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# Protective effects of curcumin and quercetin in studies on cancer: a meta-analysis study

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## ABSTRACT

**Aims:** Polyphenolic chemicals, such as quercetin and curcumin have anti-cancer properties due to their antioxidant and anti-inflammatory properties. Quercetin and curcumin aids in detoxification by boosting enzyme function and eliminating free radicals. We aimed to conduct a detailed meta-analysis of research articles reporting the protective effects of curcumin and quercetin in cancer studies.

**Methods:** The study was selected all studies over time carried out to date within the framework of our concept ,using various medical subject headings and databases like Elsevier, National Library of Frontiers, ResearchGate, Scopus Medicine, and Google Scholar. PRISMA guidelines was performed. The data management system played a significant role in locating and evaluating relevant articles, ensuring the accuracy and precision of the findings.

**Results:** From a total of 85 articles accessed in this analysis, 4 studies on quercetin and 3 studies on curcumin were included. The analyzed studies show that quercetin and curcumin have anti-cancer benefits through various cellular pathways. Quercetin inhibits Twist in breast cancer cells, while curcumin reduces Akt/mTOR cellular signaling, enhances Bax expression, and triggers cell death. It also prevents cell growth in human lung cancer cells and bladder cancer. Curcumin control reactive oxygen species levels, inhibit cancer cell proliferation, and stimulate apoptotic pathways. They also influence cancer development by altering cellular signaling pathways and affecting non-coding RNAs.

**Conclusion:** Our meta-analysis reports that quercetin and curcumin have the potential to be used in the treatment and prevention of cancer, it may be useful to investigate their synergistic effects.

**Keywords:** Antioxidants, cancer, curcumin, functional foods, quercetin

## INTRODUCTION

Polyphenols are natural chemicals present in plants, recognized for their antioxidant characteristics and possible health advantages. They are present in fruits, vegetables, tea, coffee, red wine, and plant-based diets.[1] They are a diverse category of natural bioactive phytochemicals that are found extensively distributed. These are characterized by aromatic rings attached to hydroxyl groups in their structure.[2] Polyphenols have demonstrated supplementary advantageous impacts on human health, in addition to their antioxidant action.[3] Epidemiological studies have shown that consuming dietary polyphenols can help protect against various types of cancer, as well as acute and serious ailments like cardiovascular diseases and osteoporosis, neurodegenerative diseases, and diabetes mellitus. Oxidative stress is linked to the development of many disorders.[4] Polyphenols are crucial in regulating the excessive formation of reactive oxygen species (ROS) and decreasing oxidative stress by adjusting the redox signaling pathways. Polyphenols have both antioxidant and pro-oxidant effects, with the latter being linked to their ability to induce apoptosis in cancer cells. Depending on their dosage and the specific cellular environment, polyphenolic substances can function as antioxidants or pro-oxidants.[5]

Polyphenols are crucial as they counteract free radicals, which can lead to cellular harm and play a pivotal role in chronic diseases such as cardiovascular illnesses, cancer, and neurological disorders. They possess anti-inflammatory characteristics that aid in the prevention and management of inflammatory disorders. Polyphenols are associated with cardiovascular benefits, including decreased blood pressure, enhanced blood vessel function, and reduced risk of heart disease.[6] They can also enhance cognitive function and lower the likelihood of neurodegenerative illnesses. Polyphenols support gut health by functioning as prebiotics, stimulating the proliferation of healthy gut flora. Polyphenols are bioactive substances present in plant-based foods that provide many health benefits such as antioxidant, cardiovascular, neuroprotective, and gastrointestinal health-promoting effects. Various classes within this category are categorized according to their structures, with polyphenols encompassing phenolic acids, stilbenes, flavonoids, lignans, and curcuminoids.[7]

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### Quercetin

Quercetin (3,30,40,5,7-pentahydroxyflavone), the predominant flavonoid present in plants, fruits, and vegetables, originates from the Latin term "quercetum," which translates to oak forest. It is sometimes referred to as 3,30,40,5,7-pentahydroxy-2-phenylchromen-4-one.[8] Quercetin exists in two forms: as an aglycone or a glycoside. The presence of a functional glycosyl group connected to the skeleton impacts its solubility, absorption, and actions within a living organism. Quercetin glycoside in its conjugated form is absorbed more efficiently.[9] Quercetin offers several health advantages because of its antioxidant and anti-inflammatory characteristics. It functions as an antioxidant by eliminating free radicals and preventing oxidative stress, safeguarding cells from harm caused by ROS. Quercetin regulates inflammatory pathways, decreasing the likelihood of chronic conditions such as arthritis and cardiovascular disorders. It enhances cardiovascular health by enhancing blood vessel activity, reducing blood pressure, and maybe decreasing LDL cholesterol levels.[10] It boosts the immune system by increasing the effectiveness of immune cells and encouraging a well-regulated immunological reaction. Quercetin might possess neuroprotective qualities by diminishing oxidative stress and inflammation in the brain, which could help prevent neurodegenerative conditions such as Alzheimer's disease.[11]

### Curcumin

Curcumin[1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione; diferuloyl methane] a component found in turmeric and utilized in traditional herbal medicine, is produced through a process involving DCS synthesizing feruloyldiketide-CoA and a curcuminoid scaffold (CURS) converting esters into curcuminoid structures.[12] While CURS has limited synthesis activity, combining it with DCS enhances efficiency. Curcumin performs keto-enol tautomerism, with the keto form being predominant in neutral and acidic conditions, and the enol form being stable in alkaline environments. Low bioavailability and hydrophobic properties result in inadequate absorption through the gastrointestinal tract. Contemporary encapsulation methods shield curcumin from deterioration, enhance water dispersal, and enhance bioavailability.[13] It offers several health advantages because of its anti-inflammatory and antioxidant characteristics. It blocks NF-kappaB, a protein that triggers genes associated with inflammation, hence decreasing inflammation on a molecular level. Curcumin is a powerful antioxidant that eliminates free radicals, protecting cells from oxidative harm. It can reduce symptoms and enhance joint function in illnesses such as osteoarthritis and rheumatoid arthritis. It can potentially penetrate the blood-brain barrier and be used to prevent or cure neurodegenerative conditions like Alzheimer's disease. Curcumin enhances cardiovascular health by enhancing endothelial function, decreasing inflammation, and serving as an antioxidant. It can aid in preventing and treating cancer by disrupting the formation, expansion, and dissemination of cancer cells and blocking angiogenesis.[14]

### Anti-Cancer

Quercetin and curcumin, polyphenolic chemicals, are essential in cancer development as they regulate different cellular pathways such as proliferation, differentiation as well as apoptosis, and reactions to oxidative stress. Their anti-cancer properties are associated with their alteration of signaling pathways such as mTOR, PI3K, MAPK and Akt, as well as their impact on and oncoproteins such as RAS as well as tumor-suppressing protein particularly p53.[15] Polyphenols impact the expression and changes of the p53 gene, influencing its roles in DNA damage response, apoptosis regulation, cell cycle control, and senescence. Recent investigations have found that several chemicals have anti-cancer properties, with some demonstrating strong inhibition of proliferation in breast cancer cells. Curcumin blocked the PI3K/ mTOR/Akt signaling processes, reduced BCL-2 expression, and enhanced expression of Bax and cleavage of protein caspase-3.[16]

Quercetin and curcumin are natural chemicals characterized for their antioxidant and anti-inflammatory qualities, and have been researched for their potential in reducing toxicity. Quercetin functions as an antioxidant by neutralizing free radicals and decreasing oxidative stress, particularly acting as cytoxicity agents against cancer.[17] Quercetin has demonstrated anticancer qualities in laboratory experiments, however its function as a cytotoxic agent for cancer is intricate and reliant on the setting. Quercetin can trigger cell death, hinder the growth of cancer cells, and exhibit anti-angiogenic properties by reducing the development of new blood vessels that aid in tumor progression and spread. The antioxidant and anti-inflammatory effects of this substance may help in its possible anticancer capabilities by decreasing oxidative stress and inflammation. The effects of quercetin can be considerably influenced by its concentration, the specific form of cancer, and experimental settings. Quercetin's bioavailability can be limited, which makes achieving therapeutic levels by food difficult.[18]

Curcumin has also been studied for its potential anti-cancer properties. However, its role as a cytotoxic agent for cancer is complex and context-dependent. Curcumin's mechanisms of action include anti-inflammatory properties, antioxidant activity, apoptosis induction, and inhibition of cell proliferation. Its bioavailability is low, and achieving therapeutic concentrations can be challenging. The effectiveness of curcumin may vary depending on the type of cancer, molecular characteristics of cancer cells, and other factors. Clinical trials evaluating curcumin's efficacy in cancer treatment are being conducted continuously. Some studies suggest potential benefits, while others show limited impact. It is crucial to approach these findings with caution and consult with healthcare professionals for guidance on incorporating curcumin or other supplements into their cancer management plan. Curcumin should not be considered a standalone treatment for cancer and should be discussed with a healthcare provider as part of an overall treatment strategy.[16]

It possesses anti-inflammatory properties by regulating inflammatory pathways, which aids in reducing inflammation caused by exposure to toxins. Curcumin aids the body's detoxification mechanisms by boosting the function of detoxifying enzymes and eliminating free radicals. Research indicates that the mixture of these substances may have synergistic impacts, offering improved antioxidant and anti-inflammatory assistance. Both chemicals exhibit protective properties on organs, such as the liver and kidneys, which are crucial for detoxification processes. Individual responses may vary; thus, it is important to utilize these chemicals cautiously and consult a healthcare practitioner.[18]

## METHODS

In our meta-analysis study, in which we did not specify any time period, we discussed studies from past to present indicating that Quercetin and Curcumin have protective effects in cancer research. The oldest research dated back to 1972, and studies from that day until 2023 were discussed. Detailed information is given on Figure. PRISMA Diagram and Table 1. MeSH employed in search strategy.

**Table 1. MeSH employed in search strategy**

| | |
|---|---|
| "Quercetin" AND/OR "Curcumin" AND/ OR " Management" | "Curcumin" AND/ OR "protective effects" AND/ OR "oncogenesis" |
| "Quercetin" AND/OR "antioxidant" AND/ OR "treatment " | "Quercetin" AND/OR "Dietary Compounds" AND/ OR "Oxidative Stress" |
| "Quercetin" AND/OR "Tumor suppression" AND/ OR "therapeutics of curcumin" | "Quercetin" AND/ OR "Antiproliferative" AND/ OR "Molecular Pathway" |

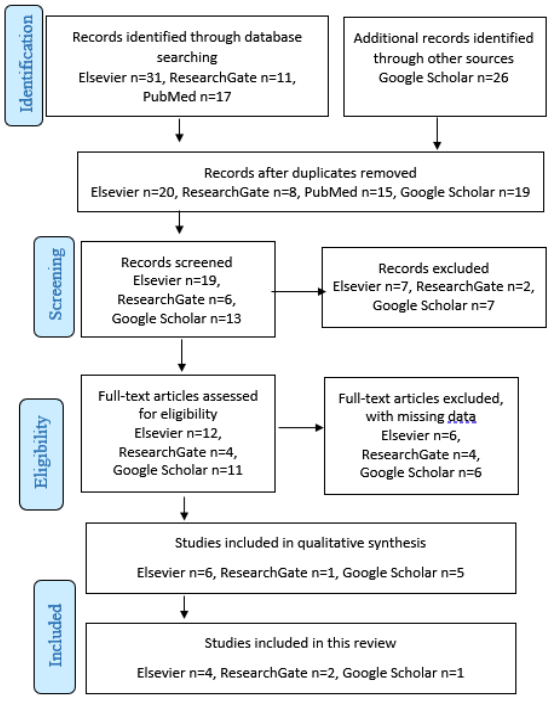


**Figure.** PRISMA diagram

Ethics committee permission is not required for this study. The researchers declare that they prepared this study in full compliance with all scientific publication ethical principles.

### Inclusion & Exclusion Criteria

The review's inclusion and exclusion criteria are set to identify the chosen and qualified studies for the study investigation to align with the subject of interest. This study examines the protective effects of curcumin and quercetin against cancer, specifically investigating the relationship between cancer and dietary components. The investigations were conducted in English and underwent peer review, demonstrating scientific rigor and accuracy through intellectual contributions across all research components. The exclusion criteria focused on excluding studies that had incomplete or missing literature. Research conducted in languages lacking translations is excluded to maintain linguistic coherence and inclusivity. The standards improve precision and accuracy, which are essential for sustaining the methodological integrity of study evaluations.

### Study Selection

In this study, research articles reporting the protective effects and anti-cancer properties of curcumin and quercetin in cancer studies were reviewed. The research is conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to ensure its effectiveness. This study was performed according to PRISMA guidelines.[19] Search tools use the "And" operator in Boolean logic to include all variables in the search and confirm their presence in several databases. Various medical subject headings (MeSH) were used to search for information in the article. The study was conducted using many scientific databases such as Elsevier, National Library of Frontiers, ResearchGate, Scopus Medicine (Pubmed), Central (PMC), and Google Scholar. This article was searched using various medical subject headings (MeSH) such as "Quercetin," "Curcumin," "anticancer," "chemoprevention," "apoptosis," "Tumour suppression," "oncocancer," "anti-proliferative," and "oxidative stress" to conduct the research. Table 1 includes the MeSH terms used to search different databases.

### Data Extraction

During the process of assisting with the methodical analysis and selecting the publications, the data management system made a substantial contribution. This contribution was significant. A methodical technique was applied in the research in order to locate and evaluate relevant articles in a rigorous manner. This was done in order to guarantee the accuracy and dependability of the findings. Throughout the entire process, the PRISMA standards were adhered to. This included conducting an in-depth analysis of the abstract and title of the paper, as well as conducting a comprehensive review of papers that were suitable for consideration, and so on. A PRISMA figure that was utilized in the process of identifying the research may be found in Figure. The meticulousness with which the appropriate clinical trial was selected and organized was the factor that ensured the dependability and precision of the findings.

## RESULTS

A total of 85 records were identified through database research, from past to present. These consisted of Elsevier=31, ResearchGate=11, PubMed=17 and additional Google Scholar=26 studies, respectively. The oldest research dated back to 1972, and studies from that day until 2023 were discussed. Thirty-eight studies consisting of controlled cell culture studies were included in the final analysis. Detailed information is given on Figure PRISMA Diagram.

The meta-analysis results are shown in Table 2. Articles analyzing the protective effects of Curcumin and Quercetin; 3 of them are studies on breast cancer, 2 on colon and rectal cancer, 1 on lung cancer and 1 on bone cancer.

Quercetin's Maximum IC50 Concentration is 290μM while minimum is 5.14μM. Maximum IC50 Concentration of Curcumin is >80μM while minimum is 1.32μM.

The protective effects of both bioactive components appear to be reported in almost all Cell stages. All other details are shown in Table 2.

## DISCUSSION

Quercetin and curcumin are polyphenolic compounds that may play important roles in regulating cancer development by managing various cellular processes like differentiation, apoptosis, the cell cycle, and responses to oxidative stress, in addition to antioxidants.[17] According to literature, Polyphenols control the expression of the p53 gene and its post-translational modifications like methylation, phosphorylation, acetylation, and ubiquitination. These modifications impact p53's roles in damage to DNA response, apoptosis regulation, cell cycle control, and senescence. Recent research has demonstrated the anti-cancer benefits of quercetin and curcumin, which can be linked to the various cellular pathways.[16] Also, Quercetin can reduce cyclin D1 and p38 MAPK phosphorylation by inhibiting Twist in MCF-7 breast cancer cells and cause G1/S arrest, leading to cell death. On the other hand, Curcumin can strongly suppress the growth of cancer cells such as MDA-MB-415, T47D and MCF-7. Curcumin can inhibit the cell cycle in M and G2 phase by reducing CDC25 levels as well as CDC25 levels and increasing p21 levels, which is a very important method to inhibit proliferation.[20]

**Table 2. Characteristics of studies**

| Study | Cancer | Compound | Subject | IC50 Concentration | Cell stage | Bioactive Effect | Result |
|---|---|---|---|---|---|---|---|
| Ranganathan et al., 2015[20] | Breast | Quercetin | MCF-7 cancer cells | 37μM | G1 arrest | Triggers cell death by inhibiting cyclin D1, p21, Twist, and phosphorylated p38MAPK. | Quercetin triggers cell death in cancerous breast cells by inhibiting Twist through the p38MAPK pathway. |
| | | | MDA-MB-231 | 100μM | | No effect | |
| Hu et al., 2018[21] | Breast | Curcumin | MCF-7 | 1.32μM | Impairment in G2/M phase | Triggers cell death via reducing CDC25 and CDC2 levels, increasing P21 expression, inhibiting Akt/mTOR phosphorylation, decreasing BCL2, and enhancing Bax and cleavage caspase-3. | Curcumin fights breast cancer by inducing an arrest in the cell cycle at the G2/M phase, blocking Akt/mTOR signalling, and promoting caspase 3 protein cleavage, resulting in cell death. |
| | | | MDA-MB-231 | 11.32μM | | | |
| | | | MDA-MB-468 | 18.61μM | | | |
| | | | MDA-MB-415 | 4.69μM | | | |
| | | | T47D | 2.07μM | | | |
| | | | SK-BR-3 | 16.39μM | | | |
| | | | BT-20 | 16.23μM | | | |
| Shen et al., 2020[40] | Breast | Curcumin | MCF-7 | 16.85μM | G1 phase was targeted | Decreases the levels of cyclin D1, cyclin E1, and CDK2. Triggers the mitochondrial apoptotic pathway. | B14 has more bioavailability as curcumin and combination with curcumin can hinder breast cancer by affecting mitochondrial apoptotic processes and cell cycle arrest. |
| | | | MDA-MB-231 | 42.01μM | | | |
| | | | MCF10A | >80μM | | | |
| Yang et al., 2016[24] | Colon | Quercetin | HT-29 | 81.65μM | G0 and G1 phase were affected | Decreases phosphorylated Akt, enhances CSN6 protein breakdown, leading to decreased levels of Myc and BCL-2, and increased levels of p53 and Bax. | Quercetin decreased the levels of phosphorylated-Akt and enhanced the degradation of CSN6 in HT-29 cells, leading to changes in the expression of Myc, p53, Bcl-2, and X proteins. |
| Shakibaei et al., 2013[25] | Colon rectal | Curcumin | HCT116 | 20μM | Antiproliferative effect in S phase | Enables mitochondrial disintegration and release of cytochrome c. | Curcumin and 5-FU may improve the therapy of chemoresistant colorectal cancer cells by targeting the NF-kB/PI-3K/Src networks and NF-kB-regulated products of genes. |
| | | | HCT116+ch3 | 5μM | | | |
| Zhaorigetu et al., 2021[28] | Lung | Quercetin | A549 | 5.14μM | G2/M cell cycle phases were affected | Upregulates Bax, downregulates BCL-2 | Quercetin triggers programmed cell death in lung cancer cells, decreases MDA levels, boosts SOD and GSHP levels, and aids in the treatment of lung damage. |
| | | | H69 | 9.18 μM | | | |
| Suh et al., 2010[41] | Bone | Quercetin | HOS | 290 μM | G1/S phase was arrested | Decrease in the expression of cyclin D1, a crucial cyclin for progression from the G1 phase to the S phase. | Quercetin induced programmed cellular death within human osteosarcoma (HOS) cells via transiently halting cells at the G1/S phase and triggering the capspase-3 pathway. |

It has been reported that curcumin inhibits proliferation and triggers apoptosis in breast cancer series. Curcumin can inhibit phosphorylation along with activation of the Akt/mTOR cellular signaling pathway. It reduces the anti-apoptotic function of BCL-2 and increases Bax expression along with the cleavage of caspase-3 protein. Additionally, Analog B14 can inhibit the cell cycle in the G1 phase and trigger the mitochondrial death process by inhibiting the expression of cyclin D1 as well as the expression of cyclin E1 and also cyclin-dependent kinase 2.[21]

Another article reports that Quercetin treatment can reduce Cyclin D1 expression in ovarian SKOV-3 cells. The decrease in cyclin D1 expression may be related to the S and G1 phase of quercetin-treated cells.[22] Similarly, Curcumin application in SKOV3 cells reduced phospho-Akt as well as PI3K concentration levels, leading to an increase in caspase-3 and an increase in Bax levels. It also suppressed its anti-apoptotic effects by reducing BCL-2 levels.[23]

Quercetin treatment in human HT-29 colorectal cancer cells caused chromatin condensation, cellular shrinkage, as well as nuclear collapse. Quercetin reduces cell viability and may trigger cell death by inhibiting the signaling axis of Akt-CSN6-Myc. It is stated that quercetin also reduces the levels of p-Akt-Thr308 by reducing CSN6 protein expression levels. This resulted in decreased Myc concentration and increased p53 levels.[24]

In another study that we discussed within the scope of meta-analysis, it is reported that Curcumin increases the effectiveness of chemotherapy in colorectal cancer. An intervention combining 5-fluorouracil and curcumin on HCT116+ch3 cancer cell resulted in the activation or degradation of PARP as well as pro-apoptotic proteins such as Bax and caspase-8. Moreover, it reduced the levels of the anti-apoptotic protein BCL-XL and the proliferative protein of cyclin D1. 5-fluorouracil increased NF-κB/Src protein kinase cellular signaling pathway, while curcumin down-regulated by inhibiting IκBα phosphorylation.[25] Also, The H446 human small cell lung cancer (SCLC) cell line had the highest sensitivity to curcumin when analyzed against HCT116, Hela or PC-9 and A549 cells. H446 effectively induced cell death, decreased BCL-2 expression, and increased Bax expression, which has a potential role in controlling cell growth. Quercetin inhibited the growth of human lung cancer cells by activating Bax and caspase-3.[26]

Quercetin is noted to inhibit the growth of T24 cells as well as human bladder cancer 5637. Treatment with quercetin may trigger apoptosis by increasing caspase-3/7 activity, leading to a high rate of DNA fragmentation in the sub-G0/G1 phase. Quercetin has dual functions in inducing apoptosis and promoting protective autophagy. This treatment led to a gradual increase in LC3-II, an autophagic marker protein, in 5637 and T24 cells, along with the production of autophagosomes. Quercetin promoted a transition from autophagy suppression by Baf1 and chloroquine to apoptosis. The data showed that the reduction in cell viability and the rise in LC3-II processing were lessened in cells treated with quercetin that had been pre-treated with N-acetyl cysteine, a scavenger of ROS. This indicates that the cytotoxic effects and autophagy triggered by quercetin were caused by the production of ROS.[27,28] On the other hand, Quercetin-losartan (a drug used to treat hypertension) hybrid can alter the cell cycle, leading to cell cycle arrest, leading to cytotoxic activities, and reducing the proliferation and angiogenesis of cancer cells in glioblastoma cultures. It is stated that quercetin can inhibit angiogenesis by reducing segment and network formation of vessels.[29] Similarly, in human glioma cells, Curcumin has shown promising anti-cancer effects by increasing ROS generation. While it reduces cell viability, it may lead to increased autophagy and cell death. Curcumin and its analogs, including demethoxy curcumin, bisdemethoxy curcumin, and dimethoxy curcumin, are noted to induce premature cell death and ROS generation via apoptosis in LN229 and GBM8401 glioma cells in vitro. Quercetin and curcumin dosage has been shown to be an important factor in inducing cell death in three different leukemic cell lines (Nalm6, K562 and CEM). While it showed low sensitivity with an IC value of 160 micromolar in breast cancer T47D cells, it led to cell cycle arrest in S phase during tumor regression.[30,31]

The articles we have discussed show that Quercetin and curcumin are compounds that can prevent the growth of cancer cells by stimulating apoptotic pathways. Quercetin can lead to DNA damage leading to increased p53 expression, decreased antiapoptotic protein BCL2, and cleavage of the apoptosis signal MCL1. The decrease in mitochondrial membrane potential causes the release of cytochrome c and SMAC/DIABLO, which in turn activates the mitochondrial intrinsic pathway. Thus, mitochondria can work more efficiently. Inhibitors of apoptosis proteins (IAPs) can be inhibited by SMAC/DIABLO, and the release of cytochrome c from mitochondria leads to the activation of caspases.[32] Also, cytochrome c plays a role in the activation of caspase-9, which in turn cleaves caspase-3 and activates it.[33] Similarly, Curcumin can lead to cell cycle arrest and apoptosis by affecting the levels of cell cycle and cell death-related proteins in acute myeloid leukemia cell lines ML-2 and OCI-AML5.[34]

Research shows that Quercetin and curcumin's anti-cancer properties affect cancer development by altering various cellular signaling pathways as well as affecting non-cancer signals such as PI3K/Akt, Wnt/β-catenin, JAK/STAT, MAPK, p53, NF-kB, and by affecting non-coding RNAs (ncRNAs).[35] Non-coding RNAs have a crucial role in various physiological processes such as chromatin restructuring, transcription, post-transcriptional modifications and signal transduction. Dysregulated non-coding RNAs may contribute to cancer development by acting as oncogenes or tumor suppressors, highlighting their potential for cancer therapy. ncRNAs, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are highly important targets in the anti-cancer properties of polyphenols. They target key oncogenes or restore tumor suppressor gene expression. In contrast to well-studied miRNAs, lncRNAs have only recently been recognized as important factors in fighting cancer.[36] It has been reported that quercetin and curcumin can modulate miRNA function by decreasing oncogenic miRNA or increasing tumor suppressor miRNA. This effect can affect multiple genes and

affect signaling pathways that regulate cell growth and death.[36] Quercetin's ability to suppress the growth of MCF-7 cells is likely due to its ability to decrease miR-21 expression and raise the production of PTEN, which are the targets of miR-21 and are crucial in the apoptotic pathway.[37] In addition, a mixture of quercetin and hyperoside inhibits the expression of miR-21 linked with prostate tumors, leading to decreased invasion, and spread of cancer PC3 cells of prostate. This combination may lead to an increase in the production of cell death protein 4 (PDCD4), an important target protein of miR-21, which is repressed by miR-21. Overexpression of miRNA344a-3p mimic along with curcumin treatment may result in increased levels of apoptotic proteins such as procaspase-9 and cleaved caspase-3 in RT4 schwannoma cells. On the other hand, Curcumin inhibits osteogenesis by upregulating miR126a-3p, which directly targets and inhibits human low-density lipoprotein receptor-related protein 6 (LRP6) expression. This effect inhibits osteogenic differentiation by suppressing the WNT signaling pathway. Therefore, long-term or high-dose use of curcumin may inhibit bone formation, resulting in decreased bone mass and density, thereby causing tumor spread.[38,39]

## CONCLUSION

The antioxidant, cardiovascular, neurological, and gastrointestinal health-promoting actions of polyphenols, such as quercetin and curcumin, are only some of the many health benefits that polyphenols provide. Through the influence that they exert on a variety of cellular processes and signaling pathways, these substances have been demonstrated to possess anti-cancer capabilities. Through processes such as triggering apoptosis, blocking cellular signaling pathways, and altering non-coding RNAs, studies have revealed that quercetin and curcumin have the potential to be used in the prevention and treatment of cancer. The protective effects of both bioactive components, especially through their strong antioxidant properties, are perhaps among the most researched functional food studies in the literature. However, elucidating the synergistic mechanisms through which the protective effects of both components on cancer and the positive/negative effects they will exert through detailed research can make a significant contribution to the literature. In addition, it is thought that it would be useful to examine these functional components with nanoparticle applications, which have become increasingly popular in recent years, and to evaluate them in detail with clinical studies that are less available in the literature, such as tumor development, angiogenesis and metastasis. Before adding quercetin and curcumin, which appear to be effective against breast, colon, and lung cancers, to cancer management strategies, detailed analyzes are required and it is important to seek advice from experts in this field.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Ethics committee approval is not required for this study.

### Informed Consent

Informed consent form is not required for this study.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Abbas M, Saeed F, Anjum FM, et al. Natural polyphenols: an overview. *Int J Food Prop*. 2017;20(8):1689-1699. doi: 10.1080/10942912.2016.1220393
2. Mancini-Filho J. Bioavailability of phenolic compounds in food and their properties in cellular protection. *Bioequiv Bioavailab Int J*. 2020;4(1):000145. doi: 10.23880/beba-16000145
3. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev*. 2009;2(5):270-278. doi: 10.4161/oxim.2.5.9498
4. Scalbert A, Manach C, Morand C, Rémésy C, Jiménez L. Dietary polyphenols and the prevention of diseases. *Crit Rev Food Sci Nutr*. 2005;45(4):287-306. doi: 10.1080/1040869059096
5. Slika H, Mansour H, Wehbe N, et al. Therapeutic potential of flavonoids in cancer: ROS-mediated mechanisms. *Biomed Pharmacother*. 2022;146:112442. doi: 10.1016/j.biopha.2021.112442
6. León-González AJ, Auger C, Schini-Kerth VB. Pro-oxidant activity of polyphenols and its implication on cancer chemoprevention and chemotherapy. *Biochem Pharmacol*. 2015;98(3):371-380. doi: 10.1016/j.bcp.2015.07.017
7. Cione E, Torre C La, Cannataro R, Caroleo MC, Plastina P, Gallelli L. Quercetin, epigallocatechin gallate, curcumin, and resveratrol: from dietary sources to human microRNA modulation. *Molecules*. 2020;25(1):63. doi: 10.3390/molecules25010063
8. Batiha GE, Beshbishy AM, Ikram M, et al. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. *Foods*. 2020;9(3):374. doi: 10.3390/foods9030374
9. Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. *Int J Med Update*. 2007;2(2):22-37. doi: 10.4314/ijmu.v2i2.39851
10. Tang SM, Deng XT, Zhou J, Li QP, Ge XX, Miao L. Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. *Biomed Pharmacother*. 2020;121:109604. doi: 10.1016/j.biopha.2019.109604
11. Shafabakhsh R, Asemi Z. Quercetin: a natural compound for ovarian cancer treatment. *J Ovarian Res*. 2019;12(1):55. doi: 10.1186/s13048-019-0530-4
12. Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – a review. *J Tradit Complement Med*. 2017;7(2):205-233. doi: 10.1016/j.jtcme.2016.05.005
13. Katsuyama Y, Kita T, Funa N, Horinouchi S. Curcuminoid biosynthesis by two type III polyketide synthases in the herb Curcuma longa. *J Biologic Chem*. 2009;284(17):11160-11170. doi: 10.1074/jbc.M900070200
14. Naama JH, Alwan GH, Obayes HR, et al. Curcuminoids as antioxidants and theoretical study of stability of curcumin isomers in gaseous state. *Res Chemic Intermediat*. 2013;39(9):4047-4059. doi: 10.1007/s11164-012-0921-2

15. Cháirez-Ramírez MH, de la Cruz-López KG, García-Carrancá A. Polyphenols as antitumor agents targeting key players in cancer-driving signaling pathways. *Front Pharmacol*. 2021;12:710304. doi: 10.3389/fphar.2021.710304
16. Wang H, Zhang K, Liu J, et al. Curcumin regulates cancer progression: focus on ncRNAs and molecular signaling pathways. *Front Oncol*. 2021;11:660712. doi: 10.3389/fonc.2021.660712
17. Khan H, Reale M, Ullah H, et al. Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions. *Biotechnol Adv*. 2020;38:107385. doi: 10.1016/j.biotechadv.2019.04.007
18. Hasan AA, Tatarskiy V, Kalinina E. Synthetic pathways and the therapeutic potential of quercetin and curcumin. *Int J Mol Sci*. 2022;23(22):14413. doi: 10.3390/ijms232214413
19. Desmoulin A, Joly E, Tran P, Derancourt C, Bertolotti A. Methodological quality of systematic reviews of the local management of anogenital warts: a systematic review using AMSTAR II, ROBIS and PRISMA. *Sex Transm Infect*. 2023;99(5):345-347. doi: 10.1136/sextrans-2023-055796
20. Ranganathan S, Halagowder D, Sivasithambaram ND. Quercetin suppresses twist to induce apoptosis in MCF-7 breast cancer cells. *PLoS One*. 2015;10(10):e0141370. doi: 10.1371/journal.pone.0141370
21. Hu S, Xu Y, Meng L, Huang L, Sun H. Curcumin inhibits proliferation and promotes apoptosis of breast cancer cells. *Exp Ther Med*. 2018;16(2):1266-1272. doi: 10.3892/etm.2018.6345
22. Catanzaro D, Ragazzi E, Vianello C, Caparrotta L, Montopoli M. Effect of quercetin on cell cycle and cyclin expression in ovarian carcinoma and osteosarcoma cell lines. *Nat Prod Commun*. 2015;10(8):1365-1368. doi: 10.1177/1934578x1501000813
23. Yu Z, Wan Y, Liu Y, Yang J, Li L, Zhang W. Curcumin induced apoptosis via PI3K/Akt-signalling pathways in SKOV3 cells. *Pharm Biol*. 2016;54(10):2026-2032. doi: 10.3109/13880209.2016.1139601
24. Yang L, Liu Y, Wang M, et al. Quercetin-induced apoptosis of HT-29 colon cancer cells via inhibition of the Akt-CSN6-Myc signaling axis. *Mol Med Rep*. 2016;14(5):4559-4566. doi: 10.3892/mmr.2016.5818
25. Shakibaei M, Mobasheri A, Lueders C, Busch F, Shayan P, Goel A. Curcumin enhances the effect of chemotherapy against colorectal cancer cells by inhibition of NF-κB and Src protein kinase signaling pathways. *PLoS One*. 2013;8(2):e57218. doi: 10.1371/journal.pone.0057218
26. Mo F, Xiao Y, Zeng H, et al. Curcumin-induced global profiling of transcriptomes in small cell lung cancer cells. *Front Cell Dev Biol*. 2021;8:588299. doi: 10.3389/fcell.2020.588299
27. Tsai TF, Hwang TIS, Lin JF, et al. Suppression of quercetin-induced autophagy enhances cytotoxicity through elevating apoptotic cell death in human bladder cancer cells. *Urol Sci*. 2019;30(2):58-66. doi: 10.4103/UROS.UROS_22_18
28. Zhaorigetu, Farrag IM, Belal A, et al. Antiproliferative, apoptotic effects and suppression of oxidative stress of quercetin against induced toxicity in lung cancer cells of rats: In vitro and in vivo study. *J Cancer*. 2021;12(17):5249. doi: 10.7150/jca.52088
29. Tsiailanis AD, Renziehausen A, Kiriakidi S, et al. Enhancement of glioblastoma multiforme therapy through a novel Quercetin-Losartan hybrid. *Free Radic Biol Med*. 2020;160:391-402. doi: 10.1016/j.freeradbiomed.2020.08.007
30. Luo SM, Wu YP, Huang LC, Huang SM, Hueng DY. The anti-cancer effect of four curcumin analogues on human glioma cells. *Onco Targets Ther*. 2021;14:4345-4359. doi: 10.2147/OTT.S313961
31. Zhou H, Ning Y, Zeng G, Zhou C, Ding X. Curcumin promotes cell cycle arrest and apoptosis of acute myeloid leukemia cells by inactivating AKT. *Oncol Rep*. 2021;45(4):11. doi: 10.3892/or.2021.7962
32. Grillone K, Riillo C, Scionti F, et al. Non-coding RNAs in cancer: platforms and strategies for investigating the genomic "dark matter". *J Exper Clin Cancer Res*. 2020;39(1):117. doi: 10.1186/s13046-020-01622-x
33. Yi J, Li S, Wang C, et al. Potential applications of polyphenols on main ncRNAs regulations as novel therapeutic strategy for cancer. *Biomed Pharmacother*. 2019;113:108703. doi: 10.1016/j.biopha.2019.108703
34. Liu H, Lei C, He Q, Pan Z, Xiao D, Tao Y. Nuclear functions of mammalian MicroRNAs in gene regulation, immunity and cancer. *Mol Cancer*. 2018;17(1):64. doi: 10.1186/s12943-018-0765-5
35. Winkle M, El-Daly SM, Fabbri M, Calin GA. Noncoding RNA therapeutics — challenges and potential solutions. *Nat Rev Drug Discov*. 2021;20(8):629-651. doi: 10.1038/s41573-021-00219-z
36. Nwaeburu CC, Bauer N, Zhao Z, et al. Up-regulation of microRNA Let-7c by quercetin inhibits pancreatic cancer progression by activation of Numbl. *Oncotarget*. 2016;7(36):58367-58380. doi: 10.18632/oncotarget.11122
37. Sohn EJ, Bak KM, Nam YK, Park HT. Upregulation of microRNA 344a-3p is involved in curcumin induced apoptosis in RT4 schwannoma cells. *Cancer Cell Int*. 2018;18(1):199. doi: 10.1186/s12935-018-0693-x
38. Pan L, Sha J, Lin W, Wang Y, Bian T. Curcumin inhibits prostate cancer progression by regulating the miR-30a-5p/PCLAF axis. *Exp Ther Med*. 2021;22(3):969. doi: 10.3892/etm.2021.10401
39. Xu W, Xie S, Chen X, Pan S, Qian H, Zhu X. Effects of quercetin on the efficacy of various chemotherapeutic drugs in cervical cancer cells. *Drug Des Devel Ther*. 2021;15:577-588. doi: 10.2147/DDDT.S291865
40. Shen H, Shen J, Pan H, et al. Curcumin analog B14 has high bioavailability and enhances the effect of anti-breast cancer cells in vitro and in vivo. *Cancer Sci*. 2021;112(2):815-827. doi: 10.1111/cas.14770
41. Suh DK, Lee EJ, Kim HC, Kim JH. Induction of G1/S phase arrest and apoptosis by quercetin in human osteosarcoma cells. *Arch Pharm Res*. 2010;33(5):781-785. doi: 10.1007/s12272-010-0519-4