# Naringenin: A Promising Flavonoid with Therapeutic Potential, Bioavailability Challenges and Advanced Drug Delivery Approaches

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## ABSTRACT

Naringenin, a naturally occurring flavonoid mainly present in citrus fruits, has attracted considerable scientific interest due to its diverse pharmacological and therapeutic properties. It exhibits significant antioxidant, anti-inflammatory, anticancer, antidiabetic, antimicrobial, antiviral, hepatoprotective, cardioprotective, and neuroprotective activities through its interaction with multiple cellular and molecular targets. The unique chemical structure of Naringenin contributes to its broad spectrum of biological effects, making it a promising candidate for the management of various chronic and metabolic disorders. However, its clinical application is greatly restricted because of poor aqueous solubility, limited permeability, extensive first-pass metabolism, and low oral bioavailability. To overcome these limitations, several advanced drug delivery systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanosuspensions, and self-nanoemulsifying drug delivery systems, have been developed to enhance its stability, bioavailability, and targeted delivery. Although these nano formulations improve therapeutic efficacy, concerns regarding toxicity, safety, dosage optimization, and long-term clinical use remain important considerations. This review provides a comprehensive overview of the chemistry, pharmacokinetic profile, bioavailability challenges, pharmacological activities, and novel drug delivery approaches of Naringenin. In addition, recent clinical investigations and future perspectives for its therapeutic application are also discussed.

**Keywords:** Naringenin, Flavonoids, Antioxidant Activity, Anti-inflammatory Activity, Bioavailability.

## INTRODUCTION

Flavonoids are a large group of naturally occurring polyphenolic compounds widely distributed in fruits, vegetables, herbs, cereals, nuts, flowers, and seeds. The term “flavonoid” is derived from the Latin word flavus, meaning yellow, which refers to the yellow pigments commonly present in plants [1]. These secondary metabolites are responsible for the various colors observed in plant tissues, including yellow, red, blue, and purple shades [2]. Flavonoids possess significant pharmacological, nutraceutical, cosmetic, and medicinal importance due to their diverse biological activities. Their beneficial effects are mainly attributed to their antioxidant, anti-inflammatory, anti-carcinogenic, anti-mutagenic, and enzyme-modulating properties [3,4].

Structurally, flavonoids consist of a basic flavan nucleus composed of two aromatic benzene rings (A and B) linked through a three-carbon heterocyclic pyran ring (C) [5,6]. Based on variations in their chemical structure and oxidation pattern, flavonoids are classified into several subclasses, including flavones, flavanols, flavanols, flavanones, flavanonols, and isoflavones. More than 4,000 flavonoids have been identified in edible plants, and they are commonly consumed in the human diet through fruits and vegetables [7]. Due to their wide range of

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biological and therapeutic activities, flavonoids are considered important natural compounds that contribute significantly to human health and disease prevention [8].

## Chemistry of Flavonoids

The fifteen-carbon skeleton of flavonoids is made up of two benzene rings (A and B, as seen in Figure 1) connected by a heterocyclic pyrane ring (C). Flavones (like flavone, apigenin, and luteolin), flavonols (like quercetin, kaempferol, myricetin, and fisetin), flavanones (like flavanone, hesperetin, and naringenin), and other classes are among them. Table 1 presents their general structures. The degree of oxidation and the pattern of C ring replacement vary throughout the different classes of flavonoids, while the pattern of A and B ring substitution varies amongst individual compounds within a class [9]

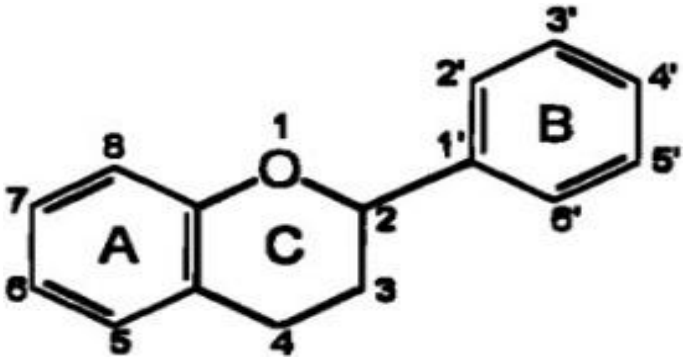
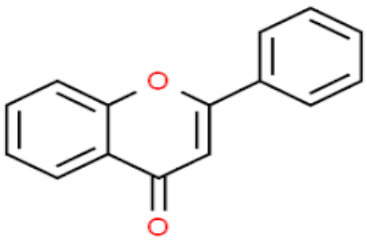
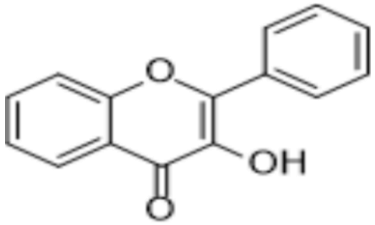



Fig.1. chemical structure of flavonoid

## Classification Of Flavonoids

| Sr.No | Name | Discription | Structure | Sources |
|---|---|---|---|---|
| 1 | **Flavones** | Flavones have a ketone in position 4 of the C ring and a double bond between positions 2 and 3. Depending on their taxonomic classification, flavones in all fruits and vegetables have a hydroxyl group in position 5 of the A ring, but the hydroxylation in other places, usually in positions 7 of the A ring or 3′ and 4′ of the B ring, can vary [10]. |  | Ginko, Carrot Vegetable Red Paper, Mint<br><br>Cerely |
| 2 | **Flavonols** | The 3-hydroxy derivatives of flavanones are known as flavanonols, or dihydroflavonols; they are a very diverse and multisubstituted class [11][12] [13][14] |  | strawberry, apple, onion, cucumber, and other fruits and vegetables |
| 3 | **Flavanones** | The C-ring of flavanones (dihydro-flavones) is saturated [15]. The main structural distinction between flavanones and other flavonoid compounds is the saturated double bond between positions 2 and 3 in the | | Citrus fruits, such as oranges, lemons, mandarins, grapefruits, |

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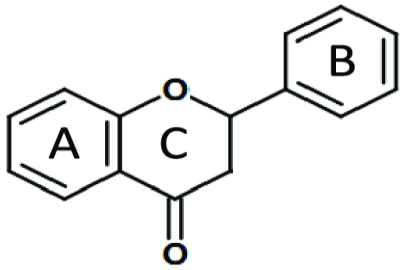
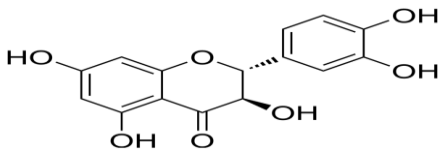
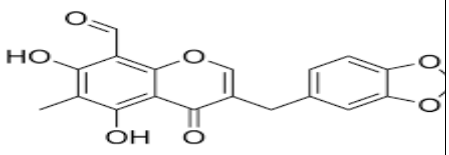
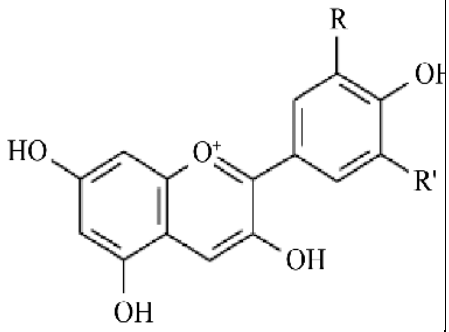
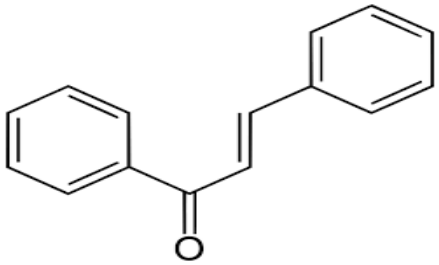
| | | | | |
|---|---|---|---|---|
| | | C-ring [16]. favanones have hydroxyl/methoxy substituents at the C3 or C4 locations of the B-ring and hydroxyl groups at positions 5 and 7 in the A-ring [17]. A disaccharidic moiety connected to the seven aglycon sites is what distinguishes flavanones [18]. |   | clementines, and limes, |
| 4 | **Flavanonols** | The 3-hydroxy derivatives of flavanones are known as flavanonols, or dihydroflavonols; they are a very diverse and multisubstituted subclass [19]. |   | Leafy Green Vegetables, Cherries, Berries.apple ,grapes. |
| 5 | **Isoflavones** | The B ring is joined to position 3 of the C ring in the subgroup known as isoflavones. They are also known as phytoestrogens because of their structural resemblance to estrogens, including estradiol [20][21] [22] |   | Red Clover, Mung Beans, Soybeans and Soy Products |
| 6 | **Anthocyanidins** | Depending on the pH of the microenvironment of the flowers, seeds, fruits, and vegetative tissues, anthocyanins—a class of soluble vacuolar pigments that are glycosylated polyphenolic compounds—can have a variety of colors, ranging from orange, red, purple, and blue [23]. Anthocyanins are crucial for human cardiovascular disease prevention, cholesterol breakdown, and optical acuity [24]. |   | Cherries, Plum, Berries, Red Blue and Purple Grapes |
| 7 | **Chalcones** | Due to their similar synthesis processes, chalcones and dihydrochalcones are categorized as flavonoids, which are flavonoid compounds with an open structure [25]. |   | Ginger, Potato,tomato, Beans,pears,apple |

**Importance of Flavonoids**

Phenolic chemicals, one of the many natural products produced by plants, are what give plant-based meals and drinks their primary organoleptic properties. They have a significant impact on fruits' and vegetables' color and flavor [26,27]. The biological pigments called flavonoids give flowers, fruit, and leaves their reddish-blue hues [28]. Plant-based foods like fruits, vegetables, tea, wine, seeds, herbs, spices, and whole grains are the primary

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source of flavonoids, a class of phytochemicals with a variety of advantageous biochemical and pharmacological qualities.

**Flavonoid Biosynthesis**

Phenylpropanoid derivatives are converted to flavonoids by condensation with malonylCoA. For instance, naringenin chalcone with a diphenylpropane (C6-C3-C6) unit is produced when p-coumaroyl-CoA (C6-C3) condenses with three malonyl-CoA (C3) molecules. This is then transformed into naringenin with the flavone (2-phenylchromen-4-one) backbone through conjugate ring closure. Numerous structural forms, such as chalcones, flavanones, dihyroflavonols, flavans, anthocyanins, flavones and flavonols, and isoflavonoids, are produced by these and further alterations [29].

**Naringenin**

Naringenin molecular formula: $C_{15}H_{12}O_5$[30] is the name given to the glycoside part of the monomer naringin, which has an interesting chemical structure.It has three rings, two of which are benzene rings joining the three carbon chains, and a basic flavonoid skeleton of 15 carbon atoms [31].The chemical name for naringenin is 4′,5,7-trihydroxyflavone, and it has a melting point of 251.0 °C and a molar mass of 272.3.[32].Naringenin is found in nature in solid form and is soluble in organic solvents such ethanol, ether, dimethylformamide, and dimethyl sulfoxide but nearly insoluble in water.[33]. Additionally, it has great therapeutic promise in the treatment of diabetes [34]. It also has strong therapeutic promise for treating diabetes[35] Naringenin's anti-inflammatory and anti-infective qualities are the main focus of current study, especially in relation to autoimmune inflammatory diseases and illnesses caused by a number of bacterial and viral infections. Naringenin's poor water solubility (5.81%) has a substantial effect on its clinical applicability and could be linked to the drug's insufficient residence time at the site of absorption [36].

**Source**

Citrus fruits, such as grapes, oranges, blood oranges, lemons, and grapefruit, are the main source of naringenin; some research has shown that grapefruit peel contains a significant amount of this compound · Citrus fruits, such as grapefruits (115–384 mg/L), sour oranges (> 100 mg/L), tart cherries, tomatoes (0.68 ± 0.16 mg/100 g), and Greek oreganol, contain naringenin.Smaller amounts can also be found in beans, bergamot, chocolate, water mint, and Drynaria. Flavonoids are found in almost all citrus fruits, although their content varies according on the fruit's kind and variety, harvest time, and environmental conditions. Humans mostly obtain flavonoids through their diet. Tomatoes and tomato-based products also contain trace amounts of naringenin. Naringenin chalcone, which is also present in fresh tomatoes, particularly in the peel, is transformed into naringenin when tomato ketchup is processed [37].

**Properties of Naringenin**

Naringenin's anti-inflammatory and antioxidant qualities are mainly ascribed to its capacity to prevent the recruitment of inflammatory transcription factors and cytokines. Its potential benefits in a number of ailments, such as metabolic syndromes, cardiovascular problems, and neurodegenerative diseases, may be attributed to these actions. For example, research has demonstrated that naringenin has cardioprotective properties and can enhance endothelial function by decreasing the size of heart infarcts and enhancing lipid profiles in animal models[38,39]

**Physicochemical and pharmacokinetic properties of Naringenin**

The molecular weight of NAR is 272.26. NAR has the chemical formula $C_{15}H_{12}O_5$ (Fig. 2). The hydrolysis of glycone forms of flavanone, like naringin or narirutin, yields this beneficial molecule. Grapefruit's bitter flavor is caused by naringin [40]. Because to the widespread breakdown, NAR has a limited bioavailability. According to earlier research, the gut flora has a high pre-systemic metabolism that produces a variety of breakdown products, including phenolic acids [41]. Since NAR is lipophilic, it most likely accumulates in tissues at quantities higher than those found in plasma. Organs like the liver and gut would most likely

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experience this buildup [42]. In male endurance athletes, its impact on metabolism was also investigated [43]. The pharmacologic value of an active substance depends on the degree of absorption or bioavailability upon ingestion, in addition to body metabolic rate and enzymatic breakdown. NAR is a lipophilic substance that dissolves in organic solvents but is nearly insoluble in water. Along with widespread degradation, the main obstacle to NAR's clinical development is its low water solubility, which results in limited permeability and poor oral bioavailability (about 5.81%) [44].

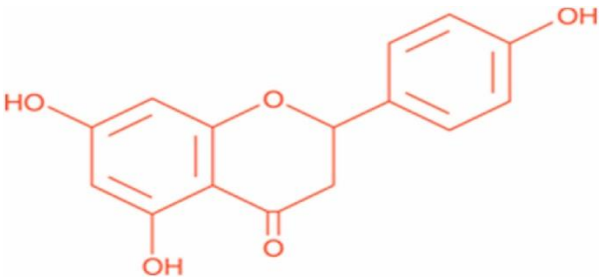
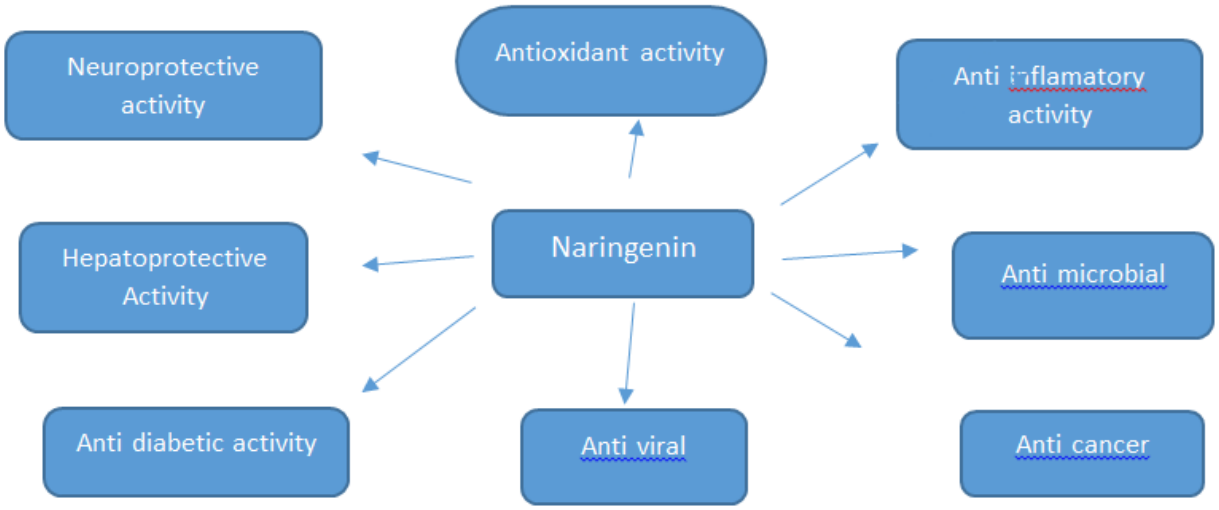



Fig 2. 2,3-dihydro-5,7- dihydroxy-2-(4- hydroxyphenyl)-4H-1-benzopyran-4

**Reported pharmacological activities of Naringenin**




**Antioxidant Activity**

The hydroxyl substituents in naringenin are primarily responsible for its antioxidant properties. It is well known that these groups react strongly with reactive oxygen and nitrogen species. A compound's activity increases with the number of -OH radicals it contains [45]. Naringenin-loaded cyclodextrin and carbon quantum dot composite nanoparticles were effectively created. The results showed that the addition of carbon quantum dots improved the antioxidant properties of the nanoparticles as well as the efficiency of naringenin encapsulation. The number of free radical units, or three in the instance of naringenin, is taken into account when calculating the amount of naringenin -OH radicals. It can help stop negative effects on lipid structures from developing when mixed with other substances. The impact of naringenin on the oxidative liver damage of Wistar rats was investigated in a study. According to the sources' findings, naringenin plus vitamins C and E proved to be a very successful treatment for cadmium hepatotoxicity [46].

**Anti-Inflammatory Activity**

Naringenin has a strong anti-inflammatory effect because it inhibits the nuclear factor-κB (NFB) signaling pathway. Nuclear factor-κB (iNOS) induces the production of interleukin 6 (IL6), interleukin 1 (IL1), cyclooxygenase 2 (COX2), tumor necrosis factor-alpha (TNF-α), and inducible nitric oxide synthase [47] The anti-inflammatory effects of various bitter substances, including naringenin, were investigated in primary

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mouse splenocytes with and without lipopolysaccharide. Naringenin treatments demonstrated the strongest anti-inflammatory effect of all the drugs examined [48]. It was shown that naringenin inhibited the generation of pro-inflammatory cytokines and the activation of nuclear factor-κB in cells stimulated with synthetic triacylated-type and diacylated-type lipopeptides, which are known to activate TLR1/TLR6 and TLR2, respectively. These findings imply that naringenin has the capacity to inhibit TLR2-mediated inflammatory responses [49].

**Hepatoprotective Activity**

It has been discovered that naringenin shares a hepatoprotective property with silymarin. Naringenin's ability to prevent rats from hepatic damage caused by dimethylnitrosamine (DMN) was examined. Oral naringenin (20 and 50 mg/kg daily over 4 weeks) significantly reduced DMN-induced damage as measured by liver weight, bilirubin levels, alanine transaminase (ALAT), aspartate transaminase (ASAT), and alkaline phosphatase (ALP). Additionally, naringerin restored the normal levels of albumin, serum, and hepatic malondialdehyde (MDA) and protein. Naringenin's hepatoprotective and antifibrinogenic properties indicate that it may be helpful in the management of hepatic fibrosis [50]

**Anticarcinogenic Effects**

Naringenin has been shown to suppress carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor growth in both in vitro and animal experiments using human cell lines and rats and mice. In addition, naringenin has been shown to suppress tumor growth in mice implanted with sarcoma S-180 and to produce dose-dependent cytotoxic and apoptotic effects in a number of cancer cell lines, indicating that it may have potential applications in tumor growth inhibition [51,52,53]. High doses of naringenin (50 percent effective concentration: 150–560 μM) also caused cytotoxic effects in human cancer cell lines. However, the creation of new flavonoids or naringenin derivatives that can cause cytotoxicity at low doses in a cell type-dependent way is necessary for the application of flavonoids as cancer chemopreventive or chemotherapeutic agents [54].

**Antimicrobial activity**

Methicillin-resistant Staphylococcus aureus (MRSA) and Helicobacter pylori are among the Gram-positive and Gram-negative bacteria that naringenin has been shown to be effective against. According to studies, naringenin can stop these diseases from growing by changing the bacterial cell membranes and interfering with the formation of biofilms [55,56,57]. Naringenin increases the antibacterial activity of traditional antibiotics like oxacillin, which results in a more significant decrease in bacterial growth and biofilm formation than each agent alone [55,59].

**Antiviral activity**

It has been demonstrated that naringenin hinders viral assembly and replication. It interacts with viral RNA and proteins, indicating that either host cell defenses or direct interactions with these components may be the source of its antiviral activities [60] . The antiviral properties of naringenin, a flavonoid primarily present in citrus fruits, have been investigated against a number of viruses, including SARS-CoV-2, the virus that causes COVID-19. Naringenin has been shown to suppress the production of angiotensin-converting enzyme (ACE) receptors, which are essential for the virus's ability to enter host cells, and to inhibit the primary protease (3CLpro) of SARS-CoV-2. Naringenin's dual effect implies that it may both reduce inflammatory responses linked to COVID-19 and ameliorate its symptoms [61].

**Antidiabetic activity**

Naringenin is a possible therapeutic agent for the management of diabetes since it improves insulin sensitivity and metabolic function. Naringenin supplementation significantly reduced body weight and insulin resistance in a human trial; after eight weeks of treatment, insulin levels dropped by 18%. The study suggested that naringenin increases metabolic rate and glucose absorption in adipose tissue, highlighting the role of peroxisome proliferator-activated receptors (PPARα and PPARγ) in mediating these effects [62].

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**Neuroprotective Activity**

Naringenin has been shown to improve cognitive abilities in Alzheimer's disease animals. By controlling several metabolic processes and lowering amyloid-beta (Aβ) aggregation, which is essential to Alzheimer's pathogenesis, it improves learning and memory impairments. Naringenin's neuroprotective actions specifically include the control of signaling pathways including PI3K/AKT/GSK-3β, which contributes to the improvement of brain insulin signaling and the reduction of Tau hyperphosphorylation [63] .Naringenin has demonstrated effectiveness in treating cerebral ischemia by lowering inflammation and oxidative damage caused by NF-κB. It has been shown to enhance neurological function and lessen infarct size and brain swelling in experimental ischemic stroke models [64].

**Naringenin Bioavailability**

Being a component of a typical diet, NRG can be found in a variety of foods. Nevertheless, NRG's hydrophobic nature hinders its biological activities, as evidenced by its poor aqueous solubility (approximately 475 mg/L) [65]. extensive gastrointestinal degradation, liver first-pass metabolism, and limited membrane transportation, all of which reduce oral bioavailability · Both passive diffusion and active transport are included in NRG absorption [66]. Human male and female pharmacokinetic parameters differed greatly, with some female pharmacokinetic parameters being noticeably greater than males [67]. Numerous investigations indicate that NRG is rapidly metabolized in vivo, mostly by conjugation into the primary NRG derivatives that circulate in plasma, glucuronides and sulphates· Furthermore, NRG-containing formulations' ultimate pharmacological qualities and shelf life may be adversely affected by its vulnerability to oxidative alterations and degradative potential in aqueous solutions · Several NRG-loaded Nano carriers with unique physicochemical compositions and biological characteristics have been developed to improve NRG stability, solubility, barrier crossing, and bioavailability at target sites in order to overcome the limitations associated with the low bioavilability. These nanocarriers have been used in a variety of conditions and diseases, with promising results and previously described applications [68].

**Challenges Related to the Delivery of Naringenin**

Many fruits, particularly citrus fruits including lemons, amla, oranges, grapefruits, and so on, contain naringenin. However, the hydrophobic structure of naringenin inhibits its biological activity, and hepatic first-pass metabolism, limited membrane transfer, considerable gastrointestinal degradation, and low water solubility all contribute to decreased oral bioavailability [69,70,71].

Because it affects the safety and therapeutic usage of naringin and naringenin, the identification of these metabolites is important. These substances have demonstrated anti-inflammatory, anti-cancer, and antioxidant qualities, among other possible therapeutic advantages. However, their bioavailability and, eventually, their efficacy may be impacted by their substantial metabolism within the body.

Furthermore, nothing is known about these chemicals' metabolic routes or how they affect human health. The whole metabolic routes of naringin and naringenin, as well as their impact on human health, require further investigation. Developing safe and efficient treatment strategies based on these chemicals would require this understanding [72]. To improve naringenin's stability, solubility, and bioavailability in particular regions, a variety of naringenin-loaded nanocarriers with distinct physicochemical and biological features have been developed. Numerous illnesses or ailments have been effectively treated using these nanocarriers, with encouraging outcomes.

Solid lipid nanoparticles, dendrimers, cyclodextrins, polymeric nanoparticles, and liposomes are examples of these nanocarriers. These nanocarriers can facilitate targeted medication administration, improve drug absorption and bioavailability, and offer protection against premature degradation. To evaluate these nanocarriers' efficacy and safety in clinical settings, more research is needed [73,74].

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**Type of Drug Delivery System for Naringenin**

Because of its poor solubility and bioavailability, naringenin, a flavonoid with considerable therapeutic promise, poses difficulties in medication delivery. To increase its efficacy, numerous sophisticated drug delivery devices have been created. These are the main categories of naringenin drug delivery systems.

**Polymeric Nanoparticles**

These are made to encapsulate naringenin, enhancing its regulated release and stability. Poly (lactic-co-glycolic acid), a natural or synthetic polymer, can be used to make them [75] Usually ranging from 1 to 1000 nm, polymeric nanoparticles are nanoscale particles composed of polymers that have the ability to contain medicines or bioactive substances on their surface or within their core.

Nanospheres, which have a solid polymeric matrix, and nanocapsules, which have a liquid core, are the two primary forms into which they can be divided [76].

**Advantage**

- **Improved Solubility and Bioavailability**: Polymeric nanoparticles that encapsulate hydrophobic medications, such as naringenin, increase their solubility in aqueous conditions, which improves the body's absorption [77]
- **Decreased toxicity:** By limiting the systemic exposure of medications, polymeric nanoparticles can improve therapeutic benefits at target areas while lowering potential toxicity [78]
- **Versatility in Formulation**: Polymeric nanoparticles can be produced using a variety of techniques, enabling customization according to the particular drug characteristics and intended release profiles [79]

**Liposomes**

Liposomes, which are lipid-based vesicles that improve solubility and shield the substance from deterioration, can contain naringenin. Improved bioavailability and sustained release are made possible by this technique. [80,81]

**Advantage**

- **Better Solubility**: Makes hydrophobic medications more soluble, which improves absorption
- **Long-lasting therapeutic** benefits are made possible by controlled release, which offers sustained medication release patterns.
- **Decreased Toxicit**y: By directing medications specifically to afflicted tissues, systemic exposure is minimized.
- **Versatility:** Adaptable to multiple delivery methods (e.g., oral, transdermal, intravenous).

**Solid Lipid Nanoparticles**

These are nanoparticles that can encapsulate naringenin while offering controlled release properties by combining solid lipids and surfactants [82,83].

**Advantage**

- **Targeted and Controlled Drug Release**: SLNs make it possible to create controlled release profiles, which let medications be administered to specific body locations at predetermined rates. This characteristic reduces adverse effects while increasing treatment efficacy.

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- **Improved Stability**: SLNs outperform conventional carriers like liposomes, which are susceptible to deterioration and leakage. For a medication to be effective over time, this stability is essential .

- **High Drug Loading Capacity**: SLNs are adaptable for a range of formulations because, in contrast to other nanoparticle systems, they can encapsulate a sizable amount of both hydrophilic and lipophilic medicines .

**Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)**

SNEDDS can increase the oral bioavailability of naringenin by forming nanoemulsions when they come into contact with gastrointestinal fluids, which improves absorption through the intestinal wall [84].

**Advantage**

- **Improved Solubility and Bioavailability**: SNEDDS significantly increase the solubility of hydrophobic drugs, which leads to better absorption in the gastrointestinal tract, especially for Biopharmaceutical Classification System (BCS) Class II drugs, which have low solubility but high permeability [85]

- **High Drug Loading Capacity**: These systems can encapsulate a high percentage of active pharmaceutical ingredients, allowing for efficient delivery and reducing the volume of excipients required

- **Reduced First-Pass Metabolism**: By promoting lymphatic transport of lipophilic drugs, SNEDDS can help circumvent hepatic first-pass metabolism, improving the drug's overall bioavailability [86].

**Nanosuspension**

Novel drug delivery methods called nanosuspensions are intended to improve the solubility and bioavailability of medications that are not particularly soluble. These are the main benefits of employing nanosuspensions.

**Advantage**

• **Improved Solubility and Bioavailability**: Hydrophobic medications dissolve far more readily in nanosuspensions, which increases their bioavailability. Faster absorption in the gastrointestinal tract is made possible by the increased surface area caused by the smaller particle size [87].

• **Decreased Dose Volume**: Nanosuspensions can reduce the volume of the supplied dose by permitting higher drug concentrations, which is beneficial for parenteral and ophthalmic applications [88].

• **Reduced First-Pass Metabolism**: The formulation may improve systemic availability by enhancing drug absorption by lymphatic transport, thereby avoiding hepatic first-pass metabolism [88].

**Potential Side Effects of Naringenin Nanoformulations**

Although naringenin nanoformulations show promise in increasing the drug's bioavailability and therapeutic effects, they may also have unintended consequences.

**Toxicity Concerns**

Although research suggests that naringenin and its nano formulations often exhibit low toxicity in a range of animal models, in-depth preclinical and clinical studies are still required to fully assess their safety profiles. In animal experiments, several formulations have shown no appreciable negative effects on major organs like the liver, kidneys, and heart [89]

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**Oxidative Stress**

Naringenin is well-known for its antioxidant qualities, but some formulations may cause oxidative stress in some situations, especially when combined with other medications or when heavy metals are present. If left untreated, this oxidative stress might worsen pre-existing diseases or lead to nephrotoxicity [89]

**Immune Response**

An immunological reaction may occasionally be triggered by the injection of nanoparticles. The long-term effects of frequent exposure to naringenin-loaded nanoparticles are still being studied, despite the fact that various formulations are made to reduce this effect. Sensitive people are susceptible to inflammation or hypersensitivity reactions [90]

**Dose Challenges**

Optimizing therapeutic results while limiting negative effects requires a precise dose regimen. Negative side effects include headaches, allergic reactions, or gastrointestinal distress could result from overdosing or incorrect formulation[91]

**Reported toxicity profile of naringenin**

Because of its limited absorption, a high dietary intake of naringenin is generally regarded as safe; but, excessive ingestion, particularly from concentrated supplements or grapefruit, can have negative effects. Its propensity to adversely interact with other drugs, especially anticoagulants, is one major worry. The cytochrome P450 enzyme CYP3A4, which is essential for the metabolism of numerous medications, can be inhibited by naringenin. These drugs' plasma levels may rise as a result of this inhibition, which could be harmful and cause negative side effects.

Although the exact toxic dose levels of naringenin in humans have not been determined, research on animals indicates that doses more than 100 mg/kg may have major biological effects, such as behavioral changes and possible neurotoxicity. Generally speaking, excessive naringenin dosages might cause gastrointestinal issues or worsen the effects of some drugs. As a result, even though naringenin has many health advantages, care should be used when taking it, particularly if it's a supplement or taken with additional medications [92].

**Recent clinical studies ongoing**

**Cardiovascular Health**

Naringenin's effects on cardiovascular risk factors, such as its capacity to reduce cholesterol and enhance endothelial function, are being studied in clinical trials. For example, a study is evaluating how naringenin supplementation affects patients with hyperlipidaemia in order to ascertain whether it is effective in lowering lipid levels and enhancing general heart health [92]

**Neuroprotection**

especially in regard to neurodegenerative conditions like Parkinson's and Alzheimer's. Its effects on neuronal protection and cognitive function in people at risk for these disorders are being investigated in ongoing clinical trials. According to certain research, dosages of about 10 mg/kg may lessen behavioral abnormalities and neuronal damage in animal models, which has led to more research on human subjects [93].

**Anti-inflammatory Effects**

Significant anti-inflammatory and antioxidant effects are demonstrated by the chemical, which also has the ability to scavenge reactive oxygen species. This raises the possibility of using it to treat disorders linked to oxidative stress and inflammatory diseases [39]

**Cancer Research**

The effectiveness of naringenin supplementation on metabolic parameters in overweight/obese patients with non-alcoholic fatty liver disease (NAFLD) is presently being evaluated in a clinical investigation. This trial may shed light on the wider health advantages of naringenin, which may be pertinent for cancer patients even though it is not specifically focused on the disease [94].

## CONCLUSION

Flavonoids, a diverse group of naturally occurring compounds, have obtained significant attention due to their numerous biological activities and health benefits. These compounds, particularly Naringenin, a flavonoid found in citrus fruits,display a wide range of pharmacological properties, including antioxidant, anti-inflammatory, and anticancer effects. The chemical structure of flavonoids, including Naringenin, allows them to interact with various cellular targets, contributing to their beneficial effects.Despite their promising health benefits, the bioavailability of Naringenin poses a significant challenge, limiting its therapeutic potential. Various drug delivery systems, including nanoformulations, have been explored to enhance its bioavailability and targeted delivery. These systems offer the potential to improve the efficacy of Naringenin while minimizing side effects, although their safety and toxicity profiles need careful evaluation. Recent clinical studies are investigating the therapeutic applications of Naringenin, particularly its role in managing chronic diseases such as cardiovascular disease, diabetes, and cancer. However, ongoing research is essential to fully understand its clinical potential, address delivery challenges, and ensure its safety in long-term use. while Naringenin and other flavonoids offer great promise as therapeutic agents, further studies are required to optimize their delivery, enhance bioavailability, and establish their safety and efficacy in clinical settings.

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