

Exploring the Pharmacological Potential of Naringenin and its Nanoparticles: A Review on Bioavailability and Solubility Enhancement Strategies

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Abstract. Citrus fruits are rich in different flavonoid compounds. One of them is naringenin, which exhibits a huge variety of pharmacological benefits such as anti-inflammatory, antioxidant, anticancer, and cardioprotective properties. But poor bioavailability and solubility are the main reason for its limited clinical application. To overcome these limitations, several strategies, including complexation, formulation, and nanotechnology-based approaches, have been developed to boost its solubility and bioavailability. Among these approaches, nanoparticle-based delivery systems have shown remarkable potential in improving the therapeutic efficacy of naringenin. This review is based on the recent advances in the development of naringenin nanoparticles and their incorporation into drug delivery systems. We discuss over the numerous methods used to make naringenin more soluble and bioavailable, such as complexing it with cyclodextrins, combining it with lipids and surfactants, and adding it to polymeric nanoparticles. We also highlight the In-vivo and In-vitro studies conducted to check the efficacy of naringenin nanoparticles in various disease models. Finally, we conclude that the development of naringenin nanoparticles and their incorporation into drug delivery systems can be a promising strategy for the efficient delivery of naringenin, ultimately leading to improved health outcomes.

1 Introduction

One of the most prevalent types of phytochemicals is flavonoids, which may be found in foods including vegetables, nuts, fruits, medicinal plants like, *Alpina officinarum*, *Hypericum perforatum* and *Silybum marianum*. Numerous pharmacological activities, including antitumor, antibacterial, antioxidant, antiviral and cardioprotective effects, are exhibited by flavonoids like naringenin, hesperidin, rutin, and diosmin.[1][2][3].

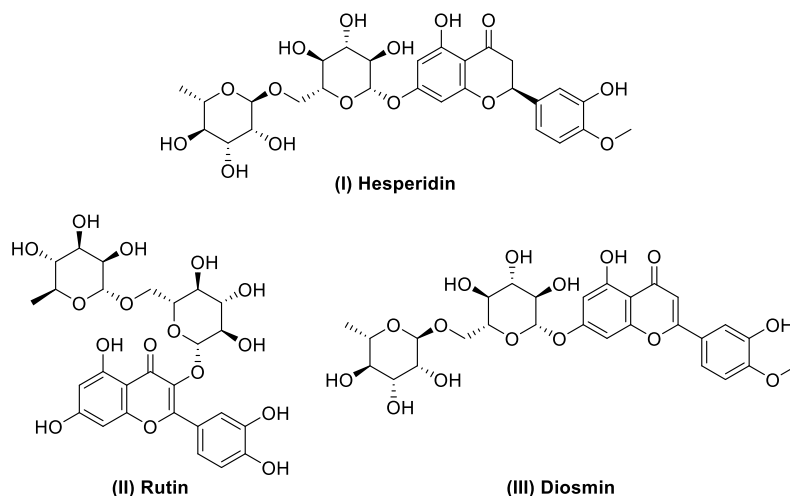


Fig. 1 Structure of some flavonoids

1.1 Naringenin

Naringenin is a type of flavonoid that belongs to the subclass flavone. It may be found in citrus fruits, bergamot, tomatoes, and other fruits, along with its glycoside form as naringin [1][2]. Chemically it is known as (2S)-5,7-Dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one (fig.1) having a M.Wt. of 272.26 (C₁₅H₁₂O₅). It possesses a broad spectrum of pharmacological properties, including antiviral, antibacterial, anti-inflammatory, anticancer, and antioxidant actions[1][2][3].

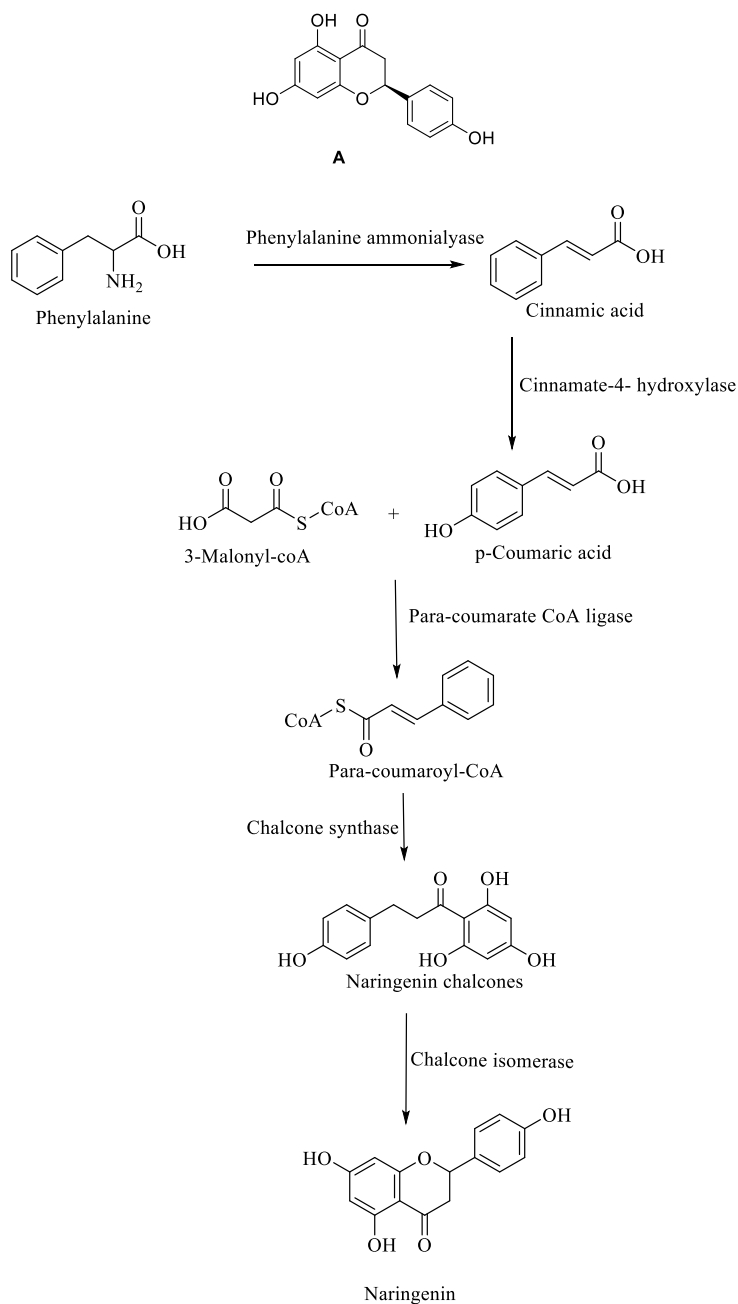


Fig. 2(A)Naringenin [(2S)-5,7-Dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one], **(B)**. Biosynthesis of naringenin from Phenylalanine

Naringenin is soluble in organic solvents such as alcohol, acetonitrile but insoluble in water[2][3]. Many different enzymes are used during its biosynthesis. Some of these are Cinnamate-4-hydroxylase, Chalcone synthase, phenylalanine ammonia-lyase (PAL), chalcone isomerase and para coumarate CoA ligase[4]. The starter unit of naringenin is composed of para-coumaroyl-CoA, which is derived from phenylalanine after the deamination of PAL. It

is then activated by a co-dependent ligase through the phenylpropanoid pathway[5]. Tyrosine is a substrate used by monocotyledonous plants to produce p-coumaric acid. They can also benefit from the flavanones found in citrus fruits like grapefruits and oranges [6][7].

2 Reported pharmacological activities of Naringenin

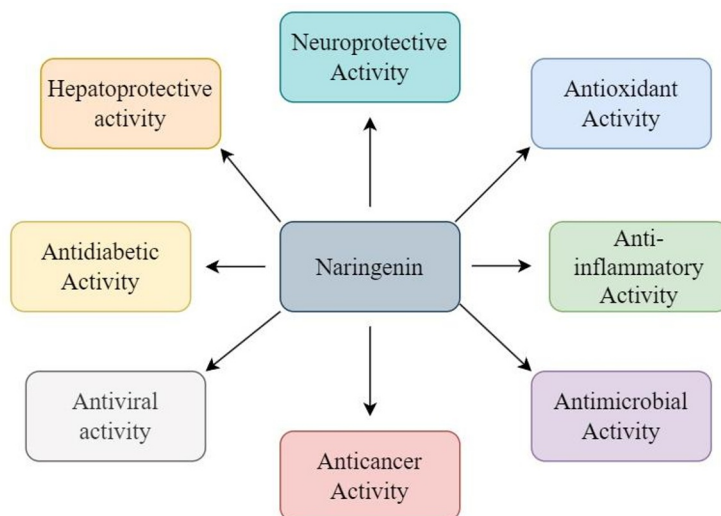


Fig. 3 Pharmacological activities of Naringenin

2.1 Antioxidant activity

The naringenin's antioxidant activity is mainly due to the presence of its hydroxyl substituents. These groups are known to be highly reactive to the reactive nitrogen and oxygen species. The more -OH radicals that are present in a compound, the more activity it has [8]. The number of naringenin -OH radicals is determined by considering the number of free radical units i.e., 3 in the case of naringenin. When combined with other compounds, it can help prevent the development of harmful effects on lipid structures. In a study conducted on Wistar rats, the effects of naringenin on the animals' oxidative liver toxicity were studied. Results from the sources identified that the combination of naringenin and vitamins C and E was highly effective in treating Cadmium-hepatotoxicity[9].

In this work, composite nanoparticles of carbon quantum dots and cyclodextrin loaded with naringenin were successfully developed. According to the findings, adding carbon quantum dots enhanced both naringenin encapsulation effectiveness and the antioxidant activities of nanoparticles. [10]. The DPPH test was used to analyze the free radical scavenging power of naringenin and pectin-naringenin conjugate. It was focused on converting these free radicals into stable compounds. The yellow colour of the DPPH solution is caused by the presence of antioxidants, which lowers the concentration 87d of the chemical. The results revealed that the pectin-naringenin combination has a higher ($P < 0.05$) free radical scavenging power than the free naringenin. This conclusion is attributed to the increased water solubility of the conjugate [11].

2.2 Anti-inflammatory activity

The inhibition of the nuclear factor- κ B (NFB) signalling pathway results in the significant anti-inflammatory action of naringenin. Interleukin 6 (IL6), Interleukin 1 (IL1), Cyclooxygenase 2 (COX2), Tumor necrosis factor-alpha (TNF- α), and inducible nitric oxide synthase are all induced by nuclear factor- κ B (iNOS) [12]. Different bitter compounds, such as Naringenin, were studied for their anti-inflammatory properties in primary mouse splenocytes in the presence or absence of lipopolysaccharide. Among all the substances tested, naringenin treatments had the most potent anti-inflammatory action [13]. The findings from a research paper reveal that naringenin has antinociceptive and anti-inflammatory actions in vivo by reinforcing the neural system's pain tolerance, providing a scientific foundation for its use in pain relief and the treatment of inflammatory illnesses [14].

On immune cells such as macrophages, naringenin inhibits leukocyte recruitment, oxidative stress, nuclear factor- κ B activation, and the generation of pro-hyperalgesia cytokines. However, naringenin reduces pain via modulating Transient receptors potential channels such as Transient receptor potential melastatin 8 (TRPM8), Transient receptor

potential vanilloid 1 (TRVP1), Transient Receptor Potential Cation Channel Subfamily M Member 3 (TRPM3) as well as activating a Nitric Oxide Signalling pathway that causes nociceptor neuron hyperpolarization. As a result, naringenin is a potential analgesic, anti-inflammatory, and antioxidant molecule [15]. The main goal of this study was to see if naringenin changes the inflammatory responses elicited by toll-like receptor 2 (TLR2). Naringenin was found to inhibit the activation of nuclear factor- κ B and the production of pro-inflammatory cytokines in cells stimulated with synthetic triacylated-type and diacylated-type lipopeptides known to activate TLR2 and TLR1/TLR6, respectively. These results suggest that naringenin has the ability to suppress inflammatory responses mediated by TLR2 signal transduction. [16].

2.3 Antimicrobial activity

A recent research study has discovered that naringenin has a significant impact on the reproduction of *P. nicotianae*, as observed through microscopic examination. The study determined that the effective concentrations of naringenin required to inhibit the production of *P. nicotianae* sporangia were 2.01 mg/L and 6.62 mg/L, which is notably lower than the effective concentration (EC50) required to inhibit mycelial growth. In addition to inhibiting mycelial growth, naringenin also downregulates cell growth and reproduction-related genes in *P. nicotianae*, as determined by reverse transcription quantitative polymerase chain reaction (RTqPCR). These findings indicate that naringenin not only reduces mycelial growth but also suppresses reproduction in *P. nicotianae* [17]. The naringenin-nano silver conjugate was created in a single phase of green synthesis, which included sunlight exposure validated by UV spectroscopy. The anticancer and antibacterial potential of the biosynthesized naringenin-nanosilver combination was investigated. A recent study revealed that the antibacterial potential of the tested substance was significantly increased by 5.8-6.14 times against Gram-positive bacteria like *S. aureus* and *Bacillus subtilis*. Additionally, the substance showed an increased antibacterial potential of 4.5-13.6 times against Gram-negative bacteria like *Pseudomonas aeruginosa* and *E. coli* [18]. To treat illnesses brought on by bacteria that are multidrug-resistant, new antimicrobial medicines are required. A recent study has reported that novel O-alkyl derivatives of naringenin and related oximes, which include new compounds featuring O-hexyl chains and a naringenin core, have demonstrated effectiveness against several clinical strains of antibiotic-resistant bacteria. These bacteria include vancomycin-resistant *Enterococcus faecalis*, beta-lactam-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*, clarithromycin-resistant *Helicobacter pylori*, and methicillin-resistant *Staphylococcus aureus* [19].

2.4 Anticancer activity

Naringenin has been shown to have anticancer action against a different of cancers, including those found in the colon, liver, lung, stomach, prostate, breast, and other organs. Naringenin has been shown to protect against cancer caused by chemicals. Naringenin protected hamsters against (7,12-Dimethylbenzanthracene) DMBA-induced mouth cancer and mice from N-nitroso diethyl amine-induced liver cancer. In this work, I observed that naringenin also reduced chemically produced skin cancer in a mouse model of two stages of skin carcinogenesis. Protection was demonstrated at both the initiation and promotion stages. In DMBA-induced cutaneous papilloma, naringenin therapy reduced pathogenic characteristics such as branching and layering [20].

In addition to acting against cancer cells, Naringenin can also help relieve the symptoms of patients suffering from the disease by acting as an effective alternative therapy. Its pleiotropic properties make it an ideal drug for treating malignancies [21]. A study conducted to measure the anti-tumour activity of Naringenin on breast cancer cells employed the MTT test, where the amount of formazan production was measured. The results showed that the viability of MDA-MB-231 cells is in a dose-dependent manner [22]. The goal of this research was to determine how naringenin affected the growth of lung cancer cells. The result showed that treatment with Naringenin at 24 and 48 hours significantly decreased the migration of A549 cells. Furthermore, transwell and healing experiments revealed that the effects of naringenin on migration were dose-dependent. Finally, a zymography study revealed that the drug inhibited the activity of various protein activities [23].

2.5 Antiviral activity

The main active component of the plant *T. angustifolia* is naringenin, and its inhibition rate is significantly higher 92.85% at 50mg/kg dose. In dose-dependent manner, naringenin was able to improve the survival of infected crayfish by preventing the white spot syndrome virus from reproducing. It also significantly decreased the viral loads in the animals. Naringenin can reduce the levels of critical viral genes, such as the *ie1*. Research has shown that the drug can decrease the expression of *ie1* by affecting the activity of its transcription factor, the Stat gene. In addition, it can inhibit the replication of the virus by targeting different immune-related genes, such as the Heat Shock Protein 70 (Hsp70), antioxidants such as cytosolic manganese Superoxide Dismutase (cMnSOD), Glutathione S-Transferase (GST), mitochondrial manganese Superoxide Dismutase (mMnSOD), and Catalase (CAT). In addition, the study also evaluated the expression of anti-inflammatory factors such as Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2), and B-cell lymphoma-2 (Bcl-2) Inhibitor-1 (BI-1) and pro-apoptosis-related factors such as Bax. [24].

A study revealed that naringenin and its derivatives can act against influenza infection. They also exhibited cellular absorption of certain flavanones. The researchers concluded that the compound's steric effect plays a significant role in their effectiveness. The prenyl group, which is the substituent of naringenin, plays a significant role in its cell permeability [25]. The use of naringenin prevented Huh7.5 cells from infection with four different dengue virus strains. It also inhibited the replication of the virus. In addition, tests performed using the RepDV-3 and RepDV-1 replicon systems revealed that naringenin can limit viral replication. Even after 24 hours following infection, the activity of the drug was still observed. Dengue virus serotype-4-infected monocytes exhibited anti-dengue virus activity using naringenin. This finding supports the possibility that this drug can be used to inhibit the reproduction of this virus [26].

The study reported on the synthesis and characterization of regioselective naringenin mono-7-O-ethers and mono and di-fatty acid esters. The researchers also evaluated the anti-ZIKV activity and antiproliferative activities against melanoma and breast carcinoma cells of the synthesized derivatives. The findings revealed that the ether derivatives had significant activity, with IC50 values ranging from 6.76, 18.5, and 22.6 M to 28.53, 45.1, and 32.3 M for ZIKV, B16-F10, and 4T1, respectively. Additionally, the lipophilic ethers exhibited specific inhibition of ZIKV replication in human cells. These results suggest that the synthesized derivatives could potentially be used in the treatment of ZIKV and cancer [27].

2.6 Antidiabetic activity

The use of naringenin to treat diabetes has been shown to provide various benefits, such as reducing the incidence of hypoglycaemia and enhancing the effectiveness of the drug in reducing inflammation. It has also been shown that this drug can act on different cellular mechanisms, such as reducing the proliferation of cells and reducing inflammation. This study aims to identify the various characteristics of this drug and its potential therapeutic application [28]. Only one of the four flavonoids extracted from a Japanese edible chrysanthemum known as Kotobuki exhibited biological activity. The skeleton of the flavanone is the single bond between the 2 and 3 carbons. Because of this, naringenin's activity was greater than that of naringenin-7-O-glucoside, it was suggested that the presence of O-glucose at position seven inhibited it [29].

Naringenin's effects on the uptake and utilization of glucose by various tissues, including muscles and adipose tissue, suggest that it can help decrease the absorption of glucose by the renal and intestinal brush barriers. It also lowers the synthesis of triglycerides and glucose in hepatocytes. Studies have shown that naringenin can enhance the ability of the pancreas to detect and react to glucose, as well as preserve the surviving beta-cell population. In addition, it can cause plasma levels of naringenin to increase significantly [30].

A type of diabetes that can appear during pregnancy is known as gestational diabetes. It can lead to higher maternal morbidity and metabolic syndrome in offspring. Currently, there are only a few treatment options available for women with this condition. Naringenin is found in tomatoes and citrus fruit, and it has been known that it can protect against diabetes. In a study, researchers discovered that this substance could be useful in treating gestational diabetes. The researchers used a mouse model to analyze the effects of naringenin on various aspects of the condition. The researchers discovered that naringenin significantly lowers the body weight and blood glucose levels in mice that have been diagnosed with gestational diabetes. It also increased their glucose tolerance and insulin levels. In addition, it can improve the perinatal outcomes of these animals by boosting litter size and lowering birth weight. The researchers concluded that naringenin could be used as a potential treatment for gestational diabetes [31].

2.7 Hepatoprotective activity

In a recent study, the administration of naringenin was found to improve metabolic parameters, suppress hepatic steatosis, and regulate the expression of genes involved in lipid metabolism, including Stearoyl-CoA Desaturase-1 (SCD1), Carnitine Palmitoyltransferase-1 alpha (CPT1 α), Fatty Acid Synthase (FASN), and Peroxisome Proliferator-Activated Receptor alpha (PPAR α). Naringenin also inhibited hepatic inflammation and reduced hepatic fibrosis and cell senescence as evidenced by decreased macrophage recruitment and levels of Interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF- α) and reduced hepatic oxidative stress by suppressing Reactive Oxygen Species (ROS) generation and normalizing the activities of antioxidant enzymes. Moreover, the use of naringenin significantly improved the activity and expression of Sirtuin 1 (SIRT1) protein, increased levels of other liver enzymes such as the Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 alpha (PGC-1 α) protein and Nuclear Factor kappa B (NF- κ B) deacetylation. An in vitro study also demonstrated that naringenin reduced the accumulation of lipids and inflammation [32].

Currently, the most commonly used medications for the clinical treatment of non-alcoholic fatty liver disease (NAFLD) are hypoglycaemic medicines, lipid-lowering pharmaceuticals, and insulin sensitizers. However, the safety and efficacy of these medications when taken over an extended period remain unknown. Additionally, these medications are not specifically designed to treat NAFLD but rather address underlying conditions such as hyperglycaemia or hyperlipidaemia. Recent research has shown that naringenin, a natural substance with antioxidant, anti-inflammatory,

antifibrogenic, fibrinolytic, anticancer, and antiviral capabilities, maybe a valuable treatment option for various liver diseases. Studies have demonstrated that naringenin reduced inflammation and fat build-up by blocking NLRP3 activation in hepatocytes and decreased expression of markers of macrophages in the livers of mice fed a methionine-choline-deficient (MCD) diet. However, naringenin was less effective in the livers of NLRP3^{-/-} animals[33]. Furthermore, naringenin prevented the high level of NLRP3 expression induced by LPS, which could reduce inflammation in Kupffer cells (KCs). Improved inflammatory activation in KCs may result in a reduced release of pro-inflammatory cytokines. Despite these promising findings, further fundamental and clinical investigations are needed to validate the use of naringenin as a treatment for NAFLD and other liver diseases in humans. It should also be noted that naringenin is a natural substance and not a specifically designed medication for liver diseases[12][33][34].

The study indicated that the use of naringenin nanoparticles made from serum albumin significantly increased liver accumulation. They also improved the tolerance of the liver cells to pro-inflammatory and high-oxidative stress stimuli. NGNPs were able to reduce the severity of the infection and prevent liver cell death in models of acute liver disease [35]. The quick production process of these nanoparticles offers a promising alternative to traditional therapy. It has been demonstrated via research papers that pre-treatment with naringenin promotes survival, enhances liver function, and reduces LPs/D-Gal-induced liver damage. The induction of autophagy is the origin of naringenin's hepatoprotective effects [36].

2.8 Neuroprotective Activity

A study has shown that Naringenin has a neuroprotective effect on C57BL/6J mouse models with MPTP-induced neurotoxicity, which is a model for Parkinson's disease. Mice treated with Naringenin orally showed a reduction in oxidative stress compared to mice treated with MPTP alone. Additionally, Naringenin has been found to improve motor performance in mice with MPTP exposure, while also reducing neuroinflammation and providing neuroprotection. The results of the study indicate that Naringenin could be a promising treatment option for Parkinson's disease.[37]. A follow-up study revealed that the optimized nanoemulsion of naringenin was able to be formulated successfully. The small particle size, the spherical shape, and the narrow PDI of the nanoemulsion were the characteristics that made it an effective neuroprotective agent. The study found that the neuroprotective effect of free naringenin was not as strong as that of the nanoemulsion with naringenin. More research is needed to confirm the effectiveness of this treatment in a real-world setting. The study's results indicated that the use of naringenin nanoparticles could be used as a potential treatment for Alzheimer's disease[37][38].

Controlling autophagy is a crucial aspect of managing the progression of neurodegenerative diseases. A study has shown that pre-treatment with Naringenin and Naringenin-solid lipid nanoparticles may reduce STZ-induced neurotoxicity by preventing autophagy and enhancing mitochondrial membrane potential (MMP). Naringenin-solid lipid nanoparticles have demonstrated better neuroprotective effects than free Naringenin due to their enhanced ability to penetrate PC12 cells. However, to achieve desired target specificity, surface-modified solid lipid nanoparticles need to be developed. Future pre-clinical and clinical trials should focus on evaluating the safety and efficacy of Naringenin-solid lipid nanoparticles in patients with neurodegenerative diseases [39]. When exposed to carbaryl toxicity, Neuro 2A cells that had been pre-treated with naringenin exhibited better outcomes. Naringenin treatment was found to preserve the integrity of the mitochondrial membrane potential while reducing oxidative stress by decreasing ROS. Furthermore, it was observed to upregulate the anti-apoptotic gene and increasing the expression of Bcl2 while downregulate the pro-apoptotic genes BAX and Caspase-3. These suggest that naringenin may be a useful agent in preventing or treating neurological disorders associated with carbaryl toxicity [40].

3 Challenges related to the delivery of Naringenin

Naringenin is available in a variety of fruits, especially citrus fruits such as lemon, amla, oranges, grapefruit, etc. However, naringenin's hydrophobic nature hinders its biological activities and reduced oral bioavailability is caused by significant gastrointestinal degradation, hepatic first-pass metabolism, constrained membrane transfer, and low water solubility [41][42][43]. A recent study has shed light on the metabolic fate of naringenin and naringin in the human body. The study identified twelve metabolites of these compounds in kidney microsomes and human liver, indicating that these compounds undergo extensive metabolism in the body. These metabolites include hesperetin, naringenin-O-glucuronide, rhoifolin, naringenin, hesperidin, eriodictyol, apigenin, naringenin-O-glucoside, and 5,7-dihydroxy chromone, neoeriocitrin, naringin[42][43].

The identification of these metabolites is significant because it has implications for the therapeutic use and safety of naringin and naringenin. These compounds have been shown to have potential therapeutic benefits, including anti-inflammatory, anti-cancer, antioxidant properties. However, their extensive metabolism in the body may affect their bioavailability and ultimately their effectiveness. Furthermore, the metabolic pathways of these compounds and their effects on human health are still not fully understood. Additional research is needed to elucidate the complete metabolic pathways of naringin and naringenin and their effects on human health. This knowledge will be critical in developing safe and effective therapeutic interventions based on these compounds [44].

Numerous naringenin-loaded nanocarriers with unique physicochemical properties and biological characteristics have been created to enhance naringenin's stability, solubility, and bioavailability in specific areas. These nanocarriers have been successfully used to treat various conditions or diseases, yielding promising results. Such nanocarriers include solid lipid nanoparticles, dendrimers, cyclodextrins, polymeric nanoparticles, liposomes. These nanocarriers can provide protection against premature degradation, enhance drug uptake and bioavailability, and enable targeted drug delivery. Further studies are required to analyze the safety and effectiveness of these nanocarriers in clinical settings. [41][42][43][44][45].

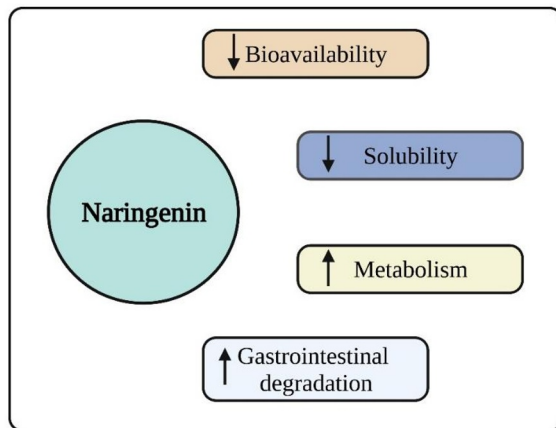


Fig. 4 Delivery limitations of Naringenin

4 Naringenin Nano-sized delivery systems

4.1 Polymeric nanoparticles

Polymeric nanocarriers have been utilized as effective drug delivery systems for several decades, particularly for delivering medications to specific organs. Several polymeric nanocarriers have been developed, including polymeric micelles, dendrimers, nanogels, and other nanovesicles. Dendrimers are highly branched, nanoscale polymers that have a well-defined size and shape, making them useful for targeted drug delivery. Nanogels are cross-linked polymer networks that can entrap both hydrophilic and hydrophobic drugs, and other nanovesicles such as liposomes and exosomes can also be utilized for drug delivery. These polymeric nanocarriers can enhance drug solubility and stability, protect drugs from premature degradation, and enable targeted delivery to specific organs or tissues. Further research is needed to optimize these polymeric nanocarriers for clinical applications [46][47][48].

The study reports that the oral bioavailability and anticancer efficacy of naringenin, a flavonoid with potential anticancer properties, can be enhanced using a drug-loaded polymeric nano-delivery system. Specifically, the study synthesized and physicochemically examined naringenin-loaded eudragit E100 nanoparticles (NRG-EE100-NPs system) and assessed their effectiveness in treating colorectal cancer *in vivo* using tumor-bearing BALB/c mice. The NRG-EE100-NPs system was found to have favourable physicochemical properties, with an ideal polydispersity index, high percent entrapment efficiency, and a mean particle size suitable for oral administration. Compared to free naringenin, the NRG-EE100-NPs system showed a significant increase in bioavailability and cytotoxicity, with a 96-fold and 16-fold increase, respectively. This indicates that encapsulating naringenin in a cationic-polymeric nanoparticle system can increase its potential as an anticancer agent for treating colorectal cancer. Overall, this study highlights the potential of using nano-delivery systems to improve the effectiveness of natural compounds with therapeutic potential, such as naringenin, for the treatment of cancer [49].

In a study paper, it was discovered that naringenin-loaded PLGA nanoparticles had overcome the drug's poor bioavailability and insolubility in water. These are created and identified using a variety of biological instruments. The nanoparticles demonstrated a 70% packing effectiveness. In an experimental rodent model, the nanoparticles looked to be more successful than the free medication at reducing the diabetogenic effects of STZ, including hyperglycaemia, hyperlipidaemia, and carbonyl- and iron-mediated oxidative stresses [50].

In this study, researchers used dextran sulphate (DS) and chitosan (CS) to create polymeric nanoparticles that can enhance the solubility of hydrophobic substances such as naringenin. These nanoparticles has a spherical shape with dimensions of 337.2 ± 48.27 nm and a zeta potential of 34.4 ± 7.45 mV. The association between the polymer and medication was confirmed using FTIR tests. *In vitro*, drug release experiments showed that unbound naringenin was

quickly released with 80% after 36 hours, while CSDS-Nar released only 51% of the drug during the same period. The MTT test results indicated that treatment with CSDS and CSDS-Nar significantly reduced the cell viability of MCF-7 cells, with percentages of 45% and 8%, respectively, at higher doses. Overall, the research findings suggest that the use of DS and CS in the formulation of polymeric nanoparticles can effectively enhance the solubility of hydrophobic substances and improve drug release. However, caution must be taken in using these nanoparticles as they can significantly impact cell viability, particularly at higher doses [51].

In a study conducted by Md. Habban and Sandeep, the sonication tailoring technique was utilized to increase the cytotoxic effect of naringenin against pancreatic cancer. The researchers successfully created naringenin-loaded nanoparticles using the emulsion-diffusion evaporation method, which was then optimized using a 2-factor and 3-level BBD experimental design. Results from the MTT test revealed that the naringenin nanoparticles had significantly higher cell-inhibition effectiveness compared to free naringenin. The IC50 values of free naringenin were found to be 119.68, 84.75, and 73.2 (g/ml) after 24, 48, and 72 hours of incubation, respectively, while for naringenin nanoparticles, they were 48.89, 44.70, and 32.08 (g/ml) during the same period. Furthermore, the findings demonstrated that naringenin nanoparticles had a significantly higher cytotoxic impact than free naringenin throughout the entire incubation period ($p < 0.05$). Overall, the study suggests that the sonication tailoring technique can enhance the bioavailability and cytotoxic effect of naringenin against pancreatic cancer. The use of naringenin-loaded nanoparticles can also significantly increase its cell-inhibition effectiveness compared to free naringenin, highlighting the potential of this approach for the treatment of pancreatic cancer [52].

The particles containing Paclitaxel and naringenin were prepared by a process that involved hot-melt emulsifying and homogenization. They then weighed and were added to a molten mass, which kept fluctuating at an ambient temperature of 850 degrees Celsius. The particles were treated with a modified surface, which was then coated with a cyclic glycan reaction peptide. The optimal combination of the finished product's composition was selected. The produced SLNs exhibited improved drug release rates and efficiency, as well as better cellular and cell-to-cell interactions. The results of the study indicated that the improved absorption and efficacy of the nano formulations were beneficial for treating various cancer types [53].

A study was conducted on rats having streptozotocin-induced diabetic condition to compare the effects of free naringenin and naringenin-loaded poly D, L lactide-co-glycoside (N-PLGA) nanoparticles on glycosylated haemoglobin level, insulin level, oxidative stress, and dyslipidemia parameters. The diabetic rats were treated with 10 milligrams per kilogram body weight of either free naringenin or N-PLGA nanoparticles containing 10 milligrams of naringenin. Results from the study showed that the N-PLGA-treated group had a significant reduction in glycosylated haemoglobin level, an increase in insulin level, and an improvement of dyslipidemia and oxidative stress parameters compared to the free naringenin-treated group. This suggests that the use of N-PLGA nanoparticles to deliver naringenin can enhance its therapeutic effects in the treatment of diabetes. Overall, the study highlights the potential of using N-PLGA nanoparticles to improve the efficacy of naringenin in treating diabetes, which could potentially lead to the development of new and more effective treatments for this condition [54].

In a study aimed at formulating elastic liposomes loaded with naringenin, varying amounts of Tween 80 and cholesterol were used. The control group included a saturated naringenin in aqueous solution and 5mg/ml solution of naringenin in 10% Tween 80. The results demonstrated that the skin permeation of naringenin was significantly enhanced in the liposomes loaded with it, compared to the control groups. The activity of saturated aqueous solution was 11.8 times lesser than elastic liposomes loaded with naringenin, containing medium levels of cholesterol and high levels of Tween 80 showed the highest drug deposition in the skin. These results suggest that elastic liposomes can be a productive step in the improvement of the skin permeation of naringenin [55].

Research was conducted to increase the bioavailability and solubility of naringenin using liposomes as a drug delivery system. The researchers dissolved 0.3 g of phospholipid and different quantities of naringenin in 20 mL of ethanol to create a clear and transparent solution, and then prepared naringenin-loaded liposomes using a thin-film dispersion technique. This study marks the first time that a naringenin-loaded liposome was effectively created. Following liposomal packing, the solubility of naringenin significantly increased, and the oral bioavailability of a compounded drug was significantly higher in rodents than that of unbound naringenin. This result suggests that the use of liposomes as a drug delivery system for naringenin could potentially enhance its therapeutic effects by improving its solubility and bioavailability. Overall, this result highlights the potential of using liposomes to deliver naringenin and improve its therapeutic efficacy, which could lead to the development of new and more effective treatments for various conditions [56].

Naringenin-loaded cyclodextrin nanoparticles have been developed pharmacologically to enhance the solubility and bioavailability of naringenin. The nanoparticles are composed of a CD core and a naringenin shell, which allows for the controlled release of the drug. In-vivo and In-vitro study shows that naringenin-loaded cyclodextrin nanoparticles have improved pharmacokinetic properties and increased bioavailability compared to free naringenin. Additionally, the nanoparticles have shown potential as an anticancer agent, with increased cytotoxic activity than free naringenin in cancer cells. Naringenin-loaded cyclodextrin nanoparticles represent a promising drug delivery system for enhancing the solubility, bioavailability, and efficacy of naringenin as a potential therapeutic agent [57].

4.2 Nanoemulsion

The study discussed in this article focused on improving the solubility and bioavailability of naringenin, using a self-nanoemulsifying drug delivery system (SNEDDS). The SNEDDS was designed and characterized, and In-vivo and In-vitro evaluations were conducted. The results showed that the nanoemulsion of SNEDDS had a diameter of less than 50 nm, and the stability of the drug was confirmed through centrifugation and freeze-thaw cycling. The drug release rate from the SNEDDS was higher than that of pure drugs, and the area under the concentration curve of the drug increased significantly. The enhanced bioavailability and drug release from the SNEDDS formulation can be attributed to the small size of the droplets and the enhanced solubility of the drug [2].

To enhance the bioavailability and solubility of naringenin, lipid nanoemulsions were designed to target vascular cell adhesion molecule-1 (VCAM-1) in a mouse model of lipopolysaccharide-induced inflammation. In vitro studies showed that the nanoemulsions were more effectively taken up by inflamed human umbilical vein endothelial cells (HUVECs) than non-inflamed HUVECs, demonstrating their targeting ability to VCAM-1. The results suggest that naringenin-loaded lipid nanoemulsions targeted to VCAM-1 have greater potential for theranostic purposes in the treatment of inflammation compared to free naringenin [58]. This study aimed to enhance the bioavailability of naringenin in the brain by utilizing a combination of chitosan and poloxamer-407 to improve its mucoadhesive properties. In vivo, permeation was conducted to compare the effectiveness of the two formulations. Results showed that the Poloxamer-Chitosan nanoemulsion had a significantly higher permeation rate than the free naringenin. The use of this nanoemulsion may be a promising approach for improving the delivery of naringenin to the brain and enhancing its therapeutic efficacy in treating neurological disorders [59].

A nanoemulsion formulation of naringenin was developed to improve its bioavailability for the treatment of Parkinson's disease. The formulation was prepared using the aqueous titration method, wherein a predetermined amount of naringenin was dissolved in the oily phase using a vortex mixer. A fixed amount of surfactants was added to the mixture while continuously stirring it with a magnetic stirrer. The study showed that the treatment with the nanoemulsion of naringenin was more effective in reversing the signs and symptoms of Parkinson's disease compared to the free form of the drug [60]. This study aimed to develop a naringenin nanoemulsion with an enhanced anticancer activity using Box-Behnken experimental design to optimize the formulation. The effectiveness of naringenin nanoemulsion as an anti-cancer agent was assessed in A549 lung cancer cells using various techniques, including cell viability assays, enzyme-linked immunosorbent assay, and flow cytometry. The study results revealed that the cytotoxicity of naringenin nanoemulsion in A549 lung cancer cells was concentration-dependent, and it was more potent than free naringenin. Based on these results, it can be noticed that the stabilized naringenin nanoemulsion may serve as an efficient drug delivery system, improving the therapeutic effectiveness of naringenin for treating lung cancer. [61].

To improve the ocular bioavailability of naringenin and paclitaxel, particles were prepared using high-speed homogenization and hot-melt emulsification methods. The particles were added to a molten lipid mass at a constant temperature, and a chemical modification process was used to modify the surface of the particles with a cRGD peptide. The optimal composition was selected, and the particles were self-assembled into nanocomplexes on a thin sheet, which was then dissolved in a Phosphate Buffered Saline solution. Sterile filtering was performed to meet the standards of eye drops, resulting in a 17PF-naringenin nano-complex ophthalmic solution that is suitable for creating PVP-complexing watery eye drops quickly and sustainably in large quantities [62].

4.3 Nanosuspension

In the following study, the focus was on exploring the potential of naringenin as an anti-osteoporotic agent by investigating its effect on the synthesis of osteocalcin in MG-63 cell lines. Osteocalcin is a crucial protein that plays a vital role in the regulation of bone metabolism. Osteoblasts synthesize and secrete this protein during bone formation in the bone remodeling process. The study findings demonstrated that the use of naringenin suspension had a considerable impact on the synthesis of osteocalcin in MG-63 cell lines. This suggests that naringenin may have potential as an anti-osteoporotic agent by promoting bone formation through the stimulation of osteocalcin synthesis. However, as the bioavailability of naringenin is poor, further studies are required to evaluate the effectiveness of naringenin in vivo and to develop effective delivery systems that can improve its bioavailability [63].

The aim of this investigation was to enhance the clinical utility of naringenin by creating a novel generation of nanosuspensions utilizing a blend of PVP K-90 and polyvinylpyrrolidone as stabilizers. The minimum particle size of the nanosuspensions was determined to be 117 ± 5 nm, with a zeta potential of -14.6 ± 5.6 mV. The sonication time, drug concentration, and stabilizer concentration had an impact on the particle size. The in vivo pharmacokinetic research indicated that the naringenin nanosuspensions had a 1.8 to 2 times higher absorption rate than the pure drug. Based on these findings, it can be concluded that nanosuspensions could be an encouraging drug delivery system for naringenin, improved dissolution with high absorption in the gastrointestinal tract [64].

The goal of this investigation was to improve the physicochemical properties and bioactivity of naringenin nanosuspensions. The materials were prepared by varying the concentrations of different types of surfactants and were

subjected to ultrasonication. The water solubility of two different types of nanosuspensions, free and naringenin-loaded, was analyzed at pH 7.0. The results indicated that the free nanosuspensions had higher water solubility than the naringenin-loaded nanosuspensions due to their smaller particle size. Additionally, the resistance time of the free nanosuspensions was found to be longer than that of the naringenin-loaded nanosuspensions. These findings suggest that the use of suitable surfactants and ultrasonication can enhance the bioactivity and physicochemical properties of naringenin nanosuspensions [65].

Chitosan was used in different amounts to create chitosan-loaded naringenin nanoemulsions. First, 1% acetic acid in purified water was used to make the chitosan solution. Later, 0.5%, 0.75%, and 1% of chitosan were used to create chitosan-loaded naringenin nanoemulsions by substituting the chitosan solutions for the aqueous phase of the formulas and rapidly mixing for 10 minutes. As a result, it could be said that naringenin containing nanoemulsion compositions based on chitosan would offer a fresh perspective on the therapy of chronic wounds and new optimism. The chitosan coating of the formulated naringenin nanoemulsion could be a foundation for accelerating wound repair [66].

The study aimed to prepare naringenin nanosuspension using a miniaturized media-milling method and investigate its effects on reducing acute cough in mice. The process involved dissolving tocopherol polyethylene glycol in water and ultrasonically dispersing naringenin in another vial containing water. In vivo, experiments revealed that a 30 mg/kg oral dose of naringenin nanosuspension significantly reduced the frequency of acute cough in mice. The cough frequency was reduced by 31.8% compared to the original drug, and the cough incubation period was increased by 42.5%. Moreover, the nanosuspension exhibited a good sputum-expelling effect, as demonstrated by an increase in phenol red secretion by 42.1% compared to the original drug and 23.9% compared to the positive drug. Based on the outcomes of the study, it can be inferred that naringenin nanosuspension holds potential as a viable drug delivery system for the treatment of acute cough and other respiratory disorders [67].

The study was based upon the development of a naringenin nanosuspension using the high-pressure homogenization technique with D- α -Tocopherol polyethylene glycol succinate 1000 and to evaluate its anticancer properties against the MCF-7 cell line. The findings indicated that the naringenin nanosuspension treatment resulted in a significant increase in mitochondrial membrane potential, intracellular ROS, lipid peroxidation status (TBARS), caspase-3 activity levels while Nanosuspension of naringenin lowers the growth stimulating hormone GSH level than free naringenin treatment in MCF-7 cell line. Moreover, the treatment with naringenin nanosuspension prolonged the life span and reduced the number of cancer cells and tumor weight in tumor-induced mice. The findings suggest that the use of a naringenin nanosuspension has the potential to be an effective anticancer treatment, potentially outperforming free naringenin.[68].

4.4 Inorganic nanoparticles

The aim of this study was to explore the potential of naringenin, a flavonoid found in citrus fruits, in the treatment of lung injury caused by silver nanoparticles. In both In-vivo and In-vitro models, the researchers assessed the impact of naringenin on apoptosis, ferroptosis, and inflammation in lung cells. The findings revealed that naringenin treatment effectively reduced apoptosis, ferroptosis, and inflammation in lung cells exposed to silver nanoparticles. Additionally, the study showed that naringenin upregulated the Nrf2/HO-1 pathway, which is essential for safeguarding cells against inflammation and oxidative stress. In conclusion, the study results as the naringenin holds promise as a therapeutic agent for treating lung injury caused by silver nanoparticles. However, further study is necessary to validate these potential clinical use of naringenin [69].

4.5 Other nano formulations

This article describes the creation of a dual-layered nanohydrogel that can be used for the delivery of naringenin to patients with colorectal cancer. The preparation and optimization of the amino acid complex known as the naringenin-Soy protein resulted in the formulation's optimal ratio of interaction. The second layer, which was incorporated into a gel-forming process, utilized the complex in an aqueous solution. The most optimal nanosuspensions were selected using a combination of methods, such as gel sedimentation, pH-selective targeted systems, and sustained-release techniques. They were then characterized using various characterization tools. It features a pH-responsive outer layer and an inner layer that is filled with protein-polysaccharide particles. The pH-sensitive outer layer can be utilized to selectively release a drug in the colon, which results in enhanced absorption and lower side effects. The researchers noted that this technology could be useful in treating colon cancer [70].

In this study, nanocapsules were prepared using a mixture of ethanolic organic phase and aqueous phase containing NAR, lecithin, and chitosan. Captisol-surface-adsorbed NCs were also created by mixing Captisol with unloaded or loaded NCs at varying concentrations.[71] Different formulations were created by altering the positive/negative charge ratio, which was determined by the equivalent amine group concentration.[72] Cytotoxicity tests showed that Naringenin was not toxic to Caco2 cells when associated with Nanocapsules, in contrast to its free form, highlighting the cytoprotective effect of the formulation.[73] The study also demonstrated that Naringenin-loaded Nanocapsules were able to inhibit biofilm formation by up to 60%.[74] These findings suggest that Nanocapsules could be a

promising drug delivery system for Naringenin, with potential applications in the prevention and treatment of biofilm-associated infections.[75] Further research is needed to validate these findings and to explore the clinical potential of Naringenin-loaded Nanocapsules[76].

5 Conclusion

Naringenin is a natural compound found in fruits such as grapefruits, oranges, and lemons. It has been extensively studied for its numerous health benefits, including anticancer, antioxidant, anti-inflammatory, and neuroprotective properties. However, the therapeutic potential of naringenin is limited due to its poor solubility and bioavailability, which affects its absorption and distribution in the body. Various approaches have been developed to improve the bioavailability and solubility of naringenin, including the use of nanoparticles such as nanosuspensions and nanocapsules. These nanoparticles can increase the surface area of naringenin, which improves its dissolution and bioavailability. Moreover, the nanoparticles can protect naringenin from degradation and enhance its stability in the body. Several studies have demonstrated the potential of naringenin nanoparticles in various therapeutic applications. For example, naringenin nanosuspensions have been shown to improve the absorption and bioavailability of naringenin, which enhances its therapeutic efficacy in treating respiratory diseases, acute cough, and cancer. Similarly, naringenin nanocapsules have been shown to prevent the development of biofilms, which are associated with various infectious diseases. Despite the promising results, further research is needed to fully understand the pharmacological potential of naringenin nanoparticles and their translation into effective clinical applications. This includes optimizing the formulation and dosing of naringenin nanoparticles, investigating their toxicity and safety profiles, and exploring their therapeutic potential in various disease models. In conclusion, the development of naringenin nanoparticles represents a promising approach to enhance the therapeutic potential of this natural compound. Naringenin nanoparticles have the potential to improve the solubility and bioavailability of naringenin, which can enhance its efficacy in treating various diseases. Further research is needed to fully explore the pharmacological potential of naringenin nanoparticles and to develop effective clinical applications.

6 References

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