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Article Review : Understanding the Mechanistic Role of Flavonoids in Cancer Prevention and Treatment

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Abstract

Cancer is one of the major causes of death in the world. The existing treatment methods mainly utilize surgery, chemotherapy and radiotherapy; these treatment methods are widely utilized, but do not work well with some types of tumors because of their very expensive nature, side effects and adverse reactions. Anti-cancer agents that have been developed recently are effective yet costly. Consequently, it is now vital to find alternative candidate drugs that will improve the efficacy of treatment and decrease the cost of therapy. Food dietary bioactive compounds have become the focus of attention as fast absorbed phytochemicals with the potential to regulate cellular activity and possibly have preventive and/or therapeutic effects on cancer. One of the key groups of bioactive compounds which are food- and beverage-derived has been reported to be flavanols, which are also known as flavonoids, which are candidate anticancer agents. The mechanistic study can be used to narrow down lead candidates to subsequent in vivo examination. Flavonoids comprise a group of polyphenolic compounds of varied chemical structures that occur naturally. These pigments help plants to resist ultraviolet (UV) radiation and act as attractants to pollination and seed scattering. Flavonoids are common in the plant kingdom and they are frequently eaten by humans. The curiosity about medicinal plants has increased, and it has triggered the assessment of the medicinal preparations to become modernized to the business realm. The importance of the flavonoids has been derived because of the availability of many of them in most of the foods that are readily available like fruits and vegetables, and because of the wide range of biological and pharmacological activities, which are deemed desirable in lowering the rate of occurrence of various ailments, anti-allergic, anti-inflammation, anticancer and cardiovascular protection. It is known that flavonoids have anticancer effects which work in various ways. As such, the clarification of the anticancer properties of flavonoids would assist in identifying the potential candidates in the identification of new anticancer agents, in addition to the preparation of anticancer drugs using natural and/or traditional medicine.

Keywords: Flavonoid, Cancer, Anti-cancer, Anti-angiogenic,

Introduction

Cancer is a rather ideal biological example of a biological environment where the possible effect of flavonoids on the cellular processes related to the disease and the physiological pathways that underlie these effects can be assessed. The numerous oncological mechanisms which are directly connected with the cancer usually evolve through the complex pathways where the major role is played by the altered cellular absorption of the key nutrients. It is interesting to note that the direct utilization of flavonoids by cancerous cells, to satisfy oncogenic requirements is an event which has hardly been recorded in the literature. Therefore, the need to determine their potential beneficial contribution to the processes in cells, whether it results in the stimulation of their growth or, vice versa, their death, becomes unquestionable. As a matter of fact, flavonoids are considered to be one of the most heterogeneous classes of dietary phenolic, and comprehensive studies of their biological properties indicate that the effects of the mentioned substances are apt to play a significant role in regulating the behavior of the oncogenic cells. The outcome of this interaction is usually adverse change of otherwise desirable cellular phenotypes. Consequently, special emphasis is then directed towards the mechanistic processes by which these food components evoke modifications in the manifold of cellular activities which are especially pertinent to certain events taking place under cancer-stimulating circumstances. Such states include basic procedures like cellular growth, regulated cell death (apoptosis), and autophagic procedure. **(Drețcanu et al., 2022; Ponte et al., 2021).**

Chemical Diversity and Sources Flavonoids

The most widespread type of polyphenols is the flavonoid, which includes two benzene rings connected by a heterocyclic pyran or chroman ring **(Ponte et al., 2021)**. Depending on the level of saturation and oxidation of the central ring flavonoid is further classified into flavones, isoflavones, flavanones, flavonols, anthocyanidins, and flavans. They are found naturally in fruits, vegetables, tea, red wine, and cocoa and color flowers, fruits, and leaves. Dietary flavonoids have effects on human health, and a lot of research has been conducted on their connection with preventing cancer. Flavonoid are chemical compounds (2-phenyl-1,4-benzopyran derivatives chemical defined) that offer a framework of chemical modification and allows biological activity(s). The structure-activity relationships have been attributed to flavonoid anticancer effects **(Bendokas et al., 2020; Drețcanu et al., 2022).** Anticancer properties Preclinical studies implicate flavones, flavanones, flavan-3-ols, isoflavones, flavonols and chalcones. Form-Activity-Structural: There are four key flavonoid skeletons having chemical substituents that interact with regulating the cancer-relevant cell-signaling pathways.

Mechanistic Structures within Cancer Biology.

Various mechanistic models can be used to outline cancer biology and the many-faceted interactions between flavonoids and it. The signs of cancer extend the fundamental principles of aberrant cell growth and differentiation and give a mechanistic vocabulary to the flavonoid functions found below **(Ponte et**

al., 2021). The best-known paradigms suggest six universal features of cancer, and countermeasures of the so-called avoided ones, and prescribe eight crucial enabling ones. Space considerations make it impossible to present a complete hallmarks-of-cancer or enabling-characteristics schema, but specific actions of flavonoids can be readily mapped onto known hallmarks and networks. The Flavonoid affects many well-established signaling pathways that are known to be major facilitators of cancer because they interact broadly and conditionally. The PI3K/AKT/mTOR axis is well-modulated and influences cell growth, survival, and autophagy, whereas the MAPK pathway is regulated and controls a variety of processes, such as proliferation and apoptosis. NF-KB and STAT3 signal transduction favor inflammations, immune evasion and metastasis; flavonoids have significant impact on these networks and the key upstream regulators include TNF-a, IL-6, and IL-8. Further blockage of downstream cancer-promoting signals is also prevented by preventing constitutive activation of the RASERK sub pathway. Adaptability of flavonoid modus operandi in different cell contexts is exemplified by their elaborate radio protective activity, which is most evidently pronounced but not uniformly embraced by cancer agents. **(Lopes et al., 2025; Jannati et al., 2025).**

Flavonoid anticancer Mechanisms.

Rapid growth of the cancer cells is one of the characteristics of the cancer **(Ponte et al., 2021)** that is linked with the deregulation of the cell cycle advancement. Cyclin overproduction typically occurs in cancer cells to guarantee unregulated cell growth, whereas the levels of cell-cycle inhibitors are undermined in the transcription **(Chahar et al., 2011)**. The passage of the G1 phase to S phase involves cyclins D and E. G2/M transition is caused by cyclins A, E, and B, and CDK2 and CDK1. Diverse flavonoids are able to prevent cells at the G1 or G2 stages or accelerate the progression to the S phase. Luteolin, epicatechin, morin, quercetin and 5,7-dihydroxyflavone are flavonoids that cause species and time-dependent G2/ M arrest.

Flavonoids cause apoptosis by mediating the intrinsic or extrinsic pathway, or by autophagy. Bcl-2 family proteins control the intrinsic pathway. The apoptotic machinery is mainly associated with caspases. The synthesis of Bcl-2 family members into pro-apoptotics stimulates the discharge of cytochrome c to the mitochondrion, resulting in the activation of caspase-9. Bid cleavage is caused by the activation of caspases-8 through death receptors in the extrinsic pathway. Free Bid moves to mitochondria which controls the mitochondrial pathway. Flavonoids have the ability to activate the autophagic process and, as well, to play a role in their anticancer activity. Markers used to determine the presence of autophagic flux are microtubule-associated protein 1 light chain 3 (LC3) and p62 protein **(Jeong et al., 2022 ; Lossi, 2022; Yang et al., 2021).**

Flavone, naringenin, genistein, chrysin, and biochanin A are flavonoids that prevent the epithelial to mesenchymal transition (EMT), which is critical in cell metastasis. The mechanism of action of Flavonoids is mediated by the transcriptional factors, Snail and Slug, by down regulating Wnt pathway. Treatment of flavonoids has been reported to suppress celladhesion protein E-cadherin, cell matrix isolating proteins fibronectin and vimentin, or proteinase matrix metalloproteinase-2. Exposure of flavonoid significantly suppresses the migratory and invasive behavior of cancer cells **(Hemmati et al., 2025; Proença et al., 2023).**

4.1. Regulation of Cell Cycle and Cell Proliferation

Flavonoids have anticancer effects due to their ability to regulate cell proliferation and cell cycle. Cell cycle is a sequence of specific stages in which cells proceed to attain division and replication. The progression is strictly regulated by control points at which it is determined whether the environmental conditions allow the further development. Four stages (G1, S, G2 and M) are observed in the cell-cycle of the mammalian cells after the point of cell-cycle initiation **(Ponte et al., 2021).** The G1/S and G2/M transitions are inhibited by arresting at the G1/S and G2/M stage, respectively, to prevent DNA synthesis and mitosis, respectively **(Matsuno et al., 2005)**. Cyclins and cyclin-dependent kinases (CDKs) are involved in cell cycle control, including cell-cycle checkpoints. Flavonoids have cell-cycle effects by inhibiting the cell-cycle at different stages in the pathway resulting in cell-cycle arrest in cancer cells. Quercetin causes arrest of G 1/S-phase by down-regulation of CDK2 and cyclins D1 and E, and up-regulation of the cyclin-dependent kinase inhibitor p21 **(Chahar et al., 2011; Song et al., 2014)**. Isoquercetin leads to the G2/M-phase arrest, and the reduction of CDK1/cyclin B1 expression kaempferol leads to G1/S- and G2/M-phase arrest and cell death in human gastric carcinoma cells. Overall, flavonoid compounds can also mediate the G1/S and G2/M arrest by different mechanisms that include repression or activation of certain cyclins and/or CDKs, which affect the cell proliferation and the cell cycle successfully **(Barra et al., 2022; Pang et al., 2021; Shendge et al., 2021).**

4.2. Apoptosis and Autophagy induction.

The accurate control of the apoptotic apparatus has a significant role in cellular homeostasis and carcinogenesis prevention. Apoptosis may occur through two major pathways: the intrinsic pathway, which is triggered by intracellular stimuli, and the extrinsic pathway, which is triggered by extracellular signals. Pro-apoptotic Bcl-2 family proteins, including Bax and Bak, cause the mitochondrial outer membrane permeabilization (MOMP) in the intrinsic pathway, resulting in the release of cytochrome c in the cytoplasm.

In the extrinsic pathway, interaction of death receptors (e.g. DR4, DR5, TNFR1) triggers the downstream caspases through sequential recruitment of death domain-binding adaptor proteins and initiation caspases. The two pathways lead to the executioner caspases (mainly caspase-3), which initiate the typical morphological characteristics of apoptosis. In addition to causing apoptosis, flavonoids may also have anti-cancer effects by regulating autophagy, a highly conserved catabolic process in the breakdown of damaged organelles, misfolded proteins and invading pathogens **(Ponte et al., 2021).** Autophagy, in the normal cells, prevents cancer progression. Nevertheless, in well-established tumor, autophagy may cause release of pro-survival signals and add to therapy resistance, making autophagy a pro-tumorigenic process **(Chahar et al., 2011).** Flavonoids are able to prevent the autophagic flux by either promoting the establishment of double-membrane phagophores or blocking the initial and terminal phases of autophagy thus having anti-cancer effects **(Silva et al., 2023).**

4.3. Proliferation of Cancerous Cells Inhibited

Epithelial- mesenchymal transition (EMT) is a process in physiology vital in early development, wound healing or tissue maintenance. Recent research indicates that cancer cells induced with EMT aberrantly encourage metastasis . EMT phenotypic markers consist of a decrease in cytokeratin, e-cadherin and occludin and loss of epithelial markers and increase of vimentin, fibronectin and n-cadherin, typically seen in a mesenchymal cell. This can be initiated by factors of growth, which include TGF-B and EGF, pro-

inflammatory cytokines or intracellular signalling pathways including PI3K/AKT, MAPK/ERK and -catenin that is a known target of flavonoids Certain flavonoids have very potent inhibitory effects on the TGF-b induced EMT prevent the expression of mesenchymal markers and recover the expression of epithelial markers in cancer cells. Moreover, the expression of CXCR4 chemokine receptor in a range of cancer cells following TGF- B treatment may be suppressed by various flavonoids,
and CXCR4 is also implicated in the TGF- B-stimulated acquisition of mesenchymal phenotype. CXCR4 inhibition or silencing can prevent TGF- 8 -mediated invasion in cancer cells treated with flavonoid **(Evers et al., 2021)**.

The aberrant communication between microenvironment and cancerous cells is experienced by cancers. These interactions are facilitated by a repertoire of soluble and membrane-bound molecules and influence tumor cell proliferation, apoptosis and invasion. Gap junction (GJ) is a common pathway that is constituted by connexin (Cxs) which enable intercellular exchange of small molecules (<1 kDa), including cAMP, IP3, amino acids, and promote paracrine signalling. **(Khater et al., 2022)**.

In cancer cells, GJ formation and dysfunction may be caused by the deregulation of Cx expression that can lead to the deterioration of GJ intercellular communication. Meanwhile, Cx- based aberrant signalling may also play a part in promoting cancer via autocrine signalling. Guava flavonoids increase the Cx43 expression in cancer cell lines and simultaneously reinstate GJIC. GJIC recovery by flavonoids is linked to a reduction in proliferation, less formation of the soft agar colony, and prevention of tumorigenesis in nude mice. Other molecules that can be modified by Flavonoids include Protocadherin 7, which is also a part of GJIC. It is because of these reasons that Guava flavonoids are being looked at in the development of dietary strategies aimed at disrupting the cancerous transformation in cells that are exposed to pro-carcinogenic agents **(Jamieson et al., 2023; Kubatka et al., 2021; Siddiqui et al., 2021).**

4.4. Anti-angiogenic Effects

One of the most important proangiogenic factors is known as vascular endothelial growth factor (VEGF) which induces the growth, migration and differentiation of endothelial cells via its receptor, VEGFR **(Khater et al., 2022)**. increased VEGF and VEGFR expression is associated with low prognosis in a number of cancers and blocking the VEGF/VEGFR axis prevents tumor neovascularization and malignancy**.** Many flavonoids have anti-angiogenic effects by inhibiting pro-angiogenic signals, such as VEGFR2, epidermal growth factor receptor (EGFR), matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), and related signalling pathway, e.g., MAPK/ERK, PI3K, HIF1-alpha/Akt and IL-6/STAT3**.** Flavonoids also lower the presence of hypoxia-inducible factors in other hypoxia models, which inhibit the increase in pro-angiogenic mediators which are regulated by hypoxia-inducible factors (**Khan & Mukhtar, 2013**). Such wide range of targets places flavonoids in a position to bypass resistance mechanisms**,**
that develop when other pro-angiogenic factors are up-regulated **(Lin et al., 2025; Wang et al., 2025; Wei & Zhang, 2024).**

4.5. Regulation of Oxidative Stress and Inflammation.

Cellular redox state and activity is controlled by intracellular redox balance between reactive oxygen species (ROS) and antioxidants. The increase in ROS reacts with the macromolecules leading to the oxidative stress, macromolecular damage and significant cellular changes that cause cancer.

Flavonoids regulate ROS, either as antioxidants or pro-oxidants in a particular situation and these effects can facilitate or suppress the various phases of carcinogenesis. The role of appointment of the Nrf2-

antioxidant response element (ARE) signaling axis in flavonoid-mediated ROS regulation and associated anticancer effects is also significant. Research has shown that flavonoid increase Nrf2 activity and address Nrf2-regulated genes. Quercetin stimulates the Nrf2 and causes NQO1 and GCLM to have a great effect on ROS levels and malignancy via the Nrf2/ARE axis. In addition to the redox homeostasis mechanisms that are also regulated by flavonoids and balance the adjustment of ROS, other intracellular and extracellular processes of cancer development are also influenced by flavonoids, especially during the early stages of cancer progression when genetic alterations occur.

NF-kB transcription factor regulates a massive proportionality of pro-inflammatory genes that promote tumor progression. By interfering with tumor-promoting information at key stations of the NF-KB-mediated inflammatory pathway, superfluous inflammation that accompanies the unregulated repair of tissue and the development of tumor, Flavonoids suppress the activation of tumor promoters **(Ponte et al., 2021; Xi et al., 2022).**

4.6. Flavonoid Regulation of Epigenetics.

The extensive set of anticancer effects, produced by flavonoids, can be explained by the complex and multifaceted processes of the epigenetic regulation. Epigenetics is the term which implies the changes of gene expression which are both hereditary and reversible and occur without any modification of the genetic code itself. The most important processes, which are involved in these changes, are DNA methylation, histone modification, and non-coding RNA (ncRNA) interaction. These three processes have been shown to be greatly influenced and affected by flavonoids, as these constitute a major and potent mechanism by which they have been shown to promote many anticancer effects. The knowledge of these interactions will help researchers learn more about the way flavonoids can be used to prevent and treat cancer **(Busch et al., 2015; Fatima et al., 2021).**

4.7. Disruption of Signaling Pathways (PI3K/AKT, MAPK, NF-B, statistin T3 -W)

In line with their myriad modulatory impact, flavonoids disrupt various signaling pathways that are involved in cancer initiation, cancer promotion and progression. These include the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase/extracellular regulated kinase (MAPK/ERK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) and signal transducer and activator of transcription 3 (STAT3)-networks and are the most active in mechanistic roles **(Malik et al., 2025).** An example of this convergence is the flavonoids that include quercetin, kaempferol and apigenin, which regulate the PI3K/AKT pathway. Another quercetin, kaempferol and apigenin target pathway is the MAPK pathway. NF- -compounds, such as luteolin and apigenin, induce NF- kB, and others, such as galangin and morin, use more of the mechanism of action of STAT3 interference.

These pathways are not autonomous, they have a mutual effect on the other one, and are more or less active in particular cellular conditions, which highlights the need to investigate further the role of flavonoid on these networks.

Pharmacokinetics, Bioavailability and Delivery Strategies.

The effect of molecular structure, physicochemical properties, food matrix, dietary patterns, drug interactions, host-related parameter, and metabolic fate are some factors that affect flavonoid bioavailability **(Ponte et al., 2021)**. The efficacy of oral effective dosing of micromolar concentrations of flavonoids is preclinical despite the fact that oral administration may not result in pharmacologically active

concentrations in tissues Clinical applications Opportunities A number of ongoing trials on flavonoids in cancer highlight opportunities **(Mignet et al., 2013)**.

Controlled-release polymers were used, which increased plasma half-life, and decreased GI morbidity, thus improving efficacy and tolerability **(Arroo et al., 2017)**.

The use of flavonoids in the treatment of cancer has a lot of potential, although at present, there is only a small quantity of preclinical and clinical evidence to substantially justify its effectiveness in this regard. The formulations which are effective targeting intestinal absorption, systemic exposure, and bioavailability are greatly desired. On the same note, new mechanisms that will help to deliver flavonoids locally to the individual tumor sites are paramount to increase treatment results. An example is that liposomes containing quercetin were found to enhance in vivo anticancer activity and safety. Also, nanoparticles that increase the circulation time of flavonoids, enhance their intake into tissues, and allow the delivery of hydrophilic compounds co-delivery have a significant impact on increasing quercetin efficacy. Significant alterations aimed at improving lipophilicity are critical in enabling complexation to appropriate excipients which can greatly improve cellular uptake and general anticancer efficacy. Nevertheless, the scope of preclinical evaluation of prodrugs is still in its early stage; thus additional investigations on structural modifications that would allow intracellular hydrolysis and sustained release of the active compounds can be used to further enhance the action and efficacy of flavonoids in relation to cancer.

Preclinical Data and Translational Consequences.

The cancer disease is a terrifying world-wide health priority, with one out of every four deaths in the United States estimated to be a result of cancer. Environmental factors have a significant effect on the etiology of diseases but preventive and curative drugs are not affordable to all people, and the regulation of supplements is a restrictive form **(Iriti & Varoni, 2013)**. In general terms, flavonoids may be considered as polyphenolic plant compounds the biosynthesis of which is catalyzed by chalcone and flavonoid synthases **(Ponte et al., 2021).**

The natural and anthropogenic sources of flavonoids are fruits, vegetables, beverages, herbs, seeds, spices and orally consumed cosmetic products. Flavonoids have extensive physiological action; an example of this is the effect on neuroendocrine and vascular systems exhibited by flavonoids in wine; research in human intervention has indicated that flavonoids of different origin can potentiate metabolic, immunological and neuromodulatory actions. Nevertheless, anticancer effects of flavonoids are perhaps the most desirable. Cellular or animal models have supported the anticancer properties of many flavonoids such as quercetin, kaempferol, rutin, genistein, daidzein, myricetin, naringenin, luteolin, apigenin and flavones and flavonols of green tea. These studies also reveal important processes of such potential and suggest that organosulfur compounds of garlic, including diallyl sulfide, would also add to the existing anticancer activity of flavonoids **(Ferdous & Yusof, 2021; Shah et al., 2023).**

Evidence and Problems of Clinical Translation.

The largest category of polyphenols in the plant-based food comprises flavonoids, which are found in a variety of edibles, including fruits and vegetables, as well as grains, herbs, tea, wine, and juices. As secondary metabolites they afford a shield against ultraviolet radiation, pathogens, give desirable smells, tastes and colors, and offer foliage and fruit peels protection. Flavonoid concentration is different across

plant species, soil, weather, and parts of plants: in leaves and fruit peels, this concentration is high **(Ponte et al., 2021).** Flavonoids chemically consist of a skeleton of fifteen carbon atoms, with two benzene rings attached by a three-carbon heterocyclic chain which has oxygen. It is further divided into six primary subclasses according to the oxidation state of the central carbon: flavones, isoflavones, flavanones, flavonols, anthocyanidins and flavans. There are also many synthetic analogs of these compounds and other minor flavonoids which are not part of the 6 groups which have been investigated. When applied to cancer and other cancer-related pathologies that are marked by an over-growth and invasion of the cells, flavonoids seem to induce anti-oxidant stress-reduction processes and anti-cellular damages. These measures have possible preventive and treatment properties. The vast majority of evidence, however, is of fairly low relevance in vitro, of cellular, or of animal studies. Very little of the clinical studies has been done to give any form of corroboration, which explains the dire necessity of controlled clinical trials to help understand the possible benefits to human health. There has been a growing interest in flavonoids as anticancer agents over the past few years, in part due to epidemiological reports that have suggested that they have certain links with cancer. Population exposure trends also have constant stimulation to explore their applicability, understand the mechanisms, and whether they can provide adjunctive or support strategies **(Iriti & Varoni, 2013).**

Safety, Toxicology, and Dose Response.

Flavonoids are not very toxic to mammals including human beings, and no side effects have been recorded in case of dietary intake. In larger doses, flavonoids may be poisonous to model organisms (mice and rats) with effects including decreased body weight and increased liver weights. Anti-carcinogenic effects of flavonoids have also been shown at these doses to have an anti-cancer effect in pre-clinical studies which has demonstrated a broad therapeutic index of flavonoid actions. Moreover, the dose-dependent modes of action of flavonoids render their classification as anti-cancer rather complicated and care should be taken when conducting an extrapolation of the findings of the study on the research doses to the clinically applicable doses **(Drețcanu et al., 2022).**

The combinations of flavonoids include (−)-epicatechin with curcumin or daidzein with genistein have been reported to have good anti-carcinogenic effects in mice **(Ponte et al., 2021)** It is also observed that these combinations also act to alter carcinogenicity pathways in different manners than the activities of the compounds alone and is an example of interaction in biological processes.

Intake studies tend to center on the dietary exposure, and usual intake amounts because of the high consumption of food products that contain flavonoids. It has been reported that food items like apples, oranges, red wine, coffee, legumes and tea contain high flavonoid and bioavailability and therefore clinical dosage of flavonoid-based therapies may be between 50 mg and 3 g per day.

Future Flavonoid Research Needs on Oncology.

Flavonoids have a wide range of anticancer activity in different mechanisms and signal transduction pathways, but there are still important gaps in knowledge. Even though significant advances have been achieved in the definition of biopharmaceutical properties, pharmacokinetics, and bioavailability, there is limited knowledge regarding factors that affect cellular uptake, intracellular targeting, and metabolic fate in cancerous and normal cells. There is also high expectations of translational research and

biopharmaceutical implementation due to extensive preclinical studies, but there is still an essentially dormant clinical trial environment worldwide. These high bioactivity levels at the cellular level have not always been translated into clinical usefulness and therefore the importance of mechanistic data to narrow down the structure activity relationship and context dependency is important.

Considering the strong potential of mechanistic involvement, the future research should examine the targets behind the anticancer effects of particular flavonoids in particular cancer cells. Certain questions are transcriptional effects on genes like c-Myc, survivin, VEGF, Nrf2 and pro-inflammatory cytokines; control of cell cycle by cyclins A, D and E; deregulation of Wnt signaling using Axin-2 and inhibition of multiple signaling pathways. The role of flavonoids in engaging oncogenic signaling pathways, including PI3K/AKT, MAPK, NF- -conducted by flavonoids, as well as STAT3, also merits further clarification. High-throughput screening (HTS) may select candidate flavonoids including monomeric and aglycone flavonoid and glycosylated flavonoids that each of them is committed to flavonoid-based cancer therapy **(Alquraishi & Alzeyadi, 2022).**

Conclusion

Flavonoids are polifenols biomolecules, which have exceptional anti-cancer properties, and hence they are of great interest in nutrition as well as in medical research. These are food-derived compounds, which are highly known to protect against cardiovascular problems as well as chronic diseases. In addition to these advantages, flavonoids are especially characterized by a high level of stimulation of the immunity of plants, their adaptation to different pathogenic agents and predators, and the effect on the degradation of photochemical processes. They also participate in the production of some compounds that may prevent the repair of the DNA in the cells of humans, which is essential to keep the cells intact. Besides these properties, flavonoids are also very crucial in the regulation of microbial communities and have a transcriptomic activity not only in plants but also in mammals. Flavonoids can enhance their anticancer actions in biological pathways in many ways. Some of these pathways involve activating the process of programmed cell death (apoptosis) which is normally impaired in cancer cells. Moreover, flavonoids can suppress cellular senescence mediated by p21 and prevent several cancer-related signaling pathways in cancer stem cells and counteract the activity of a microRNA-210 that is a regulator of many cancer-initiating processes induced by hypoxia. In the future it is crucial to ensure that scientific research should be directed towards investigating other signaling pathways that could be affected by flavonoids and also it is important that research should be directed towards the development of safe derivative compounds that are able to exploit their positive effects. Moreover, the comprehensive identification of target structures to be controlled by transcriptomic, proper evaluation of the real transcriptomic coverage in mammalian systems, the study of the mechanism by which flavonoids control microbial communities, and the knowledge of their species-specific toxicological characteristics are all aspects of research that require more study. These studies may result in future treatment approaches which capitalize on the potent effects of flavonoids.

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