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ANTICANCER MECHANISMS OF CUCURBITACINS AND CAROTENOIDS: MODULATION OF JAK/STAT, NF-κB, AND p53 SIGNALING PATHWAYS

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ANNOTATION: This article analyzes, at the molecular level, the multivalent anticancer mechanisms of cucurbitacins and carotenoids against cancer cells. Cucurbitacins, belonging to the class of natural triterpenoids, exhibit antiproliferative and antiangiogenic activity by inhibiting the phosphorylation of STAT3/STAT5 signaling pathways, blocking the nuclear translocation of NF-κB, and reducing the expression of inflammatory mediators. Carotenoids, on the other hand, enhance apoptosis by reducing oxidative stress, limiting DNA oxidation processes, and activating the tumor-suppressor p53 pathway. The synergistic effect of both classes leads to cell cycle arrest, reduced metastatic potential, and attenuation of inflammation within the tumor microenvironment. The analyzed scientific sources demonstrate that cucurbitacins and carotenoids are recognized as promising natural bioactive agents in cancer therapy through their modulation of the JAK/STAT, NF-κB, and p53 pathways. This study provides a scientific foundation for the development of next-generation phytotherapeutic agents based on phytochemical compounds.
Keywords: Cucurbitacins, carotenoids, STAT3/STAT5, JAK/STAT pathway, NF-κB, p53 signaling pathway, antiproliferative activity, apoptotic mechanisms, antiangiogenic activity, oxidative stress, cancer therapy, phytochemical modulation.

INTRODUCTION

Modern oncology has established a new paradigm over the past decade based on molecularly targeted therapy. Extensive investigation of signaling pathways such as JAK/STAT, NF-κB, and p53-which regulate cancer cell growth, invasion, and metastasis, revealed that numerous natural compounds have the ability to modulate these complex networks. In particular, cucurbitacins found in Cucurbitaceae (gourd family) plants and carotenoids belonging to the class of yellow-orange pigments have gained significant scientific attention due to their profound effects on molecular processes associated with cancer development [1].

Cucurbitacins are natural triterpenoid compounds that were historically described in ancient Eastern medicine as “bitter cucumber substances.” Today, their strong antiproliferative, antiangiogenic, and apoptotic activities are well established due to their influence on vital pathways such as STAT3, STAT5, NF-κB, MAPK, and PI3K/Akt. Selective inhibition of the STAT3 pathway, in particular, is one of the main mechanisms by which cucurbitacins suppress cancer cell proliferation and disrupt the inflammation-driven tumor microenvironment.

In contrast, another natural class-carotenoids (β-carotene, lutein, zeaxanthin, lycopene)-plays an important role in cancer pathogenesis through their antioxidant activity, reduction of DNA oxidation, and activation of the p53 pathway. Their ability to neutralize free radicals and induce G_1–S cell-cycle arrest has been documented as a protective factor in breast, lung, prostate, and gastrointestinal cancers [2].

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In cancer development, the NF-κB signaling pathway functions as a "torch-bearing driver," regulating inflammation, cell survival, and metastasis. Blockade of this pathway by cucurbitacins and its attenuation through oxidative stress reduction by carotenoids represent two different yet complementary strategies in modulating the tumor microenvironment.

Therefore, studying the combined or independent mechanisms by which cucurbitacins and carotenoids influence the JAK/STAT, NF-κB, and p53 pathways is one of the most promising directions in developing new therapeutic strategies based on natural molecules against cancer. The molecular-level interaction of these phytochemical compounds with these pathways not only deepens the understanding of tumor pathogenesis mechanisms but also enables the development of potentially highly effective, low-toxicity bioactive supplements and phytopharmaceuticals.

From this perspective, the present study is aimed at analyzing, based on scientific sources, the modulatory effects of cucurbitacins and carotenoids on cancer cell signaling pathways, as well as deeply evaluating their molecular targets and therapeutic prospects [3].

LITERATURE REVIEW

"Anticancer Mechanisms of Cucurbitacins and Carotenoids: Modulation of JAK/STAT, NF-κB and p53 Pathways." The molecular mechanisms governing cancer progression are highly complex and consist of interconnected signaling networks that regulate cell proliferation, apoptotic processes, inflammation, angiogenesis, and DNA repair systems. The literature demonstrates that in recent years, interest in bioactive components of natural substances has sharply increased due to their ability to selectively modulate these pathways. Cucurbitacins found in Cucurbitaceae plants and carotenoids present in vegetables and fruits possess particularly high anticancer potential because of their multi-directional effects on the key pathways regulating cancer cell growth and survival.

One of the most important molecular mechanisms of cucurbitacins (types B, E, I, D) is the inhibition of the JAK/STAT signaling pathway. Excessive activation of the transcription factors STAT3 and STAT5 enhances proliferation, anti-apoptotic activity, and immune evasion mechanisms in many tumors. According to scientific research, cucurbitacin B halts STAT3 phosphorylation, blocks its nuclear translocation, and thereby reduces the expression of tumor-promoting genes such as Bcl-2 and Cyclin D1. This results in cell-cycle arrest at the G2/M phase and enhancement of apoptosis in cancer cells [4].

The NF-κB signaling system is another major pathway determining the "inflammatory readiness level" of the tumor microenvironment. Through NF-κB activation, genes involved in inflammation and metastasis, such as IL-6, TNF-α, COX-2, and MMP-9-become upregulated. Cucurbitacins suppress this pathway in two main ways: (1) inhibiting the proteolysis of IκB-α, resulting in NF-κB being "retained" in the cytoplasm, and (2) limiting the nuclear translocation of the p65 subunit. As a result, inflammation, angiogenesis, and invasion around the tumor decrease significantly. Literature describes cucurbitacin I as an especially potent anti-metastatic compound.

Carotenoids-β-carotene, lycopene, lutein, and zeaxanthin-play an important role in the early stages of cancer pathogenesis due to their antioxidant capacity. Their main activities include neutralizing reactive oxygen species (ROS), reducing lipid peroxidation, and preventing DNA oxidation. Numerous studies demonstrate that carotenoids induce cell-cycle arrest at the G_1 phase through activation of the tumor-suppressor protein p53 and direct DNA-damaged cells

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toward apoptosis. Lycopene, in particular, is recognized as one of the most promising natural modulators of the p53-dependent apoptotic pathway in prostate cancer [5].

The effects of carotenoids on the NF-κB pathway are primarily mediated by lowering oxidative stress. When ROS levels decline, NF-κB activation is significantly reduced, resulting in decreased production of inflammatory mediators and a slowdown of angio-metabolic processes within tumor tissues. Thus, carotenoids enhance anti-inflammatory and anti-angiogenic effects while complementing the antiproliferative activity of cucurbitacins.

Moreover, numerous in vitro studies show that the combination of cucurbitacins and carotenoids produces a synergistic (mutually strengthening) effect. While cucurbitacins halt proliferation through STAT3 inhibition, carotenoids reduce oxidative stress and increase cellular sensitivity to apoptosis. The convergence of these two mechanisms forms a powerful therapeutic model that sharply decreases cancer cell survival [6].

CONCLUSION

In conclusion, the literature confirms that cucurbitacins and carotenoids influence the three major pathways regulating cancer progression-JAK/STAT, NF-κB, and p53-as multi-target, potent, and relatively selective modulators. Their natural origin, low toxicity, and pathway-rich mechanisms of action continue to increase interest in their application in phytotherapy, nutraceutical research, and new-generation cancer treatment models. The literature reviewed within this study demonstrates that cucurbitacins and carotenoids exert multi-directional anticancer effects by targeting the three key signaling pathways critical for cancer development/STAT, NF-κB, and p53. Their molecular activities are closely linked to restricting cancer cell proliferation, enhancing apoptosis, reducing inflammatory mediators, and restoring DNA protection mechanisms. First, the influence of cucurbitacins on the STAT3/STAT5 pathway represents one of their strongest therapeutic mechanisms. When STAT3 is highly active, cell proliferation, angiogenesis, and anti-apoptotic processes intensify. Cucurbitacin B, E, and I block STAT3 phosphorylation and inhibit its nuclear translocation. This leads to decreased expression of tumor-supporting genes such as Bcl-2, survivin, and Cyclin D1. Thus, cucurbitacins effectively "disconnect cancer cells from their growth program."

The accumulated scientific data confirm that cucurbitacins and carotenoids exert strong and multi-directional anticancer effects. Their primary molecular targets are the JAK/STAT, NF-κB, and p53 pathways. Cucurbitacins block STAT3 activation, sharply limiting tumor cell proliferation, invasion, and inflammation. Carotenoids reduce oxidative stress, activate the p53 pathway, and drive cancer cells into apoptotic death. A shared feature of both classes is their ability to suppress inflammation and angiogenesis through inhibition of the NF-κB pathway. The synergistic effects of these two groups allow simultaneous targeting of multiple stages of cancer pathogenesis, making them highly promising natural therapeutic agents.

The research findings indicate that phytopreparations developed on the basis of cucurbitacins and carotenoids may serve as highly effective, low-toxicity, and physiologically compatible therapeutic options by modulating key molecular mechanisms involved in cancer development. Therefore, deeper investigation of these natural compounds—including their bioavailability, synergy, dose safety, and clinical applicability-remains one of the most promising directions for future cancer therapy.

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