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Plant Secondary Metabolites in Cancer Treatment: A Mini Review

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Abstract

Plant-based medicines have been utilized since ancient times to treat a variety of human and animal illnesses one such disease is cancer. Cancer is a multistage process that involves the uncontrolled and sudden division of cells and is one of the primary causes of death. Over the past few years, plant secondary metabolites have gained substantial attention for their potential role in cancer treatment and cure. These metabolites, due to their diverse chemical structures and biological activities have shown to have potential in the treatment of cancer with minimal side effects. These bioactive compounds are produced by plants as a defense mechanism against herbivores and pathogens, and they have been found to exhibit anti-cancer properties in vitro and in vivo. They demonstrate their anticancer activities by eliminating free radicals, triggering apoptosis, and blocking angiogenesis in cancer cells. Over the years, a number of plant-derived compounds have demonstrated potential anticancer effects in vitro and in vivo. This mini-review seeks to offer an overview of current research on plant secondary metabolites and their potential use in cancer therapy. The review discusses the many types of plant secondary metabolites that have been studied for their anti-cancer activities, such as alkaloids, flavonoids, terpenoids, and phenols. The review also examines these metabolite's methods of action, which include apoptosis induction, cell cycle arrest, and angiogenesis suppression. Overall, plant secondary metabolites hold considerable promise as a source of new anti-cancer drugs, but more study is needed to fully realize their potential.

Keywords: Anticancer; Plant Secondary Metabolites; Terpenenoid; Phenolic Compounds

Abbreviations: SM: Secondary Metabolites; SOD: Superoxide Dismutase; GPx: Glutathione Peroxidases; NRF2: Nuclearfactor E rythroid-related Factor.

Introduction

Cancer stands as the foremost cause of mortality globally, with 14.1 million new cases and million deaths reported in 2012. Despite these alarming figures, there has been a 23%reduction in death rates since 1991. In 2015 alone, cancer claimed 8.8 million lives worldwide, marking it as the primary cause of death in 21 US states. Projections suggest a further surge, with an estimated 20 million new cancer cases anticipated worldwide by 2025 [1]. To tackle this global issue, scientists over the world have turned their attention to plants and their products for

the treatment of cancer. During this time, plant secondary metabolites appeared as a promising precursor for cancer treatment. These compounds have been shown to trigger apoptosis in cancer cells and even inhibit angiogenesis. All plant species can create secondary metabolites (SM). Plants evolve new genes to produce secondary products, which may explain the majority of changes in gene function across genomes. Plants have thousands of metabolites, but only a handful belongs to the "primary" metabolic pathways. The remaining metabolites serve no use in the plant and are termed as secondary metabolites (SM) [2].

The bulk of these metabolites is generated by five precursor pathways: acetyl coenzyme A (polyketides such anthraquinones and flavonoids), active isoprene (terpenoids), and shikimic acid (aromatic amino acids, cinnamic acids, tannins, and indole). Many of these secondary metabolites are therapeutically active against many cancer cell types. These products oftenare seen to hinder or even induce directions in the cancer cells which are vital for their survival. For many years, commercial products like Paclitaxel (Taxol) and Docetaxel (Taxotere) have been vital in cancer treatment. Paclitaxel is extracted from the Pacific yew tree (*Taxus brevifolia*), whereas Docetaxel comes from the European yew tree (*Taxus baccata*). These compounds are widely used in chemotherapy due to their powerful anticancer effects, effectively treating various cancers. Studies done by Danielle et al. (2020),highlight that almost 70% of anticancer drugs which are developed and are under process are actually plant-derived [3]. These biomolecules may be classified into various categories, eachperforming a distinct and particular function in plant nutrition as well as cancer prevention. Some of them are:

- Terpenoids
- Phenolic compounds
- Alkaloids
- Glucosinolates
- Saponins

In plants, these secondary metabolites defend plants from predators, competition, and abiotic challenges such as UV radiation, ozone, low temperature, wounds, and toxins. They play a crucial function in reproduction by attracting pollinators and dispersers as well. Over time, research has discovered that these particles, in addition to being helpful to plants, operate as important competitors and inhibitors in a variety of biochemical processes that might influence cancer cell activity.

Significance of Plant Secondary Metabolites in Cancer Treatment

It has been clear over the years that to prevent cancer there needs to be extensive use of techniques that involve modulating the carcinogen activation, inhibiting carcinogen binding to DNA, suppressing oxidative DNA damage, and normalizing cell signaling to prevent malignant transformation, growth, invasion, and metastatic potential. Many in vitro studies reported across the world have revealed that these biomolecules have the tendency and potential to modulate uncontrolled cancer growth and proliferation and induce apoptosis, reducing abnormal activation of intracellular signal transduction networks. Korkina & Kostyuk (2012), in their works have highlighted that various plant-derived phytoestrogens (isoflavones, lignans, Coumestans, and Resveratrol) act as potential ligands for the estrogen receptors in cancer cells thereby competing with endogenous estradiol in these cells [4].

Besides this another way to target these cancer cells is through using chemotherapeutics. Conventional cancer chemotherapies typically focus on tumor cells by disrupting either DNAor mitotic activities. With the advancements in molecular oncology, there has been groundbreaking discovery that reveals key pathways for targeted chemotherapy against cancer cells. This line of action comprises drugs like cyclin-dependent kinase inhibitors, mitogen-activated protein antagonists, proteasome inhibitors, and substances that encourage cell death and inhibit blood vessel formation. Keeping this in mind it has been seen that in most clinical trials, plant polyphenols like quercetin, catechins, resveratrol, and curcumin enhance the effectiveness of chemotherapy in fighting cancer [4]. Commercial products like curcumin (isolated from *Curcuma longa*) serve as a potent anti-inflammatory product that hasbeen used to treat cancer over the years. Besides these, products like Resveratrol (isolated from grapes, berries and peanuts) have potential anticancer properties which have been tinderresearch very recently.

Certain secondary metabolites, specifically phenolics, have demonstrated particularly potent activity against cancer cells. These compounds have anti-diabetic properties as well as anti-cancer properties which make them very useful to cure a wide variety of diseases. Phenolics derive their anticancer properties from their ability to regulate glucose metabolism, effective anti-oxidant properties, and modify endogenous defense mechanisms such as superoxide dismutase (SOD), glutathione peroxidases (GPx) and also help to regulate nuclear factor erythroid-related factor (NRF2) [5]. Studies done by Srinivasulu, et al. (2018), show that these biomolecules also have the ability to inhibit cell proliferation by blocking cascade signaling involving CDKs and also block angiogenesis factors like VEGFs [6]. Many studies have reported that during the enzymatic reaction of polyphenols, phenoxyl radicals areproduced. These radicles may lead to ROS activation and DNA oxidation which in turn leads to membrane damage and alter the receptor orientation in many cancer cells, thereby making them suitable anti-tumor agents [7]. Plants like *Vitis vinifera* and

Camellia sinensis are knownto actively produce polyphenols. These compounds have been extensively researched for their potential as anticancer agents and have demonstrated promising results by triggering apoptosis in cancer cells.

Apart from this, it is well known that inflammation plays a crucial role in cancer progression. Vast literature studies have revealed that many inflammatory cells within the inflammation microenvironment release cytokines which are essential for angiogenesis and also promote metastasis of tumor cells [8]. Studies done in various animal models have revealed that secondary metabolites like polyphenols show anti-inflammatory activities. These biomolecules work by inhibiting pro-inflammatory enzymes like NADPH oxidase, COX (Cyclooxygenase) and LOX (Lipoxygenase) (Table 1). This inhibition blocks the activity ofarachidonic acid derivatives which in turn again blocks the supply of inorganic mediators which leads to the release of ROS and RNS in cells thereby blocking inflammation [7].

Secondary Metabolites	Examples	Mode of Action	References
Terpenoids	Thymol,D-Limonene, Ursolic Acid, Phytol	-cause cell cycle arrest and mitochondrial depolarization	[9]
		-inhibits Raf and Ras signaling pathway	
		-induce autophagy and ROS production	
		-induce apoptosis by increased oxidative stress	
		-inhibits cell growth	
Phenolic Compounds	Curcumin, Resveratrol,	-Inhibit cell proliferation and angiogenesis,	[10]
		-increase cellular apoptosis	
		-induce autophagy	
Alkaloids	Berberin, Evodiamine, Vincristine	-inhibits kinases and proteinases	[11]
		-activates p53 causing apoptosis and cell arrest, -synthesis of intracellular ROS,	
		-induce autophagy	
Glucosinolates	Sulforaphane, Glucoraphanin	-Maintain low levels of systemic oxidative stress	[12]
		-inhibit cell cycle progression	
		-block angiogenesis	
Saponins	Soyasaponins, Escin	-induce caspase dependent-apoptosis	[13]
		-promotes cell differentiation	
		-induce immune-modulatory effects	
		-trigger anti-proliferative and anti-angiogenetic activity	
		-show pro-antioxidant activity along with antioxidant activity	

Table 1: Secondary metabolites and their mode of action against cancer cells.

Besides polyphenols another class of secondary metabolites has shown effective results against cancer, these are Terpenoids or isoprenoids. These biomolecules like polyphenols also show anti-inflammatory, antioxidant, neuroprotective, and anticancer properties. Studies have shown that these chemicals treat cancer by targeting key metabolic pathways (e.g., ACC1, PKM2, enolase, HK, and GLUT) and cross-linked pathways (PI3K/Akt/mTOR/AMPK) [14]. Therefore it is very evident that plants and their metabolites have been identified as a promising source of novel anticancer drugs that can substantially help to combat cancer.

Conclusion

The use of plant secondary metabolites holds great potential for the treatment of cancer. Targeting cancer metabolism and specific receptor-ligand interaction provides a valuable avenue for targeting cancer therapies. These bioactive compounds in plants have been extensively

studied for their anti-cancer properties particularly targeting these pathways and interactions which are involved in cancer development, making them an attractive option for cancer treatment. Furthermore, the use of plant secondary metabolites is associated with minimal side effects, making them a safer alternative to conventional cancer therapies. Despite their effectiveness in various in-vitro studies more research is needed to fully understand the mechanisms of action and the potential side effects of these compounds. The majority of these biomolecules often suffers from instability within the cells and also reduced bioavailability. Further research is necessary to enhance the effectiveness and durability of these plant derivatives against cancer. Overall, the findings of this mini-review suggest that plant secondary metabolites have a promising future in the field of cancer treatment, and theydeserve further exploration and investigation.

Declarations of interest

The authors declare that there are no conflicts of interest.

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