

REVIEW

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Receptor tyrosine kinases as a therapeutic target by natural compounds in cancer treatment

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Abstract

Background: Receptor tyrosine kinases (RTKs) are single-pass transmembrane proteins that play significant roles in regulating cellular processes, including cell division and growth. Overexpression and mutations of RTKs have been found in clinical manifestations of different forms of cancer. Therefore, RTKs have received considerable interest as a therapeutic biomarker in the treatment of cancer cells.

Main body of the abstract: Comprehensive data on RTKs, pharmacological and biological properties of natural compounds were systematically searched up to 2021 using relevant keywords from various databases, such as Google Scholar, PubMed, Web of Science, and Scopus. The scientific search by various standard electronic resources and databases unveils the effectiveness of medicinal plants in the treatment of various cancers. In vitro and in vivo studies suggested that bioactive compounds such as flavonoids, phenols, alkaloids, and many others can be used pharmacologically as RTKs inhibitors (RTKI) either by competing with ATP at the ATP binding site of the tyrosine kinase domain or competing for the receptor extracellular domain. Additionally, studies conducted on animal models indicated that inhibition of RTKs catalytic activity by natural compounds is one of the most effective ways to block the activation of RTKs signaling cascades, thereby hampering the proliferation of cancer cells. Furthermore, various pharmacological experiments, transcriptomic, and proteomic data also reported that cancer cells treated with different plants extracts or isolated phytochemicals exhibited better anticancer properties with minimal side effects than synthetic drugs. Clinically, natural compounds have demonstrated significant anti-proliferative effect via induction of cell apoptosis in cancer cell lines.

Short conclusion: An in-depth knowledge of the mechanism of inhibition and structural characterization of RTKs is important to the design of novel and selective RTKIs. This review focuses on the molecular mechanisms and structures of natural compounds RTKI targeting vascular endothelial growth factor, epidermal growth factor receptor, insulin receptor, and platelet-derived growth factor while also giving future directions to ameliorate the scientific burden of cancer.

Keywords: Receptor tyrosine kinases, Cancer, Natural products, Signal transduction, Flavonoids

Background

The use of chemotherapeutics has been buoyed by the need to stop rapidly dividing cells in the management of tumors via the activation of apoptotic factors and muddling of the cell cycle, thus inhibiting mitosis. Deject fully, traditional chemotherapy agents lack the required

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specificity against cancerous cells while also posing a considerable amount of damage on uninfected/beneficial myelocytes or gametocytes [1, 2]

However, this worry has been subdued by the emergence of small molecule kinase inhibitors, characterized by their specificity and selectivity, downregulation of oncogenesis activation proteins, and making their receptor unavailable for binding [3, 4].

As years dwindle, the focus has been shifted on tyrosine kinase as a critical player in tumorigenesis. Specifically, receptor tyrosine kinase (RTK) is a transmembrane receptor upon which dimerization occurs when extracellular signal molecules bind to it [5]. This signal molecule acts as a neurotransmitter, in that they are selective and specific in binding and exhibit no distinct structural variability. Examples include EGF, PDGF, VEGF, etc. [6].

RTK signaling has been cached in the growth and progression of cancerous cells. They activate the growth factors, stimulate cell proliferation, and prevent apoptosis from occurring in cancerous cells [6]. Generation of a phosphorylated cytoplasmic domain tyrosine residue is a recurring theme in RTK activation, thus serving as a communication node during transduction. Binding of small extracellular protein leads to the activation of domain receptor tyrosine kinases which activates the cascades ascribed for cell migration (p53-dependent activation of ERK, PI3K/Akt), upregulating anti-apoptotic cascade (NF- κ B & COX-2), Notch1/ Her1 and Hey 2 activation, thus resulting in the metamorphosis into oncogenic cells [7–9].

The application of scientific tools, over the years, has allowed an in-depth analysis of the structure and possible mechanism of RTK, bringing about novel therapeutic techniques that could act as kinase inhibitors. Although the positive results have been achieved over time, the development of resistance by cancerous cells is yet to be overcome [10].

Due to the obdurate property of cancerous cells, coupled with the worrisome adverse responses caused by chemotherapeutic agents to the immune system, the use of natural compounds could be the nostrum in overcoming this barrier. Natural compounds such as flavonoids, terpenoids, polyphenols, and alkaloids have increasingly attracted attention as studies have revealed their anticancer, antioxidant, and cardio-protective activity over time. Their ability to modulate ERK, PI3k/Akt cascade, NF- κ B activities, and JNK cascades amidst others is entirely plausible [11, 12].

In this study, we deciphered the structure of RTK while explaining its signaling and activation mechanisms. Furthermore, several natural compounds as a therapeutic agent targeting RTK in cancer treatment are accentuated.

Novel devices capable of linking structure–biological function activity of natural compounds in a targeted manner are, however, advised to be worked upon.

Main text

Receptor tyrosine kinases

Receptor tyrosine kinases (RTKs) are membrane proteins that aid cell communication with their extracellular milieu, thereby playing a pivotal role in signal transduction, cellular processes, and pathogenesis of different cancer cells. RTKs exist primarily in a single subunit form; however, some such as insulin receptors exist in dimeric form. The structure of RTKs consists of a monomeric transmembrane domain, an extracellular amino (N) terminal composed of ligand binding regions, and an intracellular terminal area flanked by the carboxyl (C) region (13). The hydrophobic part of the transmembrane terminal contains 25 to 38 amino acid residues following active site analysis. The extracellular modules varied considerably in different RTKs subfamily as well as serine/threonine kinases. RTKs are classified on the molecular basis of their natural bound ligand and structural property. Furthermore, the subfamilies of RTKs are characterized by structural diversity of the native conserved elements present at the extracellular region, including immunoglobulin (Ig)-like or epidermal growth factor (EGF)-like domains, fibronectin type III repeats, or cysteine-rich regions. The receptor-ligand complex results in induced conformational change [13, 14].

The major component of the signal transduction pathways is the growth factors, including endothelial growth factor receptor (EGFR), insulin growth factor receptor, fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and insulin-derived growth factor receptor (IGFR). The binding of the growth factor to the extracellular domain activates the RTKs by triggering the receptor dimerization [15]. Clayton et al. [16] reported that binding of IGFR and EGFR induces changes in the dimer and monomer forms of the RTKs, respectively, stimulating cell signaling and RTKs activation. The RTKs can be activated by multiple ligand binding to the extracellular domain. Three of the four human epidermal growth factor receptors (EGFR/HER) receptors, for example, react to a family of ligands generated by 13 genes and splice variants. The mechanism underlying RTKs activation involves phosphorylation of the tyrosine monomer by its neighboring receptor, thereby conducting chemical signals through the plasma membrane [17]. After phosphorylation of the tyrosine kinases, Src homology 2 (SH2) domain and phosphotyrosine binding (PTB) domain active sites for ligands are defined. The mechanism of tyrosine residue

phosphorylation at the activated tyrosine kinase domain generates binding sites for phosphotyrosine binding (PTB) and Src homology 2 (SH2) domains. Furthermore, the signal transduction pathways evolved via phosphorylation and activation of SH2 and PTB protein [18].

In a systematic review of RTKs carried out by Metibemu et al. [19], the autoinhibition and activation of RTKs were reported. c-Src, soluble tyrosine kinase, phosphorylate the tyrosine kinase domain at the resting form of RTKs, leading to cell signaling. Thus, phosphorylation helps to prevent autoinhibition by the juxtamembrane domain (Fig. 1). The mutation in the amino acid residues of the juxtamembrane has been linked to the progression of carcinoma cells. The central paradigm of the RTK activation is the phosphorylation of the intracellular tyrosine amino acid residues, forming the basis of cell communication in series of signaling cascades.

Vascular endothelial growth factor receptor

Vascular endothelial growth factor receptor (VEGFR), formerly known as vascular permeability factor, is synthesized by the fibroblast involved in angiogenesis and vasculogenesis [20]. VEGF denotes the subfamily and structural-related VEGF polypeptides. VEGFRs activate signal transduction pathways through three structural analogs of VEGFs: VEGFR1 (Flt-1) expressed in macrophages and monocytes, VEGFR2 (KDR/Flk-1), and VEGFR3 (Flt4) found in endothelial cells of vascular tissues and lymphocytes [21]. The VEGF family can be classified into five growth factors VEGFA (the prototype, also known as VEGFA165), VEGFB, VEGFC, VEGF-D, and placenta growth factor (PIGF). Although the VEGF family has been reported to be homodimeric polypeptides, heterodimer forms of VEGF and PIGF have been reported naturally [22]. The family of VEGF performs diverse functions. VEGF A is primarily involved in blood vessels and lymphangiogenesis while binding to the first receptor of VEGFs. VEGFs also function in the regulation of vasodilation through an indirect release of nitric acid [23]. The mechanism of VEGF A in the homeostatic regulation of vasodilation is not yet known. VEGF B and C control the embryonic formation of the circulatory system and lymphatic vessel formation. VEGF D, also called c-fos-induced growth factor, is a glycoprotein involved in stimulating lymphangiogenesis and potential endothelial cell growth and survival. VEGF C and D binds specifically to VEGF receptor 3 [21, 24].

The VEGFs have numerous clinical applications; for example, overexpression of VEGF A has been studied in breast cancer prognosis and damage to blood vessels in the central nervous system [25]. Stacker and Achen [26] reported that VEGF D had been used as a diagnostic

biomarker in rare hereditary diseases such as angiosarcoma and lymphangiomyomatosis.

Epidermal growth factor receptor

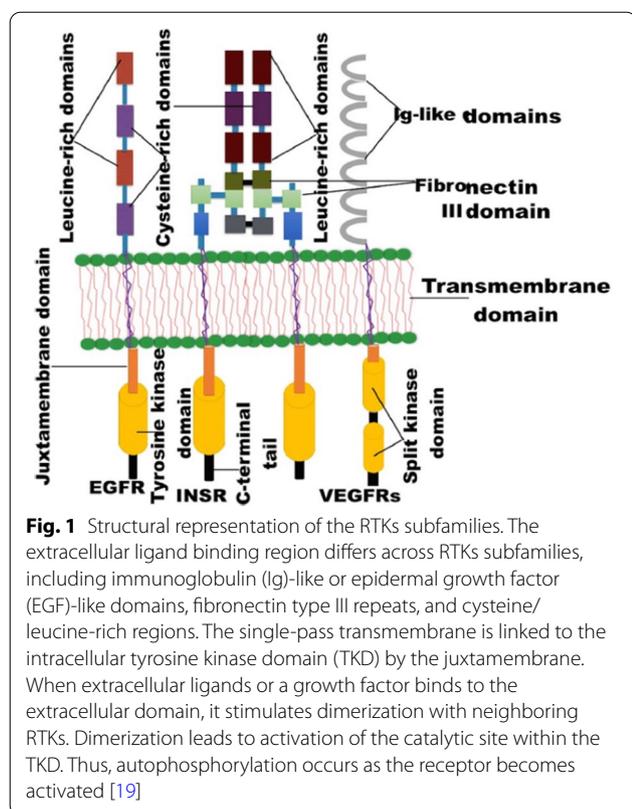
The epidermal growth factor is a tyrosine (EGFR) kinase that plays a crucial role in the proliferation of tumor cells. It is a transmembrane protein that belongs to the ErbB family of receptors overexpressed in different cancer carcinomas. EGFR is composed of four members that are similar in structure and cellular functions: ErbB1 (EGFR or HER1), ErbB2 (HER2), ErbB3.

(HER3) and ErbB4 (HER4) [27]. According to phylogenetic studies, the human epithelial receptor consists of 11 species and is classified based on binding to the four EGFR members, including transforming growth factor α that binds to HER1, epidermal regulators that bind to both HER1/HER4 and Neuregulin that binds HER3 and HER4 [28]. The phosphorylation of downflows is mediated by signaling protein and catalyzes series of signaling cascades including PI3K–PTEN–AKT, MAPK, ERK, and JAK/STAT pathways, thereby inducing tumor cells, DNA synthesis, and angiogenesis [29].

The structural characterization of HER in oncogene has led to novel therapeutic agents against different cancer cells, including lung and colon cancer. The first generation inhibitors of EGFR are erlotinib and gefitinib. Afatinib and osimertinib are the second and third generations of EGFR inhibitors [30]. Immunotherapy has also proved to be potent inhibitors of EGFR by developing monoclonal antibodies, notably Cetuximab [31]. Jorissen et al. [32] investigated the mechanism involved in ligand-receptor binding and the complex system of the signaling pathways. Thus, abnormal activation of EGFR, including Shc, Ras/MAPK pathway, JAKs, and STATs pathways, has several pathophysiology-related diseases, particularly cancer cell proliferation [33].

Platelet-derived growth factor receptor

Platelet-derived growth factor receptor (PDGFR) is tyrosine kinases, and it encodes four platelet-derived growth factor (PDGF) genes (PDGFA, PDGFB, PDGFC, and PDGFD) that have been mapped out genetically on different chromosomes locations in humans and mice [34]. PDGF is a dimer with a disulfide linkage to A and B polypeptide chains. The receptor of the PDGF can exist in two isoforms, either as a homodimer (PDGF-AA, PDGF-BB) or heterodimer (PDGF-AB) in a ligand-dependent manner. The intracellular region and the extracellular site contain a tyrosine kinase domain and five immunoglobulin-like domains [35]. According to Shen et al. [36], cellular functions, including embryogenesis, cell division, and inflammation, stimulate PDGF binding to their respective



receptors. Furthermore, PDGF has been found predominantly in smooth muscle cells, connective tissues, astrocytes, fibroblast, and keratinocytes and, to a large extent, brain neurons, kidney, and mammary endothelial cells [19, 35]. In a study carried out by Andrae et al. [37], the expression of PDGF is downregulated by the following signaling pathways, STAT Ras/mitogen-activated protein kinase (MAPK), PI-3 kinase, and phospholipase- γ (PLC γ) pathways. Because of the PDGF's pivotal role in developing tumor cells, one of the most effective ways to halt PDGF signaling is to inhibit the ATP competitive tyrosine kinase domain [37]. There has been no specificity in the mechanism of action of the available PDGFR inhibitors, including imatinib, nilotinib, and sunitinib, although they have been reported to be effective in disrupting the signaling cascades. Inhibition of PDGFR by small molecules or natural products has not gained much attention; however, immunological techniques in blocking PDGF signaling have been developed [13, 17].

Insulin receptors

The insulin receptor is a transmembrane protein that plays a vital role in the biochemical metabolism of carbohydrate, lipid, protein, and its abnormal regulations can cause various clinical diseases, including cancer and diabetes mellitus. It is a polypeptide hormone that is

produced in the β -cell of the pancreas [38]. Insulin has been of the most extensively studied protein because of its therapeutic role in treating diabetic patients, and it is the first protein to have its primary amino acid structure sequenced. Several biophysical techniques, including cryo-electron microscope, have been utilized to elucidate the structure of the insulin receptor [39]. Scapin et al. [40] carried out the structural characterization of the insulin receptor complex using a high resolution of single-particle CryoEM analysis. The insulin receptor consists of an α and β chain, which exist in their heterodimer forms and is found at the exterior of the plasma membrane. The amino terminal of the β -chain contains three regions: tyrosine ATP-dependent kinase, transmembrane terminal, and a juxtamembrane. The activation of insulin receptors occurs through insulin growth factor analogs' binding, the disulfide-rich IGF-1 and IGF-2 [41]. IR autophosphorylates the insulin receptor substrate (IRS), driving the activation of signaling pathways, including ERK/PI-3-K/RAS/MEK/ pathways [42].

Natural compounds as RTKs inhibitors

Natural compounds have been utilized in folklore medicine, pharmaceutical sciences, and many other related medical fields since time immemorial in treating several diseases, including neurodegenerative disease, cancer, diabetes, and inflammations. They are categorized into various classes (Fig. 2) and their therapeutic potential has been studied and documented in several continents such as Asia, Europe, and Africa [43]. Many well-known drug candidates are derived from plants. For example, Artemisinin isolated from the bark of *Artemisia annua* has been influential in the treatment of malaria. Also, the anticancer drugs: Paclitaxel, docetaxel, Cabazitaxel are plant-based derived compounds used to treat different cancer cell lines [44]. Fidy et al. [45] have reported the anticancer property of the β -caryophyllene, a natural compound in the family of sesquiterpene. The mechanism of action of natural compounds on different signaling pathways and how it induces cell death in various metabolic diseases have been studied extensively [46] (Fig. 3).

Flavonoids

Flavonoids are secondary phytochemicals derived from dietary sources such as fruits, grains, tea, wine, and vegetables. Flavonoids are grouped into seven: flavanones, flavones, isoflavones, flavanols, flavonols, flavanolones, and anthocyanins. The chemical structure of flavonoids contains a 15-carbon backbone with two benzene rings linked together by a heterocyclic oxygen-embedded ring [47]. Substitution reactions, including hydroxylation, methoxylation, and glycosylation in the

subclass of flavonoids (Fig. 4), have led to their diversity. Although flavonoids are poorly absorbed and rapidly metabolized representing a low bioavailability rate, they have demonstrated various biological functions, mainly antioxidant, metal chelators, anticancer, and anti-inflammatory agents [48].

Quercetin is a glycoside chemically known as 3,3',4',5,7- pentahydroxyflavone (C₁₅H₁₀O₇) and one of the most ubiquitous polyphenolic flavonoids present in fruits and vegetables. Quercetin and its derivatives have been helpful in the treatment of cancer, allergies, inflammation, and viral diseases [49]. Zheng et al. [50] investigated that the anti-metastatic and anticancer effect of quercetin against various tumor cells such as leukemia, lung and colon cancer, and breast cancer may be due to its inhibitory potential on enzyme-catalyzed reaction involved in carcinogenesis. Quercetin induced cell cycle arrest at G1 phase and apoptosis in human breast cancer MDA-MB-453 cells in a dose and time-dependent manner. Furthermore, quercetin inhibits cellular growth significantly during the G2 phase in breast cancer MCF-7 cells through a time and concentration-dependent manner [51].

VEGFR-1 and VEGFR-2 are fundamental in the formation of the angiogenesis process by regulating cell growth and proliferation. In a study conducted by Zhao et al. [52], quercetin selectively inhibits VEGFR-2 mRNA with maximum effect at a concentration of 100 and 200 μm. The anti-angiogenic activity of quercetin has also been

expressed in the downregulation of signaling pathways of VEGFR-2, ERK, and p38MAPK. However, further in vivo studies are required to establish quercetin angiogenic property [53, 54]. Sun et al. [55] reported the molecular mechanism underlying the combined effect of quercetin and metformin in cancer cells. The result shows that co-treatment of quercetin and metformin triggers apoptosis by inhibiting the VEGF/Akt/PI3K pathway in prostate cancer cells. Quercetin has also proven to be effective as combined chemotherapy with irinotecan to treat gastric cancer cells by blocking growth factor receptors [53]. Furthermore, Donnini et al. [56] demonstrated the various angiogenic effect of quercetin and its structural analog, quercetin-3-o-glucoside, on VEGF-activated endothelial cells.

EGFR signaling pathway plays a significant role in the progression of metastatic prostate cancer, making it a novel target in various cancer cells. Quercetin blocks prostate cancer cell growth through the EGF receptor by homeostatic regulation of several cell adhesion molecules, including vimentin, E-cadherin, and N-cadherin [57]. Previous studies show that quercetin and quercetin 3-O-glucoside downregulate the expression of EGFR in a cirrhotic animal model, pancreatic tumor cells, and EGFR-mediated signaling pathway [58].

Recent studies demonstrated that quercetin and silibinin could disrupt cell growth in prostate cancer cells by inhibiting the IGF-1 and IGFBP-3 through apoptotic cell death in G and S phases [59]. Additionally,

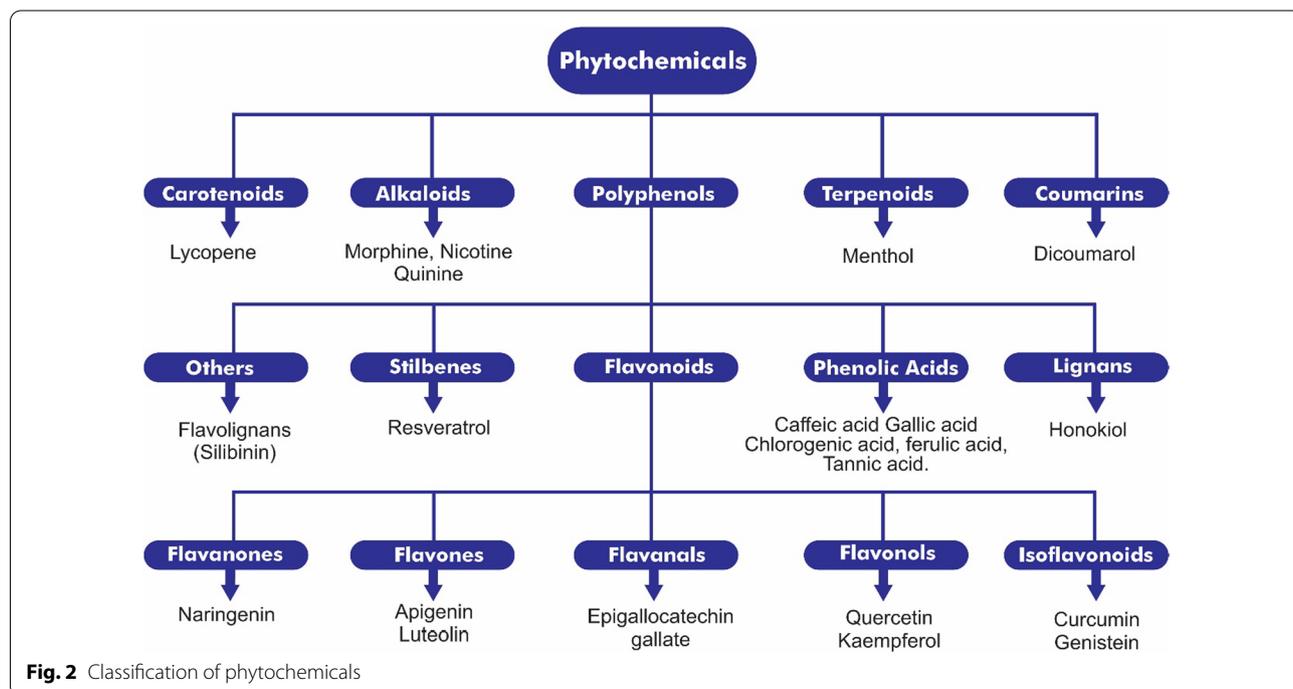
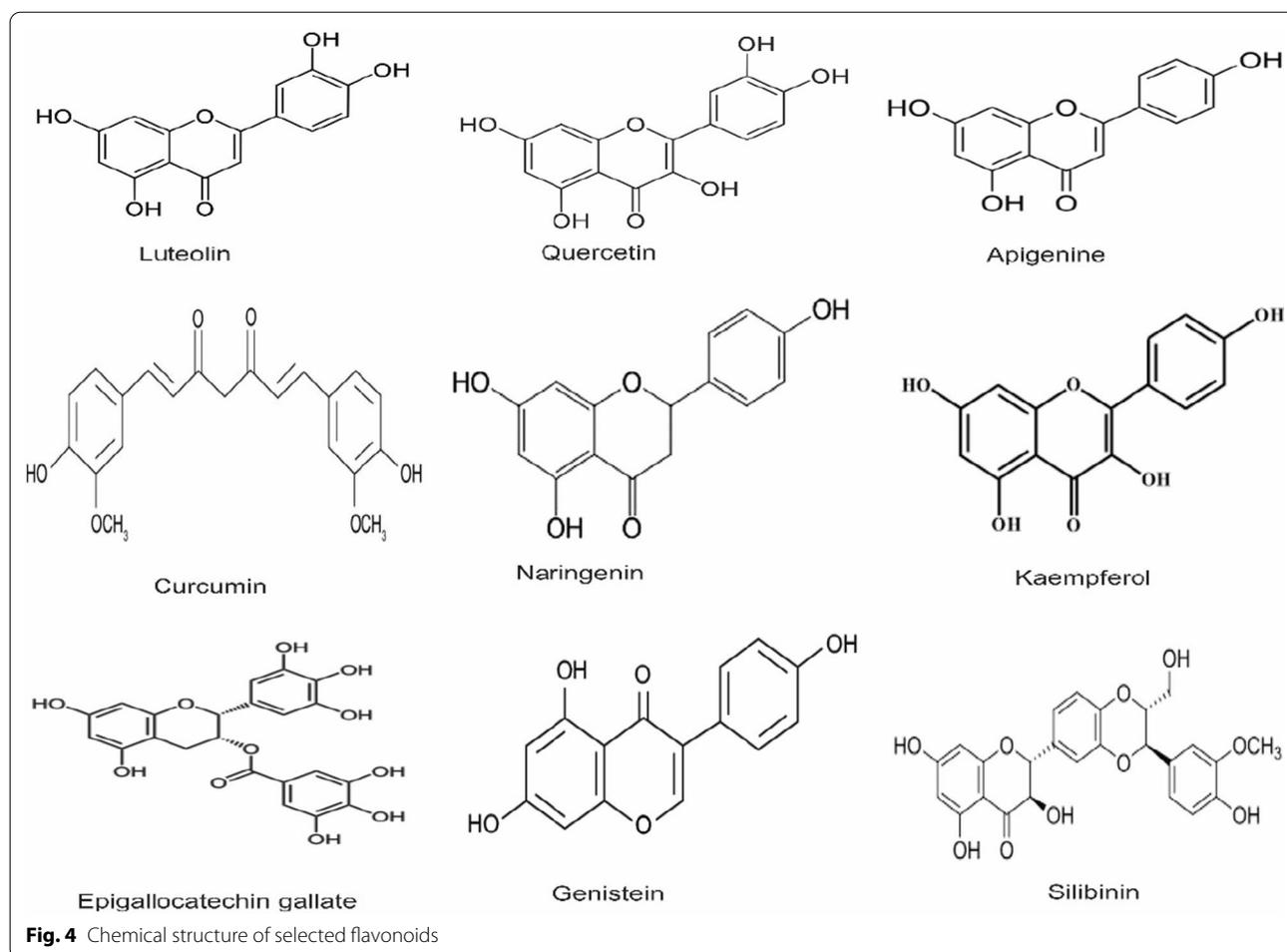


Fig. 2 Classification of phytochemicals



plants work as epigenetic regulators and are used in support of conventional anticancer therapy. Phenolic acids can exist freely or bond with other molecules like esters and ethers (Fig. 5). The major anticancer components in the phenolic acid structure are the aromatic ring, unsaturated, substituted chains, and the number and position of the free hydroxyl groups [69–71]. They are potent in affecting cancerous cells due to their antioxidant activity and ability to inhibit cell proliferation by preventing essential protein synthesis such as receptor tyrosine kinases, thereby inducing apoptosis and stopping cellular migration and metastasis [70, 72, 73] demonstrated the potency of some phenolic compounds in the inhibition of receptor tyrosine kinases of cancerous lung cells.

Phenolic acids alter the initiation and progression of cancer by modulating genes regulating key processes such as the oncogenic transformation of normal cells, growth and development of tumors, and angiogenesis and metastasis [74]. They are found to downregulate oncogenic survival kinases such as PI3K and Akt; cell proliferation regulators such as Erk1/2, D-type cyclins,

and cyclin-dependent kinases (CDKs); transcription factors including the STATs, histone deacetylase, and growth factors VEGF, FGFR1. They also regulate tumor suppressor proteins: tumor suppressor proteins p53, PTEN, p21, and p27. Furthermore, they control reactive oxygen species (ROS) and alter cell proliferation and apoptosis [74].

Caffeic acid

Caffeic acid (CA) has been found to target receptor tyrosine kinases (RTK) in cancer treatment. The epidermal growth factor receptor (EGFR), an example of RTK, is a cell-surface receptor for epidermal growth factor. Caffeic acid suppresses the phosphorylation of EGFR in breast cancer cells [75]. The gene elevation of EGFR is associated with poor prognosis in OSCC [75, 76]. Cyclooxygenases (COX-1 and COX-2) are enzymes involved in forming prostanoids; their mRNA and protein level are regulated in OSCC and high-risk premalignant oral lesions [77]. Treatment with caffeic acids inhibits the

proliferation of COX-2 in human oral squamous carcinoma cells. This treatment inhibits EGFR and COX-2, which prevents the development of oral cancers [78].

Vascular endothelial growth factor (VEGF) is also a class of RTK that promotes choroidal neovascularization (CNV) that leads to a severe loss of sight. CA inhibits the production of VEGF in retinal pigment epithelial cells (RPE cells) under hypoxic conditions. Sung et al. [79] carried out in vitro experiment by exposing human RPE cells to hypoxia with or without caffeic treatment; CA was found to suppress the hypoxia-induced production of VEGF in the RPE cells through the inhibition of reactive oxygen species (ROS) production and phosphoinositide 3-kinase (PI3K)/AKT and hypoxia-inducible factor-1 α (HIF-1 α) expression. This shows the promising effects of CA in the treatment of CNV.

CA is found to target platelet-derived growth factor receptor (PDGFR) in coronary artery cancer through its underlying mechanism on human coronary smooth muscle cells (SMCs). CA inhibited proliferation and migration of PDGF and induced apoptosis [80]; it alters the activation of AKT1, MEK1, and ERK1/2 signaling molecules at 10–60 min after CA treatment. CA triggered the activation of cytochrome C from mitochondria to cytosol, upregulated the proapoptotic gene Bax, and downregulated the antiapoptotic gene Bcl-2. The mitochondrion-dependent apoptotic signaling pathway is precipitated by CA, which created anti-proliferation, antimigration, and proapoptotic effects on human SMCs after PDGF stimulation [80].

CA suppresses the growth of breast cancer by targeting insulin receptors in the estrogen. Estrogen receptor (ER) is sensitive to the caffeic acid; it induced cell death in MCF-7 with reduced prosurvival Bcl-xL levels but increased active caspase-7 and cleaved PARP, leading to apoptosis [81]. CA reduced the insulin-like growth factor-I receptor (IGF-IR) and pAkt levels in both ER(+) and ER(-) cells. This effect disrupts the progression of the cell cycle and enhanced cell death.

Gallic acid (GA) shows anti-tumorigenic effects in TKI-resistant non-small cell lung cancer (NSCLC); lung cancer patients have benefited from GA as it demonstrated the tumor-suppressive effect for TKI-resistant cancer compared to the TKI-sensitive one. GA blocks the proliferation of epidermal growth factor (EGF), which induces downstream signaling pathways leading to tumor growth [82]. In the experiment of Ai et al. [83], lung cancer cells were cloned and labeled; H1650 was inhibited by GA through loss of phosphatase and tensin homolog (PTEN). Also, mutation of K-ras caused by GA suppressed the growth of the H358 cancer clone.

Gallic acid

GA is found promising for the prevention and therapy of ovarian cancer by targeting the VEGF. Based on concentration, GA inhibits the activation of VEGF and suppressed in vitro angiogenesis. GA downregulated AKT phosphorylations and HIF-1 α expression, and the luciferase assay results suggest that the PTEN/AKT/HIF-1 α inhibition is responsible for VEGF suppression by GA [84].

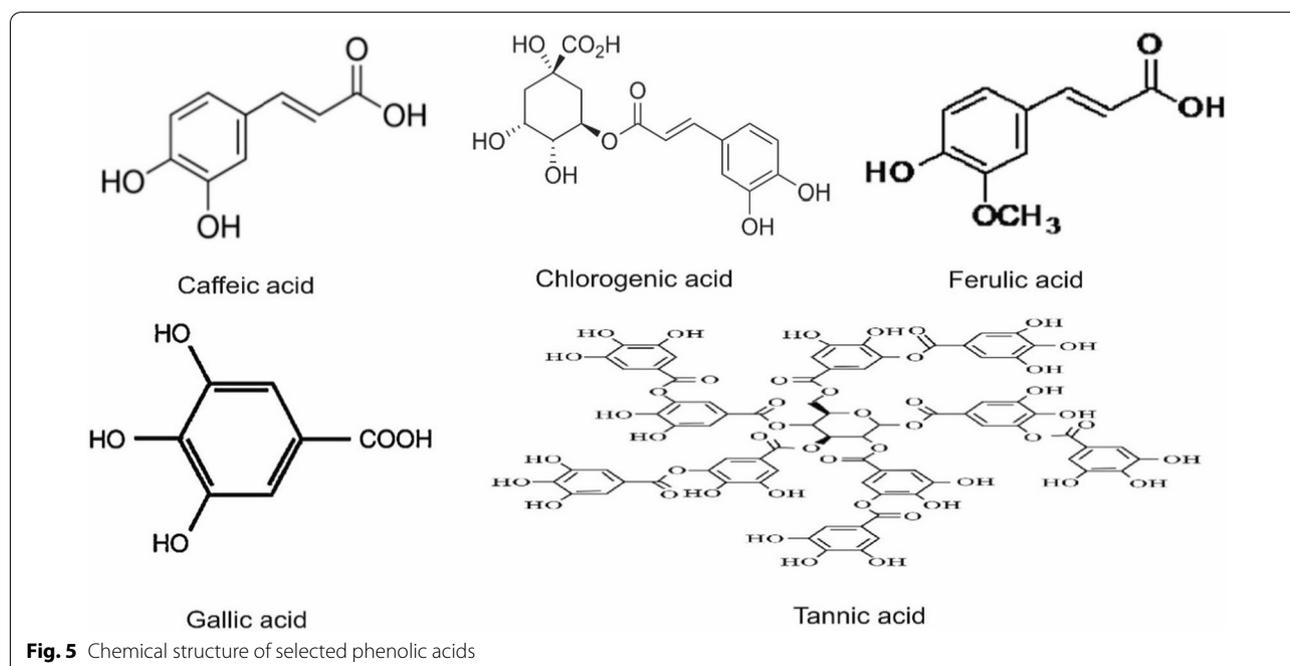


Fig. 5 Chemical structure of selected phenolic acids

GA inhibits ligand binding and the subsequent tyrosine phosphorylation of the platelet-derived growth factor β receptor (β PDGFR), which plays a critical role in the pathogenesis of atherosclerosis. PDGF is involved in all phases of atherogenesis and artery cancer. GA inhibits the association of the β PDGFR with specific signaling molecules, including RasGAP, PLC γ , PI3K, and SHP-2, in response to PDGF-BB [85].

Previous studies suggested that the anti-proliferative effect of GA may probably be due to its potential to control oxidative stress associated with cancer cells [86]. Targeting the insulin receptor, GA produces significant levels of H₂O₂ and O₂ in human promyelocytic leukemia HL60 and its resistant sublines HL60/VINC and HL60/MX2 cells; leading to apoptosis of cancer cells [87, 88].

An experiment on non-small cell lung cancer of mutated EGF receptor harbored in parental HCC827 cells. Treatment with chlorogenic acid (CGA) revealed that EGF is targeted in treating non-small cell lung cancer by inhibiting the clone HCC827C2 growth of the cancerous cell at a concentration of 20 μ M, thereby prevents the further proliferation of the cancer cell [73].

Vascular endothelial growth factor (VEGF) activates a series of signaling pathways by binding to its receptor (VEGFR2) for proliferation effects in endothelial cells [89, 90]. This binding serves as a promising target to suppress tumor growth. The CGA scavenges the ROS, which weakens the VEGFR2-mediated signaling and phosphorylation of VEGFR2, extracellular signal-regulated kinase 1/2, and serine-threonine kinase [91].

The *in vitro* studies in liver cancer show that PDGF could induce NOX subunits (p47phox and gp91phox) expression, ROS production, p38 and ERK1/2 phosphorylation, the activation of HSCs, and the manifestation of profibrotic genes. CGA is found promising in the treatment of liver cancer through the inhibition of signaling pathways of PDGF. It suppresses the PDGF-induced profibrotic action by inhibiting the NOX/ROS/MAPK pathway [92].

Glucose metabolic disorders are sometimes associated with the occurrence and progression of cancer. Inhibiting the insulin receptor, CGA suppressed the activities of α -amylase and α -glucosidase and reduced the postprandial blood glucose concentration. CGA suppresses postprandial hyperglycemia by inhibiting α -glucosidase, and its action is similar to that of acarbose, miglitol, and voglibose [93].

Ferulic acid

Ferulic acid (FA) has been reported to be of importance in cancer therapy by targeting the RTK. *In vitro* examination in human breast cancer cells inhibit epidermal growth factor receptor (EGFR) through downregulation of Tyr 1068 autophosphorylation; molecular docking analysis revealed that FA form hydrogen bond interaction with Lys 745 and Met 793 and thereby exhibit stronger hydrophobic interactions with multiple amino acid residues at the EFGR kinase domain [94]. This result gives a good effect of FA in treating breast cancer through the alteration of EFGR proliferation.

Anticancer activity of ferulic acid is observed in the docking of the molecules of tyrosine kinase and VEGF-2 proteins *in silico*, which inhibits VEGF expression on the CAM model. This related to cancer cell inhibition, which is presented by inhibition of neo-vascularization and endothelial cell growth in blood vessels, showing that FA is a promising anticancer therapeutic agent at an early stage [95].

PDGF is a promising target in the destruction of cancer cells by FA through the up-regulation of hypoxic-induced factor (HIF) 1 α mRNA and protein, which serves as the inhibitor of PDGF in humans umbilical vein endothelial cells (HUVECs) [96].

FA prevents the growth of cancerous cells through the target of the insulin receptor. Atomic force microscopy shows that FA inhibits insulin amyloid fibril. FA suppresses the characteristic conformational transition from α -helix to β -sheet, leading that FA protects the native structure of insulin and prevents the conformational change required for its amyloid fibril formation *in vitro* [97].

Tannic acid

Tannic acid (TA) has been reported to have anticancer activity through apoptosis. Reactive oxygen species destroy cellular structures through the reaction with biological molecules and thereby induce cancer; the scavenging activity of tannic acid prevents the ROS from prolonging tumor cells [98]. Tannic acid inhibits EGF by competing with the ATP; it was docked into the ATP-binding pockets of the EGF receptor and led to cancerous cell death [99]. The experiment made by Darvin et al. [99] revealed that the EGFR-stimulated growth of breast cancer cells was inhibited in the presence of tannic acid.

VEGF plays an essential role in angiogenesis, vascular development, vascular permeability, and embryonic hematopoiesis. It also promotes proliferation, survival,

migration, and differentiation of endothelial cells [100]. VEGF as a target in the destruction of cancerous cells has been promising as it increases the cell membrane expression of CXCR4, which binds to stromal-cell-derived factor-1 (SDF-1), leading to the proliferation of cancer. In human breast cancer, TA alters the proliferation of VEGF, thereby decreases the expression of CXCR4 and interrupts its binding to SDF-1 [101].

Platelet-derived growth factors play a significant role in cancer. It has been an important target in cancer therapy; TA is shown to inhibit the conventional isomers of PDGF isoforms α , β I, and β II in mouse epidermal cell lines by binding to the regulatory domain of PDGF [102, 103]. TA targets insulin receptors in cancer cells by inhibiting insulin-induced glucose transport. TA is also found to inhibit the expression of essential genes for adipogenesis [104]. Studies revealed that tannic acid inhibits insulin-stimulated autophosphorylation of the insulin receptor in streptozotocin-induced diabetic rat on a concentration basis [105].

Alkaloids

Alkaloids are one of the largest groups of natural compounds classified based on their nitrogen contain atoms at different molecule positions (Fig. 6). Alkaloids constitute structurally diverse and unrelated biomolecules. Many of the well-known alkaloids, including quinine, nicotine, morphine, and apomorphine, possess significant therapeutic potential such as antimicrobial, anticancer, antioxidant, and antispasmodic [106, 107].

Opioids have been effectively used in treating pain in cancer patients, and their effect on vascular endothelium has been studied extensively. The pharmacological function of opioids has to be characterized majorly in the central nervous with little focus on their non-neuronal systems [108]. Opioids function by activating specific μ opioid receptors (MORs), G-protein coupled receptors associated with several cellular functions, including cell differentiation, proliferation, and survival. Opioids such as morphine have demonstrated clinical applications in cancer therapy [109]. Zhao et al. [110] discovered that long-term use of morphine therapy phosphorylates EGFR more rapidly at tyrosine 845 in c-Src-dependent Src-dependent internalization. Administration of morphine significantly reduced the growth of tumor cells in MCF-7 breast cancer cells via inhibition of the VEGFR signaling pathway [108]. Further studies have shown that exposure of human oral cancer HSC-3 cells to morphine downregulates VEGFR expression, thereby disrupting cell proliferation. In hypoxic conditions, morphine impairs angiogenesis by inhibiting the primary stimulator of angiogenesis, VEGFR [111, 112]. However, Lu et al.

[109] suggested that morphine promotes carcinogenesis by stimulating the EGFR signaling pathway. Therefore, several *in vivo* studies are required to establish the anticancer effect of morphine. Other alkaloids such as quinine and nicotine inhibit signaling pathways. However, their cytotoxic effect has primarily been reported in atherosclerosis, with little focus on their anticancer activity. Nicotine has been shown to promote cell proliferation in human glioma cells through activation of EGFR [113, 114].

Stilbenes

Stilbenes are a group of polyphenols and have received significant interest due to biological functions, chemical structures, and pharmacological activities. The characterization, clinical applications, and molecular mechanisms of resveratrol and its structural analog have been reported. Stilbenes undergo different secondary metabolites modifications to produce its structure derivatives, such as glycosylation, methoxylation, and oligomerization. Stilbenes are novel compounds for drug development and have demonstrated antioxidant, antitumor, antimalarial, and anti-inflammatory [115–117].

Resveratrol (3, 5, 4'-trihydroxystilbene) (Fig. 7) is a natural phytoalexin present in plants, and dietary sources possess several biological functions, including anti-proliferative, anti-inflammatory, and antioxidant. Consumption of resveratrol has been associated with a reduced risk of cancer and heart diseases [118]. Literature data demonstrated that administration of resveratrol at high concentration suppresses insulin in an animal model. Resveratrol inhibits angiogenesis induced by VEGFR via blocking Src tyrosine kinase, which phosphorylates vascular endothelial cadherin [119, 120]. Furthermore, resveratrol isolated from grapefruit has been shown to inhibit the downstream PDGF-R activation and EGFR signaling pathway selectively. A previous study indicated that treating human HaCaT and A431 cells with resveratrol and its methylthio-derivatives reduces overexpression of EGFR in tumor cells [121]. Zhang et al. [122] investigated the anticancer effect of resveratrol on living MCF-7 cells. The result proposed that resveratrol inhibits EGFR dependent ERK activation in a dose-dependent manner. However, the molecular mechanism underlying resveratrol action on cell proliferation is not well understood [123].

Lignans

Lignans are a class of naturally occurring secondary plant metabolites produced from the dimerization of two phenylpropanoid units (Fig. 8). Lignans are present majorly in their form, although their glycosides derivatives can

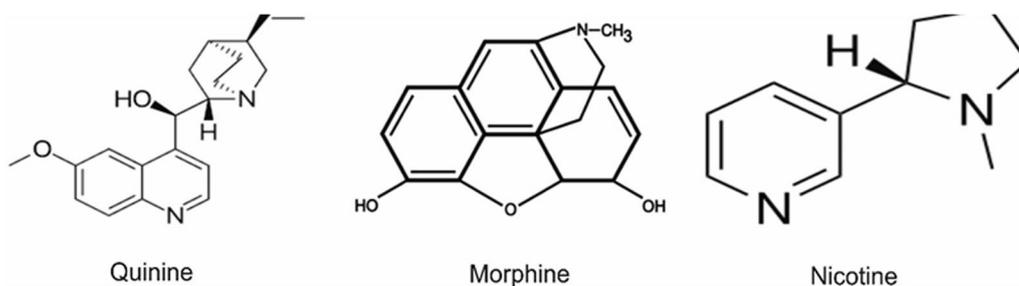


Fig. 6 Chemical structures of selected Alkaloids

also be present in minor conditions. They play a crucial role in plant defense mechanisms against diverse biological pathogens due to their biological properties. The anti-proliferative and cytotoxic effect of lignans has been the most studied among their biological functions. Silymarin, silydianin, and silychristin are flavonolignans with hepatoprotective activity [124–126].

Honokiol is a bioactive natural compound isolated from the bark of *Magnolia*. Previous studies have identified the therapeutic activity of honokiol, including anti-angiogenesis, an antioxidant, anti-inflammatory, anti-proliferative, and broad spectrum of antimicrobial [127]. Liposomal honokiol has been shown to inhibit tumor cell progression by downregulation of VEGFR-3 and induced apoptosis in cancer cell lines. Furthermore, the study suggested that honokiol effectively treats lung cancer through direct inhibition of angiogenesis and lymphangiogenesis via downregulation of vascular growth factors, VEGFR-2 and VEGFR-3 [128]. Honokiol demonstrated inhibitory potential against EGFR signaling cascade in head and neck squamous cell carcinoma (HNSCC) by arresting cellular proteins of the G0-G1 phase in a dose-dependent manner [129, 130]. Park et al. [130] reported that honokiol block the proliferation of MDA-MB-231 cells through downstream inhibition of c-Src/ EGFR-induced signaling pathway.

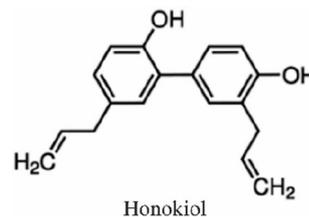


Fig. 8 Chemical structure of Honokiol

Conclusions

Natural compounds have substantially been characterized as a secondary metabolite of plants, demonstrating biological and pharmacological properties in preventing the progression of tumors and adjunct cancer therapy. Given the fundamental role of RTKs in signal transduction pathways that leads to tumorigenesis, several RTK inhibitors have been developed to effectively treat cancer. Furthermore, the use of natural products as ATP-competitive inhibitors of RTKs can reduce side effects and lower toxicity associated with small molecules such as imatinib, gefitinib, and erlotinib. Translational studies have always proven to be a barrier in scientific research, as only few are embarked on. It is no news that the pharmacological potential of natural products in the treatment of several metabolic diseases have been properly documented. As such, future studies should translate the natural products studied in this review into *in vivo* studies and if possible, clinical trials. However, synergistic relationship between several phytochemicals could prove efficient in managing cancer. Thus, studies on the synergistic mechanism of action of several natural compounds in the management of cancer could pave a novel path in ameliorating the jab thrown by the oncogenic ring in cancer.

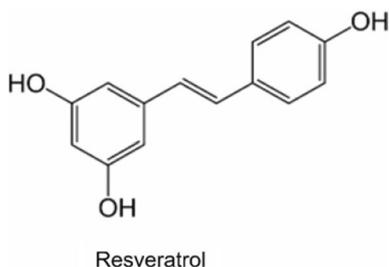


Fig. 7 Chemical structure of Resveratrol

Abbreviations

RTK: Receptor tyrosine kinases; EGFR: Endothelial growth factor receptor; PDGF: Platelet-derived growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; COX: Cyclooxygenases; ERK: Extracellular signal-regulated kinase; PI3K: Phosphoinositide 3-kinase; PKB: Protein kinase B (PKB) also known as Akt; JNK: C-Jun N-terminal kinases; IGF1R: Insulin growth factor receptor; PTB: Phosphotyrosine binding; SH2: Src homology; TKD: Tyrosine kinase domain; HER: Human epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog; MAPK: Mitogen-activated protein kinases; NSCLC: Non-small cell lung cancer; H₂O₂: Hydrogen peroxide; SDF-1: Stromal-cell-derived factor-1; JAK: Janus kinases; STAT: Signal transducer and activator of transcription proteins; PLC γ : Phospholipase- γ ; CryoEM: Cryo-electron microscope; IRS: Insulin receptor substrate; CDKs: Cyclin kinases; FGFR: Fibroblast growth factor receptor; HIF-1 α : Hypoxia-inducible factor-1 α ; SMCs: Smooth muscle cells.

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Authors' contributions

TAB conceived and designed the work. TAB, OMI, and AOA collected data, wrote the original draft, reviewed and edited. COO, ZAT, OAS, and OTA assisted with data collection and editorial works. DAO supervised the project. All authors read and approved the final manuscript.

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