

**Review Article**

**A REVIEW ON BIOACTIVE PHYTOCHEMICALS AND IT'S MECHANISM ON CANCER TREATMENT AND PREVENTION BY TARGETING MULTIPLE CELLULAR SIGNALING PATHWAYS**

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**ABSTRACT**

In developing and developed countries, cancer is a significant health problem in people. Cancer becomes the second greatest cause of death in human after cardiovascular disease. However, significant advancements in modern cancer therapies have a beneficial impact on survival, chemotherapy and radiation therapy. Plants fulfill our basic needs to continue life and provide natural products that help to cure disease. The medicinal plants are readily available and have no toxicity as compared to modern drugs. Phytochemicals act on metabolic pathways and inhibit tumor growth, the development of cancerous cells, and replication by different mechanisms. Apigenin's chemo-preventive and anticancer activities have been demonstrating in numerous studies. Curcumin is a polyphenolic compound isolated from the *Curcuma longa* plant. EGCG, a polyphenol in black, white, and green tea is a chemo-preventive effect against many cancers by targeting multiple pathways. Normal cell growth and cell proliferation are closely regulated processes. The JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway controls gene expression during different processes, including proliferation, initiation, and apoptosis. The transcription factors are associated with the growth of cancer cells and control a cellular function in the disease. Mitogen-activated protein kinase (MAPK) is a class of serine and threonine kinase that includes ERK (extracellular regulated kinase), JNK (c-Jun N-terminal kinases), and p38. This review paper describes natural phytochemical compounds, their molecular targets and mechanisms of action.

**Keywords:** Cancer, Medicinal plants, Phytochemicals, Signaling pathways

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**INTRODUCTION**

Hippocrates, a Greek physician, was the first to name cancer, combining the Greek words "carcinoma" and "cancer." The term "karakinos" is used for a tumor. Cancer comes to be the second most significant source of death in humans after cardiovascular disease. In both developed and developing countries, cancer is an unusual common health complication. Every year, an estimated 10.9 million new cancer cases, 6.7 million deaths, and 24.6 million human living with different types of cancer globally [1]. Because of late observation and low treatment effectiveness, cancer has developed resistance to the chemotherapeutic drug and unsatisfactory treatment. Radiation therapy or chemotherapy causes side effects like sickness, exhaustion, hair loss, vomiting, depression. It also affects the immunological system, kidney, urinary tract, gastrointestinal organs, neurologic and psychological changes [2].

Plants fulfill our basic needs to continue life and provide natural products that help in curing disease. In the traditional system like Ayurveda, Unani plants are used as medicines for primary health care and provide many novel compounds used for preventing and curative treatment to modern science [3]. In addition, researchers in developing countries have discovered plant species with anticancer properties that have been used in herbal medicine. Moreover, medicinal plants are less expensive than current drugs and have no toxic effect [4].

Compounds isolated from plants play a different role in cancer medication; for example, Epipodophyllotoxin, camptothecin, combretastatin, taxol and vinca alkaloids. Vindesine (VDS) and vinorelbine (VRLB) are vinca alkaloids that are semi-synthetic analogs. The vinblastine, vincristine, and vinca alkaloids are chemotherapeutic drugs, were isolated from *Catharanthus roses* [5].

**Natural phytochemicals used as cancer chemo-inhibitory and therapeutic substance**

Phytochemicals are active compounds isolated from various medicinal plants that have been found to have chemotherapeutic

effects on cancer cell lines. Phytochemicals act on metabolic pathways and inhibit tumor growth, cancer cell development, and replication through various mechanisms [6].

**Apigenin**

Apigenin is a flavonoid compound that naturally originates in many plants and helps suppress HeLa cells multiplication. Apigenin has chemo-preventive and anti-cancerous properties. The ERK/AP-1/COX-2 pathway was inhibited by apigenin, which inhibited COX-2 activity in PMA-induced breast cancer cells. Apigenin suppresses Helicobacter pylori-induced inflammation. It promotes IKB expression in gastric cancer cells while suppressing COX-2 and NF-kB activity [7]. In prostate cancer cells of human, apigenin decreased the activity of NF-kB and its responsive genes. Apigenin inhibited the PGE2 level in colon cancer cells. Apigenin disrupts the leptin/leptin receptor pathway in a non-small cell lung cancer cell line, resulting in cell death [8].

**Berberine**

Berberine is a plant-derived alkaloid with anticancer and chemo-preventive properties. Clinical experiments for different disorders, including skin, intestine, breast, and oral cancers, are ongoing. Berberine inhibits several signaling cascades in colon cancer cells, including STAT3 and MMP2/MMP-9 [9]. COX and mTOR (mammalian target of rapamycin) pathways blocked by berberine. The various functions of berberine are arresting the cell cycle, inducing the apoptosis pathway, inhibiting the NF-kB pathway, and repressed COX-2 expression at the mRNA and protein level in colon cancer cells (HT-29). Berberine targets NF-kB/COX-2 and activates the apoptosis pathway in oral cancer cells [10]. In melanoma cells, berberine induces the expression of AMPK and inhibiting the ERK signaling pathways and COX-2 expression [11].

**Curcumin**

Curcumin is a polyphenolic compound originate from the *Curcuma longa* plant (1, 7-bis [4-hydroxy-3-methoxyphenyl]-1E,

6Eheptadiene-3, 5-dione). Curcumin suppresses tumor cell development by controlling different cell signaling pathways, including tumor suppressor pathway (p21, RB, p53), caspase activation (caspase-8, 3, 9), cell cycle (cyclin D1 expression), mitochondrial pathway of apoptosis, extrinsic apoptosis pathway, PI3-K/Akt cell survival pathway, and mitogen-activated protein kinase pathway [12]. In lung cancer cells, curcumin hinders the IFN-induced activation of COX-2 and NF-kB activity. Curcumin inhibits IL-6, IL-1, and other pro-inflammatory mediators through an NF-kB, AP-1, and MAPK dependent pathway. Curcumin was discovered to have anti-inflammatory properties. In human prostate cancer cells, the proteins of Akt and mTOR pathways, their downstream targets, are phosphorylated by curcumin [13].

#### Epigallocatechin-3-gallate

EGCG is a polyphenolic compound in green tea; it is also found in small amounts in white and black teas. It has a chemo-preventive activity against different cancer by targeting multiple pathways. Anti-cancer effect of EGCG shown in various cancer like brain, prostate, cervical, and bladder [14]. *In vitro*, EGCG prevented skin cancer cells. EGCG slows down the Bcl-xL and its antiapoptotic protein activity. COX-2 is repressed by EGCG, which inhibits by blocking the PI3K/AKT pathway. EGCG inhibits its gene products such as VEGF and c-Myc. EGCG suppressed cell emigration in melanoma cells [15].

#### Fisetin

Fisetin is present in onions, strawberries, persimmons, apples, and cucumbers. It is an anti-inflammatory compound with anticancer effects. Fisetin prevents carcinogenesis in HCT-116 cells [16]. Fisetin inhibits the COX-2/iNOS and NF-kB signaling pathways in skin cancer. Fisetin inhibited adherence, emigration, and aggression by lowering the amount of nuclear factor kappa B (NF-kB) and activator protein-1 (AP-1). Fisetin inhibited cell viability by causing arrest in the G1-phase of the cell cycle and disrupting Wnt/catenin signaling in lung cancer cells [17].

#### Genistein

Fava beans, coffee, lupine, kudzu, and soybeans contain genistein, a form of isoflavone. Antiangiogenic, antioxidant, and anthelmintic properties have been discovered in genistein. Genistein inhibits DNA topoisomerase II activity and interrupts the activity of the tyrosine kinase enzyme [18]. Genistein has been indicating to be involved in the medication of leukemia in *in vivo* and *in vitro* research. Genistein induces the apoptosis pathway and inactivates NF-kB in a lung cancer cell line (H460). In addition, genistein's activation of the cell cycle is interrupted in breast cancer cells [19].

#### Kaempferol

Brussels sprouts, broccoli, grapefruit, witch hazel, tea, apples, and other plants contain the flavonoid kaempferol. It has been used in the medication for lung and pancreas cancer. It has been studied for its antiangiogenic activity, antitumor, and free-radical scavenging properties. Kaempferol is a flavonoid with antitumor, antioxidant properties, and also capacity to cause apoptosis in cancer cells [20]. Kaempferol inhibits CDK1 and thus prevents the G2/M stage of the cell cycle in human breast cancer cells. In MCF-7 cells, kaempferol effectively induced PARP cleavage, accompanied by a reduction in Bcl2 protein expression and multiplied in Bax protein expression [21]. As an aryl hydrocarbon receptor (AhR) blocker, kaempferol inhibits the PI3K-Akt pathway, which may be helpful in the treatment of esophageal cancer [22].

#### Lycopene

Lycopene is a carotenoid with anti-cancer properties and can be found in onions, red carrots, red papayas, and watermelons. Foods rich in lycopene, such as tomatoes, can slow down the possibility of prostate cancer. Lycopene has been appearing to have antioxidant and chemo-inhibitory effects in prostate cancer. Lycopene is poorly soluble in water but highly soluble in organic solvents. However, cancer-preventive enzymes, including phase II detoxification enzymes, are responsible for their anti-cancer properties. Lycopene

has been appearing to have antioxidant and antimutagenic activity. In addition, lycopene protects the body from chemical toxicity [23].

#### Quercetin

Quercetin is a flavonoid. It is found in licorice leaves and fruits that have anti-cancer, anti-inflammatory, and polyphenol properties. Quercetin has anti-estrogenic effects, which slow down metastasis of breast cancer cells [24]. Quercetin controls cancerous cell development by stimulating tumor suppressor genes, initiating apoptosis pathways, and slowing down angiogenesis. Quercetin inhibited proliferation, reduced PGE2 levels, and increased apoptosis in HCA-7 human colon cancer cells during colon carcinogenesis [25].

#### Resveratrol

Resveratrol, a polyphenolic molecule, is found in grapes, peanuts, red wine, dark berries, and other plants [26]. Many research studies conducted over the previous decade have appeared that resveratrol can hinder or delay the enlargement of disorders like cancer. It has chemoprevention capacity against many stages of cancers, such as beginning, development and progression. Resveratrol caused COX-2 intranuclear aggregation in breast cancer cells and allowed COX2 with Ser15-phosphorylated p53. In colon epithelial cells (HT-29), resveratrol suppressed the synthesis of Prostaglandin E2 (PGE2) by inhibiting COX-2 enzyme activity [27]. Resveratrol inhibits NF-kB function, blocks tumor necrosis factor, increases COX-2 activity and increases the immunoregulatory cytokines in liver cells. Resveratrol suppresses the development of breast cancer by inhibiting IκB kinase/NF-kB signaling and induces the expression of COX-2. Resveratrol also activates the tumor suppressor gene p53 [28].

#### Ursolic acid

Ursolic acid, a natural triterpenoid compound found in plants, is being investigated as a cancer treatment agent. Ursolic acid stops cancer from spreading by blocking many signaling pathways [29]. For example, ursolic acid downregulates COX-2 activity and cleaved poly (ADP-ribose)-polymerase, which activates the apoptosis pathway in liver cancer cells (HepG2) [30]. In addition, ursolic acid inhibits cellular growth, increases apoptosis, and stops the cell cycle in gastric cancer cells [31].

### Molecular-level attack for natural chemo-inhibitory substances

#### Apoptosis

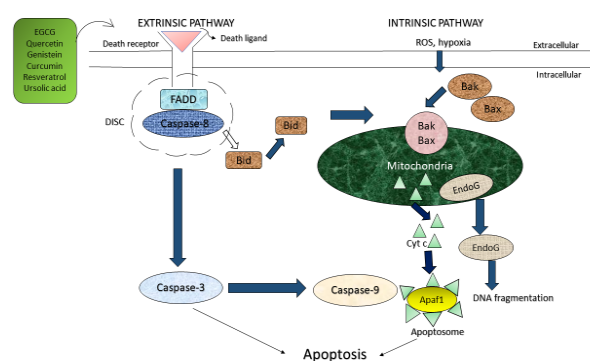
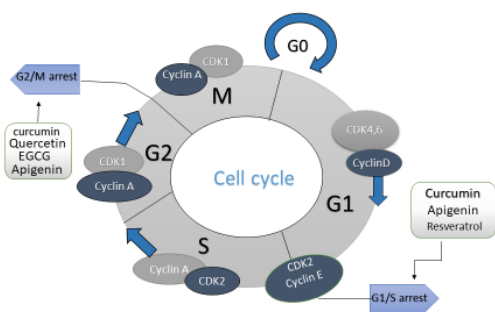


Fig. 1: In various cancers, phytochemicals activate the mechanism of the apoptosis pathway

The two most general types of cell death are necrosis and apoptosis. External damage, the disappearing of the plasma membrane or its biochemical supports causes necrosis or cell death. Uncontrollable cell development and decreased apoptosis are a marker of cancer. Programmed cell death via apoptosis cascade is necessary for the proper development of multicellular organisms. The morphological and biochemical changes in the apoptosis pathway are chromatin condensation, inter nucleosomal DNA fragmentation, the origination of apoptotic bodies, and cell shrinkage [32]. Apoptosis can destroy genetically modified, pre-cancerous, or cancerous cells. Several

natural plant compounds were originally developed as antiviral or anti-inflammatory agents. Still, as our perception of cancer mechanisms improves, the antitumor properties of different phytochemicals are becoming more commonly accepted and used [33]. In various cancer cells, EGCG can increase the apoptosis pathway and inhibit the cell cycle. These effects of EGCG in cell lines were in millimolar and micromolar concentrations [34]. Quercetin prevents cellular proliferation by inducing the intrinsic pathway of apoptosis in different cancer. It enhanced the activity of the pro-apoptotic Bcl-2 class of proteins and triggered caspase-9 and caspase-3 but not caspase-8 [35]. Red wine contains resveratrol, which is an antioxidant. It also decreased the activity of antiapoptotic protein Bcl-2 while increasing the pro-apoptotic Bcl-2 class. The Bcl-2 class contains Bid, Bax, Bad, and Bak proteins. In BGC-803 cancer cells, ursolic acid promotes DNA fragmentation, upregulating caspase3, -8, and -9 and downregulating Bcl-2 expression [fig. 1] [36].

### Cell cycle



**Fig. 2: Mechanisms of cell cycle prevent initiate by phytochemicals in different cancer**

Cell growth and proliferation are tightly controlled processes in normal cells, and cell cycle dysregulation can result in unregulated cell proliferation and contribute to the malignant phenotype of tumor cells [37]. Cancer cells lack cell cycle regulation. Cell cycle checkpoints regulate cell growth, differentiation of cells, DNA replication, and apoptosis. Many phytochemicals have been occurring to hinder cancer cell development by controlling cell cycle proteins. Additionally, cell cycle checkpoints G1/S and G2/M are essential targets in cell cycle regulation [38].

Curcumin caused G2/M and G1/S phase in HOS cells to prevent D1 cyclin, cdc2, and cyclin B1 downregulation. Quercetin arrests G2/M by upregulating p73, p21 and waf1 while downregulating cyclin B1 in a human cancer cell line. Resveratrol promotes cell cycle inhibition and aggregation of cells in the G0–G1 phase in Pancreatic cancer cells. Resveratrol arrests cell cycle in G2-M and S phases and degradation in pancreatic cancer cells [39]. Apigenin inhibits Huh7 cell development, initiates the G2/M cell cycle prevention, and increases the rate of the apoptosis pathway. Apigenin prevented the enlargement of leukemia cells by allowing them to join the G2/M phase (myeloid HL60 cells) and the G0/G1 phase (non-myeloid HL60 cells, erythroid TF1 cells). In multiple myeloma cells, isothiocyanates promote cell cycle prevention in the G2/M phase and phosphorylation of conserved serine residue in the histone H3 [40].

### JAK-STAT pathway

The JAK-STAT (Janus kinase, signal transducer, and activator of transcription) pathway controls gene expression during initiation, enlargement, migration, and apoptosis [41]. STAT proteins were originally identified as cytoplasmic transcription factors, only translocated to the nucleus upon Jak-mediated phosphorylation and dimerization. When epidermal growth factors and cytokines interact, they generate homodimers or heterodimers that move to the nucleus of the cell and regulate genes [42]. The anti-apoptotic and proliferative properties of STAT3 in cancer cells have been connected to a poor prognosis. Stat3 dysregulation has been connected to increased breast cancer cell enlargement, survival, and metastasis. In myeloma, the Bcl-xL and Mcl-1 are anti-apoptotic

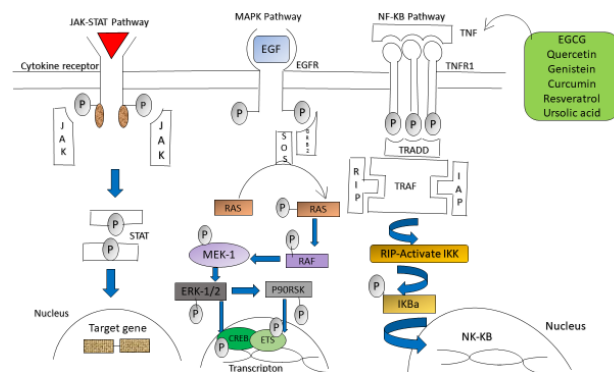
proteins that were overexpressed in myeloma cells where integral Stat3 activity was promoted by Interleukins [43]. By reducing VEGF and Stat3 activation, epigallocatechin gallate reduces gastric cancer origination and angiogenesis. In hypopharynx carcinoma and breast cancer cells in human, epigallocatechin gallate slows down Stat3 stimulation [44]. Cu (2+)-oxidized LDL-induced endothelial apoptosis was reduced by quercetin through the Jak2-Stat3 pathways. *In vitro* treatment of activated T cells with quercetin inhibited IL-12-induced tyrosine phosphorylation of Jak2, Tyk2, Stat3, and Stat4, which results in IL-12-induced T cell proliferation and Th1 differentiation [fig. 3] [45].

### MAPK pathway

Mitogen-activated protein kinase (MAPK) is particular to serine/threonine kinases that include JNK, ERK (extracellular regulated kinase), and p38. They control several processes like cell development and enlargement of cells by transferring cell signals to the nucleus. Transmitting cell signals to the nucleus affects gene expression that controls cell processes like cell development, differentiation, and multiplication [46]. The epidermal growth factor receptor (EGFR), estrogen receptor (ER), and tumor necrosis factor-alpha (TNF) are the most considerable downstream effectors. Components of MAPK pathways, for example, PI3K, Ras, and Akt, are mutated in human cancer. Raf-mediated chemotherapeutic drug resistance induces paclitaxel in breast cancer cells. B-Raf has been occurring to evolve in cancer such as thyroid and breast cancer. Curcumin down regulates EZH2 by activating three important members of the mitogen-activated protein kinase (MAPK) pathway: c-Jun NH2-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 kinase [47]. Ursolic acid suppresses the EGFR/MAPK pathway, slows down the enlargement of colon cancer cells, and activates the apoptosis pathway. In osteosarcoma cells, ursolic acid activates the MAP kinase pathway, inducing caspase-dependent apoptosis, significantly inhibited by ERK1/2 inhibitor treatment [fig. 3] [48].

### NF-kB pathway

The transcription factors are related to cancer growth and control a different cellular cascade in the disease. NF-kB inducers include tumor necrosis factor-alpha, lipopolysaccharide, reactive oxygen species (ROS), and Interleukin beta [49]. Rel/NF-kB transcription complexes are found in an inactivated state in the cytoplasm of most cells, where they are attached to an inhibitor (IκB). Many stimuli can rapidly activate these transcription complexes from their inhibitors and allowing them to translocate to the nucleus [50]. The transcription factor NF-kB controls the expression of genes impenetrable in cancer invasion, angiogenesis, and metastasis. As an effect, inhibitors of NF-kB activity have been occurring to be helpful in cancer medication [51].



**Fig. 3: Effect of phytochemicals on signaling pathway in different cancer**

Resveratrol suppressed the NF-kB-regulated gene, inhibiting apoptosis and preventing caspase-3 activation. Tumor necrosis factor promotes phosphorylation of the NF-kB. Resveratrol inhibits

TNF-promoted phosphorylation and nuclear transfer of the NF- $\kappa$ B p65 subunit [52]. Curcumin inhibits the transcription factor NF- $\kappa$ B and slows down the phosphorylation of I $\kappa$ B $\alpha$ . NF- $\kappa$ B initiated the apoptosis pathway and repressed the I $\kappa$ B kinase, preventing proliferation [fig. 3] [53].

## CONCLUSION

Major cancer therapeutics are radiation therapy and chemotherapy, which cause severe side effects such as hepatic toxicity, nausea, vomiting, etc. Natural plant products can lower the toxicity of radiation therapy and chemotherapy. This review gives information about different phytochemicals and their anticancer activity by targeting apoptosis, cell cycle, JAK-STAT, MAPKs, and NF- $\kappa$ B activation *in vitro* research.

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## ABBREVIATIONS

JAK-STAT-Janus kinase-signal transducer and activator of transcription, MAPKMitogen-activated protein kinase, ERK-extracellular regulated kinase, JNK-c-Jun N-terminal kinases, VDS-Vindesine, VRLB-vinorelbine, NF- $\kappa$ B-nuclear factor-kappa B, AP-1-activator protein-1, AhR-aryl hydrocarbon receptor, EGFR-The epidermal growth factor receptor, ER-estrogen receptor, TNF-tumor necrosis factor-alpha, ERK-extracellular regulated kinase, EZH2-zeste homolog 2, ROS-reactive oxygen species

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Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

The authors declared that they have no conflict of interest.

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