Rutin in Cancer Treatment: Unraveling its Molecular Targets and Therapeutic Potential

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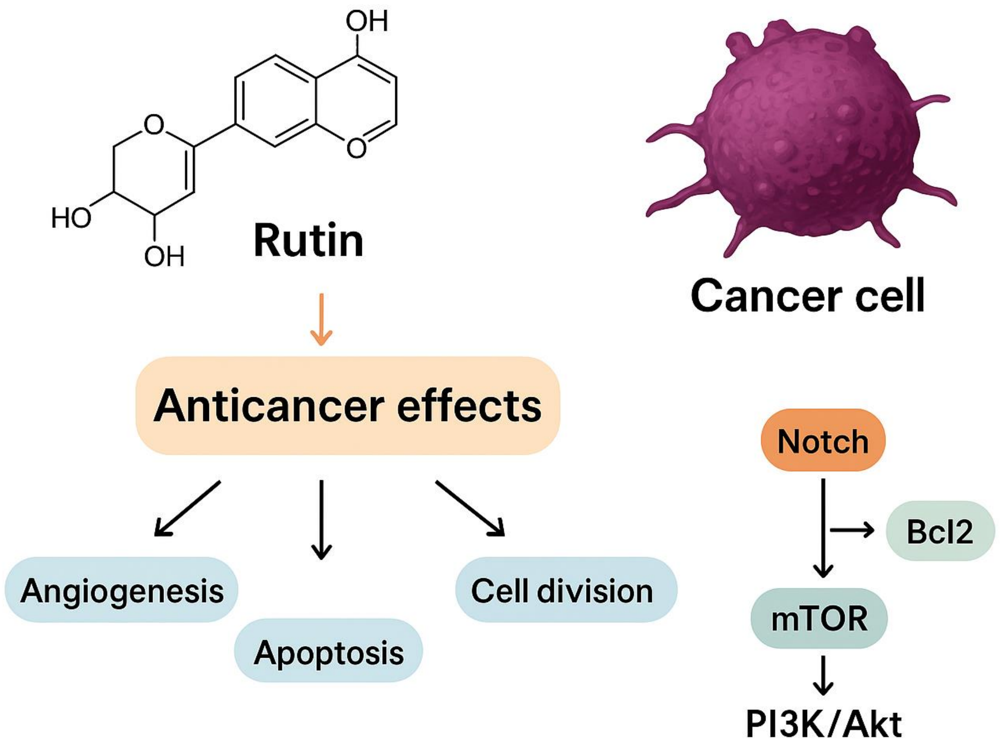
Highlights:

- Rutin, found in fruits and vegetables, has antioxidant, anti-inflammatory, and anticancer properties.
- It modulates cancer signaling pathways including angiogenesis, apoptosis, cell division, and metastasis.
- Rutin targets key cancer pathogenesis molecules like Notch signaling, Bcl2, mTOR, and PI3K/Akt.
- It inhibits cancer cell proliferation and migration by affecting pro-angiogenic factors like VEGFA.
- Rutin induces apoptosis, mitigates oxidative and endoplasmic stress, and shows potential in combination therapy.

Abstract

Cancer remains a leading cause of mortality worldwide, exacerbated by delays in diagnosis and treatment during the coronavirus disease 2019 (COVID-19) pandemic. Traditional cancer therapies, such as surgery, chemotherapy, and radiation, though effective, often entail significant side effects due to their non-specific targeting of fast-dividing cells. This has spurred interest in alternative treatments to mitigate toxicity and enhance efficacy. Natural compounds, particularly flavonoids like rutin, have emerged as promising candidates due to their low toxicity and diverse pharmacological effects. Rutin, found in various fruits and vegetables, possesses antioxidant, anti-inflammatory, and anticancer properties. This review highlights the multifaceted anticancer effects of rutin, which operates through modulation of various signaling pathways implicated in cancer initiation and progression, including angiogenesis, apoptosis, cell division, and metastasis. Rutin's ability to target key molecules and pathways involved in cancer pathogenesis, such as Notch signaling, Bcl2, mTOR, and PI3K/Akt, underscores its potential as a therapeutic agent. Moreover, rutin demonstrates anti-angiogenic effects, inhibiting the proliferation and migration of cancer cells by modulating pro-angiogenic factors like VEGFA. Rutin, a multifunctional compound, has shown potential in cancer therapy by inducing apoptosis and mitigating oxidative and endoplasmic stress in cancer cells. Combinational therapy with rutin has shown promising results in enhancing anticancer effects while minimizing adverse effects. Rutin also exhibits intriguing effects on autophagy, potentially offering novel avenues for cancer treatment. It also promotes autophagy and modulates key signaling pathways, suggesting broader applications beyond cancer therapy. Further research is needed to fully harness its therapeutic benefits.

Keywords: rutin, cancer, apoptosis, autophagy, combinational therapy, angiogenesis.



1. Introduction:

Cancer is the top cause of mortality for those under 85 years old in the US and the second-leading cause of death overall. Due to health care facility closures, changes in employment and health insurance, and anxiety about contracting COVID-19, the coronavirus illness 2019 (COVID-19) pandemic delayed the diagnosis and treatment of cancer in 2020 [1]. This is a systemic illness that affects the entire body environment by gradually disrupting metabolic, immunological, neuroendocrine, and possibly microbiological processes [2].

For patients with cancer diagnoses at various stages, surgery, chemotherapy, and radiation therapy have long been the standard of care. Chemotherapy is often administered to cancer patients either before to or following surgery. Chemotherapeutic drugs target fast-dividing malignant cells, but they also damage fast-replicating normal cells in the bone marrow, gastrointestinal system, and hair follicles. Chemotherapy damages organs and systems in a number of ways, such as direct toxicity, indirect toxicity caused by liver metabolites, immune system suppression, decreased oxygen delivery, and inflammation. The organs and systems impacted determine the particular negative consequences and damage manifestation. Chemotherapy doses are frequently restricted as a result of these adverse effects, which lowers the anti-cancer treatment's effectiveness. The treatments currently in use to lessen these side effects are insufficient because they too have negative side effects [3]. As such, there is a need to decrease the side effects to maintain full-dose chemotherapy. Thus, developing new, improved, safer, and more specific therapies is essential for cancer patients. In recent decades, several approaches have emerged to diversify cancer treatment beyond standard chemotherapy [4]. Therefore, it is essential to look for safer and more efficient chemoprevention and therapy methods in order to improve patients' quality of life and overall therapeutic outcomes. Since natural compounds have the potential to be multitargeted medications, they are of great importance in preventing related adverse effects in cancer treatment. A increasing body of research indicates that the cytostatic effects of natural products stem from their capacity to regulate oxidative stress, inflammation, autophagy, and apoptosis, hence preventing or lessening the toxicity that goes along with them [5].

The safety, low toxicity, and easy availability of phytochemicals have led to a recent surge in interest in their application in cancer therapy. It is thought that phytochemicals and their derivatives offer interesting ways to improve the effectiveness of treatment and lessen side effects in cancer patients [6]. Flavonoids can be found in fruits, grains, tea, wine, and vegetables. Flavonoids have few adverse effects and may help prevent diseases including cancer, heart disease, neurological disorders, and eye diseases that are intimately linked to oxidation and inflammation because of their antioxidant, anti-allergy, and anti-inflammatory properties. Therefore, despite the fact that flavonoids may be used as therapeutic agents to treat various illnesses, little is known about their pharmacological actions [6,7]. Ruta graveolens is the plant that initially contained the flavonoid rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnogluc8osideis). Rutin is found in the peels and pulp of citrus fruits, including grapefruit, orange, lime, and lemon. One of the greatest foods to include in your daily diet is buckwheat, according to experts. In the form of daily consumption of fruits, vegetables, and plant-based goods like wine and tea, rutin is one of the most prevalent dietary flavonoids. Flavonoids included in plant nutritional supplements have anti-inflammatory, antioxidant, and cell cycle detection properties that all help suppress cancer by preventing the growth of new cells, triggering apoptosis, and stimulating cell division. Rutin functions as a significant chemopreventive agent, as demonstrated by a number of recent investigations [8, 9]. This review presents a forward looking on rutin targets a number of signalling pathways involved in the initiation and spread of cancer, including angiogenesis, apoptosis, cell division, and metastasis. Because rutin compounds can alter these pathways, they may prove to be effective new therapeutic agents in the fight against cancer.

2. Anticancer effects of rutin

In the process of creating novel medications, natural substances have shown to be valuable research instruments. Flavonoids are naturally occurring polyphenolic compounds found in plants. Because of their biological features, flavonoids have shown great promise in the prevention and treatment of human disorders, including cancer [10]. Cancer is a diverse disease that grows aberrant cells that infiltrate and spread to other sections of the body due to unchecked proliferation and a disrupted cell cycle. The primary internal causes of cancer are oxidative stress, hypoxia, genetic alterations, and loss of apoptotic function; the external causes are associated with increasing stress, pollution, smoking, radiation, and UV radiation. The primary features of cancer cells include altered metabolism, disrupted cell cycles, frequent mutations, immune response resistance, persistent inflammation, metastasis development, and angiogenesis induction. There is growing evidence that varying degrees of mitochondrial dysfunctions and metabolic abnormalities determine cancer as a metabolic illnes. Reactive oxygen species (ROS) production, metabolic control, cell death signalling, and the production of cellular energy are all crucial functions of mitochondria. The primary metabolic changes in tumour cells include elevated aerobic glycolysis, acidosis, decreased lipid metabolism, elevated ROS production, and reduced enzyme functions. This directly results in an acidic extracellular environment that is more conducive to inflammation, increased glutamine-driven lipid biosynthesis that upregulates the pathways involved in the initiation and metastasis of tumours, decreased cardiolipin levels in membranes that impair enzyme activities, hyperpolarized mitochondria, and other effects that are correlated with the malignancy and invasiveness of cancer cells [11]. *Acalypha indica L*. contains rutin, a polyphenol with strong antibacterial, anticancer, and antioxidant qualities. HR-MS and NMR were used to characterized the rutin after it was isolated using Soxhlet extraction and purified using column chromatography and HPLC. Disc diffusion was used to measure the antibacterial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*. Breast cancer cells MDA-MB-231 and MCF-7 were used to test for cytotoxicity. Binding to human protein disulphide isomerase (PDI) was assessed using molecular docking. Rutin had the highest antibacterial activity against S. aureus, with inhibition zones ranging from 5.0 to 9.2 mm. With IC50 values of 22.31 ± 1.28 µg/mL (MCF-7) and 20.43 ± 0.81 µg/mL (MDA-MB-231) at 24 hours, it demonstrated cytotoxicity that was dose- and time-dependent. Strong affinity for human PDI was found by docking study (−5.84 kcal/mol, Ki = 52.19 µM) [29].

3. Rutin in signaling pathway

Precision medicine in cancer therapy uses molecular changes in cancer genes and related signalling pathways as a guide for novel therapeutic approaches. These days, it is well acknowledged that signalling pathways and molecular networks play crucial roles in carrying out and regulating significant pro-survival and pro-growth cellular activities. As a result, they are primarily responsible for the start of cancer as well as prospective treatments for it [12].

The molecular components of signalling networks have drawn increased attention in cancer therapy in recent years. The significance of Notch signalling in cervical cancer is rarely discussed in articles; nonetheless, in the context of aberrant cell signalling with carcinogenesis, a number of tumour types have been related to an aberrant Notch signalling cascade. The Notch signalling pathway was formerly believed to be important in regulating cell division, apoptosis, and human cancer. Several studies have shown that aberrant Notch signalling cascades are present in a variety of carcinomas. Early-stage increased Notch receptor expression and ligand-protein interaction have been linked to cervical cancer. As a result, concentrating on these essential Notch signalling pathway elements could be a helpful tactic for creating a better, more efficient cervical cancer therapy regimen [13].

According to Lins et al. (2020), rutin makes tumour suppressor proteins such p21, FOXO3a, KIP1, and CIP/WAF more expressed. The higher expression of these identified tumour suppressor proteins in cancer cells provided additional encouraging evidence for growth halt. Rutin treatment prevented cisplatin (CP)-induced ovarian damage in a mouse model by reducing antioxidant activity and the phosphorylation of FOXO3a and PTEN [14]. In addition, Talebi et al. (2021) evaluated the effects of rutin on Bcl2, cleaved caspase, cleaved PARP, and mTOR expression in a rat model of surgically induced endometriosis. In order to prevent AkT phosphorylation, they reported that rutin interfered with the mTORC2 complex and the PI3K-ATP binding domain. Rutin induced programmed cell death by altering the expression levels of caspase, Bax, and Bcl-2 [15]. Rutin's antitumoral effect at various doses on EAC solid tumours via AgNOR (argyrophilic nucleolar regulatory region). This resulted in a decrease at 25 mg concentration in the expression of the signalling pathway PI3K/AKT/mTOR, which was important for the cell cycle at the cellular level [16].

4. Rutin in angiogenesis

The creation of new blood vessels, or angiogenesis, is a dynamic and intricate process that is controlled by a variety of pro- and anti-angiogenic chemicals. It is essential for the growth, invasion, and metastasis of tumours [17]. Numerous pro-angiogenic molecules, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2), platelet derived growth factor (PDGF), apelin (APLN), ephrins, angiopoietins, and chemokines, as well as their corresponding receptors, are known to stimulate vessel formation in tumours. These factors efficiently cooperate at various stages of tumour angiogenesis because they are frequently produced simultaneously [18].

The anticancer effects on MDA-MB-231 and MCF-7 breast cancer cell lines' proliferation, metastasis, and angiogenesis have been assessed by Hajimehdipoor et al. [19]. They came to the conclusion that rutin both promoted cell migration and proliferation. Additionally, rutin downregulated CDH1 and THBS1 and raised MKI67, VIM, CDH2, FN1, and VEGFA. It also boosted the expression of the proteins N-cadherin and VEGFA and lowered that of E-cadherin and thrombospondin 1. According to their research, rutin can promote pro-angiogenic activity, migration, and proliferation in two distinct breast cancer cell lines through an EMT-related mechanism. Rutin might cause apoptosis in HeLa cancer cells in a dose-dependent way by suppressing the expression of E6 and E7 mRNA and elevating pRb, Bax/Bcl-2, and p53, with little harmful effects on normal cells, according to research by Pandey et al. [20]. The key factors causing cervical cancer to proceed are E6 and E7 (HPV oncoplayers), who also have a significant early-stage function in carcinogenesis including proliferative signalling maintenance, tumour suppressor escape, telomerase activation, induction of angiogenesis, and metastasis. Conversely, rutin's ability to downregulate or suppress the production of E6 and E7 may offer a viable and secure treatment option for cervical cancer.

5. Rutin in apoptosis

Cancer is a complicated set of diseases mostly brought on by genetic abnormalities, apoptosis, escape, and changes in signalling pathways. Abnormal cell division/proliferation and delayed programmed cell death are its defining characteristics. A range of morphological characteristics are seen in apoptotic cells, including cell shrinkage, blebbing of the plasma membrane, condensation of chromatin, and finally DNA fragmentation. The development of cancer research has shown that one of the main factors contributing to the genesis and spread of cancer is apoptosis. Furthermore, a number of studies have demonstrated a clear correlation between medication resistance, tumour spread, and malignant transformation and abnormalities in the apoptotic pathway. There are two main signalling routes that can control the onset of apoptosis: the mitochondria-dependent intrinsic system and the extrinsic pathway involving death receptor. The main molecules regulating these pathways include caspases and members of the Bcl2 family. In addition to being the source of issues, apoptosis is an important target for cancer treatment and has been used in clinical settings for numerous treatment approaches [21].

At a minimum concentration of 12.5 μg/mL, rutin strongly inhibits triple negative breast cancer (TNBC) cells when combined with chitosan to form a multifunctional biopolymer known as rutin-chitosan nanoconjugate. As a result, they were able to demonstrate cell death by apoptosis experiments, such as the use of dual labelling and nuclear fragmentation of treated TNBC cells. According to their findings, the rutin-chitosan nanoconjugate that was created was successful in inhibiting TNBC cells, and this is seen as a potentially fruitful new avenue for cancer treatment [22]. Additionally, by modifying genes linked to apoptosis (Bax, Bcl2) and the cell cycle (Cyclin D1 and CDK4), rutin significantly downregulated the expression of Notch-1 and Hes-1 and induced apoptosis, thus stopping the progression of the cell cycle. Thus, it was determined that rutin might be regarded as a strong therapeutic agent for the treatment of cervical cancer [23].

6. Rutin in endoplasmic and oxidative stress

One of the most important biological processes in the advancement of cancer is oxidative stress (OS), which is characterised as a redox imbalance favouring oxidant burden. Because cancer cells typically have greater oxidant levels, controlling redox state with pro-oxidant therapy and/or antioxidant therapy proposes a dual therapeutic approach [24].

According to Suganya et al. [9], endoplasmic stress is a crucial factor in apoptosis that is brought on by cell death. Both the rutin and doxorubicin combination and the two drugs alone have been used to assess the targeted TNBC. Rutin therapy alone was able to up-regulate the ER stress genes ASK 1 and JNK, as well as growth arrest and DNA damage resinses. According to their research, rutin by itself is more potent than doxorubicin, which causes ER stress-mediated cell death. The fact can be used to TNBC's advantage by using rutin as a medication instead of the toxic side effects of chemical-based treatments.

7. Rutin in combinational therapy

Recently, a lot of researchers have focused on combination therapy—the main therapeutic technique for cancer therapy that involves combining two or more therapeutic medications. Antioxidant combinations have been shown to boost antiproliferative and anticarcinogenic effects when compared to monotherapy in cancer treatment. Strong anticancer medication rutin functions by stopping the development of cancer cells and the production of proteins that lead to the spread of tumours [25]. According to Hoai et al. (2020), rutin prenanoemulsion has the potential to suppress cancer cell lines, such as the A549 lung and colon cancer cell lines. Furthermore, rutin prevented the alteration of proteins by lipid peroxidation products through its antioxidant-promoting actions. Moreover, it led to the formation of rutin-protein adducts, which support the Nrf2/ARE antioxidant pathway, intracellular and extracellular signalling, and so on, all of which help to lessen the effects of UV-induced oxidative stress [26]. However, research by Suganya et al. (2022) suggested that rutin is an effective treatment for TNBC; the results clearly showed that ER stress is a critical factor in cell death-induced apoptosis, and studies on gene expression amply supported these conclusions; as a result, rutin can be used to target TNBC and can be used alone even in the absence of doxorubicin. As a result, rutin can be used to treat TNBC without causing any of the negative side effects that come with drugs that contain chemicals [9].

8. Rutin in autophagy

The process of autophagy involves a cell ingesting its cytoplasmic proteins or organelles, encapsulating them in vesicles, and then fusing with lysosomes to produce autophagic lysosomes, which then breakdown the contents and replenish particular organelles. An important factor in atherosclerosis is autophagy. Inhibiting the PI3K/Akt signaling pathway promotes autophagy and reduces the generation of foam cells. By promoting macrophage autophagy, inhibition of the PI3K/Akt/mTOR axis can protect against lipid buildup and polarization change. Moreover, the development of atherosclerotic plaques is linked to mTOR. Rapamycin, a mTOR inhibitor, can limit mTOR activity in macrophages while simultaneously reducing plaque inflammation, whereas mTOR stimulates the development of foam cells. Furthermore, by boosting autophagy, mTOR inhibition can aid in the stabilization of atherosclerotic plaques. Plaque inflammation can be reduced by inhibiting the PI3K/Akt/mTOR pathway, which also enhances foam cell cholesterol export and encourages autophagy [27].

Li et al. (2022) have found that rutin could both improve and decrease the production of reactive oxygen species (ROS) and inflammatory factors in ox-LDL-induced M2 macrophages. Moreover, oil red O staining suggested that rutin reduced the formation of foam cells. Rutin also decreased the p62 expression while raised the quantity of autophagosomes and the LC3II/I ratio. Rutin may also strongly blocked the PI3K/ATK signaling pathway. They also concluded that rutin has the potential to cure atherosclerosis because it suppressed foam cell production and ox-LDL-mediated macrophage inflammation by promoting autophagy and modifying PI3K/ATK signaling [28].

9. Conclusion

Cancer remains a significant health challenge globally, with delays in diagnosis and treatment exacerbated by the COVID-19 pandemic. Traditional cancer treatments such as chemotherapy, while effective, often come with significant side effects due to their non-specific targeting of both malignant and normal cells. This underscores the urgent need for safer and more efficient therapies to improve patient outcomes and quality of life. Natural compounds, particularly flavonoids like rutin, have garnered attention for their potential in cancer therapy due to their multitargeted properties and low toxicity. Rutin, found abundantly in various fruits and vegetables, has shown promising anticancer effects through its ability to modulate various cellular pathways involved in cancer initiation, progression, and metastasis. Studies have demonstrated rutin's efficacy in targeting key signaling pathways implicated in cancer development, such as Notch signaling, apoptosis regulation, angiogenesis, and oxidative stress. By modulating these pathways, rutin exhibits antitumoral effects, inhibiting cell proliferation, inducing apoptosis, and suppressing angiogenesis. Furthermore, rutin has shown potential in combination therapy, enhancing its anticancer effects when used alongside other therapeutic agents. Its ability to target cancer cells while sparing normal cells suggests it as a promising candidate for cancer treatment with fewer adverse effects. Moreover, rutin's role in autophagy modulation presents additional avenues for therapeutic intervention, particularly in diseases like atherosclerosis where autophagy dysregulation plays a significant role.In conclusion, the multifaceted anticancer effects of rutin make it a compelling candidate for further research and development in cancer therapy. Its natural origin, low toxicity, and potential for combination therapy highlight its significance in the quest for safer and more effective cancer treatments. Continued investigation into rutin and other phytochemicals may pave the way for innovative and personalized approaches to cancer management, ultimately improving patient outcomes and quality of life.

Notes

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Conflicts of Interest: The authors have no potential conflicts of interest to disclose.

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Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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