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Review Article

Flavonol quercetin: Immunomodulatory and anticancer properties

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Abstract

Background: Cancer is one of the critical, challenging problems in a clinical setting among non-infectious diseases and poses a considerable burden to the community for its highest fatalities and associated morbidities. Immunotherapy has paid much attention to curbing cancer and protecting against advanced metastasis. Nutritional sources have been well known for their anticancer properties for centuries, although they have exhibited multiple intricated mechanisms to deter this disease. Immune-based therapy is getting popular in modern days to fight against various illnesses, including cancer. In recent years, numerous in vitro and clinical trials have been carried out regarding the potential use of flavonoids in cancer therapy; however, the results and achievements are still controversial and obscure. More research on immune-mediated anticancer therapy has to be done to understand more explicit mechanisms of how plant-derived compounds modulate immune cells and subsequent clinical uses. Flavonol quercetin is one of the most tested flavonoid compounds that stimulate immune cells and offer significant immune-mediated anticancer activities.

Objectives: This review summarizes an updated overview of quercetin, focusing on its anticancer effects. In addition to its chemistry and sources, quercetin's immunomodulatory properties and common signaling mechanisms have also been described and proposed the possible research gap for further investigation and future research.

Methodology: This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The following subject headings were applied during the literature search; global cancer incidence, flavonoids, flavonol quercetin, immunotherapy, and anticancer properties of quercetin. The eligibility criteria and study design were considered according to the inclusion and exclusion criteria.

Conclusion: This review will provide a new comparative view regarding quercetin's immunomodulatory and anticancer activities. Moreover, we conclude that quercetin plays a crucial role in eradicating cancer cells and modulating immune cells' activity based on the literature. It is worthwhile to extensively investigate quercetin's anticancer and immunomodulatory effects in clinical settings.

Keywords: Cancer, flavonol, quercetin, anticancer, immunomodulation

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Introduction

Among non-communicable diseases (NCDs), cancer imposes the most devastating effect on human survival. This dreadful disease inflicts a severe health problem in all populations, regardless of wealth or social status. This notorious disease is also the cause of about 30% of all premature deaths from NCDs among adults aged 30-69. Lung cancer stands as the most frequently diagnosed cancer among all cancer types (11.6% of all cases), followed by female breast (11.6%) and colorectal cancers (10.2%). Lung cancer contributes to the highest mortality (18.4% of all deaths), followed by colorectal (9.2%) and stomach cancers (8.2%) [1].

According to World Health Organization (WHO), cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body, and spread to other organs called metastasis, a major cause of death from cancer [2]. Cancer control interventions include primary prevention, screening, early diagnosis, multimodal treatment and survivorship, and palliative care. Cancer management is generally more complex than other diseases, even other NCDs. This life-threatening disease already accounts for one in six deaths globally, and the burden continues to rise not only on the individuals and families but also on the communities, health systems, and government economies [3].

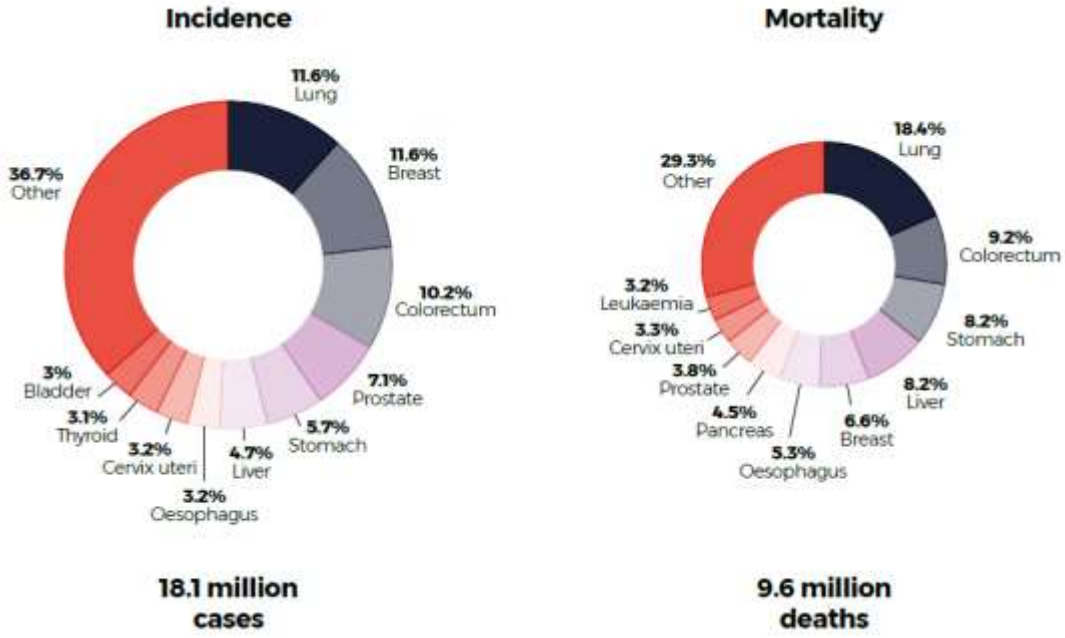

Figure (1). Distribution of cases and deaths by the leading 10 cancer types in 2018 for both sexes (WHO, 2020).

Cancer treatment options include radical surgery, chemotherapy, immunotherapy, endocrine therapy, radiotherapy, or a combination [4]. Cancer remission and relapse cases are extremely common in clinical settings, despite the availability of advanced medications and sophisticated dissection techniques. A novel approach involving immune-cell-mediated cancer therapy has been widely adopted for cancer treatment by utilizing innate immune cells. Immunotherapy treatments work in various ways. Some immunotherapy treatments assist the immune system in stopping or slowing cancer cell growth. Others aid the immune system in destroying cancer cells or preventing cancer from spreading to other parts of the body [5]. Genetic modification of immune cells, among other methods, offers hope for alternative anticancer treatment. T cells and natural killer (NK) cells are the most commonly studied immune cells. Furthermore, cytokine-induced immunomodulation has the potential to be used in cancer immunotherapy [6,7]. Scientists have studied the potential benefits of plant-derived polyphenols as an alternative cancer treatment, immune cell modulation, and genetic modification. Because of the unfavorable side effects of genetically modified immune cells, naturally occurring polyphenols, particularly flavonoids, have received much attention for their anticancer and immunomodulatory properties.

Flavonoids are a diverse group of benzo-pyrone derivatives with a diphenylpropanes-like carbon skeleton. They are classified into six groups based on their molecular structure: flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins. Several cell lines and animal models have demonstrated that flavonoids have positive protective effects in the development of cancer and neurodegenerative disorders, owing to their antioxidant activity, ability to influence the expression of several detoxifying enzymes [8], and ability to modulate protein signaling cascades [9]. Flavonoids can inhibit specific carcinogenic pathways, deter cell proliferation, and induce apoptosis in various cancer cells.

Flavonoids have long been studied for their anticancer properties, attributed to their ability to quench reactive oxygen species (ROS) and other radicals. Tea catechins, particularly epigallocatechin gallate (EGCG), react with superoxide, hydroxyl, peroxyl, and peroxynitrite radicals [10]. Resveratrol, found in red wine, grapes, and peanuts, is a scavenger of superoxide and peroxynitrite radicals [11], and genistein, derived primarily from soy, can scavenge exogenous or endogenous hydrogen peroxide in cell models [12]. In terms of flavonoids as chemoprevention in humans, contrasting results have been reported; indeed, some studies found an inverse relationship between total dietary flavonoid intake and cancer risk [13,14], whereas others found no association [15]. Among all, flavonol quercetin paid much attention to its ability to kill cancer cells [16,17] and modulated immune cells' activities in killing transformed cells [18,19].

Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were followed in this systematic review. During the literature search, the following subject headings were used: global cancer incidence, flavonoids, flavonol quercetin, immunotherapy, and quercetin anticancer properties. The inclusion and exclusion criteria were used to determine the eligibility criteria and study design. The current review included systematic reviews of in vivo and in vitro studies, primary studies of in vivo and in vitro studies related to quercetin, other research study designs (such as observational studies; observer reliability studies), and guideline documents as secondary sources of information. This article excluded quercetin's other properties, such as anti-inflammatory, anti-diabetic, cholesterol-lowering, and wound healing effects.

Chemical properties of flavonol quercetin

Flavonol is distinguished by the presence of a hydroxyl group at position 3 on its backbone. Several flavonol subclasses exist; however, quercetin, myricetin, fisetin, and kaempferol play critical roles in anticancer activity [20,21,22]. Among these compounds, quercetin possesses strong anti-cancer and immunomodulatory properties [23]. The estimated daily dietary intake of quercetin in most European countries [24] is 30mg, and its bioavailability is dependent on whether the conjugated or unconjugated form is present in the food. Indeed, quercetin obtained from plants is quercetin-glucose conjugates (quercetin glucosides), which are absorbed in the enterocytes' apical membrane. When quercetin glucosides are absorbed, they are hydrolyzed to produce quercetin aglycone, which is then metabolized by enterocytic transferases to the methylated, sulfonylated, and glucuronidated forms [25]. Quercetin metabolites are then transported to the intestinal lumen and then to the liver, where other conjugation reactions form the major quercetin-derived circulating compounds in human plasma, quercetin -3-glucuronide and quercetin -3-sulfate [26,27]. According to studies on quercetin bioavailability, the highest blood quercetin level ranges from 3.5 to 5.0 µmol/L when quercetin is absorbed in glucosides. However, quercetin absorption is poor in the glucoside-unconjugated form, with a peak plasma level of 0.33 µmol/L [28].

(A) (B)

Figure (2). The basic structure of (A) flavonol and (B) quercetin. (Diagram adapted from Mlcek, Jurikova, Skrovankova, & Sochor, 2016)[29]

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a polyphenolic flavonoid abundantly present in various citrus fruits and green leafy vegetables. The estimated molecular weight of this flavonol is 302.236 g/mol. Quercetin is synthesized from the amino acid phenylalanine, and the steps in the biosynthesis of quercetin are shown in Figure (3).

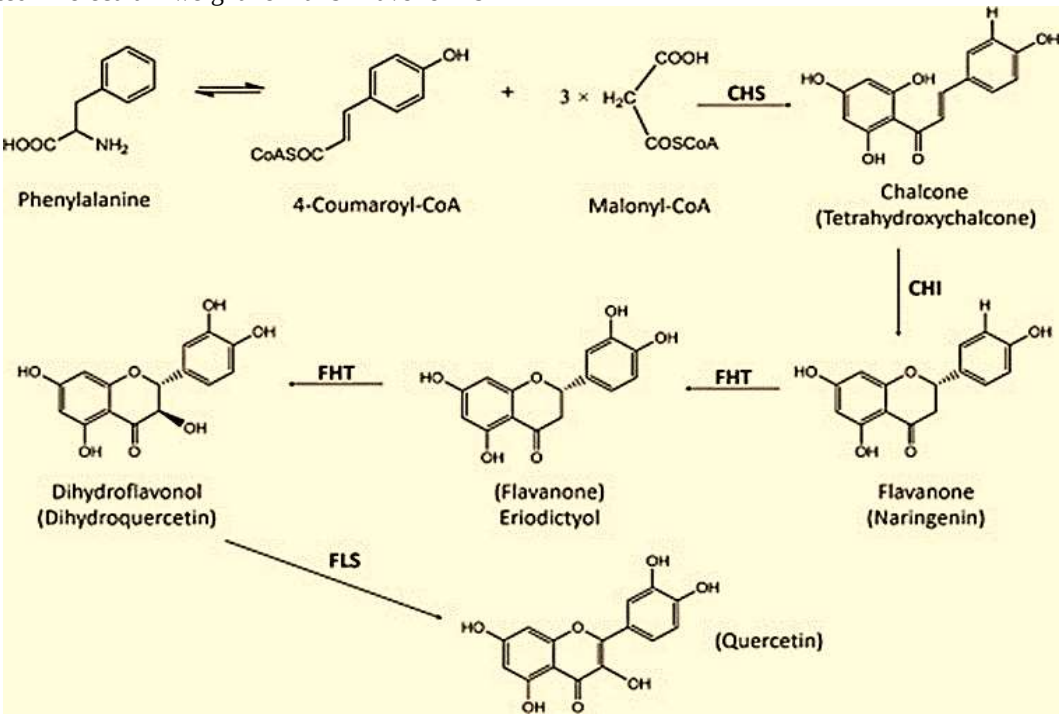

Figure (3). Steps in quercetin biosynthesis. (Diagram adapted from Yamagata, 2019)[30] CHS= Chalcone synthase, CHI= Chalcone isomerase, FHT= flavone hydroxylase, FLS= flavonol synthase.

This flavonol exerts various biological effects, including antioxidant, anticancer, antiviral, apoptosis-inducing, protein kinase C-inhibitory, cell cycle modulatory, and angiogenesis inhibitory effects [31,32]. Quercetin is an essential dietary flavonol, abundant in various fruits and vegetables as well as seeds, nuts, onion, green tea, and red wine grape [33,34]. The eight common sources of quercetin are displayed in Figure (4).

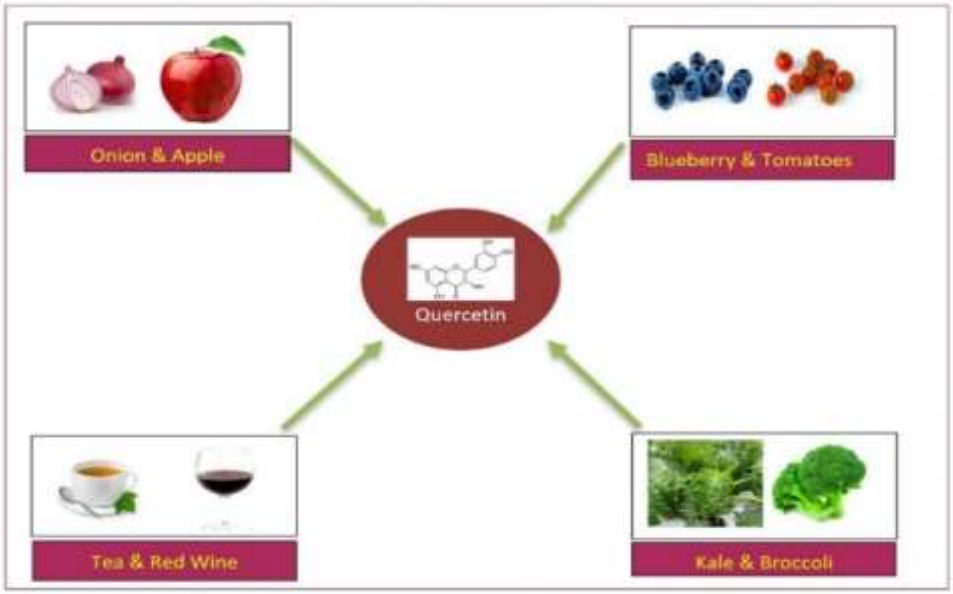

Figure (4). Schematic diagram showing the eight rich sources of flavonol quercetin.

Anticancer and Immunomodulatory properties of quercetin

Quercetin's anticancer properties are based on its ability to inhibit mitotic processes and reduce proliferation by modulating cyclins, pro-apoptotic, PI3K/Akt, and mitogen-activated protein kinase (MAPK) molecular pathways. This pentahydroxy flavonol also has biphasic, dose-dependent properties. At low doses, this flavonol acts as an antioxidant, providing chemopreventive benefits; however, at high concentrations, quercetin acts as a pro-oxidant, favoring chemotherapeutic effects [35,36]. There have been conflicting reports on the effects of quercetin on NK cells. Through induction of NK cell group-2 D (NKG2D) ligands, quercetin-treated K562 (leukemia cell line), SNU1 (Seoul National University gastric cancer cell line), and SNU-C4 (colorectal cancer) cells showed increased susceptibility to NK-92 cells. According to a study conducted by Bae and colleagues, the induction of NKG2D ligands with the decrease of HSP70 protein by quercetin may provide an appealing strategy to improve the efficacy of NK cell-based cancer immunotherapy [37]. Another study found that quercetin increased NK cell activity in BALB/c mice treated with quercetin after being injected with WEHI-3 lleukemiacells. Furthermore, NK cell activity in leukocytes isolated from the spleen was increased, resulting in increased killing activity, which was determined with YAC-1 target cells [38].

The flavonol quercetin, on the other hand, inhibited NK cell killing activity in human peripheral blood lymphocytes at concentrations as high as 100 µmol/L. After a 30-minute pretreatment with quercetin (10-100 µmol/L), NK cells were added to K562 target cells and incubated. Reduced cytolysis was observed and suggested to be caused by quercetin inhibiting Ca2+ channels and Na+/K+ ATPase activity [39]. Similarly, in community-dwelling adult females, quercetin supplementation at 500 and 1000 mg/day for 12 weeks significantly increased plasma quercetin levels but did not affect the innate immune function or inflammation [40]. A Finnish study also suggested that pre-treating NK cells with myricetin could improve their ability to kill K562 erythroleukemia cells. This increase in NK activity was observed to be dose-dependent. Treatments with the structurally similar quercetin, which lacks one hydroxyl group, did not affect NK activity [20].

The latest research on quercetin's anticancer and immunomodulatory effects is listed in tables (1) and (2).

Table (1). Anticancer properties of quercetin on various types of cancer

Compound	Cancer cells	Mechanism	Observation	Ref
Quercetin and cisplatin	Human oral squamous cell carcinoma cell Lines (OSCC)	Quercetin down-regulates NF-κB suppression of anti-apoptotic protein IAP	Quercetin promotes cisplatin-induced apoptosis in human OSCC	[41]
Quercetin dihydrate	Human prostate cancer cell lines (PCa)	Quercetin led to apoptotic and necrotic cell death in PCa cells by affecting the mitochondrial integrity and disturbing the ROS homeostasis	Quercetin exerts its anticancer effects by modulating ROS, Akt, and NF-κB pathways.	[42]
Quercetin	Human colon cancer cell lines	Quercetin induces apoptosis in human colon cancer cells through inhibiting NF-κB pathway, as well as down-regulation of B-cell lymphoma 2 and up-regulation of Bax	The apoptotic effect of quercetin on cancer cell lines was observed in a dose-dependent manner.	[43]
Quercetin	P39 chronic myelomonocytic leukemia cell line	Quercetin induces Bcl-2, Bcl-xL, Mcl-1 downregulation, Bax upregulation, and mitochondrial translocation, triggering cytochrome c release and caspases activation -induced the expression of FasL protein -increased cell arrest in the G1 phase of the cell cycle, with a	Quercetin caused pronounced apoptosis in P39 leukemia cells.	[44]

		pronounced decrease in CDK2, CDK6, cyclin-D,-E, and -A proteins, decreased Rb phosphorylation and increased p21 and p27 expression		
Quercetin and Curcumin	Four cancer cell lines, A549, HCT116, MCF7 and A375	The two flavonoids down-regulate Wnt/β-catenin signaling pathway proteins, DVL2, β-catenin, cyclin D1, Cox2, and Axin2 They also induce apoptosis by down-regulating BCL2 and inducing caspase 3/7 through PARP cleavage	Quercetin and curcumin inhibit cancer cell proliferation synergistically, and Wnt/β-catenin signaling and apoptotic pathways are partly responsible for antiproliferative activities.	[45]
Quercetin and ellagic acid	Three leukemic cell lines (CEM, K562, Nalm6), two breast cancer cell lines T47D and EAC	Quercetin induces S phase arrest followed by apoptosis in cancer cells	Quercetin induced significant toxicity in both leukemia and breast cancer cell lines	[46]
Quercetin	CEM (lymphocytic), U937 (monoblastic) and HL-60 (promyelocytic)	Quercetin does not influence intracellular signals induced downstream of CD95 ligation in leukemic cell lines.	Quercetin acts as an anti-tumor drug by exerting a strong pro-apoptotic activity on leukemic cells	[47]
Quercetin/lanthanum complex	Human cervix carcinoma cell line	The complex renders pro-oxidative effects and the formation of single-strand and double-strand DNA breaks into cancer cells	The Q/La complex showed the strongest cytotoxic effect	[48]
Quercetin	Nine tumor cell lines (colon carcinoma CT-26, prostate adenocarcinoma LNCaP cells, human prostate PC3 cells, pheochromocytoma PC12 cells, breast cancer MCF-7 cells, acute lymphoblastic leukemia MOLT-4 T-cells, human myeloma U266B1 cells, human lymphoid Raji cells and ovarian cancer cells	Quercetin induces apoptosis of all the tested cancer cell lines. Moreover, quercetin significantly induced the apoptosis of the CT-26, LNCaP, MOLT-4, and Raji cell lines, as compared to the control group	Quercetin inhibits the growth of a panel of 9 cancer cell lines with various IC50 values.	[49]
Quercetin	Human MDA-MB-231 breast cancer cells	It also reduced protein expression levels related to tumorigenesis and cancer progressions, such as aldehyde dehydrogenase-1A1, C-X-C chemokine receptor type 4,	Quercetin suppresses breast cancer stem cell proliferation, self-renewal, and invasiveness.	[50]

		mucin 1, and epithelial cell adhesion molecules.		
Quercetin and Luteolin	A431-P cells and A431-III cells	The two flavonoids not only ablate the Ribosomal protein expression but also block Akt/mTOR/ c-Myc ssignalingpathway.	Luteolin and quercetin seem to have the inherent potential to attenuate tumor metastasis.	[51]
Quercetin and Luteolin	Du145 prostate tumor cell line	Depressed the malignancy of highly invasive Du145-III cells, vasculogenic mimicry VM, anchorage-independent spheroid formation, and expression of specific cancer stem cell markers	Luteolin and quercetin were able to target cancer stem cells and prevent cancer cell invasiveness	[52]
Quercetin and curcumin	Triple-negative breast cancer (TNBC) & ER+ breast cancer cell lines	Combined treatment of quercetin and curcumin induces BRCA1 promoter histone acetylation * BRCA1 knockdown induced cell survival and cell migration in ER+ cells were significantly decreased.	Combined treatment of quercetin and curcumin acts synergistically to induce anticancer activity against TNBC cells by modulating tumor suppressor genes	[53]
Quercetin	HepG2 cell line inoculate BALB/c female mice	Through the regulation of cyclin D1expression	Quercetin significantly inhibits HepG2 cell proliferation,	[54]
Quercetin	Triple-Negative Breast Cancer (TNBC) cells	Quercetin-induced apoptosis via targeting the de novo fatty acid synthesis is likely through a caspase-3 dependent mechanism coupled with modulation of FASN and β-catenin expressions	Quercetin treatment-induced anticancer/apoptotic effects against TNBC cells	[55]
Quercetin and doxorubicin	Cancer stem cells (CSC) from HT29	induced G2/M arrest in the HT29 cells and to a lesser extent in CSCs.	Adding quercetin to Dox chemotherapy is an effective strategy for treating both CSCs and bulk tumor cells.	[56]

Table (2). Immunomodulatory properties of quercetin.

Compound	Immune cells	Mechanism	Observation	Ref
Quercetin loaded hydrogel	Macrophage	Quercetin upregulates SRY-box-9, aggrecan, and collagen type II alpha 1 chain of normal chondrocytes Qu promotes macrophage M2 polarisation, reduces inflammation, and inhibit ECM degradation by downregulating the expression of inducible nitric oxide synthase (iNOS), matrix metalloproteinase-13 (MMP13), and (MMP1) in degenerative chondrocytes	Quercetin promotes cartilage formation and anti-inflammatory activities by polarisation of macrophage to M2 type, effectively inhibit the degradation of ECM, and repair the defective cartilage tissue.	[57]
Quercetin	cultured human macrophage	The metabolic processes proposed to reflect flavonoid-mediated immunomodulation of macrophages included the downregulation of glycolytic	It revealed key metabolites and metabolic pathways involved	[19]

		activity, reprogramming of the TCA cycle, and increased antioxidant protection	in macrophage responses to quercetin providing novel insights into immunomodulatory activities.	
Oral Quercetin + azathioprine	rheumatoid arthritis patients	Quercetin significantly reduced IL-6, complement protein 3 (C3) & (C4) levels, and elevated IL-10 level Quercetin reduces the level of intercellular adhesion molecule-1	Quercetin and azathioprine combined treatment resulted in dose-dependent immunomodulatory actions regarding its effect on cytokines, sICAM, and complement proteins	[58]
Quercetin	Human monocyte-derived dendritic cells	Quercetin attenuates the pro-inflammatory phenotype and function of DCs Quercetin induces immune modulator CD83, as well as Dab2, ILT-3,-4, -5, and the ectonucleotidases CD39 and CD73 by tolerogenic DCs Quercetin-treated DCs showed an enhanced capacity to induce Tregs in DC-T cell cocultures.	Quercetin may represent a potential immunomodulatory agent to alter DC-mediated inflammation in the context of autoimmune disorders	[59]
Quercetin	Induced fibrosis in Wistar male rats	Quercetin elicits antioxidant properties to block NF-κB activation and, consequently, reduce cytokine IL-1. Quercetin reverses fibrosis by decreasing TGF-β levels, hepatic stellate cell activation, and promoting the ECM's degradation by increasing metalloproteinases.	Quercetin is capable of reversing a well established cirrhosis by blocking the pro-oxidant processes and by downregulating the inflammatory and profibrotic responses	[14]
Quercetin	Ovalbumin-induced asthma-Alloxan-induced diabetes Adult male Balb/c mice	Quercetin significantly decreased eosinophils, and interleukin-4 while increasing interferon-gamma	Quercetin altered Th1/Th2 immune balance, ultimately leading to the alleviation of allergic inflammation in the lungs of the mice.	[60]
Quercetin	Arbor Acre broiler	Quercetin increases the secretion of immunoglobulin A, interleukin-4, IgM, complement component 4 And tumor necrosis factor-α (TNF-α). Quercetin supplementation significantly increased complement component 3 & expression of TNF-α, TNF receptor-associated factor-2 (TRAF-2), TNF receptor superfamily member-1B (TNFRSF1B), nuclear factor kappa-B p65 subunit (NF-κBp65), and interferon-γ (IFN-γ) mRNA, Qu significantly decreases the expression of NF-κB inhibitor-alpha (IκB-α) mRNA	Quercetin improved immune function via the NF-κB signaling pathway	[18]
Quercetin	NK-92 and lung cancer cells	Quercetin significantly increased the NK-cell-mediated cytotoxic activity against lung cancer cells	Flavonoid quercetin possessed some significant immunomodulatory actions	[61]

		But the killing is not associated with NK cells' cytotoxic granules secretion	on NK cell cytotoxic activity toward lung cancer therapy	

Although quercetin modulates various molecular mechanisms to exert its anticancer properties, many researchers proposed a common molecular signaling mechanism through which this flavonol exerts its anticancer effect. Inhibiting intracellular kinase enzymes is essential in preventing cancer growth and metastasis. Several pathways regulate metabolic reprogramming in cancer cells, including the phosphoinositide 3-kinase/protein kinase-B (PI3K/Akt) pathway, promoting increased glucose uptake and glycolysis. The PI3K/Akt pathway regulates cell angiogenesis, metabolism, growth, proliferation, survival, protein synthesis, transcription, and apoptosis by transducing the signal across messengers that activate Akt [62,63]. By acting through AMP-activated protein kinase (AMPK), Akt participates in pathways that regulate nutrient availability. By sensing nutrient and extracellular energy changes, AMPK regulates glucose and lipid metabolism. AMPK is an energy sensor that is activated when AMP levels in the cell are high. Stresses that increase ATP consumption or decrease ATP production cause an increase in the AMP: ATP ratio, which promotes AMPK activation [64]. Under metabolic stress, AMPK can promote metabolic plasticity by stimulating alternative metabolic pathways such as mitophagy and fatty acid oxidation [65]. AMPK activation, on the other hand, can inhibit cell growth by inducing a p53-mediated cell cycle arrest and, as a result, downregulating the activity of the mammalian target of rapamycin C1 (mTORC1). Akt activation promotes hexokinase 2, which interacts directly with the mitochondrial pore to prevent the release of apoptotic proteins [66].

Table (3) Common mechanisms quercetin portrays in exerting anticancer property.

Type of study	Target cell	Mechanism	Observation/finding	Ref
In vivo	Myofibroblasts in the cutaneous wound of rabbit	Quercetin suppressed the signaling pathways activating RAW264.7 macrophages and dermal fibroblasts, which is associated with its inhibition of multiple tyrosine kinases to regulate the pathways	Quercetin inhibits the inflammatory and fibrotic responses to tissue damage by targeting multi-kinases could be the action mechanism to support its broad efficacy for various chronic disorders.	[67]
In vitro	BL21-Gold (DE3) competent cells	Quercetin acts as a lipid substrate competitive inhibitor, and it interacts with important residues of the active-site pocket of sphingosine kinase (SK) through hydrogen bonds and other non-covalent interactions.	Quercetin forms a stable complex with SphK1 without inducing any significant conformational changes in the protein structure.	[68]
In vitro and in vivo	-JB6 Cl41 cells and A549 lung cancer cells -A549 tumor-bearing mice	Quercetin inhibited aurora B activities by directly binding with aurora B in vitro and in vivo	Injection of quercetin in A549 tumor-bearing mice effectively suppressed cancer growth	[69]
In vitro	UV-B-irradiated B16F10 melanoma cells	Quercetin markedly attenuated MEK-ERK signaling, influenced PI3K/Akt pathway, and potentially enhanced the UVB-induced NF-κB nuclear translocation.	treatment of ultraviolet (UV)-B-irradiated B16F10 melanoma cells with quercetin resulted in a dose-dependent reduction in cell viability and increased apoptosis.	[70]
In vitro	Non-small cell lung cancer lines, the melanoma	Quercetin significantly reduces the activity of kinases that are	Quercetin partly exerts its anticancer activity through	[71]

	line, the glioblastoma lines, the colon cancer line, the breast cancer Line and the prostate cancer Line and melanoma line	involved in the control of mitotic processes such as tyrosine kinases, tyrosine kinase-like kinases, serine/threonine protein kinases, casein kinases, cAMP-dependent protein kinases, calcium/calmodulin protein kinase II kinases, and cyclin-dependent kinase (CDK), mitogen-activated protein kinase (MAPK)	the inhibition of the activity of a large set of kinases	
In vitro	Human breast carcinoma cell lines, HCC197	Treatment with Qu completely suppressed constitutively activated Akt/PKB phosphorylation at Ser-473 in HCC1937 cells.	Bioflavonoid Qu inhibits the PI3K-Akt/PKB pathway, similar to that of the commercially available LY, selective PI3K inhibitor.	[72]
In vitro	Tetradecanoylphorbol-13-acetate (TPA)-induced transformation of JB6 promotion-sensitive mouse skin epidermal cells.	Quercetin inhibited mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK) 1 and Raf1 kinase activities and subsequently attenuated TPA-induced phosphorylation of ERK/p90 ribosomal S6 kinase	Quercetin exerted more potent inhibitory effects than PD098059, a well-known pharmacologic inhibitor of MEK. Resveratrol did not affect either MEK1 or Raf1 kinase activity	[73]
Molecular docking	Serine/threonine kinases are involved in tumorigenesis.	Both quercetin and isoquercitrin exhibited good binding energies and interacted with aspartate in the highly conserved Asp–Phe–Gly motif.	quercetin's ability to inhibit the activity of Aurora kinases in several cancer cell lines by the quercetin-forming interactions with the hinge region in aurora kinase	[74]

Conclusion and recommendation for future research

Quercetin is a flavonol with high potential in cancer research due to its chemopreventive effects, demonstrated in vitro and in vivo models. This flavonol produces biphasic, dose-dependent effects. Lower doses of quercetin primarily act as an antioxidant, providing chemopreventive effects; however, at higher concentrations, quercetin acts as a pro-oxidant, potentially providing chemotherapeutic effects. This review depicts the potential effects of quercetin on cancer cells and immune cells, as well as the underlying mechanism of action. According to the literature review, quercetin's anticancer properties are mediated by direct toxicity and apoptotic mechanisms. In contrast, its immunomodulatory action is primarily achieved by increasing the number of immune cells or by regulating various intracellular signaling pathways of immune cells, such as cytokine production, cytotoxic granules secretion, and deterring immune cells from free radical injury.

As previously discussed, immunotherapy has focused heavily on controlling cancer and preventing advanced metastasis. Hundreds of studies on quercetin's anticancer and immunomodulatory effects to eradicate abnormally transformed cells have been conducted. Despite numerous in vivo and in vitro studies, quercetin as the sole anticancer agent has yet to be approved. In other words, more research is needed to determine the specific immunomodulatory action and anticancer effect that will be officially endorsed and approved by the FDA. Countless clinical trials have been conducted in recent years, but the results and achievements have remained controversial and obscure. More advanced research into the anticancer effects of quercetin should be conducted, with a primary focus on the role of quercetin on cancer stem cells.

Furthermore, the anticancer properties of quercetin on various molecular and signaling mechanisms should be investigated further, with a focus on the effect on microRNAs, sphingosine kinase, the mammalian target of rapamycin (mTOR) pathway, the C-X-C chemokine receptor type 4 (CXCR4), and the C-C chemokine receptor type 7 (CCR7) as targeted cancer therapy. Despite its numerous positive effects, quercetin's use in clinical settings remains limited, which may be due to its very low solubility, poor absorption, and rapid elimination. To better target tissues and organs, various approaches

to micro-and nano-delivery for quercetin therapeutic formulations should be investigated and evaluated and enhance therapeutic efficacy.

Conflict of interest

All authors declare that there is no conflict of interest. Therefore, the authors alone are responsible for the content of the paper.

Authors' contributions

AMO was responsible for study design, literature search preparation, and manuscript revision. MNMN and OML helped in study design, literature search, and manuscript preparation. NS was responsible for the critical review and editing of the manuscript. All the authors approved the final version of the manuscript.

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