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Harnessing the Antineoplastic Potential of Benzyl Isothiocyanate: Phytochemical-Based Therapeutic Strategy Towards Cancer

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Abstract: Cancer remains a pressing global health issue, with its burden intensified by factors such as increased life expectancy, urbanization, and shifts in environmental and lifestyle patterns. Defined by unregulated cell growth, invasive behavior, and the ability to metastasize, cancer continues to be a principal cause of death and disease globally. In response, there has been growing interest in natural phytochemicals as adjuncts or alternatives to traditional cancer therapies, largely due to their broad-spectrum biological activities and relatively lower toxicity. Benzyl isothiocyanate (BITC), a naturally occurring compound released from glucosinolates in cruciferous vegetables and papaya seeds via myrosinase action, has emerged as a potential anticancer agent. A wealth of preclinical evidence supports BITC's efficacy in cancer prevention and treatment, attributing its effects to mechanisms such as apoptosis induction, disruption of cell cycle progression, suppression of metastasis, and regulation of oncogenic signaling cascades. Recent advancements in nanotechnology have further enhanced BITC's therapeutic potential by improving its stability, bioavailability, and selective toxicity toward malignant cells while sparing normal tissues.

Keywords: *Phytochemical, Benzyl Isothiocyanate, Nano-Formulation, Anti-Neoplastic Effect, Cancer Cell.*

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I. INTRODUCTION

A. Cancer:

Health-related issues continue to pose a substantial burden on global health systems, adversely affecting economic development, diminishing life expectancy, and contributing to increased mortality rates (Bray et al., 2012). Among these, cancer remains one of the most pressing public health threats worldwide. It is marked by the loss of normal growth control, leading to the unchecked proliferation of cells due to disruptions in cell cycle regulation (Saini et al., 2020). In a healthy organism, cellular division and replacement are governed by precise molecular checkpoints. However, cancer arises when these regulatory pathways are altered through genetic mutations or epigenetic modifications, resulting in sustained cell division and tumor development. As the disease progresses, cancerous cells acquire the ability to invade adjacent tissues and spread to distant sites via the blood or lymphatic systems, a process known as metastasis (Hanahan et al., 2011). The shift from normalcy to malignancy involves a complex series of molecular and cellular alterations, collectively termed malignant transformation or progression (Bhat et al., 2024).

Tobacco consumption and excessive alcohol intake are among the leading contributors to cancer-related mortality worldwide. In addition to these, several other risk factors—including infections, obesity, poor dietary habits, sedentary lifestyle, exposure to ionizing radiation, and environmental pollutants—have also been implicated in carcinogenesis (Anand et al., 2008). These agents exert their effects primarily by inducing partial or complete alterations in cellular gene expression. It is estimated that only about 5–10% of all cancer cases result from inherited genetic mutations, while the majority are attributed to environmental and lifestyle factors. Early detection through screening and

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recognition of clinical signs such as persistent lumps, abnormal bleeding, chronic cough, unexplained weight loss, and changes in bowel habits plays a crucial role in improving prognosis (Sadikovic et al., 2008).

Despite notable progress in medical research and oncology, cancer continues to pose a significant global health burden, with many therapeutic strategies showing limited long-term efficacy. Current treatment approaches typically involve surgical resection, often in combination with radiotherapy, chemotherapy, or targeted molecular interventions (Debela et al., 2021). Chemotherapeutic regimens utilize various drug classes, such as antimetabolites like methotrexate, DNA-damaging agents such as cisplatin and doxorubicin, microtubule inhibitors including taxanes, hormone-based therapies, and a range of molecularly targeted drugs (Choudhari et al., 2020). The effectiveness of these therapies largely depends on cancer type and stage at the time of diagnosis. However, challenges such as tumor relapse, resistance to chemotherapeutic agents, and toxicity to normal cells remain prevalent. These limitations not only reduce therapeutic effectiveness but also negatively impact patients' quality of life. Therefore, there is a critical need to discover and develop new anticancer agents that offer enhanced efficacy and lower systemic toxicity (Anand et al., 2023).

Plant-derived phytochemicals and their derivatives have garnered significant attention as a promising alternative approach for cancer chemoprevention. Rather than targeting late-stage malignancies, these compounds primarily aim to modulate the process of carcinogenesis at its early stages (Chavda et al., 2022). Epidemiological and experimental studies suggest that regular intake of phytochemicals, coupled with a healthy lifestyle, could potentially prevent over two-thirds of cancer cases by interfering with tumour initiation, promotion, and progression (Rudzińska et al., 2023). A growing body of evidence supports the efficacy of phytochemicals not only in preventing but also in treating various cancers, with findings indicating their ability to reduce cancer cell viability, induce programmed cell death (apoptosis), and suppress angiogenesis and metastasis (Rudzińska et al., 2023). Additionally, both *in vitro* and *in vivo* studies have demonstrated that many of these compounds exhibit superior therapeutic indices compared to conventional chemotherapeutics, often producing fewer adverse effects on healthy surrounding tissues (Singh et al., 2019).

Phytochemicals are bioactive substances produced naturally by plants as part of their metabolic processes, contributing to their sensory properties such as color, flavor, aroma, and texture (Shahidi and Hossain, 2022). These secondary metabolites form a crucial component of a plant's defense system, protecting against microbial infections, parasitic attacks, and environmental stressors (Behl et al., 2021). To date, over a thousand phytochemicals have been identified from various plant sources, including leaves, roots, seeds, and fruits (Khan et al., 2020). Major classes of these compounds include carotenoids, polyphenols, flavonoids, isoflavones, phytosterols, saponins, and specific polysaccharides (Thakur et al., 2020). These bioactives are known for their potent antioxidant activity and possess a broad spectrum of pharmacological properties, including antimicrobial, antiviral, antiallergic, anti-inflammatory, antidiabetic, and anticancer effects (Rahman et al., 2019). Furthermore, several phytochemicals exhibit protective effects on critical organs, demonstrating hepatoprotective, neuroprotective, and nephroprotective activities when challenged with toxic agents (Dwivedi et al., 2022). Their anticancer potential is often attributed to their ability to modulate cellular signaling pathways, regulate gene expression, and enhance immune system function (Chen and Liu, 2018).

Numerous studies have highlighted the antineoplastic potential of isothiocyanates (ITCs), a class of naturally occurring compounds characterized by the –N=C=S functional group. These bioactive molecules are primarily derived from cruciferous vegetables belonging to the Brassicaceae family, such as broccoli, Brussels sprouts, cabbage, and cauliflower (Petropoulos et al., 2017). Among the various ITCs, BITC has garnered significant attention due to its broad pharmacological activities. BITC is predominantly found in Alliariapetiolata and papaya seeds (Ali et al., 2018), and is biosynthesized via the enzymatic hydrolysis of glucosinolates (GLS) by the myrosinase enzyme—a reaction responsible for the characteristic pungent odor of these plants (Petropoulos et al., 2017).

BITC has demonstrated multiple therapeutic properties, including antioxidant, anti-inflammatory, antifungal, and notably, anticancer activities, as evidenced by extensive preclinical investigations. Its antitumor efficacy is attributed to its ability to modulate several key hallmarks of cancer, such as uncontrolled proliferation, resistance to apoptosis, angiogenesis, and metastatic progression (Wang et al., 2022).

This review comprehensively discusses the anticancer mechanisms of BITC, emphasizing its molecular targets and pathways involved in tumor suppression. Furthermore, the paper explores advanced nanotechnological strategies that have been developed to enhance the bioavailability and therapeutic efficacy of BITC in oncological applications.

B. BITC and Pharmacological Overview:

Isothiocyanates (ITCs) are biologically active compounds predominantly found in cruciferous and radish family vegetables such as broccoli, cauliflower, Brussels sprouts, watercress, and radish (Avato & Argentieri, 2015). These compounds are formed through the enzymatic hydrolysis of glucosinolates, a class of Thio glycoside conjugates, upon tissue disruption such as chewing or cutting (Shakour et al., 2022). The enzyme myrosinase, a β-Thio glucoside glucohydrolase, catalyzes this hydrolysis, resulting in various ITCs including allyl isothiocyanate (AITC), sulforaphane (SFN), BITC, and phenethyl isothiocyanate (PEITC) (Getahun et al., 1999). Among these, BITC is recognized for its potent pharmacological activities and is primarily present in cruciferous vegetables. It is a lipophilic compound with a strong pungent odor and

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has a molecular formula of C_8H_7NS (molecular weight: 149.21) (Ali et al., 2018). In vivo, BITC undergoes biotransformation via conjugation with glutathione, followed by enzymatic processing through glutathione-S-transferase (GST), leading to the formation of a mercapturic acid derivative (Hinchman et al., 1994). Approximately 62% of administered BITC is eliminated in urine as this N-acetylcysteine conjugate (Lamy et al., 2011).Structurally, BITC contains an electrophilic carbon within its -N=C=S group, which contributes to its ability to induce oxidative stress by generating reactive oxygen species (ROS), potentially leading to DNA damage (Minarini et al., 2014). Current research highlights the multifaceted bioactivity of BITC, including its antimicrobial and anticancer properties.

II. MATERIALS AND METHODS

A thorough literature review was performed using Google Scholar with the search terms “benzyl isothiocyanate (BITC),” “anticancer,” and “nano-formulation” to identify pertinent studies published up to November 2024. In light of the consistently high global cancer mortality and the demand for innovative therapeutic agents, BITC has emerged as a compound of interest due to its promising anticancer activity. A growing body of both in vitro and in vivo research supports its effectiveness against a wide range of malignancies. This review presents a critical analysis of recent findings on the molecular mechanisms through which BITC exerts its anticancer effects, particularly its influence on key signaling pathways involved in apoptosis, cell proliferation, cell cycle regulation, and autophagy. The aim is to provide an up-to-date evaluation of BITC's therapeutic relevance and mechanistic insights within the context of cancer treatment.

III. ANTICANCER ACTIVITY OF BITC

A. Selective Cytotoxicity Against Cancer Cells:

BITC, a bioactive compound found in cruciferous vegetables such as mustard, broccoli, and cabbage, exhibits pronounced anticancer properties through selective cytotoxicity. Research indicates that BITC effectively induces apoptosis and suppresses proliferation in multiple human cancer cell types, including those of the breast, prostate, and pancreas, while sparing normal, non-transformed cells. This selectivity is primarily associated with BITC’s ability to modulate critical cellular processes, including oxidative stress via reactive oxygen species (ROS) generation, mitochondrial membrane potential disruption, and inhibition of oncogenic transcription factors such as NF-κB and STAT3 (Kim et al., 2010; Xiao et al., 2014). Furthermore, BITC interferes with cell cycle progression by inducing arrest at the G2/M checkpoint and alters the balance of apoptotic regulators—upregulating pro-apoptotic Bax and downregulating anti-apoptotic Bcl-2 proteins (Singh et al., 2009). These multifaceted actions underscore BITC’s promise as a selective chemopreventive and therapeutic agent in oncology.

B. Inducing Intracellular Reactive Oxygen Species (ROS) Generation:

BITC, a phytochemical with potent anticancer properties, induces apoptotic cell death in human oral carcinoma cells predominantly by altering the intracellular redox balance(Yeh et al., 2016). BITC treatment leads to a marked elevation in intracellular (ROS) levels across various cancer cell types. One of the key mechanisms involves BITC's interaction with glutathione (GSH), a principal intracellular antioxidant. BITC reacts with the thiol group of GSH to form dithiocarbamates, thereby enhancing oxidative stress and modulating redox-sensitive signaling pathways that culminate in programmed cell death.

Additionally, BITC exerts a dual effect on the GSH system: it not only depletes intracellular GSH but also upregulates glutathione S-transferase (GST) activity, further impairing the antioxidant defense and promoting ROS accumulation in malignant cells (Sahu et al., 2009). Furthermore, the binding of BITC to GSH can prevent its interaction with nucleophilic amino acid residues in proteins, contributing to widespread cellular dysfunction and damage (Mi et al., 2011).

Elevated ROS levels under BITC treatment also cause DNA damage, which activates DNA damage response kinases, particularly the ATM (ataxia telangiectasia mutated) pathway. This leads to the phosphorylation of downstream targets such as Chk2 and the tumor suppressor protein p53, ultimately triggering apoptosis. These events are characterized by G2/M cell cycle arrest and are supported by increased expression of phosphorylated ATM (p-ATM), Chk2 (p-Chk2), p53, p21, phosphorylated Cdc2 (p-Cdc2), and cleaved PARP (Yeh et al. 2016).

C. Changes in Mitochondrial Function:

BITC exerts potent pro-apoptotic effects by targeting mitochondrial function. It markedly impairs mitochondrial membrane integrity, promoting the cytosolic release of apoptosis-inducing factor-1 (AIF) and endonuclease G (Endo G), as observed by Lee et al. (2018). Mitochondrial dysfunction further elevates intracellular levels of reactive oxygen species (ROS), such as hydrogen peroxide, thereby enhancing oxidative stress. This oxidative milieu facilitates the nuclear translocation of AIF and Endo G, leading to DNA fragmentation, disruption of the cell cycle, and initiation of programmed cell death. Additionally, BITC-induced apoptosis involves both mitochondrial cytochrome c release and the activation of caspase cascades, suggesting the engagement of both caspase-dependent and caspase-independent apoptotic pathways (Liu et al., 2015).

D. Inhibition of Epithelial-Mesenchymal Transition (EMT):

Epithelial–mesenchymal transition (EMT) is a fundamental cellular process that significantly contributes to cancer development and metastasis. During EMT, epithelial cells acquire mesenchymal characteristics, resulting in diminished cell–cell adhesion, disruption of apical–basal polarity, and elevated migratory and invasive capabilities. This transition is marked by the suppression of epithelial markers like E-cadherin and the induction of mesenchymal

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proteins such as vimentin and fibronectin. These molecular alterations facilitate tumor progression, enhance metastatic potential, and are often linked to resistance against conventional cancer therapies (Ribatti et al., 2020).

BITC, a naturally occurring isothiocyanate, has been shown to suppress EMT in several cancer models. BITC treatment restores epithelial characteristics by upregulating E-cadherin and tumor suppressors such as p53 and retinoblastoma (Rb) protein in both estrogen receptor-positive (MCF-7) and -negative (MDA-MB-231, 4T1) breast cancer cells, as well as in aggressive pancreatic cancer cells like PC-45. Moreover, BITC effectively downregulates mesenchymal markers and key transcriptional repressors of E-cadherin, including Snail and Slug, even in the presence of pro-inflammatory cytokines like TNF-α and TNF-β. These effects suggest that BITC interferes with cytoskeletal dynamics and reduces cancer cell motility, thereby hindering metastatic potential (Trudel et al., 1992).

E. Inhibition of Matrix Metalloproteases (MMP) Activity:

The degradation of extracellular matrix (ECM) components by proteolytic enzymes such as matrix metalloproteinases (MMPs) is a pivotal event in the metastatic progression of tumors. Specifically, MMP-2 and MMP-9 play key roles in the enzymatic breakdown of type IV collagen in the basement membrane, thereby facilitating cancer cell invasion and dissemination. Experimental studies employing gelati zymography, reverse transcription polymerase chain reaction (RT-PCR), and western blotting have shown that BITC suppresses the expression of MMP-2 and MMP-9 in various cancer cell lines, including HT29 (colorectal carcinoma), SK-Hep1, and HepG2 (hepatocellular carcinoma) (Lai et al., 2010; Wang et al., 2010). Additionally, BITC has been reported to influence Notch signaling in breast cancer cells by elevating the levels of cleaved forms of Notch1, Notch2, and Notch4, which are indicative of active signaling. Among these, only Notch2 activation has been functionally linked to the observed inhibition of cancer cell migration, suggesting a selective role in BITC-mediated antimetastatic effects (Guo et al., 2011).

F. Chromatin Condensation and DNA Fragmentation:

BITC has been shown to induce the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, which subsequently activates the ataxia-telangiectasia mutated (ATM) signaling pathway. This activation triggers downstream phosphorylation of checkpoint kinase 2 (Chk2), ultimately leading to the stabilization and activation of the tumor suppressor protein p53. Both Chk2 and p53 play critical roles in modulating a range of target genes that govern cell cycle arrest at the G2/M checkpoint and initiate apoptotic pathways (Yeh et al., 2016).

Furthermore, molecular docking studies have demonstrated that BITC binds effectively within the active sites of methenyltetrahydrofolatesynthetase (MTHFS) and epidermal growth factor receptor kinase (EGFRK). The interaction analysis revealed key amino acid residues—namely Thr107, Pro81, and Ile111—engaging in hydrogen bonding with BITC, while additional π-interactions with its aromatic rings and functional groups contribute to binding stability. These molecular interactions likely contribute to the inhibitory effects of BITC on cancer cell proliferation and survival (Kadir et al., 2023).

G. Cell Cycle Arrest:

The progression through the cell cycle is intricately controlled by the interplay between cyclins and cyclin-dependent kinases (CDKs). A critical checkpoint exists at the G2/M transition, primarily regulated by the CDK1-Cyclin B1 complex. Upon DNA damage, checkpoint kinase 2 (Chk2) becomes activated and subsequently phosphorylates the phosphatase Cdc25C, rendering it inactive. This prevents the dephosphorylation and activation of the CDK1-Cyclin B1 complex (also known as Cdc2-Cyclin B1), leading to arrest at the G2/M phase.

BITC, a bioactive compound derived from cruciferous vegetables, has been reported to trigger Chk2 activation in Capan-2 pancreatic cancer cells. This activation is associated with a marked downregulation of Cdc25C, CDK1, and Cyclin B1, resulting in G2/M phase arrest. BITC also inhibits cell cycle progression by suppressing cyclin expression through the modulation of histone deacetylase (HDAC) activity, thereby attenuating the proliferation of pancreatic cancer cells such as BxPC-3 and Capan-2 in both in vitro and in vivo models (Batra et al., 2010).

Furthermore, BITC engages the c-Jun N-terminal kinase (JNK) signaling cascade, promoting phosphorylation of the anti-apoptotic protein Bcl-2 at serine 87. This modification impairs Bcl-2's ability to bind Bax, a pro-apoptotic factor, thereby enhancing apoptotic sensitivity and reinforcing the G2/M checkpoint arrest (Miyoshi et al., 2004).

H. Induction of Autophagy:

Autophagy is a precisely regulated catabolic mechanism in which cellular debris and dysfunctional organelles are broken down and recycled through the lysosomal pathway. Treatment with BITC has been shown to trigger autophagic responses by promoting the conversion of LC3-I to its lipidated form LC3-II, indicative of autophagosome formation and autophagic flux activation. *In vivo* studies using BITC-treated xenografts revealed hallmark features of autophagy, including increased LC3 cleavage, downregulation of p62, elevated Beclin 1 levels, and oxidative modification of Atg4. These molecular events were associated with FoxO1-driven autophagic cell death in MDA-MB-231 and MCF-7 breast cancer cell lines (Shima et al., 2022).

In prostate cancer models, BITC treatment in Rv1 and PC3 cells led to LC3 aggregation, suggesting impaired autophagosome-lysosome fusion. Moreover, the suppression of mTORsignaling, a central regulator of autophagy under stress conditions, was evident by reduced total mTOR activity and decreased phosphorylation at Ser2481 over a

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24–72 h treatment period. In lung cancer cells, BITC exposure resulted in the accumulation of LC3-II within acidic vesicular organelles (AVOs) alongside an upregulation of Atg5 expression, further supporting autophagic activation (Selvaraj et al., 2016).

In human colorectal cancer cells, treatment with BITC triggered autophagy alongside the upregulation of the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathwayand its downstream cytoprotective targets (Liu et al.). Additionally, in anaplastic thyroid carcinoma (ATC) cells, BITC enhanced the expression of the tumor suppressor PTEN, which subsequently modulated the autophagic machinery through suppression of phosphorylated mTOR, p62, and SOS1, while upregulating LC3. These molecular alterations collectively contributed to increased apoptosis and inhibition of ATC cell proliferation and invasion (Lee et al., 2013).

I. Induction of Apoptosis:

Apoptosis via the extrinsic pathway is primarily initiated through death receptor signaling involving ligands such as FasL and TNF-related apoptosis-inducing ligand (TRAIL), which interact with corresponding receptors including Fas, DR4, DR5, and TNFR. This receptor-ligand binding activates FAS-associated death domain (FADD) protein, which subsequently triggers the activation of caspase-8. The cascade continues with the activation of executioner caspase-3, ultimately leading to apoptotic cell death (Gonzalvez et al., 2010). In parallel, elevated levels of reactive oxygen species (ROS), DNA fragmentation, mitochondrial dysfunction, and energy depletion contribute to the activation of intrinsic apoptotic signaling pathways.

BITC, a naturally occurring isothiocyanate, exerts potent anticancer activity by initiating apoptosis in various chemoresistant cancer cell lines, including PaCa-2/GemR pancreatic cancer cells. Its pro-apoptotic effects are primarily mediated through the intrinsic (mitochondrial) pathway, as evidenced by elevated activities of caspase-3 and caspase-9 following treatment. BITC also triggers endoplasmic reticulum (ER) stress, which leads to increased intracellular calcium levels. The resulting calcium influx into the cytosol contributes to mitochondrial outer membrane permeabilization (MOMP), facilitating the release of cytochrome c and the activation of downstream apoptotic signaling cascades.

This mitochondrial dysfunction is intricately regulated by the Bcl-2 protein family. BITC disrupts the equilibrium between antiapoptotic (Bcl-2, Bcl-xL) and proapoptotic (Bax, Bak) members, thereby favoring apoptosis. Notably, BITC upregulatesBax in MCF-7 cells and enhances Bak expression in both MCF-7 and MDA-MB-231 cells, contributing to mitochondrial depolarization and cytochrome c release. Concurrently, a decrease in Bcl-2 and Bcl-xL expression further facilitates apoptotic progression. These molecular changes are accompanied by an increased expression of proapoptotic effectors such as BID, BAX, and BAD, reinforcing the intrinsic apoptotic mechanism (Kaufman et al., 2014).

Furthermore, BITC modulates the p53 tumor suppressor network. In cells harboring mutant p53, BITC promotes the expression of p73—a functional homolog of p53—and disrupts its interaction with the mutant form. This interference restores p73 activity, enabling the transcription of proapoptotic genes (Qian et al., 2022). BITC also activates liver kinase B1 (LKB1), which cooperates with both p53 and p73 to enhance their recruitment to DNA promoter regions, amplifying the expression of apoptotic targets via a positive feedback loop (Xie et al., 2017).

J. Inhibition of Angiogenesis:

Angiogenesis plays a critical role in tumor progression by facilitating cancer cell proliferation, invasion, and metastasis to distant sites. BITC has been shown to suppress tumor angiogenesis, thereby inhibiting tumor growth and metastasis. In MDA-MB-231 breast cancer xenograft models, BITC treatment significantly reduced neovascularization within the tumor tissue, highlighting its anti-angiogenic potential. Vascular endothelial growth factor (VEGF), a key pro-angiogenic factor commonly upregulated in aggressive cancers, promotes survival and proliferation of both normal and tumor-associated endothelial cells. BITC exposure led to a marked decrease in VEGF secretion and downregulation of VEGF receptor 2 (VEGFR-2) expression in MDA-MB-231 cells (Warin et al., 2010).

Similarly, in hepatocellular carcinoma models induced by diethylnitrosamine (DEN), BITC treatment inhibited VEGF release in hepatoma cell lines. This suppression of VEGF was associated with reduced expression of signal transducer and activator of transcription 3 (STAT-3) in liver tissues. Hepatocyte growth factor (HGF), known to promote angiogenesis via activation of the c-Met receptor and downstream PI3K/Akt and STAT-3 signaling pathways, was also suppressed by BITC. Specifically, BITC downregulated the HGF/p-Akt/STAT-3 axis, leading to impaired angiogenicsignaling. Furthermore, BITC inhibited HGF secretion within the tumor microenvironment and abrogated STAT-3-mediated VEGF expression (Pratheeshkumar et al., 2012). These findings collectively indicate that BITC exerts its anti-angiogenic effects through multifaceted inhibition of key signaling molecules involved in vascular development in tumors.

K. Regulation of Signalling Pathways:

- *Regulation of Wnt/β-Catenin Pathway*

Dysregulation of Wnt/ β-catenin signalling pathway is a major hallmark of cancer progression. Wnt stimulation inhibits degradation of β-catenin by degradation complex and increased cytoplasmic β-catenin level significantly increases expression of cyclin D1 and c-Myc genes resulting cell proliferation and migration. In several studies it was revealed BITC treatment increases the expression of APC and GSK-3β indicating activation of degradation complex. This complex phosphorylates β-catenin leading to its degradation by proteasomal complex indicating tumour-preventive and tumour-inhibitory role of BITC (Lecarpentier et al; 2019). Additionally, BITC also markedly decreased β-catenin by downregulating FOXH1 expression and supresses

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tumorigenesis. Collectively, these findings indicate that benzyl isothiocyanate (BITC) suppresses β-catenin-mediated transcription of cyclin D1 and subsequently inhibits cell proliferation, a process that involves the nuclear translocation of the p65 subunit in human colorectal carcinoma cells (Cai et al., 2014).

➢ *Regulation of MAPK Pathway*

Activation of the Akt and MAPK signaling pathways plays a central role in promoting cell proliferation, survival, and drug resistance by initiating the transcription of downstream genes. BITC, a bioactive compound derived from cruciferous vegetables, has been shown to disrupt these oncogenic signaling cascades. Specifically, BITC downregulates the expression of key MAPK family members—including ERK1/2, p38, JNK, and MAPK—thereby suppressing AP-1-mediated transcription and the associated synthesis and activation of matrix metalloproteinases (Hwang et al., 2008). Interestingly, BITC simultaneously enhances AP-1 activity through the phosphorylation of c-Jun, which leads to a significant upregulation of the tumor suppressor microRNA miR-99a (Tsai et al., 2020). This miRNA directly targets the Akt/mTORsignaling axis, resulting in the induction of apoptosis in both breast and lung cancer cells.

Furthermore, BITC has demonstrated the capacity to overcome gefitinib resistance in lung cancer cells by inhibiting the activation of Akt and NF-κB pathways. In these resistant cells, components of the MAPK signaling pathway—including JNK, ERK1/2, and AP-1—were effectively modulated by BITC, underscoring its potential as a therapeutic agent against drug-resistant malignancies (s120). Additionally, BITC treatment led to the upregulation of the pro-apoptotic protein Bim, which is ordinarily suppressed by Akt via FOXO transcription factors. Inhibition of Akt by BITC promotes the nuclear localization of FOXO proteins, thereby enhancing the transcription of apoptotic genes such as Bim. This mechanism has been reported in pancreatic cancer cell lines, including BxPC-3 and PanC-1 (Boreddy et al., 2011).

➢ *Regulation of STAT-3 Pathway*

BITC induces apoptosis in human pancreatic cancer cells by downregulating both total STAT3 protein and its activated forms, phosphorylated at Tyr705 and Ser727, in a dose- and time-dependent manner. In BxPC-3 pancreatic cancer cells, a similar reduction in STAT3 mRNA expression was observed following BITC treatment. This suppression of STAT3 signaling was further corroborated by a decline in STAT3-dependent DNA-binding activity and transcriptional downregulation of its downstream anti-apoptotic targets, including Mcl-1 and Bcl-2 (Sahu et al., 2009).

IV. ANTICANCER ACTIVITY OF BITC

A. In-Vitro Anticancer Study:

Table 1 In-vitro Anticancer Study

Type of Cancer	Cell Line	Key Findings	References
Breast cancer	MDA-MB-231 and MCF-7 cells	Upregulation of epithelial markers (E-Cadherin and occludin) Downregulation of mesenchymal markers (vimentin) Suppression of vimentin, snail, slug mRNA expression Inhibition of endothelial-mesenchymal transmission.	Tsai et al., 2020
	MDA-MB-231 and MCF-7 cells	Decrease in cell viability G2/M cell cycle arrest Induction of apoptosis Increase in Bak and Bax, caspase level Decreased Bcl-xL and Bcl2 level Increased ROS generation and chromatin condensation Formation of autophagic vacuoles	Xie et al., 2017
	MCF-7, MDA-MB-231 and SUM159	Decrease in cell viability Inhibition of cell migration Activation of Notch pathway	Kim et al., 2012
	MDA-MB-231	Reduced cell viability Inhibited cell migration Suppressed nF-kB activity and HGP induced phosphorylation Suppression of Akt signalling	Kim et al., 2012
	MDA-MB-231 MCF-7 cells	Increased ROS generation Inhibition of complex-III of Electron transport chain Activation of JNK/MAPK pathway	Shima et al., 2022
	MCF-7, MDA-MB-231, SUM159 cell lines	Inhibition of cell proliferation and invasion Inhibition of FOXH1 mediated cell proliferation.	Liu et al., 2015

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		Repression of Mnt/b-catenin pathway	
	4T1 cells	Suppresses cellular proliferation, motility, and invasive potential of cancer cells. Promotes apoptotic cell death and induces arrest at specific phases of the cell cycle. Negatively regulates the Wnt/β-catenin signaling cascade. Leads to decreased expression levels of key oncogenic regulators, including cyclin D1, c-Myc, and APC.	Xie et al., 2017
	MDA-MB-231, MCF-7, MDA-MB-468, BT-474, and BRI-JM04	Formation of acidic vesicular organelles (AVO) Induction of autophagy Increased expression of FoxO1	Xiao et al., 2012
Pancreatic cancer	Gemcitabine resistant PaCa-2 cell	Decrease in cell viability Chromatin condensation Increased ROS generation Increase in caspase activity	Sahu et al., 2009
	BxPC-3, CFPAC-1 and Hs766T	TRAIL induced apoptosis	Basu and Haldar, 2009
	BxPC-3, AsPC-1, Capan-2, MiaPaCa-2, and Panc-1	Decrease in cell viability Reduced expression of STAT 3 and regulated proteins	Sahu and Srivastava, 2009
	Capan-2 cells	Inhibited cell proliferation G2/M phase arrest Apoptosis induction Inhibition of Cdk2 kinase activity	Zhang et al., 2006
	BxPC-3 and Capan-2 cells	Decrease in histone deacetylase activity Reduced nF-kB activity	Batra et al., 2010
Haematopoietic malignancies	CLBL-1, GL-1, CLB70 and CNK-89,	Decrease in cell viability Caspase dependent apoptosis Increased ROS generation	Xiao et al., 2012
	Jurkat cells	Induction of apoptosis G2/M phase arrest Bcl2 phosphorylation by MAPK pathway DNA fragmentation	Miyoshi et al., 2004
human colon cancer cells	Rapidly proliferative CCD-18 Co	Dose dependent cytotoxicity Cell cycle arrest which is negatively regulated by p53	Hwang et al., 2008
	HT-29 HCT116	Inhibited cell proliferation Inhibited beta catenin dependent cyclin D1 transcription	Abe at al.,2014
	HT 29	Inhibition of proliferation, invasion and metastasis Inhibition of MMP2/9 and uPA by MAPK pathway.	Lai et al., 2010
Thyroid carcinoma	Anaplastic thyroid carcinoma (ATC)	Decreased cell proliferation and migration Increased apoptosis and autophagy Reduced inflammation	Basilotta et al., 2024
Hepatocellular carcinoma	Bel 7402 and HLE	Induction of apoptosis Increased expression of caspase 3/8 and PARP-1 Decreased expression of MMP2/9 and CXC4. Inhibition of migration.	Zhu et al., 2017
	Hep G2 and Huh-7	Antiproliferative activity Inhibition of angiogenesis Suppression of HGF and pAkt activity Reduced expression of matrix metalloproteases.	Zakaria et al., 2018
	SK-Hep 1 cells	Dose dependent suppression of cell proliferation Reduced expression of matrix metalloproteinases 2/9 Inhibition of MAPK pathway	Hwang and Lee, 2008
Oral cancer	Cisplatin resistant CAR cells	Increased cell death Increased ROS production Loss of mitochondrial membrane potential Chromatin condensation Upregulation of pro-apoptotic and down regulation of anti-apoptotic proteins.	Lee et al., 2018
	OSCC cell line	Inhibition of cell proliferation	Yeh et al., 2016

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		Apoptosis with G2/M cell cycle arrest Chromatin condensation and DNA fragmentation Increased ROS generation Decrease in mitochondrial membrane potential Activation of ATM-chk2-p53 pathway	
Prostate cancer	Hormone sensitive Rv1 and refractory PC3 cells	Decrease in cell viability Induction of apoptosis Formation of autophagosomes. Inhibition of mTOR signalling pathways. Loss of mitochondrial membrane potential caspase 3/7 activation DNA fragmentation	Lin et al., 2013 Lin et al., 2017
	BxPC-3 and Capan-2 cells	Decrease in histone deacetylase activity Reduced nF-kB activity	Batra et al., 2010
	DU-145 cells	Decrease in cell viability DNA damage Apoptosis induction ROS generation Loss of mitochondrial membrane potential and release of AIF and endo G Activation of caspases	Liu et al., 2011
	gefitinib-sensitive PC9 and gefitinib-resistant cell lines PC9/AB2 and PC9/BB4	Inhibition of proliferation Activation of intrinsic apoptotic pathway ROS generation Glutathione depletion G2/M phase arrest Suppression of Nf-kB activity	Tian et al., 2021
Head and neck cancer	head and neck squamous cell carcinoma (HNSCC)	Dose dependent cytotoxicity PARP cleavage and caspase 3 activation Activation of p38/MAPK signalling	Lui et al., 2003
Lung cancer	A459	Dose dependent inhibition of proliferation Induction of autophagy Increased expression of LC3-II and Atg 5 Increased ER stress level	Zhang et al., 2017
Bladder cancer	T24 and 5637	Suppression of IGF1R, FGFR3 and mTOR expression by miR99a	Tsai et al., 2019

B. In-vivo Anticancer Activity:

Table 2 In-Vivo Anticancer Activity

Type of Cancer	**Cell Line**	**Key Findings**	**References**
Breast cancer	MDA-MB-231 xenograft in female athymic mice	Increased expression of E-Cadherin and decreased vimentin and fibronectin protein level. Reduced metastasis	Szczyglewska et al., 2023
	MDA-MB-231 xenograft	Increase in Notch2 and Hes-1 protein expression	Uppal et al., 2020
	MDA-MB-231 xenograft	Decrease in tumour volume and increase in survival time Reduced angiogenesis marker CD31 expression Reduced migration Formation of apoptotic bodies	Warin et al., 2010
	4T1 xenograft	Tumour regression Induction of apoptosis Inhibition of metastasis and tissue invasion	Kim et al., 2012
	MDA-MB-231 xenograft	Induction and cleavage of LC3 proteins Increased expression of p62	Xiao et al., 2012
Lung cancer	A459 xenograft	Tumour regression Increased expression of autophagic markers.	Zhang et al., 2017
Pancreatic cancer	BxPC-3 xenograft	Decrease in tumour volume Increased apoptosis Reduced STAT-3 expression	Sahu and Srivastava, 2009

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	BxPC-3 xenograft	Reduced expression of cyclin D1 and histone deacetylases (HDAC1/3)	Batra et al., 2010
	BxPC-3 xenograft	Reduction in tumour volume Reduced PI3K/AKT/mTOR activity	Idrees et al., 2022
Thyroid carcinoma	ATC orthotropic model	Reduced tumour growth Inhibited endothelial-mesenchymal transition (EMT) Inhibited metastasis Induced apoptosis and autophagy	Basilotta et al., 2024
Hepatic cancer	Diethyl nitrosamine (DEN) induced tumour	Inhibited TNF-alpha expression Reduced expression of HGF Inhibited angiogenesis Inhibition of STAT 3 expression	Zakaria et al., 2018

V. NANOTECHNOLOGY IN DELIVERY OF BITC

Nanomaterials have attracted widespread attention owing to their distinct physicochemical characteristics that set them apart from their bulk-scale equivalents. These unique attributes—such as increased mechanical resilience, heightened surface reactivity, and enhanced electrical conductivity—stem from their reduced dimensions, typically within the 1–100 nm range. Such nanoscale features have been effectively utilized in medical biotechnology applications, including the design of nanomedicines, biosensing devices, targeted drug delivery systems, and platforms for cellular manipulation, contributing significantly to disease diagnosis, treatment, and management (Szczyglewska et al., 2023).

Among various nanocarrier systems, nanoparticles composed of biodegradable polymers, copolymers, liposomes, dendrimers, emulsions, and peptides have demonstrated superior therapeutic efficacy. These systems enable controlled and site-specific release of chemotherapeutic agents, thereby minimizing systemic toxicity and preserving healthy tissues. Encapsulation of drugs or bioactive molecules within such nanocarriers has been shown to significantly improve their aqueous solubility, stability, bioavailability, and therapeutic activity.

BITC, a bioactive compound with documented anticancer activity against multiple cancer cell lines, has faced limitations in clinical translation due to its poor water solubility, rapid metabolism, and low systemic bioavailability. To address these challenges, nanotechnology-based delivery systems have emerged as promising solutions to enhance BITC's therapeutic potential. Nanoformulations not only stabilize BITC in physiological conditions but also enhance its chemopreventive efficacy (Idrees et al., 2022).

A notable example involves the encapsulation of BITC within chitosan-based nanoparticles, which significantly improved its solubility and physicochemical stability. These nanoparticles had an average diameter of approximately 81.0 nm and retained stability for up to 60 days. The entrapment efficiency was reported as 64.68 ± 4.7%, indicating efficient loading of BITC into the carrier system. *In vitro* release studies revealed a cumulative release of 72.38% and 77.78% over 144 hours at pH 7.2 and 5.5, respectively, highlighting the formulation's potential for sustained drug delivery. Moreover, toxicity evaluations, including hemolysis assays, confirmed the biocompatibility and safety of the formulation, suggesting that chitosan-based BITC nanoparticles could serve as a viable approach for therapeutic applications (Uppal et al., 2018).

Recent advancements in nanotechnology have significantly improved the delivery potential of BITC, a promising bioactive compound with anticancer properties. A cerium oxide-based nanoemulsion system was developed, exhibiting a nearly spherical morphology with particle sizes ranging from 4 to 8 nm. This nanoformulation demonstrated high biocompatibility, as confirmed by bovine serum albumin (BSA) binding assays and haemolysis studies. Notably, the cerium oxide nanoparticles (CNPs) served as efficient carriers for BITC, achieving an encapsulation efficiency of 89.06 ± 2.3%. *In vitro* release studies revealed a pH-responsive behavior, with 28.5% drug release at physiological pH (7.2) over 10 hours, which increased to 41.2% under acidic conditions (pH 5.5), simulating the tumor microenvironment. This pH-sensitive release profile underscores the potential of the system to selectively deliver BITC to cancerous tissues while minimizing off-target toxicity. Moreover, MTT assays indicated enhanced cytotoxicity against MDA-MB-231 breast cancer cells, suggesting improved therapeutic efficacy (Uppal et al., 2020).

In another approach, a rhamnolipid-stabilized nanoemulsion demonstrated excellent long-term stability across various pH conditions. This formulation also exhibited high drug loading efficiency, sustained release behavior, and favorable biocompatibility. Cellular uptake experiments confirmed the successful internalization of the nanoemulsion by cancer cells, supporting its utility as an effective delivery vehicle.

An inclusion complex formed between BITC and β-cyclodextrin (β-CD) was reported to enhance the stability and achieve controlled release of BITC, further contributing to its therapeutic potential (Mottola et al., 2023).

Optimized oil-in-water BITC nanoemulsions were developed using a homogenization–sonication technique. These formulations demonstrated high encapsulation

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efficiency, low polydispersity indices, and superior colloidal stability. Compared to unformulated BITC, the nanoemulsions exhibited significantly improved solubility and dissolution profiles. Transport studies in Caco-2 monolayers showed increased apical-to-basolateral permeation, indicating enhanced intestinal absorption. Additionally, the nanoemulsions were effectively internalized by A549 (lung) and SKOV-3 (ovarian) cancer cell lines and showed significant *in vitro* antitumor activity. This study provides the first evidence that BITC-loaded nanoemulsions could improve its oral bioavailability and therapeutic potential.

Furthermore, fish skin gelatin (FSG)-based nanoemulsions of BITC achieved a notable bioavailability of 80.77%. The FSG matrix effectively protected the BITC and enabled sustained drug release, demonstrating the viability of marine-derived biopolymers in drug delivery applications.

Natural emulsifiers such as chitosan, gum arabic, soy protein isolate (SPI), and a hybrid system combining SPI with phosphatidylcholine (SPI-PC) have also been utilized to formulate BITC-loaded oil-in-water nanoemulsions. These systems not only provided excellent encapsulation and stability but also offer a biocompatible and eco-friendly alternative for nanoformulation development (Tian et al., 2021).

Alpha-tocopherol-based oil-in-water nanoemulsions were successfully developed using a combination of surfactants, specifically sodium stearoyllactylate and Tween 80, through a high-energy ultrasonication technique. The resulting formulation demonstrated notable physical stability over a period of 90 days. *In vitro* release studies revealed that approximately 50.29% of BITC was released over 36 hours. Furthermore, cytotoxicity assessment against HepG2 cells indicated that the nanoemulsion exhibited a cell viability of 24%, signifying potent anticancer potential. In a parallel approach, BITC and sorafenib (SOR) were co-encapsulated into nanoparticles (BITC–SOR-NPs) utilizing the amphiphilic copolymer methoxypoly(ethylene glycol)-poly(lactic-co-glycolic acid) (mPEG–PLGA) via a modified emulsion-based method (Sharif et al., 2017).

VI. CONCLUSION

BITC, a naturally occurring compound found in cruciferous vegetables and papaya seeds, has demonstrated significant anticancer activity both *in vitro* and *in vivo* at non-toxic concentrations. BITC anticancer effects are more pronounced compared to its structural analogues like phenyl isothiocyanate (PITC), phenethyl isothiocyanate (PEITC), and sulforaphane (SFN). The isothiocyanate functional group and alkyl side chain are crucial for its bioactivity. BITC acts through multiple mechanisms including apoptosis induction, cell cycle arrest, inhibition of migration, invasion, angiogenesis, and activation of autophagy.

These actions involve key signaling pathways such as the intrinsic and extrinsic apoptotic pathways, MAPKs (p38, ERK1/2, JNK1/2), NF-κB, Wnt/β-catenin, and PTEN/PI3K/Akt. Furthermore, BITC has shown potential in enhancing the effects of chemotherapeutic agents like cisplatin, TRAIL, and radiotherapy. It also exhibits autophagy-activating properties in various cancers including breast, colon, prostate, and lung. While resistance to BITC has been observed, combining it with NF-κB or PI3K inhibitors may help overcome this limitation. Despite promising preclinical data, BITC has not yet been evaluated in clinical trials. Some studies have reported a tumor-promoting effect in bladder cancer, highlighting the need for careful dose optimization and further investigation. To validate its therapeutic potential, detailed pharmacokinetic studies and clinical assessments are necessary to ensure its safety and efficacy as a chemo-preventive or chemotherapeutic agent.

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