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Review

Therapeutic Targeting of Regulated Signaling Pathways of Non-Small Cell Lung Carcinoma

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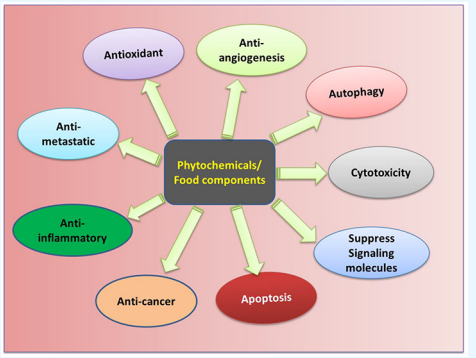
ABSTRACT: Non-small cell lung carcinoma (NSCLC) is the most common cancer globally. Phytochemicals and small molecule inhibitors significantly prevent varying types of cancers, including NSCLC. These therapeutic molecules serve as important sources for new drugs that interfere with cellular proliferation, apoptosis, metastasis, and angiogenesis by regulating signaling pathways. These molecules affect several cellular signaling cascades, including p53, NF-κB, STAT3, RAS, MAPK/ERK, Wnt, and AKT/PI3K, and are thus implicated in the therapeutic management of cancers. This review aims to describe the bioactive compounds and small-molecule inhibitors, their anticancer action, and targeting cellular signaling cascades in NSCLC. We highlighted the therapeutic potential of Epigallocatechin gallate (EGCG), Perifosine, ABT-737, Thymoquinine, Quercetin, Venetoclax, Gefitinib, and Genistein. These compounds are implicated in the therapeutic management of NSCLC. This review further offers deeper mechanistic insights into different signaling pathways that could be targeted for NSCLC therapy by phytochemicals and small-molecule inhibitors.



1. INTRODUCTION

Phytochemicals have been broadly documented and researched for their numerous health benefits.[1] These are major bioactive compounds of fruits, grains, vegetables, and other plant materials, decreasing the risk of diseases.[2,3] Diets enriched in plant foods are linked with a diminished risk of multiple diseases, including cancers.[4] Phytochemicals boost our immune system and help in combating diseases. Antioxidant phytochemicals are extensively found in cereal grains, fruits, vegetables, and medicinal plants.[5,6] Fruits such as berries, grapes, guava, sweetsop, pomegranate, persimmon, and plum are rich in antioxidants. Fruit wastes comprise high phytochemicals such as catechin, cyanidin 3-glucoside, gallic acid, epicatechin, kaempferol, and chlorogenic acid. Vegetables have high antioxidant and phenolic components.[7,8] Phytochemicals possess various chemical entities, including polyphenols, steroidal saponins, flavonoids, organosulphur compounds, and vitamins.[9] Natural polyphenols are plentiful antioxidants in human food diets, and radical scavenging actions are associated with substituting hydroxyl groups of phenolics.

Numerous phytochemicals have been recognized as potential therapeutic agents. The bioavailability of diverse compounds of interest at the targeting in the body location is a significant challenge in determining the therapeutic efficacy of the target drugs.[10] Delivery of phytochemicals with a drug can modify the action of glucuronidation or inhibit C-P450 clearance, increasing the bioavailability of active compounds at the target site. Several phytochemicals are failed at preclinical or clinical levels because these compounds are either unbalanced in the gut or show poor bioavailability.[10] There is a need for preclinical models that might imitate systemic exposure to phytochemicals with significant pharmacokinetic alterations. A detailed preclinical and clinical examination of the bioavailability of active compounds or phytochemicals is necessary to understand their therapeutic limitations. In addition, determining a compound delivery system for achieving the best efficacy level of the agent on the target organ is also necessary. Approval of phytochemicals in the human system and bioavailability for targeting cells enable their bioefficiency for protecting health.[11]

Cellular signaling pathways are complex signaling systems that govern and manage key biological processes. Tumor cells frequently show alteration in different cellular pathways as an

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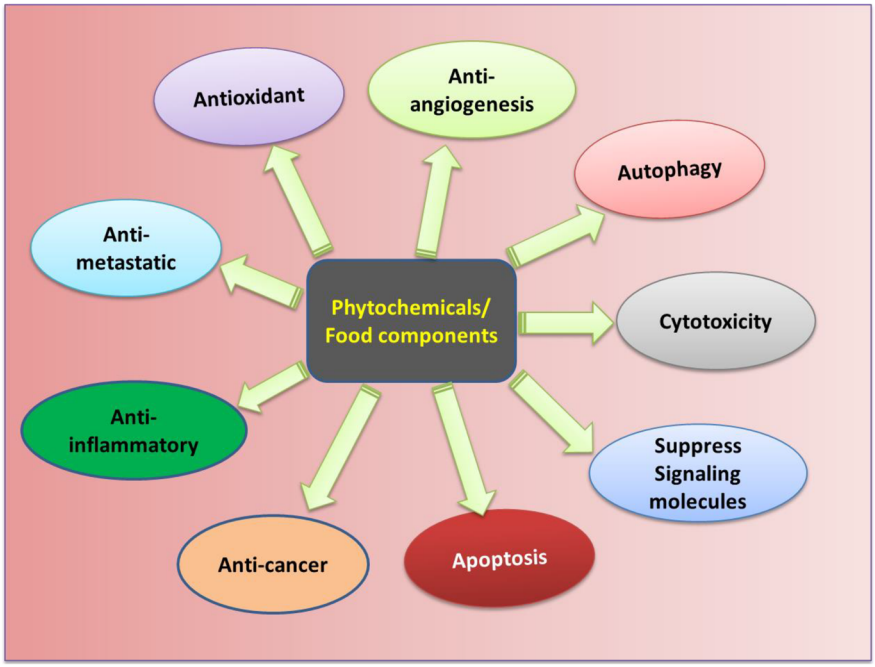

Figure 1. Natural compounds exhibit therapeutic actions. Phytochemicals show antitumor properties, principally antimutagenic, antioxidative, anti-inflammatory, and apoptosis-stimulating properties, which might inhibit tumor growth.

effect of the complex communication of cell signaling, including non-small cell lung carcinoma (NSCLC).[12] The RAS-RAF-MEK-ERK cascade controls cell survival and proliferation of the NSCLC.[13] PI3K-AKT signaling triggers cell proliferation. Hence, the RAS−ERK signaling cascade is a key downstream effector of oncogenic PI3K. Epidermal growth factor receptor (EGFR) controls ERK and STAT3 pathways.[14,15] ERK is activated via EGFR in a tumor that is linked with the inhibition of apoptosis. EGFR stimulates cellular signaling, including the MAPK, PI3K/AKT, and STAT3 pathways. RAS/MEK and PI3K pathways are connected with cell proliferation and apoptosis.[16,17] These pathways are injured in tumor cells, which endorse the cancer cells' growth and block apoptosis.

Phytochemicals benefit multiple disease conditions by regulating many cellular and molecular pathways, including the regulation of inflammation, metabolic disorder, redox potentials, and apoptosis. Polyphenols showed chemopreventive action against carcinogenesis by affecting the mechanistic target of rapamycin (mTOR)/AKT signaling.[18] These might obstruct the IκB kinase action, thus preventing translocation to the nucleus, which NF-κB persuades the expression of genes connected to apoptosis, metastasis, and invasion.[19,20] Hence, by preventing NF-κB activation, polyphenols repress the expression of diverse cell survival and proliferative genes.[21] Phytochemicals significantly stimulate cell death in several cancers by preventing the activity of the JAK/STAT pathway and activating apoptosis, which stimulates cell death by preventing constituent activation of STAT3 and decreasing regulating survivin and Mcl-1.[22,23] Polyphenols have shown a regulatory effect on MAPK signaling. Some phytochemicals show dual control of this signaling pathway by preventing activation of the MAPK pathway linked to influencing cell proliferation and influencing MAPK-associated apoptosis.[24]

Signaling cascades have been studied for therapeutic development. These cascades are suggested as promising therapeutic targets for cancer therapy.[12,25] A coordinated down-regulation of ERK and AKT is crucial for initiating cell death and anticancer action.[26] Kinase inhibitors with enhanced specificity and improved pharmacokinetics have been implicated in designing anticancer agents.[16,27,28] Hence, inhibitors that target these signalings have numerous potential utilizes, from cancer repression to proliferative diseases.[16,29] Targeting EGFR with considering mutations suggested promising benefits in developing drug-like molecules that cause enhanced expression of pro-apoptotic proteins and activate apoptosis.[30] In addition, targeting MEK and PI3K with mTOR is a better alternative than single agents for KRAS mutants in NSCLC, suggesting a beneficial treatment approach in future therapeutic development.[31]

This review provides a detailed overview of the therapeutic potential of different phytochemicals and small-molecule inhibitors in NSCLC. We further, focused molecular mechanisms of the signaling molecules in NSCLC and consequently targeted targets for potential therapeutic implications. Additionally, we elucidated the possible therapeutic use of phytochemicals and small-molecule inhibitors in NSCLC.

2. BIOLOGICAL ACTIVITIES OF PHYTOCHEMICALS

Phytochemicals have antioxidant action, antimicrobial results, modulation and detoxification enzymes, immune system incentive, reduction of platelet aggregation, neuroprotective effects, and anticancer properties.[32] Phytochemicals possess various health-promoting functions, including cancer fight.[33] These molecules are responsible for preventing diseases. Phytochemicals, as plant constituents with distinct bioactivities toward biochemistry and metabolism, are being extensively studied for their capability to provide health benefits.[34] Plant metabolites were studied on animal and human cells, exhibiting exciting biological activities. They are beneficial in pharmaceutical applications, nutrition, and dietary supplements,

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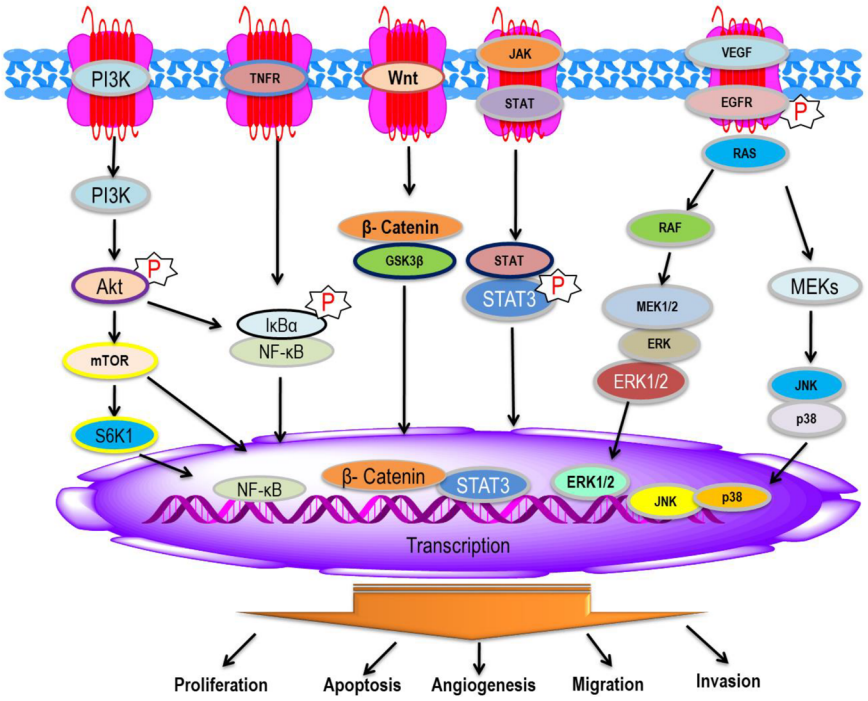

Figure 2. Signaling cascades involved in cancer development and cell proliferation. Signaling pathways control cell proliferation, survival, and differentiation by triggering the expression of multiple genes that are connected to tumor progression. Signal cascades initiate activation of the downstream pathways, which consequently starts the transcription of genes. This figure is adapted from refs[20,50,51] and drawn by using ChemBioDraw.

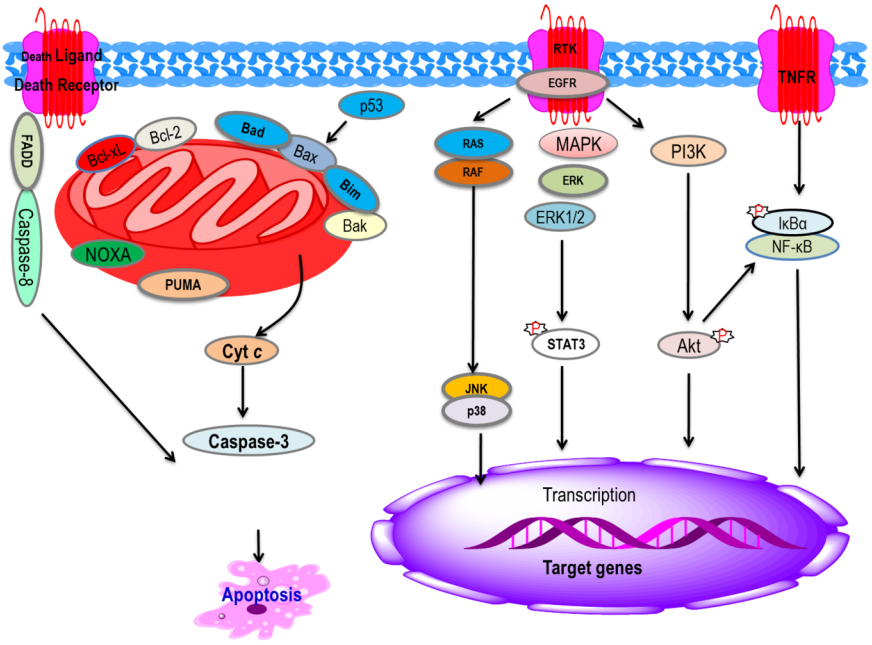

Figure 3. Cancer-linked signaling pathways. Pathways regulate cell proliferation and survival by controlling the gene expression associated with tumor development. These cascades control cell death (apoptosis) in various ways, blocking cell death from death receptors at several steps. This figure is adapted from refs[20,51,55] and drawn by using ChemBioDraw.

constantly deliberated as the source of food, diet, and medical compounds.[35]

Furthermore, the pool of phytochemicals (natural compounds) encloses an extensive range of 'bioactive' compounds. Phytochemicals might detoxify substances that cause tumor progression. They seem to neutralize free radicals, prevent enzymes that stimulate carcinogens, and trigger enzymes. Genistein inhibits the creation of new capillaries needed for cancer growth and metastasis.[36] However, considerable research is ongoing on their tumor-preventing potentials.[37] Phytochemicals prevent high blood pressure, diabetes, and macular degeneration. They show antitumor properties,

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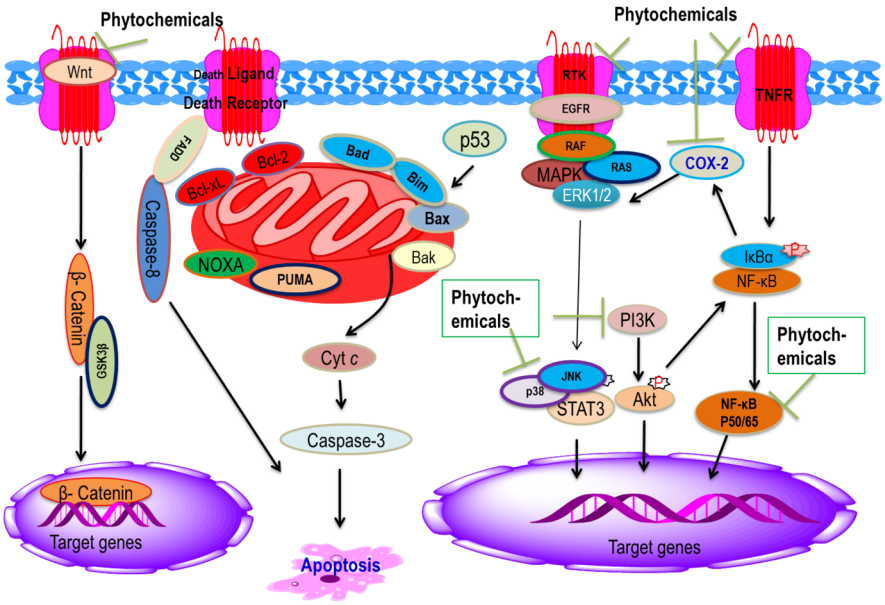

Figure 4. Phytochemicals inhibit signaling molecules and stimulate apoptosis. Rationale for targeting pathways via inhibitors for inhibiting tumor proliferation. Multiple signaling regulates the action of apoptotic proteins via post-translational mechanisms. Targeting these signaling cascades might stimulate apoptosis. This figure is adapted from refs[20,55] and drawn by using ChemBioDraw.

principally antimutagenic, antioxidative, anti-inflammatory, and cell death-stimulating properties, that might inhibit tumor proliferation. Phytochemicals exhibit several therapeutic actions by repressing the cell cycle, stimulating apoptosis, and obstructing signaling cascade critical for cancer progression.[38] Figure 1 illustrates the roles of phytochemicals in clinical therapeutics.

3. REGULATION OF CELLULAR SIGNALING MOLECULES IN NSCLC

Multiple signaling pathways are linked with several cancers, including NSCLC.[20] The RAS-stimulated signaling comprises the MAPK pathway; RAS-rapidly accelerated fibrosarcoma (RAF)-MEK-ERK pathways control cell survival and proliferation in the NSCLC. MAPK signaling pathway affects crucial functions in the carcinogenesis and treatment resistance of NSCLC cells via endorsing proliferation or preventing apoptosis of NSCLC cells.[39,40] The RAS−ERK pathway is a key downstream effector of oncogenic PI3K. ERK and STAT3 pathways are regulated and controlled by activating the EGFR pathway.[41,42] The RAS/MEK signal transduction pathway controls cell progression and apoptosis.[43,44] This pathway's mutation is commonly associated with human cancers.[45] The activation of Wnt signaling is connected with rising cancer initiation potential. The Wnt pathway is significant in developing NSCLC that found upregulated Wnt signaling. Figure 2 illustrates the regulation of Wnt signaling genes in lung cancer. These genes are regulated in the lungs of KRAS transgenic mice. Hence, these signaling molecules regulate cell survival and proliferation by regulating multiple gene expression.[2,20,46]

RAS-ERK and PI3K-AKT cascades regulate apoptosis in various ways, linked with cell cycle arrest and proliferation. The active networks associated with the KRAS-Dep phenotype in NSCLC.[47] Hyperactivation of the signaling by oncogenic mutations in the RAS-ERK and PI3K-AKT cascade perturbs the balance of antiapoptotic signals, contributing to tumor cell growth. AKT blocks many steps in cell death from death receptors.[48,49] Though, it phosphorylates FoxO3A, which leads to their cytoplasmic sequestration, thus blocking the initiation of death ligands and the Bim.

AKT activates the apoptosis inhibitor XIAP. Thus, AKT controls NF-κB that triggers numerous survival factors, such as Bcl-xL and Bcl-2.[52] AKT-induced ubiquitylation and degradation of p53 suppress p53-induced apoptosis. AKT prevents apoptosis in many tumors including NSCLCs. AKT confers drug resistance via the inhibition of apoptosis, often the first-line therapy for NSCLCs.[53] Figure 3 shows that ERK phosphorylates the NF-κB inhibitor IkBa and Bim that target them for degradation. These signaling cascades control and inhibit apoptosis in several ways.[2,20,46]

4. ANTICANCER EFFECTS OF PHYTOCHEMICALS

Phytochemicals repress the cancer progression and metastasis through diverse mechanisms and protect the healthy cells from carcinogens, dropping inflammation that might progress to tumor development, stimulating apoptosis, and inducing autophagy of the damaged cells. Phytochemicals derived from medicinal plants are assumed to be a potential option for the present antitumor drugs.[54] Phytochemicals have been used for antitumor activity in preclinical studies to clinical trials.[54]

There is evidence concerning the cellular mechanisms by which polyphenols control carcinogenesis, cancer cell growth and death, inflammation, and angiogenesis. Phytochemicals can modify the initiation of carcinogenesis progression through defense against DNA injury. Suitable lifestyle alterations could inhibit human tumors, and the diet involves around 35% of tumor mortality.[56] Polyphenols play a significant role in the antitumor action of phytochemicals. Polyphenols, ellagitannins, and epicatechin gallate exhibit anticancer functions.

Several plant-based anticancer agents are currently in clinical use. Several phytochemicals have been checked for antitumor action.[57] Antioxidant phytochemicals might prevent cell

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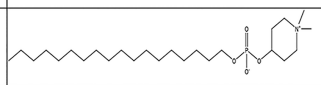
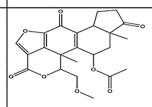
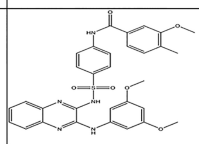
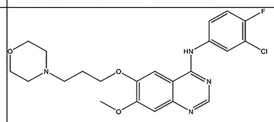
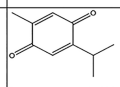
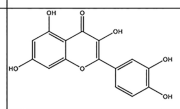
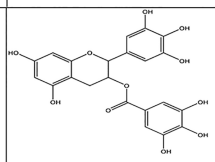
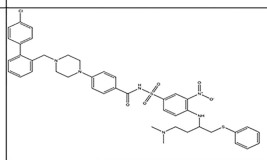
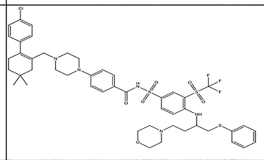
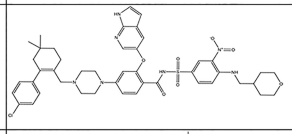
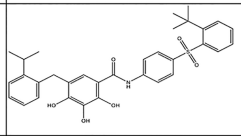
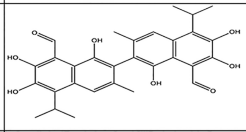
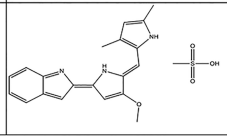
Table 1. Inhibitors/Phytochemicals and Small-Molecule Inhibitors of the Signaling Pathways for the Therapeutic Target[a]

Inhibitor	Structure (PubChem)	Inhibits signaling pathways	Clinical status	Ref.
Perifosine		AKT, NF-κB, MAPK, EGFR	Phase 1, 2	73
Wortmannin		PI3K/AKT	Pre-clinical	74
XL-765		PI3K/AKT/mTOR	Phase 1	75
Gefitinib		AKT, EGFR, ERK, STAT3	Phase 2	76
Thymoquinone		AKT, NF-κB, EGFR, ERK1/2, STAT3	Phase 2	77
Quercetin		AKT/PI3K, MAPK, Wnt/β-catenin	Phase 2	77
EGCG		NF-κB, MAPK, AKT/PI3K, STAT3, EGFR	Phase 1/2	78
ABT-737		AKT/PI3K, STAT3, EGFR	Phase 1/2	79
ABT-263		ERK1/2, JAK2-STAT3, EGFR	Phase 1/2	80
ABT-199		STAT3, EGFR	Approved for use in CLL	81
TW-37		STAT3, AKT, Notch-1	Phase 1/2	82
Gossypol		MAPK, NF-κB, VEGF, AKT, mTOR/p70S6K1	Phase 1/2	83
GX15-070 (Obatoclax)		PI3K/AKT, Ras/Raf/MAPK,	Phase 1	84

[a]Source: www.clinicaltrials.gov.

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proliferation and encourage tumor apoptosis, targeting tumor stem cells to express its antitumor capability. It can exert synergistic antitumor action with catechin against several cancer cell lines. Genistein, quercetin, and resveratrol showed a higher induction of quinone reductase. The antitumor potential of quercetin in multiple cancers has been reported.[58]

Similarly, resveratrol exerted the antitumor act via preventing cancer initiation, promotion, and development. Polyphenols encourage cell death via binding to Bcl-2 or BclxL or by changing the cellular microtubule cytoskeleton. Cocoa polyphenols stimulate cell death by enhancing the expression of caspase 3 and Bax while reducing Bcl-xL.

Phytochemicals control tissue cancer by regulating inflammation, metastasis, angiogenesis, and invasion. Figure 4 shows phytochemicals suppress cancer development through several pathways.[2,20,46] Polyphenols showed a regulatory effect on MAPK signaling. Hence we dually control this signaling pathway by preventing activation of the MAPK pathway linked to influencing cell proliferation and persuading MAPK-associated apoptosis.[24] Increased TNF-α making may alleviate cellular signaling, which might cause cells to undergoing necrosis or apoptosis. Hence, TNFR1 arbitrated signaling stimulates the activation of PI3K pathway that further promotes caspase 8/3 and BH3 interacting-domain death agonist (BID). This is pursued via the initiation of oxidative stress, necrosis, and apoptosis.[59,60] Cell scorch death may be stimulated via the activation of caspase-4/5/11 through lipopolysaccharide (LPS), which stimulates caspase-4/5/11 and eventually persuades cell scorch death.[61,62] Therefore, they defined cell scorch death as programmed cell necrosis mediated by the Gasdermin family. Thus, targeting the miRNAs via polyphenols was planned as a novel and potential approach to antitumor chemotherapy. By preventing NF-κB activation, polyphenols repress the expression of diverse cell survival and proliferative genes.[63,64] Phytochemicals significantly stimulate cell death in several cancers by preventing the activity of the JAK/STAT pathway and activating apoptosis, which stimulates cell death by preventing constituent activation of STAT3 and decreasing regulating survivin and Mcl-1.[23,65] Phytochemicals inhibit the translocation and accretion of β-catenin in the nucleus by activating GSK3.[24]

5. TARGETING SIGNALING MOLECULES IN NSCLC

Several signaling cascades are identified as potential therapeutic targets for lung cancer with the recognition of modified targeting genes.[66] The RAS/MEK/ERK and PI3K/AKT/STAT3/NF-κB signalings are majorly involved in NSCLC. These cascades are promising therapeutic targets for tumor therapy. Targeting the EGFR pathway is an attractive approach to developing personalized medicine in NSCLC.[30] EGFR activates cellular pathways, including AKT/PI3K, STAT, and MAPK cascades, and leads to improved cell proliferation. The RAS/ERK and NF-κB/PI3K/STAT3 signaling cascades have been comprehensively studied for therapeutic development. These cascades have been documented as promising therapeutic targets for tumor therapy. EGFR mutation was recognized as a rational therapeutic target.[67]

Figure 4 shows phytochemicals utilized for chemoprevention. These phytochemicals efficiently repress cell proliferation, control the cell cycle, induce apoptosis, and obstruct numerous tumorigenic signaling cascades, including PI3K/AKT and MAPK/RAS-Raf-MEK-ERK pathways.[46] Additionally, they could enhance DNA repair by the action of p21 and p53 gene results, like Bax, Bid, and Bak proteins that cause the synthesis of caspases 3, 7, 8, and 9. Hence, the initiation of apoptosis in cancer cells via the AKT/PI3K pathway is detained via a wide range of phytochemicals.[68,69] The flavonol glucoside icanin promotes cell death by ROS-mediated injury by inhibiting the STAT3 and PI3K/AKT cascades. Acting on the NF-κB/PI3K/AKT recovers the sensitivity for cisplatin of A549.[70] Flavonoids act on cells by PI3K/AKT signaling and must control cell death that activates caspase 9. Apoptosis initiation and repression of the AKT/NF-κB were associated with the regorafenib-inhibited progression of NSCLC.[71] Apoptosis stimulation and EGFR inactivation are connected to the regorafenib-increased anti-NSCLC effectiveness of cisplatin.

Phytochemicals may prevent tumors by inhibiting the PI3K, Raf, and ERK2 signaling pathways. EGFR is a major regulator of carcinogenesis.[72] EGFR signaling has the potential to repress tumor proliferation. Inhibitors of these signaling molecules are utilized for therapeutic targeting of various tumors (Table 1). Several inhibitors have been revealed as promising therapeutics for NSCLC.

6. THERAPEUTIC TARGETING OF CELLULAR SIGNALING OF NSCLC

6.1. Therapeutic Effect of EGCG. The therapeutic effects of EGCG were reported against multiple cancers. EGCG controls proliferation in SCLC cells effectively and has some effect on the limited number of NSCLC cells. Modulation of signaling via EGCG may contribute to its chemopreventive action. EGCG controls proliferation in diverse NSCLCs,[2] which was established for blocking NF-κB activity in tumor cells. EGCG blocks UVB-stimulated NF-κB activation. p50/p65 targets cleavage by caspases during EGCG-stimulated apoptosis. NF-κB is a potent target for cancer therapy. In the JB6 mouse epidermal cell, EGCG blocked the MAPK pathway.[91]

The treatment with EGCG for NHEK before UVB contact was revealed to prevent UVB-induced H_2O_2 creation associated with inhibiting the UVB-induced phosphorylation of JNK, ERK1/2, and p38. EGCG inhibits cancer cells' MAPK pathway and AP-1 action.[92] The deregulation of the MAPK pathway is observed in multiple cancers. Alteration of MAPKs via EGCG provides an attractive strategy for tumor therapy. EGCG inhibits the PI3K pathways in the TRAMP model. It diminishes proliferation, induces cell death, increases PTEN expression, and decreases p-mTOR and p-AKT expression.[55,93,94] It competently blocked hypoxia-induced factor 1 (HIF-1) assembly by preventing ERKs/AKT/PI3K pathways. EGCG participated in apoptosis induction and the inhibition of cell proliferation. EGCG may repress the expression of p-AKT through PTEN for triggering AKT/PI3K signaling.[95]

The anticancer role of EGCG results from STAT3 pathway inhibition. It blocks STAT3 activation, which led to down-regulation of the targeting gene, produces of STAT3, including Bcl-xL, Bcl-2, Mcl-1, cyclin D1, and VEGF. The inhibition of the EGFR may involve the anticancer action of EGCG in lung cancer.[96] It modifies and prevents NF-κB, ERK1/2, and AKT-mediated cascades, thus changing the Bcl-2 family protein ratio and inducing cancer caspases. EGCG initiates apoptosis and prevents EGFR, STAT3, and ERK pathways in tumors.[78,97,98] The components of the Wnt pathway play a significant role in lung cancer. However, Wnt 1 and Wnt 2 are more expressed in

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NSCLC, and their inhibition leads to apoptosis.[99] It diminished cell growth and proliferation through suppressed ERK1/2, AKT/PI3K, STAT3, NF-κB, and Wnt pathways.[2] EGCG exposure markedly diminished EGF-induced EGFR, ERK1/2, and AKT activation.

6.2. Therapeutic Effect of Perifosine. Perifosine is an alkyl phospholipid with a high oral bioavailability and excellent antitumor activity. Perifosine blocks growth and stimulates cell death in NSCLC cells. Induction of apoptosis is linked to the downregulation of AKT, which perifosine stimulated apoptosis in NSCLC cells.[100] Perifosine could block the mTOR axis in human lung cancers. Hence, perifosine considerably enhanced type II light chain 3 and rising PARP cleavage that stimulates autophagy and apoptosis.[101,102] The down-regulation of the NF-κB signaling involves the mechanism of action of Perifosine. Co-treatment with Perifosine is promising to hinder the progression of antimetabolite resistance because of NF-κB activation in cancer.[103] It is a potential new antitumor agent that blocks the EGFR/MET-AKT axis in malignant pleural mesothelioma.

A phase 1/2 clinical trial of perifosine in the management of NSCLC has been performed to establish the maximum dose of perifosine, which may be administered to contrast the gastrointestinal toxicity of diverse dose schedules and to achieve preliminary information on the response rate of perifosine in NSCLC.[102] Perifosine has shown anticancer activity via the inhibition of AKT by preventing its recruitment to the cell membrane. Perifosine has revealed a response in phase I trials for advanced solid tumors.[104,105] It is designed to target cellular membranes. Its incidence persuades membrane permeability, phospholipid metabolism, and mitogenic signal transduction, resulting in cell differentiation and cell growth inhibition in multiple tumor model systems.[106]

This drug blocks the MAPK signaling and modulates the equilibria between the MAPK and pro-apoptotic stress-activated protein kinase (SAPK/JNK) signaling. Its anti-AKT activity increases the results of other treatment agents via stimulating cell death and interfering with cell growth signals.[107] Perifosine induces expression of the death receptors DR4 and DR5, increasing JNK and c-Jun levels and promoting cell cycle arrest via induction of p21.[100,108] A combination of perifosine and TRAIL is more efficient in stimulating apoptosis and preventing cancer growth than either agent alone. Hence, clinical trials of perifosine in HNSCC had mixed results, in terms of efficiency. Furthermore, perifosine enhanced the antineoplastic action of cisplatin in several cancers, including lung cancer cells, via stimulating the apoptotic pathways;[109,110] hence, enhancing the cytotoxicity of cisplatin and demonstrating synergistic apoptosis induction in combination with etoposide, UCN-1, and HDAC inhibitors.[111]

6.3. Therapeutic Effect of ABT-737. ABT-737, a novel inhibitor of Bcl-2, shows antiapoptotic potential with a high affinity for Bcl-xL. It improves the apoptotic results in small-cell lung cancer.[112] ABT-737 stimulates caspase-3, causing cell death, which up-regulates the Noxa expression. However, the inhibition of Noxa via small interfering RNA attenuates apoptosis. It provokes the activation of caspase-3 and cleavage of PARP and stimulates cell death. ABT-737 induces Bax/Bak-mediated apoptosis, which might improve the radiosensitivity of various solid tumors.[113] Although it has promising effects, it is known for clinical trials because of unfavorable pharmacological attributes, including thrombocytopenia. However, numerous Bax-targeted antitumor agents are approved.

Multiple studies showed the promising effect of ABT-737 on cellular signaling molecules. The radio-sensitizing action of ABT-737 in preclinical studies suggested that clinical trials utilizing this approach could be useful in K-RAS mutant NSCLC.[113] Bim polymorphism is strongly associated with a poor clinical response in EGFR mutant NSCLC patients. ABT-737 significantly enhances erlotinib-mediated apoptosis and high responses to EGFR inhibitors in lung cancer patients. It blocks PI3K/AKT in tumors. Hence inhibition of Bcl-xL and Bcl-2 tremendously enhances AKT/PI3K inhibition-stimulated cell death in tumors. The AKT and p53 signalings are checked due to ABT-737 and naringenin in gastric cells. BEZ235 with ABT-737 regulated tumor apoptosis.[114] Targeting the ERK/MAPK and AKT/PI3K signaling can alter the inequity between anti- and pro-apoptotic molecules, which may comprise an effective strategy for sensitizing tumors for ABT-737. ABT-737-induced apoptosis demonstrated decreased cancer cell growth and stimulated *c*-Jun in high regulation of Bim.[115] Combined with sorafenib, it efficiently inhibited STAT3 levels, and thus recommended targeting STAT3-inducers of cell death, which might be a promising novel approach for treating cancer cells.

6.4. Therapeutic Effects of Thymoquinone. *Nigella sativa* has many precious ingredients that efficiently treat different diseases. Thymoquinone (TQ) is a potent antitumor bioactive compound in black seeds. TQ has shown antioxidative, anti-inflammatory, and antitumor effects.[116,117] TQ inhibits proliferation and angiogenesis and activates apoptosis in NSCLC.[118] It inhibited growth and diminished cyclin D1 expression in NSCLC (A549 cells). It prevents cell proliferation, induces apoptosis, and blocks the *in vivo* growth of xenograft tumors of several tumors, including lung cancer. TQ improved apoptosis by raising the Bax/Bcl2 ratio and regulating p53 in NSCLC.[119] It enhances less-regulating antiapoptotic genes and more-regulating pro-apoptotic genes in lung cancer cells. TQ-mediated apoptosis was associated with high regulation and less Bcl-xL and Bcl-2 regulation. TQ induces caspase-9, -7, and -3. It alters the activity of the Bax/Bcl-2 pathway, inducing apoptosis. TQ promotes ROS expression, leading to a diminished level of MMP, consequently liberating cyt-*c*.

TQ is regarded as an anticarcinogenic and antimutagenic mediator, and aqueous and alcohol extracts of *N. sativa* were established to be effective in inactivating MCF-7 cell growth.[120] It initiates antioxidant results in animal models. It may be exploited as a therapeutic agent in health management.

TQ is connected with several signaling pathways; TQ diminished JAK2 and EGFR phosphorylation. It induces cell death in cancer cells by preventing STAT3 signaling by inhibiting JAK2- and Src-mediated phosphorylation of EGFR-TK. It attenuated the STAT3 expression targeting genes, such as survivin, c-Myc, and cyclin-D1, -D2, and enhanced p27 and p21. It could inhibits the enzyme activity of several kinases in various tumor cells and animal models, including MAPK, PI3K, JAK/STAT, and PLK1. TQ represses the ERK1/2 that inhibited the NSCLC invasion.[121] The TQ-I3 M combination prevented lung malignancy metastasis and diminished tumor proliferation by preventing AKT/NF-κB signaling in the xenograft model. It illustrates considerable antitumor actions by up-regulation of PTEN during transcription, in which PTEN participated in stimulating p53 expression and blocking the AKT signaling. TQ modulates different genetic pathways,

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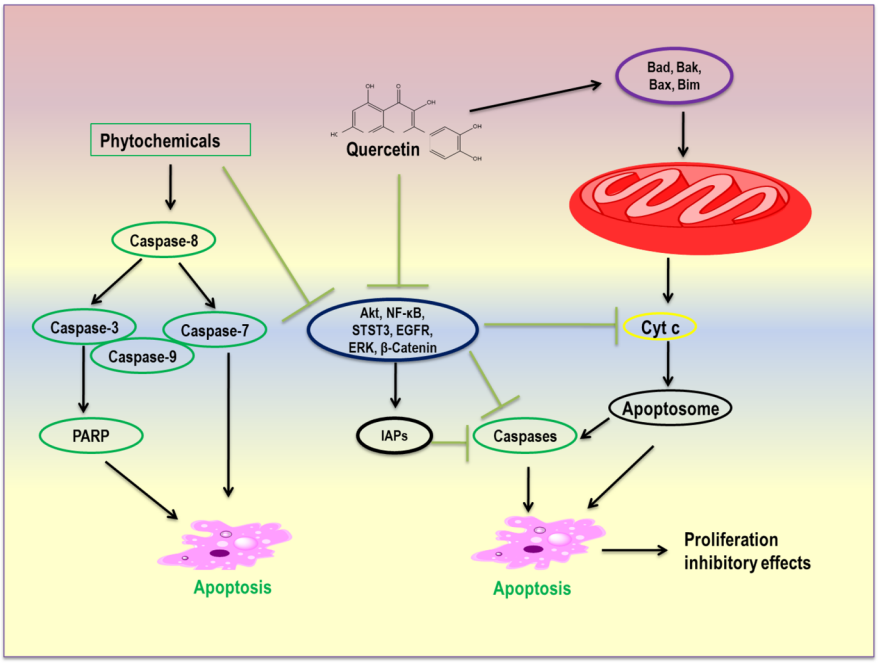

Figure 5. Effects of quercetin and phytochemicals on cancer cells. By blocking signaling molecules and stimulating pro-apoptotic proteins that trigger mitochondrial-induced caspase activation and cell death, quercetin decreases cell proliferation. This figure was drawn by using ChemBioDraw.

which prevents NF-κB activation. It up-regulates miR34a and down-regulates Rac1 expression.[122]

6.5. Therapeutic Effect of Quercetin. Quercetin (Qu) has potential antioxidant and antitumor properties such as growth factor repression, induced apoptosis, and antiproliferative activities.[123] Qu inhibits cell proliferation and stimulates apoptosis and is an antioxidant. It might alter apoptosis via downregulating Bcl-xL and Bcl-2 and upregulating Bad and Bax. Qu alters the Bax-Bcl2 pathway that arbitrates apoptosis. It enhances cell death in the caspase-3-dependent cascade by obstructing Cox-2 and triggering Bax and Bcl-2 expression. However, Qu may be a potent drug in leukemia therapy. Qu increased the cisplatin-induced apoptosis of the NSCLC H-520 cells. It performs as a chemosensitizer of lung cancer by regulating the multiple apoptosis-associated genes. Qu and TQ considerably decline Bcl-2 and stimulate Bax, which sensitizes NSCLS inducing apoptosis. Hence, it reduced Bcl-2 and Bcl-xL and enhanced Bax and caspase-3.[124]

Qu induces apoptosis of tumor cells and reveals anticancer roles. It induces apoptosis that shows potential and chemosensitivity and showed tumor inhibitory actions. Figure 5 suggests that Qu might have antitumor, antiproliferative, and apoptosis-stimulating properties.[125] Qu has effective modulation toward inflammatory agents, which block the core inflammatory enzyme COX—the function of quercetin-induced molecular regulation in suppressing NSCLC metastasis. Qu exhibited potential cytotoxic results on NSCLCs harboring the EGFR C797S mutation via blocking AXL and increasing cell death. It imitates the interfaces of ATP in the dynamic positions of RTKs. Qu inhibited cell viability, downregulated VEGFR-2, and reduced AKT, ERK, and JNK levels. It modified the AKT/AMPK pathway.[126]

The anticancer functions of Qu normally happen through the alteration of apoptosis, VEGF, AKT/ MAPK/ERK1/2, and Wnt/β-catenin signaling.[127] It modulates the AKT/PI3K and ERK pathways and prevents proteasome activity. Qu represses several cancer cells by blocking the MMP3 expression. It notably illustrates antimigratory results. Inhibition of MEK1/2, p38 kinase, or JNK abolished Qu-induced phosphorylation of c-Jun, cleavage of caspase-3 and -7, cleavage of PARP, and apoptosis. Inhibition of caspase activation completely blocked Qu-induced apoptosis. Expression of constitutively activated MEK1 in A549 cells led to the activation of caspase-3 and apoptosis. Alteration in the expression of the Bcl-2 family of proteins and activation of MEK-ERK is required for quercetin-induced apoptosis in A549 cells.[128]

6.6. Therapeutic Effect of Venetoclax. Venetoclax is an inhibitor of Bcl-2, effective in treating chronic lymphocytic leukemia (CCL).[129] Venetoclax (ABT-199) has shown clinical effectiveness in different tumor types by inducing apoptosis. It has exhibited clinical effectiveness in many hematological cancers, but this inhibitor persists in connecting to Bcl-2. It enhances BIM-dependent apoptosis and blocks tumor growth. Hence, it is a promising therapy for high Bcl-2-expressing SCLCs.[130] Venetoclax showed anticancer activity in preclinical trials. It represents the first-in-class inhibitor of Bcl-2 alert platelets.

ABT-199 works through various pathways to achieve synergistic cytotoxicity with AZD9291 in NSCLC. This may offer an efficient option in combined therapy with EGFR-TKIs to treat NSCLC.[131] Combining radiation with EGFR and Bcl-2 obstacles might be a novel move toward targeting cancer stem cells. NF-κB has been considerably low-regulated in ABT-199+ AZD9291.[131] KRAS mutation is much more frequent in NSCLC. The combinatorial approach for targeting oncogene obsession to RAS mutant cells, which include ABT199 and irinotecan, leads to RAS mutant lung tumor cells and increased apoptosis. The PI3K/AKT pathway was less regulated via the combination in KRAS mutant lung tumor cells. The results of the ABT199 and irinotecan combination are synergistic on the RAS mutant lung tumor cells.[132] ABT199 and the silencing of Bcl-2 inhibited STAT3 phosphorylation. The pharmacological

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inhibition of Bcl-2 is potent for treating Bcl-2-dependent tumors.

6.7. Therapeutic Effect of Gefitinib. Gefitinib showed effective anticancer activity in NSCLC.[133] Effectiveness and safety of two different gefitinib doses in patients with pretreated NSCLC was reported. The approved suggestion for Gefitinib has been as a monotherapy for treating metastatic NSCLC patients. The randomized phase II trial results contrasted Gefitinib with docetaxel with advanced NSCLCs. Six phase III trials expected Gefitinib's survival power only or combined with therapy in metastatic NSCLC. Thus, the activities of Gefitinib against vulnerable and resistant tumors were estimated in many documents. A study[134] observed the effect of Gefitinib in the cell growth of NSCLC cells using colony formation and MTS and examinations that demonstrated half-maximal inhibitory concentration (IC_{50}) values of 4−42 μM.

Gefitinib regulated the intrinsic pathway, connecting the activation of Bax and release of cyt-*c*. It caused a rapid increase in the level of BIM. BIM is critical to the gefitinib-induced destruction of NSCLC cells. ABT-737 enhances gefitinib-induced apoptosis. It motivates cell death via Bax activation in tumor cells.[135] It activates G1 arrest and cell death through high regulating of p27 and p21 and Bax activation. Since the down-regulation of Bcl-2 through RNAi, the effects of Gefitinib might be an innovative therapeutic plan for treating NSCLC.[136] It suppressed the Bcl-xL and Bcl-2 expressions, depicting hepatocellular carcinoma (HCC) as prone to apoptosis. The combined therapy might be a potent new treatment for lung tumor patients.[76]

Gefitinib was the first inhibitor of EGFR recognized as a clinical appliance. It is a TKI revealed for utilization in treating NSCLC patients; hence, tumors have particular EGFR mutations. It has been approved for cancer treatment and metastatic EGFR mutation-positive NSCLC.[137] A selective EGFR TKI blocks EGFR, AKT, and ERK phosphorylation, activating G1 arrest and cell death. Thus, gathering a BH3 mimetic considerably enhances the destruction of NSCLCs through EGFR TKI gefitinib. Patients with p-AKT-positive cancers who obtained Gefitinib had superior response and disease control rates. Hence Gefitinib might be most efficient in patients with basal AKT activation—however, phosphorylation of AKT and gefitinib is efficient in patients with advanced NSCLC.[136] Combinational targeting of STAT3 and EGFR may increase the efficiency of Gefitinib or other EGFR TKIs in lung tumors.

6.8. Therapeutic Effect of Genistein. Genistein is a natural product, and it is an isoflavone isolated from legumes of soybeans, lupin, and fava beans. It is associated with multiple cancers, cardiovascular disease risk, and osteoporosis.[138] It decreases breast cancer stem cells (CSCs) by less regulation of the hedgehog-signaling cascade, consequently regulating cell proliferation. Genistein stimulates cell death in NSCLC cells via a p53-independent signaling cascade and might act as an antitumor agent. Genistein increases the result of cisplatin on the inhibition of NSCLC. It is a promising drug applicant for treating and managing NSCLC.[139]

Genistein therapy is used to prevent the development of tumor cells via increasing apoptosis, inducing delayed cell cycles, and triggering signaling cascades.[140] Genistein prevents cancer growth and proliferation by downregulating the negative effect of EGF on the action of FOXO3 in a tumor model. Genistein increased the anticancer effects of Gefitinib in an NSCLC, which synergistic action could be due to enhanced inhibition of the molecular and pro-apoptotic results of EGFR. It blocks the activation of NF-kB in cancer cells. It can abolish NF-kB activation via DNA-damaging, which serves as a chemopreventive drug. Genistein decreased proliferation and enhanced apoptosis in lung tumor cells, which was connected with inhibition of the AKT/PI3K and NF-κB pathways. It is a promising chemotherapeutic agent for lung cancer.[141] It affects EGF-mediated proliferation via the cancer cells' PI3K/AKT modulation. It is a potential antiangiogenic agent, which might repress VEGF-stimulated endothelial cell activation by decreasing the role of PTK and MAPK activation. The antiproliferative actions of Genistein are attained from decreased IGFR phosphorylation and the IGF pathway, which represses cell development. Genistein decreased the action and cell proliferation, and ERK controls growth and proliferation, while p38 is strongly connected with stress and inflammatory reactions.

7. ENHANCING THE EFFECTIVENESS OF INHIBITORS WITH CHEMOTHERAPY/RADIOTHERAPY

Chemotherapy has reached a plateau of efficacy as a primary treatment modality, even if the toxicity can be effectively controlled. Emerging specific signaling and metabolic pathway inhibitors contrast with traditional chemotherapy drugs in that the latter primarily interfere with DNA biosynthesis and the cell replication machinery. To improve efficacy, combining targeted drugs with conventional chemotherapeutics has become a standard approach to testing multiple new agents in early phase clinical trials.[142] They enhance antitumor response by combining immune checkpoint inhibitors with chemotherapy of NSCLC.[143]

Classical chemotherapy frequently remains the most recommended antitumor therapy for several tumor treatments. Drugs are efficient for the treatment of multiple tumors. However, chemotherapeutic drugs may stimulate the RAS/MEK/ERK cascade through various mechanisms. Activated ERK could phosphorylate p53 and control its action. The drug might trigger the CaM-K cascade through ROS. Activating this pathway may activate the Raf/MEK/ERK pathway,[144] which plays significant functions in apoptosis. Hence the Raf/ MEK/ERK pathway might control the transcription of various important genes. Cisplatin-stimulated cell death was linked with enhanced levels of p53 and the downstream Bax.[145] MEK inhibitors obstructed cell death by blocking the cisplatin-mediated gathering of p53 and Bax proteins.

Radiotherapy is a general therapeutic plan for the treatment of several different tumors. However, the results of the pretreatment of several tumor cells with the drug were calculated.[146] However, the MEK inhibitor treatment radiosensitizes the diverse tumor cells. ERK1/ERK2 action is compulsory for cancer cells to arrest on the G2 checkpoint, which was observed. The MEK inhibitor repressed the autocrine pathway in tumor cells, which usually resulted from EGF discharge and the activation of EGFR. A549 had KRAS mutations and have been a radiosensitizer via the MEK inhibitor.[147]

The capability of an MEK inhibitor for radiosensitizing certain cells, noticeably other tumor cells without stimulated mutations in the RAS//MEK/ERK signaling growth motivation, must be observed to radiosensitization via the MEK inhibitor, like the KRAS mutation can trigger the PI3K signaling to cause therapy resistance. However, PI3K/AKT

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inhibitors sensitize the cancer vasculature to radiation.[148] mTOR and radiation participate in important functions in the regulation of autophagy. However, mTOR is inhibited through rapamycin. Increased autophagy is crucial for cell death in solid tumors and diverse mechanisms to resistance for Raf inhibitors. The BRAF mutant melanoma cells were sustained in a medium enclosing the B-Raf inhibitor that altered their reliance from B-Raf to Raf-1.[149]

8. CONCLUSIONS AND FUTURE PROSPECTS

Phytochemicals have decreased the risk of diseases, including cancer.[150,151] The antitumor and chemopreventive features of phytochemicals attract oncology researchers because of their low toxicity in healthy cells but outstanding effects in tumor cells. Several signaling molecules, including p53, EGFR, KRAS/MAPK, STAT3, NF-κB, and PI3K/AKT pathways, are involved in multiple cancers, including NSCLC. These signaling cascades participate in an essential role in cancer cell growth and proliferation.

Phytochemicals can benefit multiple disease hindrances by regulating cellular and molecular pathways and stimulating apoptosis. Signaling cascades have been comprehensively studied for therapeutic development. These signaling cascades are recognized as promising therapeutic targets for tumor therapy. These dynamic signaling pathways offer potential therapies and conflicts for drug investigation and discovery. Kinase inhibitors with enhanced specificity and improved pharmacokinetics have been considered to design and develop anticancer agents. In outlook studies, the current study must help develop novel inhibitors for p53, EGFR, KRAS/MAPK, STAT3, NF-κB, and PI3K/AKT pathways to treat NSCLC. Hence, targeting signaling pathways by inhibitors could be a promising therapy for NSCLC.

Various phytochemicals have been assessed for promising antitumor effects in preclinical and clinical studies. Some are utilized in current tumor therapy after completion of clinical trials. Therefore, clinical research assesses the efficiency of some phytochemicals, develops drugs, and conveys them to therapeutic utilization for NSCLC. Phytochemicals would serve as a therapeutic target of cancer for public health in the future. Furthermore, the creative and novel clinical trial approach should enhance our capacity to evaluate novel agents and combinations to elucidate molecular diversity and finally achieve improved outcomes. Further, in-depth mechanistic investigations and exclusive clinical trials are needed to understand the importance of phytochemicals in human health and several cancers, including NSCLC.

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ABBREVIATIONS

NSCLC, Nonsmall cell lung cancer; LADC, lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; PUMA, p53 upregulated modulator of apoptosis; PKB, AKT/ protein kinase B; PI3K, Phosphatidylinositol 3-kinase; mTOR, Mechanistic target of rapamycin; NF-κB, Nuclear factor κB; JAK2, Janus-activated kinase-2; NF-κB, Nuclear factor-κB; NEMO, NF-κB essential modifier; EGFR, Epidermal growth factor receptor; TNFR, Tumor necrosis factor receptor; RAF, RAS-rapidly accelerated fibrosarcoma; MAPK, Mitogen-activated protein kinase; ERK1/2, Extracellular signal-regulated kinase1/2; JNK, c-Jun N-terminal kinase; AP-1, Activator protein-1; KRAS, Kirsten rat sarcoma viral oncogene; EGCG, Epigallocatechin-3-gallate; STAT3, Signal transducer and activator of transcription-3

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