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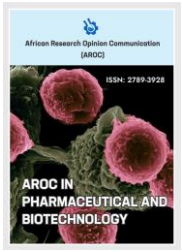
REVIEW ARTICLE

Multifunctional Natural Products in Disease Modulation: A Systems Perspective on Cancer and Cardiovascular Therapies

Adeleye A. Edema[1], Mayowa Solomon Owolabi[2], Aliyah Omotayo Abdulkabir[3], Adewuyi Hassan[4]



[1]Department of Chemistry & Biochemistry, The University of Tusla, USA.
[2]Department of Breast Cancer, Baylor College of Medicine, USA.
[3]School of Nursing, Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State, Nigeria.
[4]Department of Biochemistry, Federal University of Technology, Minna, Nigeria.

Corresponding Author:
Adeleye A. Edema
Email: adeleye07edema@gmail.com

ABSTRACT

Background: Natural products have long served as a vital source of pharmacologically active compounds, offering unique structural diversity, evolutionary optimization, and biological specificity. In this review, we examine the multifaceted roles of natural products in the prevention and treatment of cancer and cardiovascular disease (CVD), two major global health burdens. Natural products exhibit multitargeted mechanisms of action, modulating pathways related to proliferation, apoptosis, angiogenesis, inflammation, oxidative stress, and immune regulation. Classic cytotoxics like paclitaxel and vinca alkaloids continue to serve as chemotherapeutic mainstays, while non-cytotoxic phytochemicals such as curcumin, resveratrol, and EGCG influence epigenetic regulation and tumor microenvironment remodeling. In cardiovascular contexts, flavonoids and alkaloids demonstrate potent antioxidant, anti-inflammatory, and metabolic benefits through the activation of signaling pathways including eNOS, AMPK, and Nrf2. Despite promising pharmacological profiles, many natural products face clinical translation challenges due to poor solubility, low bioavailability, and regulatory limitations. Emerging strategies—such as nanoformulations, bioenhancers, synthetic biology, systems pharmacology, and AI-guided drug development—offer promising solutions to these barriers. Bridging traditional knowledge with modern scientific advances may accelerate the integration of natural products into precision medicine, establishing them as cornerstone agents in the future of therapeutic innovation.

Keywords: Cardiovascular Disease; Cancer; Natural Products; Anti-inflammatory; Antioxidants.
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1. Introduction

Natural products have long been a cornerstone of therapeutic discovery, largely due to their structural complexity, biological specificity, and ecological origin. These bioactive compounds—originating from plants, microbes, fungi, and marine organisms—offer chemical scaffolds that often surpass synthetic compounds in terms of biological compatibility and evolutionary refinement. This is particularly important in diseases such as cancer and cardiovascular disease (CVD), which are multifactorial in origin and require multi-pronged therapeutic strategies (Newman & Cragg, 2020; Atanasov et al., 2021; Li & Vederas, 2009; Harvey et al., 2015).

The remarkable structural diversity of natural products is not coincidental but the outcome of millions of years of co-evolution with biological systems. Through natural selection, these compounds have been fine-tuned to interact optimally with protein targets, enzymatic sites, and cellular membranes—often resulting in high specificity and minimal off-target effects. In contrast to synthetic drugs, which are typically engineered to act on a single molecular target, many natural products display polypharmacology, enabling them to modulate multiple targets or signaling pathways simultaneously.

This multitargeted mechanism is particularly advantageous in the management of complex diseases such as diabetes, where dysregulation involves several intersecting biological networks

(Ganesan, 2016; Dias et al., 2012; Ogunlabi et al., 2020; Adegbesan et al., 2021). Furthermore, numerous natural compounds have been documented for their ability to combat oxidative stress, suppress inflammation, and inhibit cancer progression (Onah et al., 2024; Omiyale et al., 2024a, 2024b).

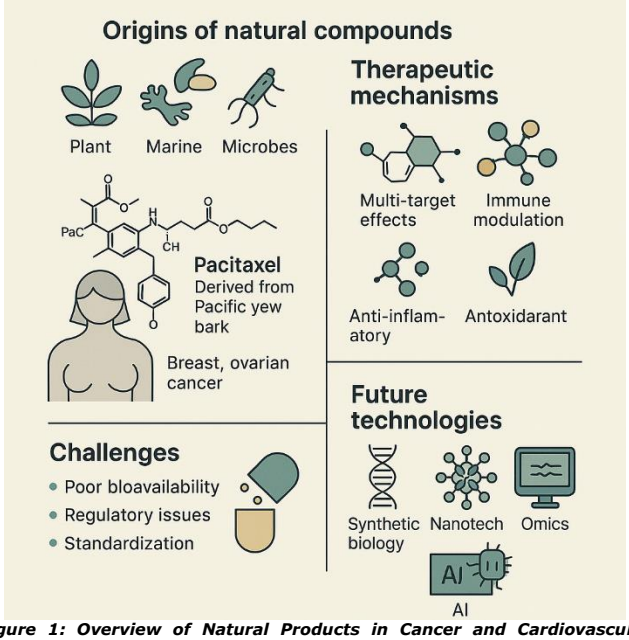

Figure 1: Overview of Natural Products in Cancer and Cardiovascular Therapy: *The top-left panel illustrates the major sources of natural compounds, including plants, marine organisms, and microbes, with paclitaxel as a representative agent derived from Taxus brevifolia. The top-right panel depicts core therapeutic mechanisms such as multi-target activity, immune modulation, anti-inflammatory effects, and antioxidant properties. The bottom-left panel outlines common challenges limiting clinical translation, including poor bioavailability, lack of standardization, and regulatory hurdles. The bottom-right panel highlights future technologies driving the advancement of natural product-based therapeutics, including synthetic biology, nanotechnology, omics platforms, and artificial intelligence (AI).*

Given the escalating burden of non-communicable diseases globally, including cancer and CVD, the healthcare system faces immense pressure to deliver effective, affordable, and safe treatments. These diseases are often characterized by chronic progression, lifestyle dependencies, and overlapping risk factors. Natural products offer an attractive solution due to their biocompatibility, cost-effectiveness in production (especially in resource-limited settings), and historical use in traditional medical systems. As modern biomedical science increasingly validates traditional knowledge through molecular and clinical investigations, the relevance of natural compounds in 21st-century medicine is being redefined—not merely as supplementary remedies but as integral components of precision and integrative medicine (Butler, 2008; Koehn & Carter, 2005).

2. Natural Products in Cancer Therapy

2.1 Classic Cytotoxics

Natural cytotoxic compounds laid the foundation for modern chemotherapy. Drugs like paclitaxel and the vinca alkaloids demonstrated that nature could yield molecules with profound antitumor efficacy. These agents act primarily on the cytoskeleton, a critical structure for cell division. Paclitaxel, for instance, stabilizes microtubules in their polymerized form, thereby preventing the normal breakdown required for mitotic progression. This leads to prolonged mitotic arrest, triggering intrinsic apoptotic pathways (Wani et al., 1971; Jordan & Wilson, 2004).

Similarly, vincristine and vinblastine—vinca alkaloids from *Catharanthus roseus*—destabilize microtubules, causing metaphase arrest. These agents not only exemplify how natural products can interfere with core cellular machinery but also highlight nature's capacity to produce molecules that influence structurally conserved processes across various cancer types (Dumontet & Jordan, 2010; Cragg & Newman, 2005).

Importantly, these compounds have undergone decades of refinement, including semi-synthetic modification and formulation improvements, to enhance delivery, reduce toxicity, and overcome resistance. Despite the emergence of targeted therapies, classic natural cytotoxics remain standard-of-care agents, often used in combination regimens (Newman et al., 2003).

2.2 Phytochemical Anticancer Agents

The role of non-cytotoxic phytochemicals in cancer prevention and therapy is a rapidly evolving field. Compounds like curcumin, resveratrol, and EGCG are not directly cytotoxic at dietary concentrations but modulate key signaling pathways that underpin tumorigenesis, such as those governing proliferation, apoptosis, inflammation, angiogenesis, and immune evasion (Aggarwal & Harikumar, 2009; Shanmugam et al., 2015).

Curcumin targets a broad spectrum of molecular effectors, including transcription factors (e.g., NF-κB, STAT3), kinases (e.g., Akt, ERK), and cytokines (e.g., IL-6, TNF-α). Its ability to induce apoptosis and inhibit angiogenesis positions it as a valuable adjuvant therapy. However, its clinical utility has been hampered by poor bioavailability, spurring the development of analogs and nanoformulations (Anand et al., 2007; Nelson et al., 2017).

Resveratrol has gained attention for its preventive properties. Beyond modulating gene expression and enzymatic activity, it activates SIRT1—a longevity-associated protein with tumor-suppressive functions. It also interferes with carcinogen metabolism and promotes DNA repair, further reinforcing its chemopreventive profile (Baur & Sinclair, 2006; Smoliga et al., 2011).

EGCG is a catechin abundant in green tea with pro-apoptotic and anti-inflammatory properties. It inhibits pathways like PI3K/Akt and Wnt/β-catenin while also exerting epigenetic

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effects, such as DNA demethylation. These properties allow EGCG to reprogram malignant cells toward a less aggressive phenotype (Yang et al., 2009; Khan et al., 2006).

2.3 Antioxidant Efficacy of ZnHCP and Organoselenium compounds in Mitigating Oxidative Stress induced cancer

In a recent study, Ogunlakin et al. (2024) synthesized a novel zinc-based compound, (Z)-((dimethylcarbamothioyl)thio)((1,1,1-trifluoro-4-oxo-4 phenylbut-2-en-2-yl)oxy)zinc hydrate (ZnHCP), and investigated its antioxidant potential using both in vitro and ex vivo models. The compound exhibited potent free radical scavenging activity—demonstrated through DPPH and nitric oxide assays—as well as ferric reducing antioxidant power (FRAP) and Fe^{2+} chelation capacity, all in a dose-dependent manner. ZnHCP's antioxidant profile was comparable to quercetin, a well-established reference compound.

Further ex vivo experiments in $FeSO_4$-induced oxidative pancreatic injury models revealed that ZnHCP significantly elevated endogenous antioxidant defenses, including catalase and glutathione levels, while reducing malondialdehyde (MDA), a biomarker of lipid peroxidation. These findings suggest that ZnHCP effectively attenuates oxidative stress by mimicking superoxide dismutase (SOD) functionality and enhancing purinergic enzyme activities. Thus, ZnHCP represents a promising antioxidant candidate with therapeutic potential against oxidative stress-related pathologies.

Organoselenium compounds, naturally present in certain plants, fungi, and microorganisms, have garnered attention for their chemopreventive properties. In our recent study (Edema et al., 2023), we explored the therapeutic potential of diphenyl diselenide—an organoselenium compound—in Wistar rats bearing mammary tumors induced by 7,12-dimethylbenz[a]anthracene (DMBA). Diphenyl diselenide demonstrated pronounced antioxidant and anti-proliferative effects, as evidenced by enhanced endogenous antioxidant defenses—including elevated levels of catalase and glutathione—and a marked reduction in lipid peroxidation. Notably, the compound attenuated tumor progression, likely through the modulation of oxidative stress pathways and activation of apoptosis signaling cascades. These findings underscore the promise of diphenyl diselenide as a bioactive agent in breast cancer therapy, combining redox modulation with effective tumor growth suppression.

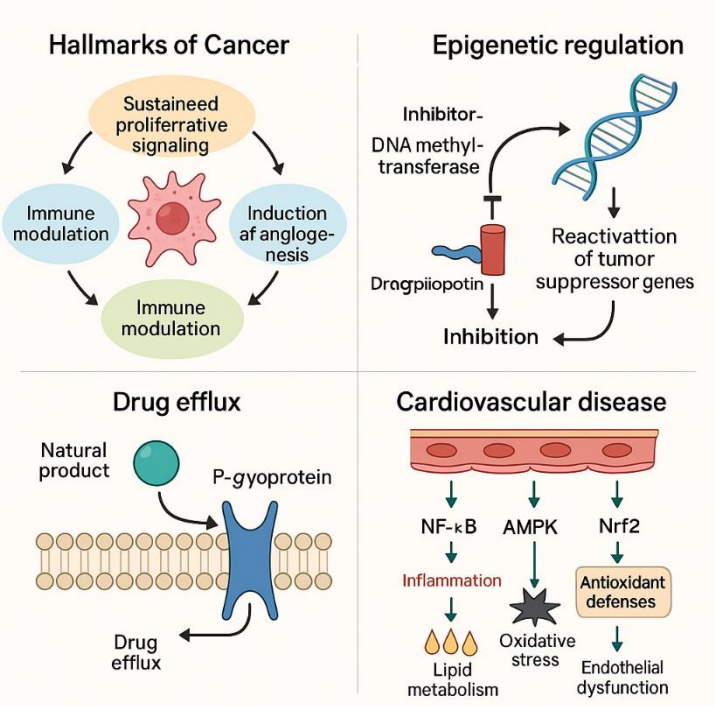

Figure 2: *Mechanistic Actions of Natural Products in Cancer and Cardiovascular Disease: This multi-panel figure summarizes the major mechanistic targets of natural products in the treatment of cancer and cardiovascular disease (CVD): Top Left (Hallmarks of Cancer): Natural compounds modulate key cancer-related processes such as sustained proliferative signaling, induction of angiogenesis, and immune evasion. These multitarget effects enable the reprogramming of the tumor microenvironment. Top Right (Epigenetic Regulation): Several natural products function as epigenetic modulators by inhibiting DNA methyltransferases and histone-modifying enzymes. This results in reactivation of tumor suppressor genes and reversal of gene silencing, contributing to tumor suppression. Bottom Left (Drug Efflux Modulation): Natural products inhibit efflux transporters like P-glycoprotein, improving the intracellular retention of chemotherapeutic drugs and overcoming multidrug resistance in cancer cells. Bottom* ***Right (Cardiovascular Disease Targets)****: In CVD, natural products regulate inflammation (via NF-κB), improve oxidative stress responses (via AMPK), and enhance antioxidant defenses (via Nrf2), thereby supporting vascular integrity, lipid balance, and endothelial function.*

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2.4 Mechanistic Insights

Natural products address several of the "hallmarks of cancer" as defined by Hanahan and Weinberg, including sustained proliferative signaling, evasion of apoptosis, induction of angiogenesis, and immune modulation (Hanahan & Weinberg, 2011). Their multitargeted nature makes them suitable candidates for overcoming therapeutic resistance, which often arises from pathway redundancy or compensatory mechanisms.

Epigenetic regulation is another key mechanism by which natural products exert anticancer effects. Many compounds influence chromatin remodeling by inhibiting DNA methyltransferases and histone deacetylases. This reactivates silenced tumor suppressor genes, promoting growth arrest or apoptosis (Link et al., 2010; Stefanska et al., 2012).

Furthermore, some phytochemicals modulate drug efflux pumps like P-glycoprotein, which are implicated in multidrug resistance. By inhibiting these pumps, they restore the intracellular retention and efficacy of chemotherapeutic drugs. The ability to influence redox balance, mitochondrial integrity, and inflammatory signaling networks further enhances their therapeutic promise (Zhou et al., 2016; Lambert & Elias, 2010).

3. Natural Products in Cardiovascular Disease (Elaborated)

3.1 Antioxidant Flavonoids

Cardiovascular diseases are closely linked to oxidative stress and endothelial dysfunction. Flavonoids, due to their polyphenolic structures, can directly scavenge reactive oxygen species (ROS) and upregulate antioxidant defenses. These actions prevent lipid peroxidation, protect vascular integrity, and improve endothelial nitric oxide synthase (eNOS) activity (Hertog et al., 1993; Schini-Kerth et al., 2010).

Hawthorn-derived flavonoids improve coronary blood flow and reduce ischemic damage by enhancing endothelium-dependent vasodilation. They also reduce myocardial oxygen demand and modulate calcium homeostasis, providing additional cardioprotection during ischemia (Tauchert, 2002; Pittler et al., 2003).

Orientin, through its antioxidant and anti-inflammatory properties, plays a protective role in myocardial ischemia-reperfusion injury—a key pathological feature in myocardial infarction and cardiac surgeries. Its effects on endogenous defense mechanisms help attenuate mitochondrial dysfunction and cardiomyocyte apoptosis (Liu et al., 2016; Gao et al., 2015).

3.2 Alkaloids and Saponins

Berberine exemplifies how a single compound can target multiple metabolic pathways relevant to CVD. By activating AMPK, it enhances insulin sensitivity, fatty acid oxidation, and glucose uptake—pathways relevant in metabolic syndrome and diabetic cardiomyopathy. It also modulates gut microbiota composition, which may further impact systemic inflammation and lipid metabolism (Zhou et al., 2008; Zhang et al., 2010).

Astragaloside IV exerts cardioprotection via activation of Nrf2, a master regulator of antioxidant response elements (AREs). By promoting expression of HO-1 and other cytoprotective genes, it mitigates oxidative injury in cardiomyocytes. Moreover, its anti-apoptotic and anti-fibrotic properties make it suitable for managing heart failure and cardiac remodeling (Su et al., 2020; Liu et al., 2013).

4. Challenges in Clinical Translation

4.1 Standardization and Quality Control

The therapeutic potential of natural products is often compromised by variability in chemical composition. Environmental factors (soil, climate), cultivation methods, extraction solvents, and storage conditions all affect bioactive compound content. This variability poses challenges for dose standardization, toxicological assessments, and reproducibility in clinical trials (Cos et al., 2006; Fabricant & Farnsworth, 2001).

Developing standardized extracts and employing marker-based quality control using techniques like HPLC, LC-MS, and NMR are necessary steps. However, the multicomponent nature of herbal preparations complicates the identification of active principles and pharmacodynamic correlations (Liu et al., 2015; Zhang et al., 2012).

4.2 Pharmacokinetics and Bioavailability

Despite their promising pharmacological activities, many phenolic natural products—such as curcumin, resveratrol, and epigallocatechin gallate (EGCG)—are hindered by poor pharmacokinetic profiles that limit their therapeutic efficacy when administered orally. These limitations include low aqueous solubility, extensive first-pass metabolism, short plasma half-lives, and poor membrane permeability (Anand et al., 2007; Walle, 2011).

Low Solubility

Curcumin has a solubility of approximately 0.03 mg/mL in water, while resveratrol exhibits similarly poor solubility. This physicochemical limitation reduces their dissolution in the gastrointestinal tract and consequently restricts absorption (Ghosh et al., 2010).

Rapid Metabolism and First-Pass Effect

Even when orally absorbed, natural compounds often undergo rapid biotransformation. Resveratrol, for example, is extensively metabolized into glucuronides and sulfates (Walle, 2011). Similarly, curcumin is rapidly conjugated to glucuronide and sulfate derivatives, leading to low plasma concentrations (Anand et al., 2007).

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Short Plasma Half-Life
Resveratrol has a plasma half-life of approximately 8 to 14 minutes, while curcumin also shows a very short systemic half-life (Shoba et al., 1998; Nelson et al., 2017).

Poor Membrane Permeability and Efflux Transporters
Curcumin and resveratrol are substrates for efflux pumps like P-glycoprotein and BCRP, which reduce net absorption (Gao et al., 2013).

4.3 Strategies to Overcome Pharmacokinetic Barriers

Nanoformulations
Nanotechnology-based carriers such as PLGA nanoparticles, liposomes, and micelles have been developed to improve solubility, bioavailability, and tissue targeting of curcumin and resveratrol (Yallapu et al., 2012; Sanna et al., 2013).

Innovative Protein Delivery in Breast Cancer Therapy
Ogunjobi et al. (2025) explore advanced protein delivery strategies—such as ligand-targeted systems, nanoparticle carriers, and bioengineered proteins—to enhance therapeutic precision and minimize systemic toxicity in breast cancer treatment. These technologies are shown to significantly improve the delivery of therapeutic proteins to tumor cells by overcoming biological barriers and targeting the tumor microenvironment, thereby increasing treatment efficacy while reducing adverse effects.

From a public health perspective, the study underscores the potential of these innovations to facilitate minimally invasive, more personalized treatments, which may enhance patient adherence and quality of life. The authors emphasize that, alongside continued technological refinement and clinical validation, integrating equitable access pathways will be crucial to ensure these interventions meaningfully impact population-level cancer outcomes.

Co-administered Bioenhancers
Piperine inhibits enzymes like UGT and SULT, and efflux transporters like P-gp, enhancing the bioavailability of curcumin by up to 2000% (Shoba et al., 1998). It also improves resveratrol absorption (Johnson et al., 2011).

Hybrid and Responsive Delivery Platforms
Smart hydrogels and self-emulsifying drug delivery systems (SEDDS) have shown improvements in the systemic exposure of resveratrol and curcumin in preclinical and clinical studies (Zhang et al., 2021).

4.4 Regulatory Hurdles in Natural Product Development
Natural products face substantial regulatory barriers due to classification as dietary supplements under laws like the U.S. DSHEA. This results in a lack of required toxicological and clinical testing compared to pharmaceutical drugs (Marcus & Grollman, 2002). The absence of harmonized regulatory guidelines and quality control undermines reproducibility and clinician confidence (Liu et al., 2015).

Another challenge is limited IP protection for natural compounds. Because native structures cannot be patented, investment incentives are low. Newer strategies include patenting semisynthetic derivatives, delivery technologies, and biosynthetic processes (Patwardhan & Mashelkar, 2009).

5. Future Perspectives: Toward Next-Generation Natural Product Therapeutics

5.1 Synthetic Biology
Synthetic biology offers a sustainable platform to produce complex natural products using microbial chassis like *E. coli* and *S. cerevisiae*, overcoming sourcing and supply limitations. For example, semi-synthetic artemisinin production has been industrialized (Paddon et al., 2013).

5.2 Multi-Omics and Precision Medicine
Omics platforms—including genomics, transcriptomics, proteomics, and metabolomics—facilitate patient stratification, biomarker discovery, and disease subtyping. These data enable personalized natural product therapies (Hasin et al., 2017; Zhao et al., 2019).

5.3 Artificial Intelligence (AI) and Machine Learning
AI can accelerate drug discovery by predicting natural compound–target interactions, identifying synergistic combinations, and optimizing chemical scaffolds (Stokes et al., 2020).

5.4 Systems Pharmacology
Systems pharmacology models how natural products interact across multiple signaling networks, which helps rationalize combination therapy and predict toxicity (Li et al., 2011; Zhang et al., 2015).

5.5 Biomarker-Driven Clinical Trials
Biomarker-guided trial designs can enhance efficacy readouts and reduce cost by focusing on responsive subpopulations (Hamburg & Collins, 2010). This is particularly promising for multi-target natural compounds.

6. Conclusion
Natural products represent a vast and underutilized pharmacological reservoir, offering structural diversity and multi-target mechanisms ideal for managing complex, multifactorial diseases such as cancer and cardiovascular disorders. Their utility is supported by centuries of traditional use and an expanding body of molecular evidence. However, their clinical potential remains largely unrealized due to pharmacokinetic challenges, regulatory ambiguities, and commercial disincentives.

To overcome these barriers, a multidisciplinary approach is required—one that leverages nanotechnology, synthetic biology, multi-omics, artificial intelligence, and systems pharmacology. Coupled with innovative clinical trial designs and regulatory reform, these strategies can enable the mainstream integration of natural products into modern, precision-based medical care.

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In summary, bridging traditional knowledge with frontier science holds the key to unlocking the full therapeutic potential of natural compounds, establishing them as cornerstone agents in the future of drug discovery.

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