INTERNATIONAL DEVELOPMENT PLANNING REVIEW
ISSN:1474-6743 | E-ISSN:1478-3401

NARINGENIN'S JOURNEY IN MODERN MEDICINE: FROM CITRUS FLAVONOID TO VARIOUS ANTI-CANCER ACTIVITIES

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Abstract

Background: Naringenin, a bioactive flavonoid mainly present in citrus fruits, has attracted considerable interest because of its wide range of pharmacological benefits, such as antioxidant, anti-inflammatory, anti-cancer, cardioprotective and anti-diabetic effects. Despite its promising therapeutic potential, naringenin faces challenges related to its poor bioavailability and rapid metabolism.

Methods: Recent advancements in drug delivery systems, including nanoformulations and liposomes, aim to overcome these limitations and enhance its clinical efficacy. Preclinical studies have demonstrated its efficacy in various disease models, like cancer, cardiovascular (CV) diseases, diabetes, and neurodegenerative disorders.

Results: Naringenin has exposed efficacy in preclinical models for numerous diseases, highlighting its potential in disease treatment, particularly in cancer treatment. The advanced drug delivery systems help advance its clinical efficacy by increasing its bioavailability and stability.

Conclusion: This review attempts to bridge the gap between laboratory research and clinical application of naringenin's anti-cancer effects by thoroughly analyzing existing knowledge and future potential.

Keywords:

Naringenin, Citrus flavonoid, Anti-cancer, Apoptosis, Cell cycle arrest, Signaling pathway.

Introduction

Plants are packed with a diverse range of tiny, beneficial compounds called flavonoids. These flavonoids are polyphenols and they're found in many of the fruits, vegetables and grains we consume regularly. These natural substances have demonstrated various biological and medicinal effects (Cavia-Saiz et al., 2010). Naringenin, is a naturally occurring flavonoid with a molecular formula of $C_{15}H_{12}O_5$ and a molecular weight of 272.25 g/mol. Naringenin, possesses a distinctive flavanone skeleton Figure 1.

This structure features three hydroxyl groups positioned at the 4^{th}, 5^{th}, and 7^{th} carbon positions, along with a single chiral center at the 2^{nd} carbon atom (Wang et al., 2014). Naringenin is mostly present in citrus fruits like grapefruits, oranges and tomatoes has attracted a lot of scientific attention (Arafah et al., 2020). Flavonoids are mainly found in almost all citrus fruits, but their amount varies depending on the type and variety of the fruit, harvest time, and environmental conditions. Table 1 shows the sources and levels of naringenin (Amin et al., 2020).

Historically, the health benefits of citrus fruits have been well recognized, with traditional medicine utilizing them for their purported health-promoting properties (Tocmo et al., 2020). Naringenin, as a major constituent of these fruits, has been identified as one of the key compounds contributing to these beneficial effects (Singh et al., 2023).

The hierarchy and significance of bioactive compounds found in citrus fruits**Error! Reference source not found.**, emphasizing their roles in promoting health and combating oxidative stress. Citrus fruits are renowned not only for their flavors but also for their abundance

of various bioactive compounds (Saini et al., 2022). Polyphenols are distinguished by their potent antioxidant properties, playing a crucial role in health maintenance. A significant subclass of polyphenols, flavonoids are celebrated for their role in reducing inflammation and promoting overall well-being (Rathod et al., 2023). Flavanones, a unique group within flavonoids, are known for their ability to combat oxidative stress effectively (Speisky et al., 2022). Prunin, a glycoside, also present in citrus fruits with its unique properties (Hădărugă and Hădărugă, 2023). Naringenin is recognized for its powerful antioxidant effects and substantial health benefits (Cavia-Saiz et al., 2010).

Over the years, research has explored naringenin's broader pharmacological effects (Arafah et al., 2020). Because of the compound's strong anti-inflammatory, anti-cancer, cardioprotective and anti-diabetic qualities, it is a good fit for several therapeutic uses in modern medicine Figure 3 (Singh et al., 2023).

The interest in naringenin's therapeutic potential can be traced back to early 20th-century studies that identified its strong antioxidant capabilities. A disruption in the body's regular balance of antioxidants and free radicals results in oxidative stress, is a major factor in the appearance of many chronic disorders. These illnesses encompass cancer, CV diseases, and neurodegenerative disorders (Sharifi-Rad et al., 2020). Naringenin's free radical-scavenging properties and strengthen the body's natural antioxidant defenses system positions it as a powerful natural remedy for oxidative stress-related conditions. Naringenin's ability to combat inflammation is especially intriguing, as chronic inflammation is a major contributor to many diseases. Research indicates that naringenin may reduce inflammation by inhibiting the synthesis of chemicals known as pro-inflammatory cytokines. It may also interfere with inflammatory signaling pathways like nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK). This dual approach could potentially reduce inflammation and offer therapeutic benefits in various conditions, including arthritis, colitis, and CV diseases (Al-Khayri et al., 2022).

Research revealed that cancer is one of the leading causes of death globally (9.9 million) (Lin and Park, 2023). Naringenin has demonstrated promising anti-cancer effects in various *in vitro* and *in vivo studies*. Research suggests naringenin anti-cancer properties, includes inducing cell death (apoptosis), slowing down cell growth (proliferation) and preventing the spread of cancer cells (metastasis) in various cancer cell lines, including breast, prostate, liver and colon cancers (Motallebi et al., 2022). Naringenin can be used as a supplementary therapy in the treatment of cancer since it can interfere with important signaling networks like PI3K/Akt and MAPK, which are essential for the proliferation and viability of cancer cells (Issinger and Guerra, 2021).

Beyond antioxidant, anti-inflammatory, and anti-cancer properties, naringenin also demonstrates significant cardioprotective effects (Yang et al., 2022). CV diseases, including atherosclerosis, hypertension, and myocardial infarction, remain leading causes of death globally (Thomas et al., 2018). In 2017, more than 17 million people died from cardiovascular diseases (CVD), nearly double the number of cancer-related deaths (Qu et al., 2024). By 2019, this number had increased to 17.9 million (Luengo-Fernandez et al., 2024). Naringenin's positive impact on

heart health is linked to its ability to regulate cholesterol levels, maintaining healthy blood pressure, and safeguard the heart muscle from damage (Alam et al., 2014). Clinical studies have explored the effects of naringenin on blood lipids. Consuming naringenin may raise HDL cholesterol while concurrently lowering triglycerides, LDL cholesterol and total cholesterol. These changes in cholesterol levels could contribute to a reduced risk of developing atherosclerosis and subsequent CV events (E Orhan et al., 2015).

Chronic diabetes mellitus, which is characterized by elevated blood glucose concentrations and a compromised response to insulin, poses a serious threat to public health (Kharroubi and Darwish, 2015). Naringenin also exhibits promising anti-diabetic properties (Rajappa et al., 2019). Research indicates naringenin's ability to regulate blood sugar level and insulin response, positioning it as a promising candidate for diabetes management (Murugesan et al., 2020). It may act by inhibiting carbohydrate-digesting enzymes, enhances the expression of glucose transporters and modulates insulin signaling pathways, thereby reducing blood glucose levels and improving overall metabolic health (Sok Yen et al., 2021).

Despite the extensive research highlighting naringenin's therapeutic potential, its clinical application faces several challenges. One of the primary limitations is its poor bioavailability, which is attributed to its poor soluble form and fast metabolism in the human system (Gera et al., 2017). Recent advancements in drug delivery systems, such as the development of nanoformulations, liposomes and other novel carriers, aim to enhance the bioavailability and therapeutic efficacy of naringenin. These strategies hold promise in overcoming the bioavailability barrier and translating the compound's preclinical success into clinical reality (Wang et al., 2017). The goal of this review is to give a thorough overview of naringenin's evolution in modern medicine from a citrus flavonoid to a possible anti-cancer drug.

Historical background

Citrus fruits, particularly grapefruit, have long been associated with a characteristic bitterness. This bitterness is primarily attributed to naringenin, which was likely linked to its medicinal properties in traditional practices (Li et al., 2023). Traditional uses of citrus fruits which contain noteworthy amounts of flavanones used in various cultures for medicinal purposes highlight the historical significance of naringenin (Mitra et al., 2022). Naringenin, was first identified by Power and Tutin in 1907, was initially classified as a chalcone. Later research, likely by Dean in 1963 or around that time, led to a more precise understanding of its chemical structure. Currently, no official recommended daily intake exists for naringenin or flavonoids in general (Zaidun et al., 2018). The interest in naringenin was initially driven by its potent antioxidant properties. Studies have shown that naringenin possesses strong free radical scavenging abilities, thereby mitigating oxidative stress and safeguarding cells from damage. This early recognition of naringenin's antioxidant capacity spurred further investigations into its potential health benefits (Cavia-Saiz et al., 2010). In addition to its antioxidant, anti-inflammatory and anti-cancer effect, naringenin's cardioprotective effects have also been extensively studied.

Challenges and limitations

Despite its therapeutic potential, naringenin faces several challenges, including poor bioavailability (15% oral bioavailability), delayed metabolism, and low water solubility (475 mg/L) (Joshi et al., 2018). Strategies to overcome these limitations include the development of nanoformulations, liposomes, and other advanced drug delivery systems to enhance its bioavailability and therapeutic efficacy.

Anti-cancer potential

Cancer, characterized by uncontrolled cell proliferation and metastasis, is a leading cause of global mortality. The Centers for Disease Control and Prevention reported 606,520 cancer deaths in 2020 and expected over 1.8 million new cases that year. Every year, the world sees close to 20 million new cancer diagnoses and roughly 10 million cancer-related fatalities (Narayana et al., 2024). Conventional cancer therapies often come with severe side effects and limitations, highlighting the need for more effective and safer alternatives (Pucci et al., 2019). Chemotherapy drugs work by helping cancer cells die through a process called apoptosis. However, these synthetic drugs often come with high toxicity, which limits their use. In contrast, plant-based treatments are usually less toxic and still offer strong medicinal benefits (Durgo et al., 2013; Ravishankar et al., 2013) Among the different types of flavonoids, naringenin, which is found in grapefruit and oranges, has been widely discussed for its potential to fight cancer (Ekambaram et al., 2008).

Mechanisms of action

Naringenin fights cancer in several ways: it causes cancer cells to die through a process called apoptosis, stops the cancer cells from multiplying and prevents the cancer from spreading to other parts of the body (Motallebi et al., 2022). Naringenin influences important pathways like PI3K/Akt, MAPK and NF-κB that control cell survival and death. Research has shown it is effective against different cancers, including breast, prostate, liver, and colon cancer (Memariani et al., 2021).

A short overview of the processes by which naringenin inhibits cancer via induction of apoptosis, regulation of the cell cycle, prevention of angiogenesis, suppression of metastasis, modification of signaling pathways and antioxidant action is shown in the Table 2.

Induction of apoptosis

Cancer development involves two main issues: uncontrolled cell growth and the failure of cells to die when they should (apoptosis). Normally, genes tightly control both cell growth and death. Some genes promote cell growth (oncogenes), while others suppress it (tumor suppressor genes) (Reed, 1999). Cancer cells pose a significant threat to human health. Thankfully, our bodies have a built-in mechanism for eliminating them: apoptosis, also known as programmed cell death. This critical process ensures the removal of unwanted or damaged cells, including cancerous ones. Apoptosis is strictly regulated by certain genes that function via two primary pathways: the intrinsic and extrinsic pathways.

The Intrinsic pathway: This internal "self-destruct" mechanism involves genes like Bcl-2-Associated X Protein (BAX), Bcl-2 antagonist/killer protein (BAK), Apoptotic Protease

Activating Factor 1 (APAF-1) and a family of enzymes called caspases. When activated, these genes trigger a cascade of events leading to the controlled dismantling of the cancer cell.

The Extrinsic pathway: This pathway relies on external signals from outside the cell. Genes like Tumor necrosis factor-related apoptosis inducing ligand (TRAIL), TNF receptor-associated death domain protein (TRADD), Fas-associated death domain protein, and Fetal alcohol syndrome (FAS) are involved in receiving these signals and initiating the apoptosis process in response to external threats like immune system attacks (Kiraz et al., 2016).

Naringenin promotes cell death by increasing the levels of proteins that trigger apoptosis, such as BAX, caspases and cytochrome c. At the same time, it reduces the levels of proteins that inhibit apoptosis, like Bcl-2 (Timucin and Basaga, 2017). This imbalance tips the scales towards cell death. As a consequence, the membranes of the mitochondria (the cell's power plants) lose their electrical charge (depolarize), allowing cytochrome c to leak out and activate caspases, ultimately leading to cell death (Parsons and Green, 2010).

Studies have shown that flavonoids, can trigger programmed cell death (apoptosis) in cancer cells. This process often involves the activation of specific enzymes called caspases, particularly caspases 3 and 9. Additionally, the expulsion of cytochrome c from the mitochondria appears to be involved. According to these results, flavonoids could eradicate cancer cells by triggering the intrinsic apoptotic mechanism (Kopustinskiene et al., 2020). It has been demonstrated that naringenin affects both the internal (mitochondrial) and exterior (death receptor) apoptotic pathways, causing cancer cells to undergo programmed cell death (apoptosis). This is supported by research demonstrating that naringenin can halt the uncontrolled growth of various cancer cell lines, including those expressing ER-α or ER-β receptors, like K562 cells, by triggering apoptosis (Oršolić and Jazvinšćak Jembrek, 2022).

Cell cycle arrest

The growth of a cell is a well-planned process that is separated into discrete stages called cell cycle. These stages include G1 (growth 1), S (synthesis), G2 (growth 2) and M (mitosis). CDKs are a class of enzymes that carefully control each stage of cell cycle. For these CDKs to be active, they need companion proteins known as cyclins. It's interesting to note that distinct cyclin and CDK combinations are necessary for different cell cycle stages. To ensure proper cell cycle progression, another set of regulatory molecules called CDK inhibitors, including p21, p27 and p57, act as a braking system, preventing CDKs from functioning prematurely. Gene alterations, or mutations, can interfere with cyclin and CDK synthesis and activity.

This disruption can lead to uncontrolled cell division, a hallmark of cancer. It's interesting to note that laboratory research indicates naringenin has significant use in the treatment of cancer. It is likely to work by stopping the cell cycle during the G0/G1 stage and causing apoptosis (Wang et al., 1999). Research has demonstrated that naringenin can prevent K562 human leukemia cells from proliferating, especially when the cells are in the G0/G1 stage of the cell cycle. This inhibition might be achieved by elevating p21/WAF1 levels, independent of p53 signaling. Additionally, naringenin appears to suppress the activity of cyclin E/CDK2 and cyclin A/CDK2 complexes (Arul and Subramanian, 2013).

Inhibition of angiogenesis

The growth and spread of tumors heavily rely on the establishment of new blood vessels called angiogenesis. Angiogenesis delivers essential nutrients to cancer cells, fueling their expansion. A delicate balance exists between proteins that promote and inhibit angiogenesis, ultimately dictating tumor progression. VEGF, basic fibroblast growth factor, interleukin-8 (IL-8) and transforming growth factor-beta (TGF-β) are a few important factors that encourage the creation of blood vessels Lugano et al., 2020; Ziyad and Iruela-Arispe, 2011).

Anti-angiogenic factors, which prevent the establishment of new blood vessels, include thrombospondin-1, angiostatin and endostatin (Mirossay et al., 2018). Flavonoids, including naringenin, also demonstrate effectiveness in inhibiting angiogenesis, further supporting their potential role in cancer therapy. Naringenin reduces angiogenesis by suppressing the production of VEGF and its receptor (VEGFR) (Li et al., 2016). This disrupts the multiplication and movement of endothelial cells, essential for forming new blood vessels. Additionally, naringenin downregulates the TGF-β pathway, further limiting the spread (metastasis) and invasion of pancreatic cancer cells. By inhibiting angiogenesis, naringenin essentially starves tumors of the blood supply and nutrients they need to grow and spread (Lou et al., 2012).

Suppression of metastasis

Cancer's ability to spread to other organs, known as metastasis, remains a significant hurdle in treatment. Naringenin tackles metastasis by blocking the production and action of enzymes called MMPs, especially MMP-2 and MMP-9. These enzymes break down the surrounding tissue, allowing cancer cells to move and invade other areas. Naringenin inhibits the capacity of cancer cells to penetrate neighboring tissues and migrate to other organs by decreasing MMP activity, which may prevent metastasis (Chen et al., 2018).

Modulation of signaling pathways

Inhibiting the PI3K/Akt pathway

Naringenin targets multiple signaling pathways critical for cancer cell survival and proliferation, including the PI3K/Akt, MAPK, and Wnt/β-catenin paths. By decreasing the phosphorylation of Akt, a key protein for cell growth and survival, it inhibits the PI3K/Akt path. This inhibition leads to decreased cell survival and increased apoptosis.

Modulating the MAPK pathway

Naringenin also influences the MAPK pathway by inhibiting the stimulation of ERK, JNK, and p38 MAPKs, ultimately resultant in lower cell proliferation and increased apoptosis.

Suppressing the Wnt/β-catenin pathway

Wnt/β-catenin is a protein that is essential for cell survival and multiplication. Naringenin reduces its levels. This reduced level hinders cancer cell survival and multiplication (Motallebi et al., 2022).

These multifaceted actions make naringenin a promising candidate for cancer therapy, potentially offering a safer and more effective alternative to conventional treatments. Many research investigations have demonstrated the effectiveness of naringenin in preventing the development and spread of malignancies in a variety of cancer variants.

Naringenin in different types of cancer

Naringenin in breast cancer

Zhao et al., 2019 studied the anticancer effects of naringenin on triple-negative human breast cancer cells (MDA-MB-231). They claimed that naringenin exhibited dose and time dependent inhibition of cell proliferation. Reduced cell growth has been linked to increased apoptosis, a notable concentration of cells in the sub-G1 stage (indicating cell death) and an arrest of the cell cycle in the G0/G1 stage. Naringenin treatment reduced tumor incidence and tumor burden by varying concentration. Additionally, naringenin modulated biochemical and antioxidant markers associated with inflammation, potentially contributing to its anti-cancer activity. qRT-PCR study confirmed that naringenin stimulate cell death via a mitochondrial-mediated apoptotic mechanism. Their findings collectively demonstrated the capacity of naringenin prevent the growth of cancer cells by causing an arrest of the cell cycle and encouraging apoptosis. Additionally, it appears to regulate mitochondrial apoptotic signaling and exhibits anti-inflammatory effects in DMBA-induced breast cancer.

James et al., 2024 investigated naringenin-7-O-glucoside's potential to target Triple-Negative Breast Cancer (TNBC) cells. A dose-related cytotoxic impact was seen on TNBC cells by the MTT assay, with an IC50 of 233.56 µg/µL. Notably, this cytotoxicity was slight on healthy Vero cells. Furthermore, wide DNA fragmentation analysis confirmed the compound's ability to induce apoptosis. Additionally, compared to control samples, TNBC cells treated with naringenin-7-O-glucoside exhibited a significant decrease in Epidermal Growth Factor Receptor (EGFR) levels. They concluded that naringenin-7-O-glucoside may interfere with key signaling pathways, like the EGFR pathway, that are crucial for cancer cell proliferation and survival.

Effat et al., 2024 investigated the combining Doxorubicin and naringin affects breast cancer cells. They focused on the JAK/STAT signaling mechanism, which is involved in the division and proliferation of cells. The team evaluated the cytotoxicity (cell death) of these compounds on MCF-7 breast cancer cells. Their findings revealed that the combination was more effective than either compound alone in inhibiting both MCF-7 cell growth and migration. This combination significantly decreases in the expression of STAT3, JAK1, Bcl-2, Survivin and VEGF, all of which promote cancer progression. Conversely, BAX levels, associated with cell death, increased. Their study concludes that combining Doxorubicin and naringin could be a more potent strategy for treating breast cancer.

Ramya Devi et al., 2023 investigated the potential of naringenin encapsulated chitosan nanoparticles to cause cell death in breast cancer cells (MDA-MB-231). The investigators treated the MDA-MB-231 with varying concentrations of naringenin and naringenin encapsulated chitosan nanoparticles. Using MTT cytotoxicity and BrdU cell proliferation assays, they observed that naringenin encapsulated chitosan nanoparticles significantly reduced MDA-MB-231 cell proliferation (by 37% and 29% after 24 and 48 hours, respectively). Therapy with naringenin encapsulated chitosan nanoparticles also led to a notable upgrade in NO content and XOD activity, alongside a downgrade in XDH levels and a rise in ROS levels. This increase in ROS was confirmed by fluorescent imaging of cells treated with naringenin encapsulated chitosan

nanoparticles, suggesting the induction of apoptosis. Furthermore, Western blot analysis revealed that high concentrations of naringenin encapsulated chitosan nanoparticles enhanced the stimulation of procaspase-3 in contrast to free naringenin. According to their research, large concentrations of chitosan nanoparticles encapsulated in naringenin can enhance procaspase-3 stimulation and oxidative stress, which would ultimately cause cancer cells to die by apoptosis and exhibit decreased cell division.

Jalalpour Choupanan et al., 2023 examined the potential for a synergistic effect between quercetin and fisetin with naringenin on breast cancer cells (MCF7 and MDA-MB-231 cell lines). Breast cancer cells were treated with various dose of quercetin, fisetin, or combinations with naringenin. Their study revealed a synergistic effect (combination index < 1) when quercetin or fisetin were combined with naringenin in both cell lines. These combined treatments significantly outperformed single treatments in reducing cell growth, suppressing migration and inducing apoptosis. Further analysis of gene expression showed an increase of miR-1275 and a decrease of miR-27a-3p. Their findings suggest quercetin and fisetin enhance the anti-proliferative and anti-migratory action of naringenin in MCF7 and MDA-MB-231 breast cancer cells.

Yıldırım et al., 2022 designed a novel drug delivery system for naringenin using pH and thermo-sensitive smart polymeric nanoparticles (NarSPNPs) to enhance its bioavailability and effectiveness against breast cancer. Physicochemical characterization confirmed the stability of NarSPNPs. Cytotoxicity and IC50 value demonstrated their efficacy as an anti-breast cancer agent with no adverse effects on human epithelial cells. Flow cytometry study further exposed that apoptosis is induced by NarSPNPs therapy.

Rhman et al., 2022 studied the possible synergistic properties of Quercetin and Naringenin (CoQN) in MCF-7 breast cancer cells. Treatment by CoQN resulted in increased cytotoxicity when compared to either Quercetin or Naringenin alone. This was observed by a decline in the production of the Bcl-2 gene, indicating a reduction in cell survival factors. Additionally, CoQN treatment led to a greater boost in caspase 3/7 activity, a key enzyme involved in apoptosis, compared to individual treatments. Furthermore, CoQN caused a more pronounced enhanced in lipid peroxidation, a marker of oxidative stress and a greater reduction in MMP compared to quercetin or naringenin alone. Their findings suggest that CoQN treatment demonstrated significantly increased cytotoxicity and reduced cell viability through a synergistic effect, likely mediated by enhanced oxidative stress, reduced MMP and increased caspase 3/7 activity, ultimately leading to apoptosis in MCF-7 cells.

Ke et al., 2017 examined the impact of naringenin on mammary tumor growth using both cell cultures and obese mice. naringenin exerted anti-cancer effects on E0771 mammary tumor cells, inhibiting their growth, activating AMP-activated protein kinase (AMPK), reducing CyclinD1 expression and ultimately inducing cell death. Analysis of treated mice revealed higher naringenin concentrations within tumors compared to surrounding mammary adipose tissue. Naringenin treatment resulted in lower body weight, decrease in adipose tissue mass, the amount of fat stored in the body, reduction in the size of individual fat cells. It correspondingly decreases in the production of inflammatory cytokines mRNA levels in both mammary and perigonadal fatty

tissues. When compare to a high-fat diet, naringenin slowed tumor growth initially but did not change the final tumor weight. The researchers concluded that naringenin may exert its effects by reducing fat and inflammation within adipose tissue, leading to a modest inhibition in tumor development.

Naringenin in cervical cancer

Lin et al., 2020 studied the anti-proliferative effects of naringenin on various cervical cancer cell lines (C33A, SiHa and HeLa). Their findings demonstrated that naringenin significantly reduced cell viability in all three cell lines, with IC50 values of 745 μM, 764 μM and 793 μM for C33A, SiHa and HeLa cells, respectively. Experiments using Annexin V FITC staining and immunoblotting techniques demonstrated a noteworthy increase in apoptosis in cells treated with higher naringin concentration. Their findings suggest that naringin kills cancer cells (CC cells) by inducing stress in the endoplasmic reticulum (ER). Naringin treatment triggered an increase in the expression of proteins that sense ER stress. This included the phosphorylation of eIF2α, a key protein involved in translation initiation. Additionally, naringin activated CHOP, a protein associated with apoptosis, alongside other pro-apoptotic proteins like PARP1 and caspase-3. Notably, pre-treating the cells with salubrinal, an inhibitor of ER stress, prevented the apoptotic effects of naringin. Naringenin further impaired the β-catenin signaling route by reducing the levels of both β-catenin and its phosphorylated form (Ser576) and GSK-3β (Ser9). Additionally, naringenin triggered arrest of cell cycle in the G0/G1 stage, a critical checkpoint for cell division. This effect was achieved through the upregulation of cell cycle inhibitor proteins p21/cip and p27/kip. According to their research, naringin inhibits cervical cancer cells through two different mechanisms: i) inducing apoptosis via ER stress and ii) disrupting the Wnt/β-catenin signaling route, causing to cell cycle arrest at the G0/G1 stage.

Naringenin in colon cancer

Zeya et al., 2022 investigated how colon cancer cell lines HCT116 and SW480 responded to the combined effects of Diosmin and Naringenin (DiNar), focusing on apoptosis and inflammatory pathways. Their study revealed that DiNar treatment acted synergistically, increased cytotoxicity, chromatin condensate, DNA breakdown and cell cycle arrest in the G0/G1 stage. The Annexin V-FITC/PI apoptosis study indicated a higher amount of cells suffering apoptosis in the DiNar treated group. Additionally, DiNar treatment more effectively regulated the expression of apoptosis and inflammatory markers. In conclusion, their findings suggest that DiNar could be more effective than Diosmin and Naringenin individually. Their results imply DiNar combination holds promise as a future treatment option for colon cancer. When compared to the colon cancer medications now on the market, it might help as a safer chemotherapy option with fewer or no adverse effects.

Naringenin in colorectal cancer

Wang et al., 2024 explored the biological properties and cellular effects of naringenin, focusing on its potential antitumor effect against colorectal cancer (CRC). Their study showed combination of naringenin and 5-fluorouracil inhibits CRC cell proliferation and promotes apoptosis. Naringenin was shown to trigger AMPK phosphorylation and help mitochondrial fusion

in CRC cells. The combination treatment significantly reduced 5-fluorouracil-induced cardiotoxicity and liver damage in mice with subcutaneous CRC and mitigated colorectal damages in AOM/DSS-induced CRC. This combination disrupts mitochondrial function by increasing the amount of reactive oxygen species (ROS) within the mitochondria and weakens the mitochondrial membrane potential (MMP). The regulation of mitochondrial dynamics through the AMPK/p-AMPK pathway enhances mitochondrial fusion and reduces fission, leading to increased apoptosis in cancer cells. Their information recommends that naringenin may inhibit CRC cell proliferation by impacting the AMPK pathway by regulating mitochondrial function and induce apoptosis in CRC cells.

Naringenin's ability to suppress the growth of CRC cells and its possible mechanism through PI3K/AKT/mTOR pathway inhibition were explored by Cheng et al., 2020. They found that naringin slowed down the growth of CRC cells depending on the dose. Naringin also caused the CRC cells to undergo apoptosis and blocked the PI3K/AKT/mTOR route based on concentration. According to their results, naringenin may be used for treating CRC since it inhibits PI3K/AKT/mTOR pathway, thereby suppressing cell growth and inducing cell death.

Naringenin in gastric cancer

Bao et al., 2016 explored the impact of naringenin on cell proliferation, apoptosis, migration and invasion of stomach cancer cells (SGC-7901). Their study revealed that naringenin suppressed the growth of SGC and PCNA levels in time and dose dependence. Additionally, cell migration and invasion significantly reduced after naringenin treatment, with MMP2 and MMP9 expressions notably downregulated. Naringenin also had a strong proapoptotic effect on SGC-7901 cells, increasing BAX and cleaved caspase-3, while downregulating Bcl-2 and Survivin. Naringenin treatment inhibited AKT phosphorylation and this suppression was slightly increased by combining naringenin and AKT inhibitor LY294002. The research demonstrated that naringenin effectively suppressed the proliferation, migration and invasion of SGC-7901 cells, additionally inducing cell death. Their findings suggest that naringenin might present a cutting-edge therapeutic approach for the management of stomach cancer.

Xu et al., 2021 study examined the naringenin potential as a treatment for gastric cancer, focusing on its mechanisms related to apoptosis and autophagy. Their study demonstrated that naringenin suppressed the development of SNU-1 gastric cancer cells. Furthermore, naringenin treatment made cell cycle arrest in the G0/G1 stage and encouraged cellular demise. Mechanism of action disclose that naringenin inhibited PI3K/AKT signaling route, triggered cellular autophagy and increased production of proteins linked to apoptosis, cleaved caspase-3 and BAX while decreasing Bcl-2. Pretreatment of SNU-1 cells with 3-methyladenine (3-MA), a compound that inhibits autophagy, notably weakened naringenin's ability to induce apoptosis and activate caspase-3. Their findings suggest that naringenin triggers apoptosis in SNU-1 cells by preventing the PI3K/AKT signaling route and inducing autophagy.

Raha et al., 2015 studied how naringin affects human AGS cancer cells. They found that naringin stopped these cancer cells from growing in a way that depended on the amount and time of exposure. Naringin did not cause the cells to die through apoptosis, as shown by no DNA

breakdown and a lower BAX/Bcl-xL proportion. The researchers used western blot analysis and found that naringin reduced the activity of the PI3K/Akt/mTOR route and increased the level of p21CIP1/WAFI. The treatment caused the cells to produce autophagosomes and cytoplasmic vacuoles the observation was supported by the increased phosphorylation of MAPKs and the overexpression of the autophagic markers Beclin 1 and LC3B. Their study revealed that naringenin prevents the growth of AGS cancer cells by inhibiting the PI3K/Akt/mTOR route and inducing autophagy via activation of the MAPK signaling cascade. Naringenin exhibits potential as a novel treatment approach for treating gastric cancer in humans.

Naringenin in leukemia

Park et al., 2008 observed the capability of naringenin to induce cell death in human leukemia THP-1 cells. Their study exposed that naringenin administration resulted in the development of apoptotic bodies in the sub-G1 stage of THP-1 cells was related to dose-dependent suppression of proliferation. Naringenin made cell death was related to improved hyperpolarization of the mitochondrial membrane likely, decreased Bcl-2, increased BAX, activating caspases and successive cleavage of poly(ADP-ribose) polymerase. Caspase-3 inhibitor z-DEVD-fmk particularly blocked naringenin's cytotoxicity and apoptotic effects, indicating caspase-3's essentiality in naringenin's cell death mechanism. The use of the caspase-3 inhibitor z-DEVD-fmk markedly decreased the cytotoxic effects and apoptosis features brought on by the administration of naringenin, indicating the critical role that caspase-3 plays in the reported cytotoxic effect. Introduction of cell death was too linked to the phosphatidylinositol 3-kinase (PI3K)/Akt pathway inactivation, with the PI3K inhibitor LY294002 increasing naringenin made cell death. According to their research, naringenin shows promise as an anti-cancer medication. Naringenin causes leukemia cells (THP-1) to undergo apoptosis by inactivating the PI3K/Akt pathway, activating caspases and damaging mitochondria.

Naringenin in liver (hepatocellular) carcinoma

Arul and Subramanian, 2013 investigated the ability of naringenin to stop the cell growth and cause cell death in human hepatocellular carcinoma cells (HepG2). They discovered that naringenin causes cell cycle arrest at the G0/G1 and G2/M stages, which inhibits the growth of HepG2 cells. This was partly because of a rapid increase in p53 levels, linked with the cell cycle arrests. Furthermore, evidence of apoptosis was observed with naringenin treatment, characterized by nuclear damage and a higher part of cell death as determined by flow cytometry. Naringenin induced apoptosis through a mitochondrial pathway. This entailed raising the BAX to Bcl-2 protein ratio, which allowed cytochrome c to be released from mitochondria and activated caspase-3 as a result. The researchers found that naringenin inhibited HepG2 cells development through two mechanisms: by suppressing cell proliferation and inducing apoptosis.

Mohamed et al., 2022 developed a nano formulation combining Naringin and Dextrin (NDN) to enhance the therapeutic efficacy of naringin against HepG2. The researchers found that NDN enhanced the biological effects of naringenin by stimulating the production of ROS and promoting anti-inflammatory responses. This was facilitated by reduced expression of nuclear factor kappa B and IL-8, leading to cell death. Apoptosis was initiated by a reduction in B-cell

lymphoma-2 protein levels and a concurrent rise in pro-apoptotic proteins, including Bcl-2-associated X protein, caspase-3, caspase-9, p53 and programmed cell death 5. Additionally, there was a decrease in the expressions of certain GTPase-activating proteins and Ras signaling and a rise in others. Their findings indicate that naringenin's in NDN nano formulation enhanced therapeutic efficacy against HepG2 cells by stimulating anti-inflammatory action, induce cell death through mechanisms involving ROS generation, DNA destruction and cell cycle disruption. The authors concluded that dextrin nanoparticles can be used as a potential carrier. NDN demonstrated superior biocompatibility and anticancer efficacy compared to unformulated naringenin when evaluated in HepG2 cells. NDN's effective anticancer activity may be attributed to dextrin's ability to sustain naringin release, suggesting dextrin as an effective nanocarrier for prolonged drug delivery.

Naringenin in lung cancer

Chang et al., 2024 explored the mechanisms underlying naringenin-induced lung cancer cell death in H1299 and A549. Their study found that naringenin treatment decreased cell survival and halted cell division in H1299 and A549. Pretreatment with ROS scavengers, such as N-acetylcysteine or catalase, inhibited naringenin-triggered apoptosis and reestablished cyclin-dependent kinase function. Naringenin further induced autophagy through the generating ROS, resulted in the initialization of the AMPK signaling route. Suppression of ROS formation attenuated naringenin-induced autophagosome accumulation and diminished LC3II/LC3I ratio and AMPK pathway activation. Naringenin demonstrated anti-tumor effects in a xenograft mouse model, characterized by reduced tumor development and increased tumor cell death. The authors' findings support the notion that naringenin possesses anti-cancer properties by suppressing the tumor development and induce cell death through mechanisms involving oxidative stress, cell cycle disruption, apoptosis and autophagy.

Mohamed et al., 2023 investigated the Naringin-Dextrin nanoformulation preventive effects towards lung cancer development caused by diethylnitrosamine (DEN)/2-acetylaminofluorene (2AAF) in male Wistar rats. They treated rats' lung tissue with naringin and nanoformulations which inhibited the growth of tumor cells. Reduced lipid peroxidation, increased glutathione peroxidase and superoxide dismutase activities and increased glutathione and Nrf2 expression were observed in lung tissues. Both treatments suppressed lung inflammation by decreasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ) and transcription factors (NF-κB), as well as inducible nitric oxide synthase, while enhancing the anti-inflammatory cytokine IL-10 expression. Naringin-Dextrin nanoformulation exhibited stronger anti-inflammatory action compared to naringin alone. Both treatment regimens knowingly downregulated Bcl-2 expression while concurrently upregulating BAX and P53 protein levels, indicating an induction of apoptosis. They also lowered the expression of proliferation marker, Ki-67, with Nar-Dx-NCs having a more pronounced effect. They concluded that dextrin effectively delivered naringenin, mitigating lung cancer induced by DEN/2AAF through reduced oxidative stress and inflammation, while enhancing apoptosis signaling.

Yan et al., 2021 tested the anticancer properties of both naringin and naringin within polymeric nanoparticles intended for lung cancer therapy (A549 and HEL-299). Research employing dual staining with acridine orange/ethidium bromide and Hoechst 33344, coupled with flow cytometry analysis, showed that lung cancer cell growth was linked to apoptosis. Naringin encapsulated within polymeric nanoparticles exhibited improved biocompatibility compared to free naringin. The authors conclude that encapsulating naringenin within polymeric nanoparticles presents a promising and safe strategy for treating lung cancer. They recommended further clinical investigations to validate their results.

Shi et al., 2021 researched naringenin's capacity to stop lung cancer cells (A549) from growing and cause them to die. Cell viability was determined to be 93.7±7.5%, 51.4±4.4% and 32.1±2.1% at naringenin concentration of 10, 100 and 200 μmol/L respectively. Naringenin resulted in a significant elevation in the apoptotic cell. Naringenin dose of 100 and 200 μmol/L reduced the size of larger wounds in cultured A549 cell models compared to untreated group. Naringenin also upregulated caspase-3 expression while simultaneously downregulate the production of MMP-2 and MMP-9. Collectively, their findings indicated that naringenin demonstrates efficacy in inhibiting the proliferation, migration and metastatic potential of A549 cell in vitro.

Naringenin in melanoma cells

Fernando et al., 2024 explored the potential of naringenin as an anticancer agent by investigating its impact on ROS generation, mitochondrial function and programmed cell death in melanoma cells. They found that naringenin was observed to decrease the viability of melanoma cells while simultaneously increasing the production of ROS. This elevated ROS level triggered cell death through apoptosis. Additionally, it induced mitochondrial impairment by increasing intracellular calcium and ROS levels within the mitochondria, while simultaneously decreasing cellular ATP production. Naringenin increased levels of pro-apoptotic proteins, comprising phospho-p53, BAX, cleaved caspase-3 and cleaved caspase-9, while decreasing the anti-apoptotic protein Bcl-2. Furthermore, naringenin triggered programmed apoptosis by triggering the c-Jun N-terminal kinase route and stimulating autophagy process. Researchers concluded that naringenin induces oxidative stress, mitochondrial dysfunction and autophagy in melanoma cells, ultimately leading to cell death. Based on the researcher's data, it indicated that naringenin might be a viable treatment option for treating melanoma.

Naringenin in metastasis cancer

Dhanisha et al., 2024 developed naringenin loaded liposomal drug delivery system mimicking macrophage cell membranes, to improve the drug delivery to the target site. Their formulation exhibited favorable characteristics including excellent biocompatibility, stable, ideal particle size, pH-related drug release kinetics and efficient cellular uptake in *in vitro* studies. The anti-metastatic properties of naringenin biomimetic nanoparticle were validated using syngeneic athymic BALB/c nude mouse models. They concluded that naringenin biomimetic nanoparticles target metastatic cells through α4, β1 integrin and VCAM1 receptors, reducing lung metastasis by modulating apoptosis, as confirmed by Western blot, semi-quantitative PCR, real-time PCR and IHC analyses.

Naringenin in oral cancer

Du et al., 2024 explored the connection between naringenin and tongue cancer. Their study results demonstrated that naringenin significantly triggered planned cell death in CAL-27 cells in a dose-related. Mechanistically, the apoptotic process was initiated by an upregulated in Bid expression and a downregulated in Bcl-xl stages, ultimately leading to elevated levels of ROS. According to their research, naringenin may be used to treat oral cancer. This is by its capability to trigger programmed apoptosis by influencing the Bid and Bcl-xl signaling pathways.

Liu et al., 2022 investigated the naringenin induces cell death in human oral squamous cell carcinoma (OSCC) cells. According to their research, naringenin stimulates endoplasmic reticulum (ER) stress via the production of intracellular ROS, leading to autophagy, a survival mechanism for the cancer cells. Naringenin triggers cell death by activating a series of enzymes (caspase cascade), disrupting mitochondria function and causing stress within the cell's internal protein production system due to excessive calcium release. The interconnectedness of apoptosis and autophagy pathways highlights the role of ROS generated by naringenin in inducing cell death in OSCC cells. Thus, their study concluded that naringenin induces programmed cell death in OSCC cells through apoptosis and autophagy. Their findings exposed that naringenin reduces OSCC viability through intracellular ROS generation, endoplasmic reticulum stress and the activation of autophagy, leads to cell death. Therefore, naringenin shows promise as a novel natural compound with antitumor effects, potentially improving current therapies for OSCC.

Naringenin in ovarian cancer

Zhou et al., 2024 researched the ovarian anti-cancer activity of naringenin and explored the fundamental cellular mechanisms responsible for its effects. Their findings showed that different naringin doses had a substantial impact on TGF-β expression levels. The downstream *Snail1*/*SMAD2* signaling pathway was also impacted, showing decreased expression as naringenin concentration increased. Overexpressing *TGF*-β increased *Snail1*/*SMAD2* expression, while reducing *TGF*-β had the opposite effect. Additionally, naringin further decreased the *Snail1*/*SMAD2* expression induced by *TGF*-β. Constant results were found once *TGF*-β agonists and inhibitors were used in animal models alongside naringin. The researchers discovered that ovarian cancer cell proliferation was suppressed by naringin in a concentration-dependent way. Furthermore, they demonstrated that naringin induced cell death by triggering the TGF-β mediated signaling cascade.

Xu et al., 2022 explored the influence of naringenin on the growth and advancement of ovarian cancer. The researchers found that naringenin decreased the amounts of the protein BCL2L1 and prevented the ovarian cancer cells' PI3K/Akt signaling pathway from being activated. In ovarian cancer cells, this led to a decrease in cell division and an increase in cell death. However, these properties were moderately attenuated by enhancing BCL2L1 and therapy with 740Y-P, a PI3K activator. In summary, their findings indicated that naringenin showed an anti-cancer property on ovarian cancer evolution by suppressing the PI3K/Akt/BCL2L1 communication pathway.

Naringenin in prostate cancer

Lim et al., 2017 studied the effect of naringenin, on prostate cancer cells (PC3 and LNCaP). Researchers found that naringenin suppressed cancer cell growth and movement, while simultaneously inducing cell death and increasing the ROS production. Naringenin treatment of PC3 cells resulted in a dissipation of mitochondrial membrane effect and an increase in BAX, accompanied by a decrease in Bcl-2. LNCaP cells did not exhibit this effect. Naringenin also reduced the phosphorylation of ERK1/2, P70S6K, S6 and P38 proteins in PC3 cells and ERK1/2, P53, P38 and JNK proteins in LNCaP cells, in a dose-dependent way. However, it increased the phosphorylation of AKT in both cell types. They also found that naringenin, when combined with the chemotherapy drug paclitaxel, enhanced its effectiveness in suppressing prostate cancer cell growth. The researchers concluded that naringenin holds promise as a potential therapeutic alternative for treating prostate cancer.

Lin et al., 2020 examined the impact of naringenin towards the spread of human prostate cancer cells, specifically PC3 and DU145 cell lines. They found that naringenin reduced the viability and movement of these cancer cells. Naringenin considerably lowered the amounts and actions of key matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9. This was confirmed through protein analysis (Western blotting), gene expression analysis (real-time PCR) and enzymatic activity analysis (gelatin zymography). Additionally, naringenin inhibited the ERK1/2 pathway, confirmed by western blotting. It also reduced the levels of ROS. Naringenin has shown promise as a prostate cancer treatment agent, but more research is required.

Erdogan et al., 2018 investigated whether combining the chemotherapy drug paclitaxel with naringin could improve the effectiveness of paclitaxel against both androgen-dependent (LNCaP) and androgen-independent (DU145 and PC3) prostate cancer cell lines. Following naringenin administration, the researchers saw a dose and time dependent decrease in cell survival. Their result was linked to cell cycle arrest and apoptosis development during the G1 stage. Naringin, at a concentration of 150 μM, significantly upregulated the mRNA production of pro-apoptotic genes including BAX, BID, caspase 3, cytochrome c, p53, p21Cip1 and p27Kip1 in DU145 cells. Conversely, the anti-apoptotic proteins survivin and livin exhibited decreased mRNA levels under the same conditions. Naringin augmented the cytotoxic potency of paclitaxel against both LNCaP, DU145 and PC3. Naringin and docetaxel combination showed a comparable similar to paclitaxel's suppressive effect on cell proliferation in cell lines. However, this synergistic effect was not observed in LNCaP cells. According to the researchers' findings, naringin functions as a chemosensitizer, amplifying paclitaxel's lethal effects on prostate cancer cells. This suggests that naringin, by itself or by combining with paclitaxel, could be a possible therapeutic approach for treating prostate cancer.

Naringenin in skin cancer

Ahamad et al., 2014 examined the anti-proliferative and apoptotic properties of naringenin on human epidermoid carcinoma A431 cells. They used various methods, including MTT assay, DNA breakdown, nuclear condensation, changes in MMP, cell cycle analysis and caspase-3 activity, to examine these effects and naringenin's ability to induce ROS and trigger apoptosis. According to their research, naringenin dramatically reduced A431 cell viability ($p<0.01$).

Concurrently, there was a dose-dependent enhancement in nuclear condensation and DNA fragmentation. Furthermore, the production of ROS was significantly elevated ($p<0.001$). Naringenin also caused mitochondrial depolarization, leading to apoptosis in epidermoid carcinoma cells. Cell cycle analysis exposed that naringenin halted cell division at the G0/G1 phase, preventing further progression. Concurrently, the activity of caspase-3, an enzyme associated with programmed cell death, increased proportionally with naringenin concentration, thus promoting cell death. Through a sequence of events, the researchers discovered that naringenin efficiently causes dead cells in epidermoid carcinoma cells. These include the generation of ROS, disruption of mitochondrial function, nuclear breakdown, DNA damage, cell cycle arrest in the G0/G1 stage and activation of caspase-3, an enzyme involved in programmed cell death.

Conclusion

Naringenin, with diverse pharmacological properties, holds significant promise as a therapeutic agent in modern medicine. Naringenin has shown significant potential as an anti-cancer agent across various studies. Its ability to inhibit cancer cell proliferation, induce apoptosis, and interfere with crucial signaling pathways underscores its therapeutic promise. The compound has demonstrated effectiveness in reducing metastasis, enhancing the efficacy of conventional chemotherapy drugs like paclitaxel, 5-fluorouracil, docetaxel, and promoting autophagy in different types of cancer cells, including colorectal, prostate and lung cancers. Moreover, naringenin's favorable biocompatibility and capacity to sensitize cancer cells to chemotherapy highlight its potential as both a standalone treatment and an adjunctive therapy. Based on the collective evidence presented, naringenin emerges as a promising compound for further clinical evaluation as a multifaceted and effective anticancer therapeutic agent.

Funding sources

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1 Naringenin sources and concentration

Source	**Naringenin concentration**
Grapefruit	115–384 mg/L
Sour orange	>100 mg/L
Tart cherries, tomatoes	0.68±0.16 mg/100 g
Citrus reticulata	3383.6 µg/mL
Citrus paradisi	230 µg/mL
Citrus bergamia	22.3 µg/mL
Citrus aurantium	19.7 µg/mL
Citrus clementina	8 µg/mL
Bergamot, cocoa, water mint, drynaria, and beans	Smaller quantities

Table 2 Naringenin's anti-cancer activity and its mechanisms of action

Anti-cancer activity	**Mechanism of action**
Induction of apoptosis	Activates intrinsic and extrinsic pathways

	Increases pro-apoptotic proteins levels Reduces anti-apoptotic proteins levels
Cell cycle arrest	Arrests cell cycle at G1 or G2/M phase checkpoints Modulates cyclins, Cyclin-dependent kinases (CDKs) and (CDK) inhibitors
Inhibition of angiogenesis	Suppresses Vascular endothelial growth factor (VEGF) and VEGF receptor expression Reduces endothelial cell proliferation and migration
Suppression of metastasis	Inhibits matrix metalloproteinases (MMP), MMP-2 and MMP-9 activity Prevents extracellular matrix degradation and cancer cell invasion
Modulation of signaling pathways	Inhibits PI3K/Akt pathway activation Suppresses MAPK pathway signaling Downregulates Wnt/β-catenin pathway
Antioxidant activity	ROS Reduces oxidative stress and DNA damage

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Figure 1 Structure of naringenin

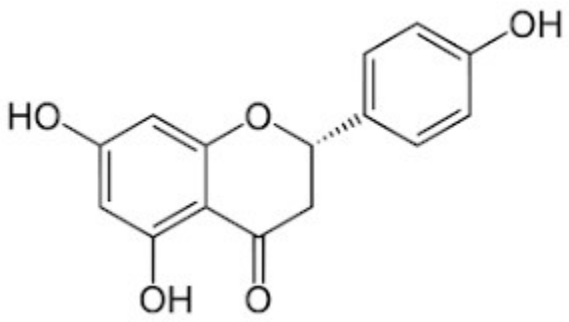


Figure 2 Bioactive compounds in citrus fruits: Health benefits and therapeutic potential

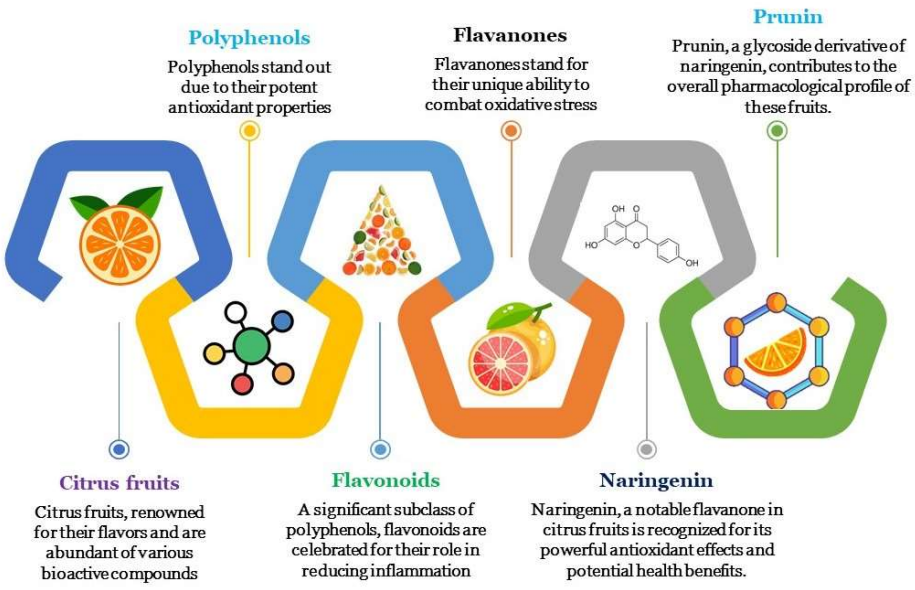
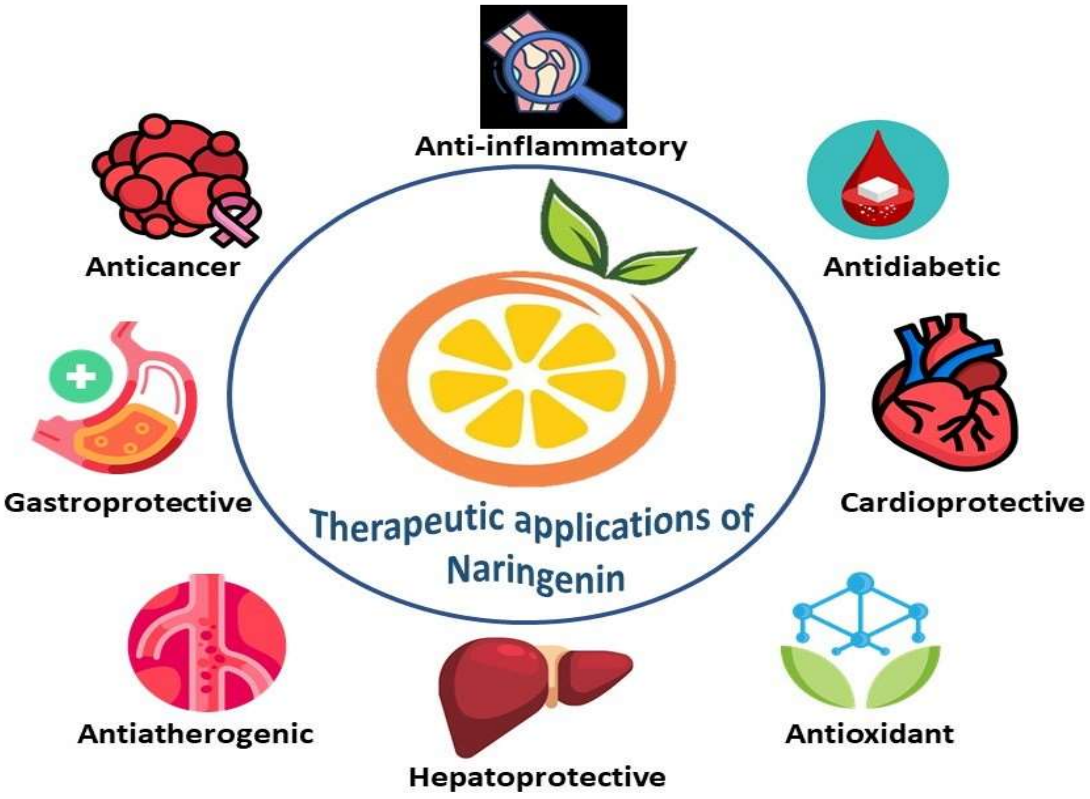


Figure 3 Therapeutic applications of naringenin



List of Abbreviations

Abbreviated Term	Definition
µM	Micromolar
2AAF	2-acetylaminofluorene
3-MA	3-methyladenine
740Y-P	A potent and cell-permeable PI3K activator
A/CDK2	Cyclin A-Dependent Kinase 2
A431, A549,	A human epidermoid carcinoma cell line
HEL-299	A human fibroblast cell line
ADP	Adenosine Diphosphate
AGS	A human gastric adenocarcinoma cell line
AKT	Ak strain transforming. It is also known as Protein Kinase B, is a group of serine/threonine-specific protein kinases that play key roles in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration
AMP	Adenosine Monophosphate
AMPK	AMP-activated protein kinase
AOM/DSS-induced	Azoxymethane/Dextran Sulfate Sodium
APAF-1	Apoptotic Protease Activating Factor 1
ATP	Adenosine Triphosphate
BAK	Bcl-2 antagonist/killer protein
BALB/c	An inbred strain of laboratory mice
BAX	Bcl-2-Associated X Protein
BAX/Bcl-xL	Members of the Bcl-2 family of proteins, which play crucial roles in regulating apoptosis (programmed cell death)
Bcl-2	B-cell lymphoma 2
BCL2L1	Bcl-2-like 1, which is a gene that encodes for the Bcl-xL protein
Bcl-xl	An anti-apoptotic protein, meaning it helps prevent apoptosis by inhibiting the release of cytochrome c from mitochondria
Beclin 1	A protein that plays a crucial role in the regulation of autophagy
BID	BH3 Interacting Domain Death Agonist
BrdU	Bromodeoxyuridine
C33A, SiHa and HeLa	Cervical cancer cell lines
CAL-27	A human epithelial cell line derived from a squamous cell carcinoma of the tongue
CDKs	Cyclin-Dependent Kinases
CHOP	C/EBP Homologous Protein
CoQN	Quercetin and Naringenin

CRC	Colorectal cancer
CV	Cardiovascular
CVD	Cardiovascular diseases
DEN	Diethylnitrosamine
DiNar	Diosmin and Naringenin
DMBA	7,12-Dimethylbenz(a)anthracene
DU145	A human prostate cancer cell line
E/CDK2	Complex formed by Cyclin E and Cyclin-Dependent Kinase 2
EGFR	Epidermal Growth Factor Receptor
eIF2α	Eukaryotic translation initiation factor 2 alpha
ER	Endoplasmic reticulum
ERK	Extracellular Signal-Regulated Kinases
ERK1/2	Two closely related isoforms of Extracellular Signal-Regulated Kinases, ERK1 and ERK2
ER-α	Estrogen Receptor Alpha
ER-β	Estrogen Receptor Beta
FAS	Fetal alcohol syndrome
G0/G1	Phases of the cell cycle
G1	Growth 1
G2	Growth 2
GSK-3β	Glycogen Synthase Kinase 3 Beta
H1299	Human non-small cell lung carcinoma cell line
HCT116	A human colon cancer cell line
HDL	High density lipoprotein
HepG2	Hepatocellular carcinoma cells
Hoechst 33344	A fluorescent dye used for staining DNA in cell nuclei
IC50	Half maximal inhibitory concentration
IHC	Immunohistochemistry
IL	Interleukin
JAK/STAT	Janus Kinase/Signal Transducer and Activator of Transcription. A critical signaling mechanism used by cells to respond to cytokines and growth factors
JNK	c-Jun N-terminal Kinases
K562	A human immortalized myelogenous leukemia cell line
Ki-67	A protein that serves as a cellular marker for proliferation
LC3B	Microtubule-associated protein 1 light chain 3 beta
LC3II/LC3I	LC3-I and LC3-II are two forms of the protein LC3 (Microtubule-associated protein 1 light chain 3 beta) involved in the autophagy pathway

LDL	Low density lipoprotein
LNCaP	A human prostate cancer cell line.
LY294002	A chemical compound that acts as a potent inhibitor of phosphoinositide 3-kinases
M	Mitosis
MAPK	Mitogen-activated protein kinase
MCF7	A human breast cancer cell line
MDA-MB-231	A human breast cancer cell line
miR-1275	A microRNA (miRNA) that plays a role in the regulation of gene expression by affecting the stability and translation of messenger RNAs
miR-27a-3p	A microRNA that plays a role in regulating gene expression by targeting messenger RNAs for degradation or inhibiting their translation
MMPs	Matrix metalloproteinases
mRNA	Messenger RNA
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NarSPNPs	Naringenin using pH and thermo-sensitive smart polymeric nanoparticles
NDN	Naringin and Dextrin
NF-κB	Nuclear factor kappa B
NO	Nitric Oxide
Nrf2	Nuclear factor erythroid 2-related factor 2
OSCC	Oral squamous cell carcinoma
p21, p27 and p57	Cyclin-dependent kinase inhibitors
p21/cip	P21 also known as Cip. It is a critical regulator of the cell cycle and functions as a potent inhibitor of cyclin-dependent kinases
WAF1	Wild-type p53-Activated Fragment 1)
p21CIP1/WAFI	Also known as CDKN1A and is a crucial regulator of the cell cycle
p27/kip	Cyclin-dependent kinase inhibitor 1B
p38	A group of mitogen-activated protein kinases
p53	A crucial tumor suppressor protein that plays a key role in regulating the cell cycle and preventing cancer.
PARP1	Poly ADP-Ribose Polymerase 1
PC3 and DU145	Both are human prostate cancer cell lines
LNCaP	Lymph Node Carcinoma of the Prostate is a human prostate cancer cell line
PCNA	Proliferating Cell Nuclear Antigen

PCR	Polymerase Chain Reaction
PI3K/Akt	Phosphoinositide 3-kinase/Protein kinase B pathway
PI3K/Akt/BCL2L1	A critical signaling pathway involved in regulating cell survival, proliferation, and apoptosis.
PI3K/Akt/mTOR	A critical intracellular signaling pathway that regulates various cellular processes, including cell growth, proliferation, survival, and metabolism
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
ROS	Reactive oxygen species
S	Synthesis
Ser576, Ser9	A specific amino acid residue that can be phosphorylated in certain proteins
SGC-7901	Stomach cancer cells
Snail1/SMAD2	Both involved in the regulation of epithelial-mesenchymal transition (EMT), a process critical in development, tissue repair, and cancer progression
SNU-1	A human gastric cancer cell line
STAT3	Signal Transducer and Activator of Transcription 3
Survivin	A protein that plays a crucial role in inhibiting apoptosis (programmed cell death) and regulating cell division
SW480	A human colon adenocarcinoma cell line
TGF-β	Transforming growth factor-beta
THP-1	A human monocytic cell line
TNBC	Triple-Negative Breast Cancer
TNF-α, IL-1β, IL-6, IFN-γ	Pro-inflammatory cytokines
TRADD	TNF receptor-associated death domain protein
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
VCAM1	Vascular Cell Adhesion Molecule 1
VEGF	Vascular Endothelial Growth Factor
VEGFR	VEGF and its receptor
V-FITC/PI	A combination of V-FITC (Annexin V conjugated with fluorescein isothiocyanate) and PI (Propidium Iodide), commonly used in apoptosis detection assays
Wnt/β-catenin	A crucial signaling pathway that regulates various cellular processes, including cell proliferation, differentiation, and embryonic development
XDH	Xanthine Dehydrogenase
XOD	Xanthine Oxidase

z-DEVD-fmk	A specific and irreversible inhibitor of caspase-3, an enzyme that plays a crucial role in the execution phase of apoptosis (programmed cell death)