



MECHANISMS BY WHICH BIOACTIVE COMPOUNDS OF ZUCCHINI (*CUCURBITA PEPO*) AND PATISSON (CUCURBITACINS AND TERPENOIDS) LIMIT CANCER CELL GROWTH AND METASTASIS THROUGH NF- κ B–STAT3 SIGNALING PATHWAYS

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Annotation: This article analyzes the chemical composition of *Cucurbita pepo* (zucchini) and its multivalent molecular mechanisms of anticancer activity. Phytochemical studies have shown that zucchini contains cucurbitacins, terpenoids, flavonoids, carotenoids, phytosterols, and immunomodulatory polysaccharides. These bioactive compounds suppress key oncogenic signaling axes such as NF- κ B and STAT3, thereby limiting proliferation, invasion, and metastasis in cancer cells. Additionally, components of zucchini reduce the expression of MMP-2/9, VEGF, and COX-2, activate apoptotic pathways, diminish oxidative stress, and enhance immune responses within the tumor microenvironment. The findings allow the evaluation of zucchini as a low-toxic, highly bioactive, and promising nutraceutical source that may be used for cancer prevention and adjunctive therapy.

Keywords: zucchini, cucurbitacin, terpenoids, flavonoids, NF- κ B, STAT3, metastasis, angiogenesis, immunomodulation, antioxidant, bioactive compounds, nutraceuticals, oncogenic signaling pathways.

INTRODUCTION

The rapid proliferation of cancer cells, their infiltration into surrounding tissues (invasion), and their spread to distant organs (metastasis) are closely associated with the persistent and excessive activation of central signaling systems such as NF- κ B and STAT3. These transcription factors regulate inflammatory mediators, anti-apoptotic proteins, angiogenesis-promoting factors, and immune-evasion mechanisms, thereby ensuring long-term survival of tumor cells. Therefore, inhibition of the NF- κ B–STAT3 axis is considered one of the most important targets in cancer therapy.

Bioactive compounds found in the fruit and peel of *Cucurbita pepo* (zucchini)-particularly cucurbitacin B, E, and various terpenoids-are attracting significant scientific interest as natural inhibitors of these signaling pathways. By reducing the activation of NF- κ B and STAT3, they suppress inflammatory signaling, activate apoptosis, and decrease the expression of several key molecules responsible for cancer progression-MMP-2/9, VEGF, Bcl-2, COX-2, and EMT markers.

The low toxicity of cucurbitacins and terpenoids, their ability to influence several molecular pathways simultaneously, and their potent anti-proliferative, anti-invasive, and anti-metastatic properties make zucchini and patisson promising phytochemical sources for cancer prevention, functional nutrition, and nutraceutical research [1].

LITERATURE REVIEW

Scientific investigations on the role of NF- κ B and STAT3 signaling in cancer pathogenesis show that these transcription factors play pivotal roles at all stages of malignancy initiation, proliferation, invasion, angiogenesis, and metastasis. When NF- κ B is excessively activated, the



expression of genes associated with inflammation and survival, such as IL-6, TNF- α , COX-2, and Bcl-2, increases; when STAT3 is activated, molecules such as VEGF, MMP-2/9, and survivin accelerate cancer spread. Additionally, NF- κ B and STAT3 mutually stimulate each other, forming a self-sustaining “inflammatory feedback loop.”

In recent years, among natural compounds, cucurbitacins and terpenoids have been widely discussed as promising inhibitors capable of disrupting this pathological loop. Literature reports indicate that cucurbitacin B, E, and I halt STAT3 at the tyrosine-phosphorylation stage and restrict its nuclear translocation. As a result, the expression of STAT3-regulated oncogenes such as Bcl-2, Cyclin-D1, and MMP-9 decreases significantly. In particular, studies in breast, liver, colorectal, and lung cancer models have reported that cucurbitacin B suppresses STAT3 pY705 phosphorylation by 60–80% [2].

The terpenoid group also plays an important role in the inhibition of NF- κ B. Literature data show that terpenoids such as limonene, α -terpineol, and β -myrcene prevent I κ B α degradation, thereby restricting nuclear entry of the NF- κ B p65 subunit and reducing the activity of inflammatory genes such as COX-2, IL-1 β , and TNF- α . Additionally, terpenoids activate caspase-3/9, which are responsible for apoptosis, restoring the cell’s natural death mechanisms.

Other studies have shown that biologically active compounds in *Cucurbita pepo* inhibit the enzymes MMP-2 and MMP-9. Since these enzymes play key roles in basement-membrane degradation and invasion, their reduction significantly decreases the metastatic potential of cancer. Furthermore, flavonoids and polyphenols in zucchini and patisson inhibit angiogenesis by lowering VEGF levels, thereby reducing the formation of blood vessels that supply the tumor. The literature highlights the low toxicity, antioxidant, anti-inflammatory, and anti-metastatic properties of zucchini compounds. These characteristics make them a natural resource that can support cancer prevention as a nutraceutical agent. The multi-target approach of natural compounds gives them an important advantage over classical chemotherapeutic agents [3].

Table 1.

Major Chemical Compounds of *Cucurbita pepo* (Zucchini) and Their Biological Properties

Chemical group	Major compounds	Chemical nature	Biological properties
Cucurbitacins	Cucurbitacin B, D, E, I	Triterpenoid steroids	Strong cytotoxicity, STAT3/NF- κ B inhibitor
Terpenoids	Limonene, α -terpineol, β -myrcene, squalene	Mono- and sesquiterpenes	Anti-inflammatory, anti-metastatic, apoptotic
Flavonoids	Quercetin, rutin, luteolin	Polyphenols	Strong antioxidant, DNA protection, MMP inhibition
Phenolic compounds	Gallic acid, syringic acid	Aromatic acids	Antioxidant, anti-mutagenic
Carotenoids	β -carotene, lutein, zeaxanthin	Lipophilic pigments	Reduces ROS, membrane protection
Phytosterols	β -sitosterol, stigmasterol	Steroid lipids	PI3K/Akt-mTOR inhibition, antiproliferative
Polysaccharides	Rhamnogalacturonan, arabinogalactan	Complex carbohydrates	Immunomodulatory, shifts M1/M2 balance
Vitamins	Vitamin C, B-	Water-soluble and	Antioxidant, immune-



	complex, E	lipophilic vitamins	enhancing
Minerals	K, Mg, Zn, Fe	Macro/microelements	Cofactors of antioxidant enzymes

Table 2.

Bioactive Compounds of Zucchini and Their Molecular Anti-Cancer Mechanisms

Bioactive compound	Target signaling pathway	Effect on cancer cells	Outcome
Cucurbitacin B/E	STAT3 ↓, NF-κB ↓	Bcl-2 ↓, Survivin ↓, Bax ↑	Proliferation ↓, apoptosis ↑
Terpenoids (limonene, α -terpineol)	NF-κB ↓, COX-2 ↓	Inflammation ↓, migration ↓	Metastasis slows
Quercetin, luteolin (flavonoids)	MMP-2/9 ↓, ROS ↓	Invasion ↓, DNA damage ↓	Metastasis ↓, anti-mutagenic
β -carotene, lutein (carotenoids)	GPX4 ↑, ROS ↓	Lipid peroxidation ↓	Ferroptosis is controlled
β -sitosterol (phytosterol)	PI3K/Akt-mTOR ↓	Cell cycle arrest	Growth is restricted
Polysaccharides	M1/M2 polarization	iNOS ↑, TNF- α ↑	The immune system eliminates tumor
Vitamin C + flavonoid synergy	Antioxidant system ↑	Protects DNA	Mutation risk ↓
Squalene	Anti-angiogenic	VEGF ↓	Inhibition of blood vessel formation
Bioactive compound	Target signaling pathway	Effect on cancer cells	Outcome

The cucurbitacins, terpenoids, flavonoids, carotenoids, and polysaccharides present in *Cucurbita pepo* (zucchini) exert a multitarget inhibitory effect on cancer cells. These compounds block oncogenic signaling pathways such as NF-κB, STAT3, PI3K/Akt, MMP, and VEGF, thereby suppressing proliferation, invasion, metastasis, and angiogenesis.

Chemical composition and anticancer activity of *Cucurbita pepo* (zucchini): an analytical approach- *Cucurbita pepo* (zucchini) is rich in biologically active compounds and demonstrates multi-centered anticancer activity through a complex of phytoconstituents such as terpenoids, cucurbitacins, polyphenols, flavonoids, and carotenoids. The synergistic action of these compounds distinguishes zucchini as a low-toxic but highly potent nutraceutical source with significant anticancer potential [4].

Cucurbitacins and their anticancer role- Cucurbitacin B, D, E, and I in zucchini are triterpenoid steroid-like compounds with high biological activity. Scientific sources report that cucurbitacins directly inhibit STAT3 and NF-κB signaling pathways in cancer cells. Suppression of STAT3 phosphorylation leads to a decrease in anti-apoptotic proteins such as Bcl-2, an increase in the Bax/Bcl-2 ratio, and the activation of apoptotic processes. Inhibition of NF-κB reduces the expression of COX-2, TNF- α , and IL-6, thereby restricting inflammation-driven proliferation,



invasion, and migration. Therefore, cucurbitacins exert a comprehensive suppressive effect against tumor cell growth, tissue infiltration, and metastasis to distant organs [5].

The effect of terpenoids on NF- κ B and their anti-metastatic activity - Zucchini contains terpenes such as limonene, α -terpineol, β -myrcene, and squalene, which belong to the class of volatile essential compounds. Terpenoids prevent the degradation of I κ B α , thereby limiting the nuclear translocation of NF- κ B and reducing the expression of COX-2, iNOS, and MMP-9. These changes lead to reduced angiogenesis (VEGF), slower migration, and decreased metastasis in tumor tissues. Studies indicate that terpenes activate caspase-3/9 and induce apoptosis in cancer cells.

Flavonoids - antioxidant protection and DNA stabilization- Flavonoids such as quercetin, rutin, and luteolin in zucchini are strong polyphenolic antioxidants. They neutralize ROS (reactive oxygen species), reducing DNA damage, mutations, and genetic instability. Enhancement of p53 activity by flavonoids leads to cell cycle arrest at the G2/M phase, which limits the proliferation of tumor cells. Additionally, flavonoids decrease MMP-2 and MMP-9 activity, thereby slowing invasion and metastasis [6].

Carotenoids - prevention of lipid peroxidation and ferroptosis regulation- The carotenoids of zucchini, including β -carotene, lutein, and zeaxanthin, are lipophilic antioxidants. They enhance membrane stability, inhibit lipid peroxidation, and reduce ROS levels. Supporting the GPX4 enzyme system stabilizes ferroptosis processes, thereby limiting oxidative stress-induced damage in cancer cells. Carotenoids also enhance immune system activity and strengthen anti-tumor immune surveillance.

Immunomodulatory effects of polyphenols and polysaccharides- Polysaccharides in zucchini possess immunomodulatory properties, inducing the transition of macrophages from the M2 (tumor-supporting) phenotype to the M1 (tumor-suppressive) phenotype. This process is accompanied by altered interleukin profiles, increased iNOS expression, and enhanced phagocytic activity. Such immune reprogramming disrupts immunosuppressive conditions within the tumor microenvironment and strengthens immune attacks against tumor cells.

The chemical composition of zucchini exerts anti-cancer effects through multi-stage mechanisms. Cucurbitacins and terpenoids inhibit the NF- κ B–STAT3 axis, suppressing proliferation, invasion, and metastasis. Flavonoids and carotenoids stabilize DNA through antioxidant defense, inhibit MMP-2/9, and prevent lipid peroxidation. Polysaccharides transform the tumor microenvironment into an immune-active state that promotes cancer cell elimination.

As a result, the phytochemical complex of zucchini creates a strong, low-toxic, multi-target anticancer potential against the development and spread of cancer.

CONCLUSION

The analyses show that *Cucurbita pepo* (zucchini), due to its phytochemical composition, effectively inhibits several key molecular pathways that govern cancer development, spread, and invasion. The cucurbitacins, terpenoids, flavonoids, carotenoids, phytosterols, and polysaccharides in zucchini reduce critical signaling axes such as NF- κ B, STAT3, MMP-2/9, VEGF, and PI3K/Akt–mTOR within cancer cells. This leads to slowed proliferation, angiogenesis, invasion, and metastasis; enhanced apoptosis; and reduced DNA damage.

The low toxicity of zucchini, its antioxidant potential, immunomodulatory activity, and simultaneous suppression of multiple oncogenic pathways make it one of the most promising natural anticancer resources. Therefore, the chemical constituents of this plant hold significant potential not only for scientific research but also for practical healthcare applications-particularly



in developing cancer-preventive functional foods, bioactive supplements, and nutraceutical preparations. The obtained scientific findings provide a strong foundation for creating supplements aimed at cancer prevention and strengthening the body's natural defense mechanisms. Development of polyphenol–carotenoid complexes, cucurbitacin-rich extracts, or terpenoid-rich nutraceutical formulations may provide combined antioxidant, anti-invasive, anti-metastatic, and immunomodulatory effects. Research and innovative developments in this field pave the way for producing new, safe, and effective anticancer bioactive supplements within the national nutraceutical industry, contributing significantly to public health protection.

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