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Potential Role of Anticancer Compounds Derived from Phytomedicines in Modulating the Signaling Pathways for Cancer Progression - A Review

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Abstract

One of the most prevalent causes of death globally is cancer, which is a consequence of uncontrolled proliferation and division of cells in the body. The role of inflammation in tumour progression has been increasingly established. It also affects epigenetic changes that promote tumour induction and promotes all stages of carcinogenesis. Chronic inflammation may result in greater damage to DNA, interfere with DNA repair mechanisms, accelerate cellular division, and induce apoptosis, angiogenesis, and invasion of the tissue. A comprehensive knowledge of the cellular and molecular signaling mechanisms of tumor-endorsing inflammation is essential for the advancement of anti-cancer medications which concentrate on the interaction between malignancy formation and inflammatory mechanisms. Several inflammatory signalling pathways have been identified as regulating inflammation, including the NF-κB signalling pathway, the JAK-STAT signalling pathway, the MAPK signalling, the PI3K/AKT/mTOR signalling and the Wnt signalling cascade. Several phytochemicals can treat cancer by altering these pathways. There are numerous classes of phytochemicals in herbal medicine that are being used therapeutically. Herbal medicine has shown to be especially beneficial for cancer patients, with many reporting a considerable increase in survivorship as a result of treatment. Cellular metabolism, tumour development, growth, proliferation, metastasis, and cytoskeletal reorganization are all regulated by aberrations in different cellular signalling pathways. The primary emphasis of the current review focuses on the phytochemical's capacity to combat cancer through modifying numerous cell signalling pathways.

Keywords: *Anticancer Activity, Cancer, Cellular Signalling Pathways, Inflammation, Phytomedicines.*

Introduction

Cancer

The human body is made up of approximately 37.2 trillion cells. The developmental process of a cell includes birth, growth, reproduction, and death. When certain body cells proliferate uncontrollably and invade other body parts, a medical condition referred to as cancer emerges. When mature cells perish from ageing or trauma, new ones enter their place. At times, damaged or abnormal cells proliferate and develop when they shouldn't, which is a consequence of an aberration in this controlled process. These cells possess a tendency to generate masses of tissue referred to as Tumours. Tumours may develop and be either benign or malignant. In addition to implanting themselves into nearby tissues, malignant tumours possess a tendency to metastasize, or spread, to distant regions of the body and establish new tumours. Neighbouring tissues are not invaded or affected by benign tumours. Following

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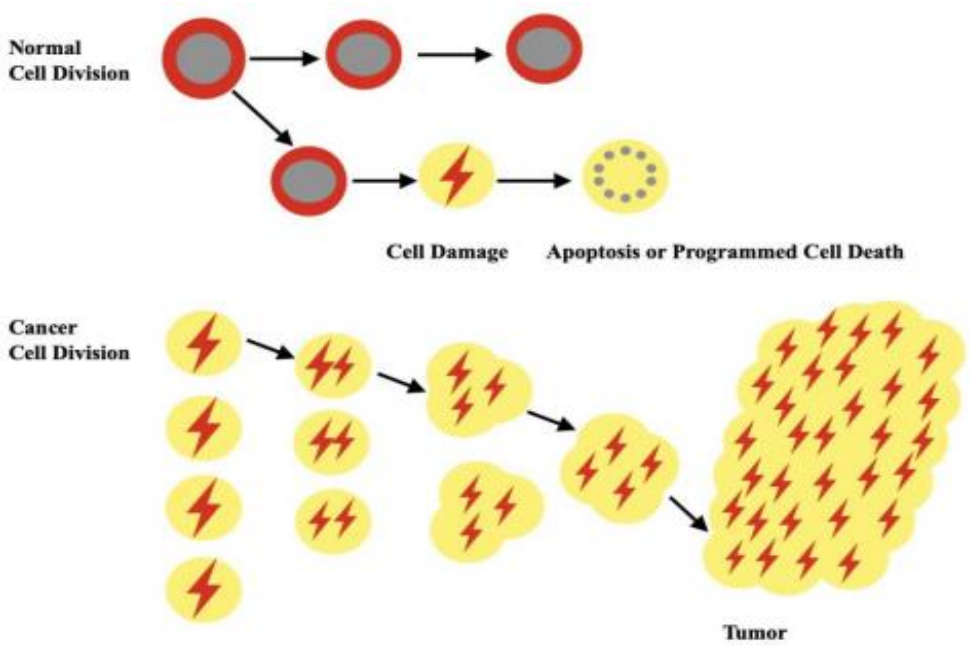
excision, benign tumours rarely regrow, however, malignant tumours can grow [1]. More than 200 cancer categories exist, each correlating to a different organ of origin. Unrestricted replication, lack of ability to respond to growth signals that cause cell division to stop, persistent angiogenesis, resistance to apoptosis, and the capacity to

invade other tissues are the hallmarks that characterise cancer. In recent times, there has been a growing investigation into several molecular-based techniques such as gene therapy, siRNA-targeted silencing, apoptosis-triggering gene expression, and wild-type tumour suppressors [2]. Calotropin targets apoptosis, glycolysis, metastasis, and proliferation in HSC-3 oral cancer cells, showing promise as a treatment [3].

Global Statistics on The Prevalence of Cancer

The projections of cancer incidence and mortality for GLOBOCAN 2020 have been developed by the International Agency for Research against Cancer. (With the possible exception of non-melanoma skin cancer, which has been estimated to be 18.1 million cases) and approximately 9.9 million deaths from cancer worldwide have been estimated for 2020. Lung cancer has been exceeded by female breast cancer as the cancer that is most likely among those diagnosed, with a total of approximately 2.3 million new cases (11.7%). Cancers of the stomach (5.6%), prostate (7.3%), colorectal (10.0%), and lung (11.4%) develop. Considering an expected 1.8 million deaths, lung cancer constituted the most common cause of fatalities associated with cancer (18%), trailing colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers [4]. Cancer poses an imminent danger to public health, society, and the economy in the twenty-first century. Approximately one in six deaths (16.8%) and one in four deaths (22.8%) around the world are triggered through noncommunicable diseases (NCDs) [5]. The International Agency for Research on Cancer forecasts that 1.36 million new cases of colorectal cancer emerged in 2012, thus ranking it the third most common cancer globally. Newer research indicates that young-onset colorectal cancer(CRC), which is mostly characterised in adults under 50, is becoming more common. In 2018, the American Cancer Society revised their recommended screening age for average-risk people aged 50 to 45 years old. Liu et al. retrieved cancer incidence data from the International Agency for Research on Cancer (IARC) in 2019, and they observed that 11 out of 12 countries had a significantly higher risk of young cancer deaths (CRC). The annual per cent changes in incidence (APCi) varied between 0.32 (95% confidence interval [CI], 0.01 to 0.64) in Italy to 9.20 (95% CI, 6.85 to 11.59) in Brazil [6]. Cervical cancer is distributed significantly worldwide; in low- and middle-income nations, over 85% of cases occur [7]. Twenty million new instances of cancer are expected in 2022; by 2050, that number is projected to rise to almost 35 million, a 77% increase. Modifications in risk factor exposure, many of which have been linked to socioeconomic development, as well as population growth and ageing, primarily due to alcohol, tobacco, and obesity, are the primary contributors to the rapidly rising incidence of cancer throughout the world. Air pollution persists to be a key contributor to environmental risk factors [8]. In OSCC and severe oral epithelial dysplasia, salivary MMP-9 levels are markedly raised, indicating that it may be a signal for malignant transformation [9].



Natural Products with Anticancer Properties

Plants have been the fundamental component of highly sophisticated medical systems for thousands of years, specifically in China and India, and they are essential to the administration of healthcare. Science offers overwhelming proof that phytochemicals have cancer-fighting properties. As reported by Newman and Cragg (2016), nearly fifty per cent of all anticancer drugs that were licensed between 1940 and 2014 were derived or sourced from natural sources [10]. These strategies work in collaboration to lower the rate of carcinogenesis by scavenging free radicals [11], prohibiting cancerous cells from surviving and proliferating [12], and diminishing tumour invasiveness and angiogenesis [13]. According to estimations from the World Health Organisation, 20% of the world's population still heavily depends on plant products for primary healthcare, with the remaining 80% receiving traditional medications [14]. The finding of compounds that kill cancer cells has been greatly aided by natural products; in fact, 60% of all clinically utilised cancer treatments may be either natural products or derived from natural sources. The National Cancer Institute (NCI), a US government organisation that has made investments in the discovery of several anticancer medications, has carried out the most extensive investigation on cytotoxic compounds found in nature [15]. A $20 million investigations campaign that lasted for several years led the American National Cancer Institute (NCI) to divide a range of foods that may prevent cancer into three categories based on epidemiological evidence, in vitro and in vivo tests, and other findings: The vegetables exhibiting the greatest degree of anticancer activity were those found in the umbelliferous category, which includes parsnips, celery, carrots, and parsley, as well as soy, ginger, garlic, and liquorice. The food groups that follow have been shown to have an average anticancer outcome: onions, linseed (flaxseed), citrus, turmeric, cruciferous vegetables (broccoli, Brussels sprouts, cabbage, and cauliflower), solanaceous vegetables (tomatoes and peppers), brown rice, and whole wheat. Oats, barley, cucumbers, and kitchen herbs including mints, rosemary, thyme, oregano, sage, and basil are all believed to have moderate anticancer action [16]. It has been suggested that employing multi-targeted photo agents

from traditional medicine is a more efficacious approach to cancer treatment and prevention than using agents that target a single molecule [17,18]. β-Sitosterol targets important apoptotic pathways and induces apoptosis in KB cells, which shows great therapeutic potential against oral cancer [19]. Higher DMFT scores, a plaque ecology that favours Streptococcus mutans, and increased caries severity are all associated with H. pylori in cavitated carious lesions [20].

Role of Phytomedicines in Signalling Pathways of Cancer

PI3K/AKT/mTOR Pathway

A key player in the regulation of quiescence, proliferation, metabolism, and the cell cycle in cancer is the PI3K/AKT/mTOR signalling pathway [21-23]. The conversion of membrane-bound phosphatidylinositol (3,4,5)-triphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2), delivering coupling sites for signalling proteins like AKT, is triggered by growth factor receptor protein tyrosine kinase activation. The mTORC2 complex phosphorylates AKT at Ser473 during the terminal stage of AKT activation. AKT stimulates the production of target proteins by activating mTOR complex 1 (mTORC1). Multiple research investigations have suggested a connection between the PI3K/AKT/mTOR signalling pathway and the biology of CRC-SCs [24]. Chen et al. showed that phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2, which is a PI3K regulatory subunit) was overexpressed in the CRC-SCs from human CRC xenografts, along with other components of the PI3K/AKT/mTOR signalling pathway [25].

Mangiapane et al. determined that high expression of erb-b2 receptor tyrosine kinase 2 (ERBB2) in colorectal cancer stem cells (CRC-SCs) is linked to the activation of the PI3K/AKT pathway, promoting acetylation in the regulatory elements of the ERBB2 gene. The above was discovered using a collection of primary cell cultures growing on spheroids obtained from 60 CRC specimens [26]. Additionally associated with a worse outcome in patients with stage II colorectal cancer is mTOR expression [27]. Additionally, a transcriptome analysis comparing the primary cultures of colorectal cancer stem cells (CRC-SCs) to those of normal stem cells revealed that the CRC-SCs demonstrate enrichment of genes associated with PI3K/AKT and Wnt signalling [28].

PTEN (phosphatase and tensin homolog) is a tumour suppressor that frequently serves as a detrimental regulator of the PI3K/AKT/mTOR pathway [29]. PTEN has frequently been discovered to be deleted, mutated, or epigenetically silenced in a variety of malignancies, which has been shown to facilitate processes like metastasis, tumour progression, apoptosis inhibition, malignant transformation, and radiotherapy resistance [30,31]. Different genetic alterations in OSCC grades are revealed by NGS, which advances minimal intervention techniques and helps with individualized therapy planning [32].

Abnormal AKT activation, which phosphorylates numerous downstream proteins notably mTOR, insulin receptor substrate 1 (IRS-1), and glycogen synthase kinase-3 beta (GSK-3β), may result from prolonged production of inflammatory cytokines which include IL-3, IL-6, and IL-7. Moreover, overexpression of vital proteins notably cyclin D1 and vascular endothelial growth factor (VEGF), which usually promote carcinogenesis, may result from stimulation of mTOR signalling [33].

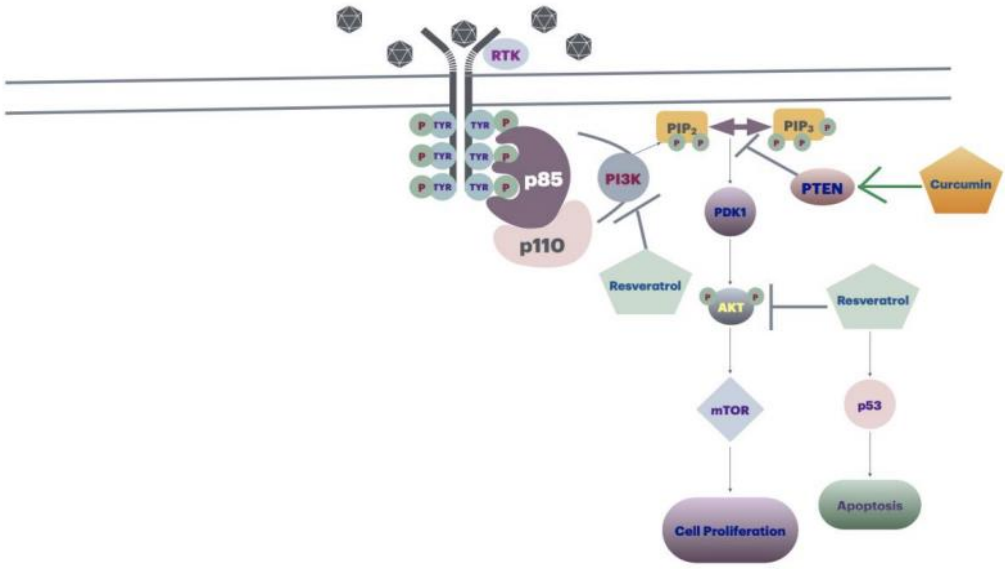


Figure 1. Role of Phytomedicines on PI3K/AKT/mTOR Pathway

Curcumin's potent antiapoptotic properties for numerous cancers have been demonstrated by its regulation of PI3K/Akt/mTOR signalling. It has been demonstrated that curcumin inhibits the ubiquitin-proteasome system, induces autophagy, and downregulates Akt protein in breast cancer cells in a dose and influenced by time manner [34]. Moreover, it has been shown that curcumin, which blocks the PI3K/Akt signalling pathway, increases autophagy and death in breast cancer cells [35]. Resveratrol suppresses the proliferation of cells by inhibiting PI3K and Akt. Resveratrol accelerates apoptosis by upregulating p53 [Figure 1][36]. Curcumin activates the pathway, represented by the green arrow mark [Figure 1][37]. A novel therapeutic option for curcumin is presented here downregulating PI3K/Akt (Akt1, Akt2) was another effect of (E)-2-(4-hydroxy-3-methoxybenzylidene)-5-((E)-3-(4-hydroxy-3-methoxyphenyl)acryloyl) cyclopentanone (CUR3d). This reduced the growth of HepG2 hepatocellular carcinoma cells [38]. According to research, curcumin suppresses PI3K/Akt signalling in pancreatic cancer cells, boosting FoxO1 expression and triggering cell cycle arrest and apoptosis [39]. Curcumin also drastically lowered the growth, immigration, and invasion of thyroid cancer cells by downregulating Akt signalling and consequently attenuating MMP1/7 and COX-2 proteins [40]. Colon cancer cells' ability to proliferate and migrate was substantially lowered by curcumin. Additionally, it triggered apoptosis by upregulating the mRNAs for caspase-3, cytochrome c, and Bax and suppressing Akt phosphorylation [41]. Curcumin suppressed cellular melanin levels and tyrosinase activity in α-MSH-stimulated melanoma cells by downregulating microphthalmia-associated transcription factor (MITF) and its downstream signal molecules through activation of PI3K/Akt [42]. The circulating exosomal miRNAs miRNA 21, miRNA 184, and miRNA 145 exhibit promise as plasma biomarkers for identifying individuals with OSMF, leukoplakia, and OSCC who are at high risk of developing malignant transformation [43].

6-Shogaol is a modest, bioactive substance that was isolated from ginger (Zingiber officinale, Roscoe). In a nude mouse model of non-small cell lung cancer (NSCLC), 6-shogaol (10 mg/kg) substantially lowered the development of NCI-H1650 lung cancer cells. A decrease in Ki-67-positive cells and an increase in terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end

labelling (TUNEL)-positive cells demonstrated a link between this and a decrease in cell proliferation and an increase in apoptosis. In vitro Akt signalling is hindered by 6-school through direct targeting of Akt1 and Akt2 [44]. Vitamin D supplementation may hasten tooth movement with less tissue damage, as evidenced by the negative correlation between salivary 1-25dihydroxycholecalciferol and IL-17A levels during orthodontic treatment phases [45].

Wnt/β-Catenin Signalling Pathway

Wnt is the name used to describe a mixture of two proteins: the Drosophila segment polarity gene, wingless, and the vertebrate homolog, integrated, or int-1 [46-47]. When Wnt adheres to LRP5 and LRP6, also known as frizzled proteins, the Wnt pathway is activated. Wnt signalling cascades are classified as either the β-catenin-dependent (canonical) or non-canonical (non-dependent) cascades. The progressive entry of cytoplasmic β-catenin into the nucleus and its stabilisation are crucial elements of β-catenin-dependent signalling.

Two key factors that considerably aid non-β-catenin signalling are planar cell polarity and small GTPase proteins. It has been demonstrated that higher discharge of TNF-α, IL-6, and IL-1β promotes the canonical Wnt/β-catenin signalling pathway. Through its suppression of the Wnt/β-catenin signalling pathway, MiR-26b could drastically decrease the release of cytokines that include TNF-α, IL-6, and IL-1β, this can help inhibit the development of malignant cells and accelerate overall apoptosis [48]. Thus, inflammation induced by Wnt/β-catenin might encourage malignancy and decrease cellular death.

Theories have suggested that certain types of cancer are associated with the activation of the Wnt/β-catenin signalling pathway. For example, the discovery that β-catenin mutations are present in about 30% of primary HCC cases leads to the hypothesis that Wnt/β-catenin signalling activity plays a role in hepatocarcinogenesis. Additionally, a minority of osteosarcoma cell lines activate the Wnt/β-catenin pathway [49,50].

Reduced production of secreted FRP1, TCF-4 (ICAT), AXIN2, and inhibitor of β-catenin could result in the activation of the Wnt/β-catenin signalling pathway and carcinogenesis through decreasing the negative factors. It implies that the stimulation of the Wnt/β-catenin signalling pathway triggered by miR-1207 may promote the development of cancer through decreasing linked negative regulators. Cyclin D1 synthesis declines when the Wnt/β-catenin signalling pathway is hindered by retinoid X receptor α (RXRα) knockdown. RXRα may additionally activate the NF-κB signalling pathway and suppress p21 levels, which will boost the expression and proliferation of cellular nuclear antigens. As a result, aberrant activation of Wnt/β-catenin and NF-κB pathways caused by RXRα could encourage the development of cholangiocarcinoma [51,52]. Consequently, these findings suggest that Wnt/β-catenin signalling activity may play a role in carcinogenesis. However complex connections in the NF-κB and Wnt/β-catenin pathways have also demonstrated this. Increased expression of β-catenin is adversely correlated with both NF-κB and hiNOS activity (human inducible nitric oxide synthase). When β-catenin is not present, there has been evidence of elevated NF-κB induction. Wnt/β-catenin signalling, therefore, plays a critical role in the pathophysiology of inflammation-linked carcinogenesis by regulating the expression of hiNOS through the NF-κB interaction [53]. miRNAs are essential in OPMDs, and they may be used as therapeutic targets and diagnostic indicators [54].

The modulation of cell survival, proliferation, and death is largely dependent on the Wnt/β-catenin system. Numerous disorders, including cancer, have been linked to the deregulation of this pathway's constituent parts [55].

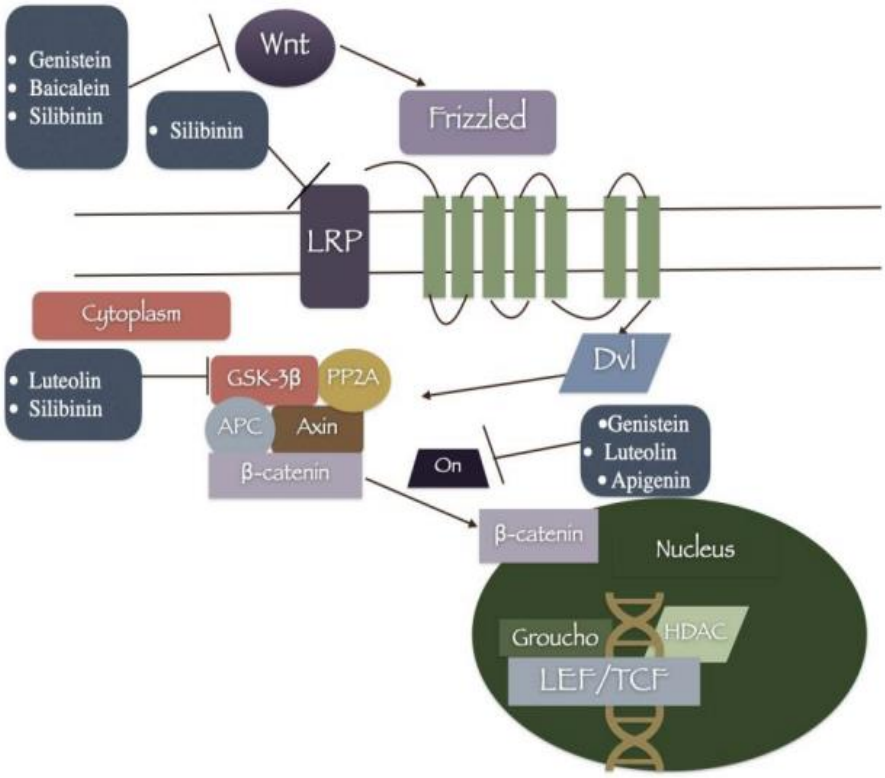


Figure 2. Role of Phytomedicines on Wnt/β-Catenin Signalling Pathway

An array of potent compounds, including genistein, baicalein, silibinin, apigenin and luteolin, have been scientifically reported to be potent inhibitors of the Wnt/β-catenin pathway in recently published studies [Figure 2][56]. Curcumin has additionally been demonstrated to hinder the proliferation of breast cancer stem cells by accelerating the production of the E-cadherin–β-catenin complex and re-establishing E-cadherin expression [57].

Additionally, curcumin's effect on ER-negative human breast cancer cells was evaluated by presenting them with the administration of heterocyclic cyclohexanone derivatives of curcumin, resulting in β-catenin levels briefly surging [58]. Curcumin-induced G0/G1-phase arrest in lung cancer by preventing NSCLC cell growth and invasion through MTA1-mediated suppression of the Wnt/β-catenin pathway [59]. Another significant curcumin metabolite, tetrahydrocurcumin (THC), has been revealed to possess anticarcinogenic and antiangiogenic impacts on colon carcinogenesis in vivo. Azoxymethane-induced reductions in Wnt-1 and β-catenin protein expression in colonic mucosa accomplish this [60,61].

An isoflavone named genistein, which mimics oestrogen is composed of soybeans. In the azoxymethane (AOM)-induced rat colon cancer model, genistein (140 mg/kg) administration suppressed the total concentration of aberrant crypts by blocking aberrant β-catenin nuclear accumulation and reducing WNT signalling genes [62]. The administration of genistein to HL-60 cells in vitro led to G2/M phase arrest and death by ROS-mediated ER stress, which lowered mitochondrial membrane potential and elevated Ca2+ production. The observed effect was caused by increased expression of ER stress-associated proteins (IRE-1α, calpain 1, GRP78, GADD153, caspase-7, caspase-4, and ATF-6α) and apoptosis-associated proteins (Bax, PARP-cleavage, caspase-9, caspase-3, Bcl-2, and Bid) [63].

Table 1. List Of Phytochemicals Employed in Cancer Treatment Which Target Cellular Signalling Pathways

Compounds	Compound Classification	Type Of Cancer/ Model	Targeted Cellular Signaling Pathways	Mechanism of action	References
Allicin	Organosulfur	Cholangiocarcinoma and Lung Adenocarcinoma cells	Suppresses the activity of the STAT3 protein and the PI3K/AKT signalling pathway	Reduces adhesion, invasion, and migration; Modulates the balance of TIMP and MMP; Suppresses AKT phosphorylation; and Increases the expression of Bax proteins, which triggers apoptosis.	[64, 65]
Apigenin	Flavanoid	Non-small cell lung cancer (NSCLC)	Hinders the PI3K/AKT signalling cascade	Suppresses Cd26 expression and the SNAIL/SLUG-mediated EMT.	[66]
Andrographolide	Diterpenoid	Non-small cell lung cancer A549 cells	PI3K/AKT signalling cascade down-regulation	Inhibiting the migration and invasion of Non-small cell lung cancer A549 cells.	[67, 68]
Baicalein	Flavanoid	Modulates ESCC, apoptosis, and senescence in colon cancer cells	Promotes the p38, ERK, and MAPK signalling pathways	Improves p38 and ERK1/2 phosphorylation, promoting senescence brought on by RAS.	[69]
Glycyrrhizin	Triterpenes	Lung cancer	Alters the NF-κB signalling	Induces TLR4, suppresses the TxA2-related pathway, and hinders HMGB1.	[70]
Luteolin	Flavanoid	Breast cancer	Suppresses the PI3K/AKT pathway.	Induces caspase-3, -7, and -9, ERK, IGF, β-catenin, GSK-3β, MMP-2 and -9, iNOS, COX-2, Bcl-2, Bax, CDK2, and cyclin D and causes damage to DNA.	[71]
Nimbolide	Triterpenes	Pancreatic cancer	PI3K/AKT/mTOR and ERK signaling pathways	Suppresses mTOR, AKT, and p70S6 Kinase phosphorylates ERK and inhibits EMT.	[72]

Pterostilbene	Polyphenol	Breast carcinoma [55], Human hepatocellular carcinoma cells [56], Breast cancer cells [57]	Inhibition of Matrix Metalloproteinase-9, p38 Kinase Cascade and Akt Activation [55] Suppressing multiple signal transduction pathways and induces apoptosis, cell cycle arrest and cytoprotective autophagy [56, 57]	Reduce matrix metalloproteinase 9 (MMP) production [55] and inhibit PI3K/Akt activation to diminish the heregulin-b1/HER-2-modified invasive and aggressive phenotype of breast cancer cells [55, 56, 57]	[73-75]
Thymol	Monoterpenoids	Oral squamous cell carcinoma	Mitochondrial mediated apoptosis	Mitochondrial dysfunction and apoptosis.	[76]
Thymoquinone	Quinone	Gastric cancer	Suppresses the phosphorylation of STAT3 and associated protein.	Diminishes the activity of c-Src and JAK2.	[77]

Investigating Phytomedicine's Potential in Precision Oncology

Configuring cancer treatment based on a patient's particular genetic, molecular, and environmental characteristics is the goal of precision oncology. Using compounds originating from plants for medicinal purposes, phytomedicine has a lot of promise in this tailored approach. Considering their potential to target specific cancer-related pathways, phytochemicals could provide highly focused therapy possibilities that are personalised to the genetic and molecular makeup of distinct tumours. The therapeutic benefits of phytomedicines can be maximised while reducing adverse effects and interactions with other treatments by modified dose and administration.

Conclusion: The Potential and Prospect of Phytomedicine in the Management of Cancer

The second most common cause of mortality internationally is cancer. Phytomedicines have demonstrated potential in the treatment of cancer by providing supplementary or substitute choices to conventional therapy. Numerous substances derived from plants have anti-cancer characteristics, such as pro-apoptotic, anti-metastatic, and anti-proliferative actions. Through the modulation of many signalling pathways implicated in the evolution of cancer, phytomedicines exhibit immense promise as anticancer agents. They offer a diverse approach to cancer therapy because of their capacity to trigger apoptosis, halt the cell cycle, lessen inflammation, prevent angiogenesis, and target important signalling pathways. To fully realise their promise in cancer management, further investigation and clinical assessment will be necessary.

Conflict of Interest

There is no conflict of interest as expressed by the authors.

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