Chapter 8
Polyphenol-Rich Formulations and Their Multi-Target Interactions With Molecular Pathways in Cancer Cells

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ABSTRACT

Cancer remains the second leading cause of death globally, with classical therapies limited by selectivity, toxicity, and resistance. This review examines polyphenol-rich preparations and their multi-target interactions in cancer cells. Polyphenols (flavonoids, phenolic acids, stilbenes, lignans) simultaneously modulate multiple targets, addressing key cancer hallmarks: sustained proliferative signaling, apoptosis

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evasion, replicative immortality, and angiogenesis. Key pathways include PI3K/Akt/mTOR, MAPK, RAS, and p53. Notable compounds like curcumin, resveratrol, quercetin, and EGCG induce apoptosis, inhibit angiogenesis, arrest cell cycle, and modulate epigenetics. Despite encouraging preclinical evidence, clinical translation faces challenges from low bioavailability, rapid metabolism, and conflicting data. Strategies include stable derivatives, nano-encapsulation, personalized medicine, and combination with established drugs. Polyphenolic compounds emerge as promising multi-target anticancer agents with low toxicity. Further research on bioavailability and trials is needed.

1. INTRODUCTION

Cancer continues to pose a significant global health burden, ranking as the second leading cause of death worldwide and accounting for nearly one in six deaths annually (World Health Organization, 2025). It encompasses a wide range of diseases characterized by abnormal and uncontrolled cell division, the ability to invade surrounding tissues, and, in many cases, metastasize to distant organs. The pathophysiology of cancer is complex and involves genetic mutations, epigenetic alterations, and dysregulation of multiple cellular signaling pathways (Chillón-Pino et al., 2024). Over time, cancer cells acquire several biological capabilities collectively referred to as the hallmarks of cancer which include sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, and activation of invasion and metastasis (Hanahan & Weinberg, 2011).

Traditional cancer treatments such as surgery, chemotherapy, and radiotherapy, while effective in many cases, suffer from significant drawbacks. Chemotherapeutic agents, for instance, are often non-selective, attacking both cancerous and healthy cells, leading to toxic side effects and reduced quality of life. Moreover, tumors can develop resistance to these therapies through various mechanisms such as efflux pumps, DNA repair activation, or pathway redundancy (Farhan, 2023; Emran et al., 2022). The limited specificity and adaptability of these therapies have underscored the need for novel, multi-targeted, and less toxic therapeutic alternatives. In this context, natural products, especially polyphenols, have gained substantial attention for their potential role in cancer prevention and treatment. Polyphenols are a diverse class of bioactive compounds naturally found in plants, and are abundant in fruits (such as berries, grapes, and apples), vegetables, teas, coffee, red wine, cocoa, herbs, and spices (Cháirez-Ramírez et al., 2021). Structurally, they are characterized by the presence of multiple phenol units and can be broadly categorized into flavonoids, phenolic acids, stilbenes, and lignans. These compounds are part of the

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