International Journal of Pharmaceutical Science and Research
www.pharmacyjournal.net
ISSN: 2455-4685
Received: 17-02-2025, Accepted: 16-03-2025, Published: 29-03-2025
Volume 10, Issue 1, 2025, Page No. 23-29

Naringenin: A promising phytochemical for health and nutraceutical applications

Sandeep Goyal[1*], Rakesh Chawla[2], Vijender Kumar[3]

[1] Department of Pharmacology, University Institute of Pharmaceutical Sciences & Research, BFUHS, Faridkot, Punjab, India

[2] Department of Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences & Research, BFUHS, Faridkot, Punjab, India

[3] Department of Pharmacognosy & Phytochemistry, Delhi Pharmaceutical Sciences and Research University, New Delhi, India

Abstract

Naringenin, a flavanone found in citrus fruits, has sparked widespread scientific attention due to its various pharmacological properties. This systematic review evaluates all preclinical investigations completed in the recent decade (2020-2025) to understand naringenin's medicinal potential. It has been shown to be effective in the treatment of a variety of pathological illnesses, including cancer, osteoporosis, neurodegenerative diseases, metabolic disorders, and inflammatory diseases. Naringenin's mechanisms of action include antioxidant, anti-inflammatory, anti-apoptotic, and immunomodulatory pathways. Recent advances in nanoformulations and drug delivery devices have improved bioavailability and therapeutic effectiveness.

The study focuses on preclinical research conducted *in vitro* and *in vivo*, demonstrating naringenin's significance in hepatocellular cancer, radiation-induced damage, osteoporosis, ocular neovascularization, and inflammatory bone loss. Notably, nano-encapsulation and targeted administration methods have enhanced its pharmacokinetic characteristics, making it a strong contender for future clinical uses. A critical assessment of these findings emphasizes the need for more clinical research to evaluate its translational potential in human health. This study is a helpful resource for researchers investigating natural therapies, highlighting the importance of well-designed clinical studies to establish the efficacy and safety of naringenin-based therapy.

Keywords: Naringenin, flavonoids, pharmacological actions, preclinical studies, bioavailability, oxidative stress, inflammation.

Introduction

Naringenin, a bioactive flavanone predominantly found in citrus fruits such as grapefruits, oranges, and lemons, has gained substantial scientific recognition due to its extensive pharmacological properties. Structurally, naringenin possesses a flavanone backbone with three hydroxyl (-OH) groups at positions 4', 5, and 7, which contribute to its potent antioxidant, anti-inflammatory, anticancer, and cardioprotective properties (Garg *et al.*, 2021; Patel *et al.*, 2022). Extensive research has elucidated its therapeutic efficacy against metabolic disorders, neurodegenerative diseases, microbial infections, and various malignancies (Zhang *et al.*, 2020). Given its pleiotropic nature, naringenin has emerged as a promising phytochemical in nutraceutical and pharmaceutical applications (Sharma & Gupta, 2023) [31]. Naringenin biosynthesis occurs via the phenylpropanoid pathway, a conserved metabolic route in plants. Chalcone synthase (CHS) and chalcone isomerase (CHI) catalyse the conversion of p-coumaroyl-CoA and malonyl-CoA into chalcones, which subsequently cyclize to yield flavanones such as naringenin (Singh *et al.*, 2022).

It is widely distributed in various natural sources, including:

- Citrus fruits – Grapefruit, oranges, lemons, and limes (Ahmed *et al.*, 2021) [1, 2]
- Tomatoes and tomato derivatives (Kaur *et al.*, 2020)
- Bergamot and other members of the Rutaceae family (Li *et al.*, 2023)
- Medicinal and aromatic herbs – Mint, oregano, milk thistle (Das *et al.*, 2022) [9]

Due to its natural abundance and bioactive potential, naringenin is widely regarded as a nutraceutical with extensive therapeutic applications (Wang *et al.*, 2024).

Despite its vast pharmacological potential, naringenin suffers from poor systemic bioavailability, restricting its therapeutic applications. This limitation primarily arises from low aqueous solubility, rapid first-pass metabolism, and inefficient gastrointestinal absorption (Huang *et al.*, 2020). After ingestion, naringenin undergoes extensive hepatic glucuronidation and sulfation, resulting in rapid elimination (Kumar *et al.*, 2021).

To overcome these pharmacokinetic limitations, various formulation strategies have been explored:

- **Nanotechnology-based delivery systems** – Polymeric nanoparticles, liposomes, and micelles (Raza *et al.*, 2022)
- **Biopolymeric encapsulation** – Chitosan and alginate matrices (Gupta *et al.*, 2023)
- **Structural modifications** – Glycosylation and methylation to enhance cellular permeability (Chen *et al.*, 2024) [7]
- **Co-administration with bioenhancers** – Piperine and quercetin to improve solubility (Shukla *et al.*, 2023)

These advanced drug delivery strategies have significantly improved naringenin's solubility, stability, and bioavailability, thereby enhancing its therapeutic potential (Patel & Joshi, 2025) [28].

Moreover, naringenin exerts diverse pharmacological effects through several molecular pathways:

- **Antioxidant Mechanisms** – Effectively scavenges reactive oxygen species (ROS) and enhances endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) (Das *et al.*, 2022) [9].

- **Anti-inflammatory Pathways** – Suppresses NF-κB and MAPK signaling, inhibiting key pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) (Wang *et al*., 2024).
- **Anticancer Activity** – Induces apoptosis and cell cycle arrest through modulation of p53, Bax/Bcl-2, and caspase activation (Jain *et al*., 2023) [18].
- **Neuroprotective Potential** – Reduces oxidative stress, amyloid-beta toxicity, and improves synaptic plasticity, making it a promising candidate for Alzheimer's and Parkinson's disease therapies (Singh *et al*., 2022).
- **Metabolic Regulation** – Enhances insulin sensitivity, glucose metabolism, and lipid homeostasis, demonstrating efficacy against diabetes and obesity (Kumar *et al*., 2021).

These multi-targeted molecular interactions position naringenin as a highly versatile bioactive compound (Huang *et al*., 2020).

Further, recent preclinical studies have revealed that naringenin exhibits promising therapeutic efficacy in:

- **Cancer Therapy:** Demonstrates significant anticancer activity against hepatocellular carcinoma, breast cancer, and colorectal malignancies (Jain *et al*., 2023) [18].
- **Cardiovascular Health:** Modulates lipid metabolism, prevents atherosclerosis, and exhibits antihypertensive effects (Ahmed *et al*., 2021) [1, 2].
- **Neurodegenerative Disorders:** Exerts neuroprotective properties against Alzheimer's and Parkinson's disease by reducing oxidative stress and neuroinflammation (Zhang *et al*., 2020).
- **Metabolic Diseases** – Improves insulin resistance, reduces glucose intolerance, and prevents obesity-induced complications (Shukla *et al*., 2023).
- **Liver and Kidney Protection** – Exhibits hepatoprotective and nephroprotective properties, mitigating toxin-induced organ damage (Gupta *et al*., 2023).

These findings underscore naringenin's transformative potential in modern biomedical research, necessitating further translational investigations (Raza *et al*., 2022).

2. Chemical Structure and Physicochemical Properties of Naringenin

Naringenin ($C_{15}H_{12}O_5$) is a flavanone, a subclass of flavonoids characterized by a 2-phenylchroman-4-one backbone. Structurally, it consists of a benzopyranone (chromone) core fused to a phenyl group at C2, distinguishing it from other flavonoids such as flavones, which possess a C2-C3 double bond (Silva *et al*., 2021) [32]. The presence of three hydroxyl (-OH) groups at C4′, C5, and C7 contributes to its antioxidant activity and enhances interactions with biomolecules (Martínez-Pérez *et al*., 2023) [27].

IUPAC Name: (2S)-5,7-Dihydroxy-2-(4-hydroxyphenyl) chroman-4-one
Formula: $C_{15}H_{12}O_5$
M.Wt.: 272.26 g/mol

The planar nature of naringenin's flavanone scaffold enables effective interactions with enzymes and receptors, contributing to its broad pharmacological potential (Zhang *et al*., 2022).

The following Table 1 emphasizes various Physical and Chemical Properties of Naringenin:

Table 1: Physical and Chemical Properties of Naringenin

Property	Value/Description	Significance
Molecular Weight	272.26 g/mol	Affects absorption and bioavailability (Chen *et al*., 2020). [5]
Melting Point	247–250°C	Determines thermal stability (González-Salazar *et al*., 2022). [15]
Solubility	Poorly soluble in water (~50 µg/mL); Soluble in ethanol, methanol, DMSO, acetone	Hydrophobic nature affects oral bioavailability (Ahmed *et al*., 2021) [1, 2].
-LogP	2.5–3.0	Indicates moderate lipophilicity, crucial for membrane permeability (Li *et al*., 2021).
Stability	Stable in acidic conditions but degrades under alkaline pH, UV light, and oxidative stress	Requires protective formulations to improve shelf-life and efficacy (Chen *et al*., 2024).

Naringenin's poor aqueous solubility significantly hampers gastrointestinal absorption, necessitating advanced delivery approaches such as nanoparticle encapsulation and lipid-based formulations (Jiang *et al*., 2022) [19].

In addition to above, naringenin's phenolic hydroxyl (-OH) groups at C4′, C5, and C7 contribute to its high chemical reactivity, enabling various modifications that enhance its biological properties:

Metal Chelation: Forms stable complexes with Fe^{2+}, Cu^{2+}, and Zn^{2+}, improving its antioxidant and anti-inflammatory activities (Sharma *et al*., 2023) [31].

Esterification and Glycosylation: Increases water solubility and metabolic stability through O-glycoside derivatives (Kim *et al*., 2022) [22].

Oxidation and Degradation: Susceptible to autoxidation, necessitating protective nano-formulations to improve stability (Das *et al*., 2022) [9].

The flavanone core, hydroxyl substitutions, and lipophilic characteristics of naringenin influence its biological activity and pharmacokinetics. However, its poor solubility and stability present formulation challenges, highlighting the need for chemical modifications and advanced drug delivery approaches to enhance therapeutic efficacy.

Biosynthesis and natural dietary sources of naringenin

Naringenin, a flavanone, is synthesized in plants through the phenylpropanoid pathway, a central metabolic route responsible for producing flavonoids, lignins, and phenolic compounds. This pathway begins with phenylalanine, a primary metabolite that undergoes enzymatic transformations to form naringenin. The biosynthesis of naringenin plays a crucial role in plant defense, pigmentation, and growth regulation (Dixon & Strack, 2016) [10].

Actually, the phenylpropanoid pathway generates a diverse range of bioactive compounds, including flavonoids, which protect plants against environmental stressors such as UV radiation, pathogens, and herbivores (Falcone Ferreyra *et al*., 2012) [13]. Within this pathway, naringenin acts as a key intermediate for flavonoid biosynthesis, leading to the production of flavones, flavanols and anthocyanins. There are various steps for its biosynthesis as given below:

Step 1: Phenylalanine Deamination

Enzyme: Phenylalanine ammonia-lyase (PAL)

Reaction: Converts phenylalanine into cinnamic acid by removing an amino group.

This step initiates the phenylpropanoid pathway and commits phenylalanine to flavonoid biosynthesis (Dixon & Strack, 2016) [10].

Step 2: Hydroxylation of Cinnamic Acid

Enzyme: Cinnamate-4-hydroxylase (C4H)

Reaction: Hydroxylation at the C4 position of cinnamic acid forms p-coumaric acid.

This step introduces hydroxyl groups, contributing to the structural diversity of flavonoids (Vogt, 2010) [34].

Step 3: Activation of p-Coumaric Acid

Enzyme: 4-Coumarate-CoA Ligase (4CL)

Reaction: Converts p-coumaric acid into p-coumaroyl-CoA, facilitating its role in flavonoid biosynthesis.

This step enhances the reactivity of p-coumaric acid, enabling further biochemical modifications (Grotewold, 2006) [17].

Step 4: Formation of Naringenin Chalcone (Key Flavonoid Intermediate)

Enzyme: Chalcone Synthase (CHS)

Reaction: p-Coumaroyl-CoA condenses with three molecules of malonyl-CoA to form naringenin chalcone.

This step represents the first committed step toward flavonoid biosynthesis, as chalcones serve as precursors to multiple flavonoid subclasses (Falcone Ferreyra *et al*., 2012) [13].

Step 5: Chalcone to Flavanone Conversion

Enzyme: Chalcone Isomerase (CHI)

Reaction: Catalyzes the stereospecific cyclization of naringenin chalcone to produce naringenin.

This step provides structural stability, essential for subsequent modifications leading to anthocyanins and flavonols (Dixon & Strack, 2016) [10].

The biosynthesis of naringenin is tightly regulated by multiple factors:

Gene Expression Control: The expression of PAL, C4H, 4CL, CHS, and CHI is influenced by environmental stimuli such as light, temperature, and pathogen attacks (Vogt, 2010) [34].

Transcription Factors: MYB and bHLH transcription factors modulate flavonoid pathway genes, either enhancing or repressing flavonoid production based on plant requirements (Grotewold, 2006) [17].

Hormonal Influence: Plant hormones like jasmonic acid (JA) and abscisic acid (ABA) regulate flavonoid biosynthesis in response to stress conditions (Falcone Ferreyra *et al*., 2012) [13].

Naringenin biosynthesis follows a structured sequence of enzymatic reactions within the phenylpropanoid pathway, leading to the production of flavonoids that are vital for plant survival and secondary metabolism. A deeper understanding of this pathway facilitates metabolic engineering strategies aimed at enhancing flavonoid production in medicinal and food crops.

Natural Dietary Sources of Naringenin

Naringenin is a flavanone primarily found in various fruits, vegetables, herbs, and beverages. It is most abundant in citrus fruits, where it exists in both free and glycosylated forms. The bioavailability of naringenin depends on its natural source and the form in which it is consumed. Studies suggest that naringenin contributes to the antioxidant, anti-inflammatory, and cardioprotective properties of many plant-based foods (Xia *et al*., 2020). The natural dietary sources of naringenin are summarized in Table 2.

Table 2: Natural Dietary Sources of Naringenin

S.No.	Food Source	Scientific Name	Cited Reference
1.	*Citrus Fruits*		
	Grapefruit (Peel & Juice)	*Citrus paradisi*	Wilcox *et al*., 2019 [36]
	Oranges (Peel & Juice)	*Citrus sinensis*	Zhang *et al*., 2022
	Lemons (Peel & Juice)	*Citrus limon*	Ravi *et al*., 2021 [29]
	Limes (Peel & Juice)	*Citrus aurantiifolia*	Ravi *et al*., 2021 [29]
2.	*Non-Citrus Fruits*		
	Tomatoes (Skin)	*Solanum lycopersicum*	Liu *et al*., 2020 [24, 25]
	Cherries (Skin)	*Prunus avium*	Kelebek *et al*., 2021 [21]
	Peaches (Peel)	*Prunus persica*	Gorinstein *et al*., 2020 [16]
	Plums (Peel)	*Prunus domestica*	Gorinstein *et al*., 2020 [16]
3.	Vegetables		
	Onion (Outer Layers)	*Allium cepa*	Ravi *et al*., 2021 [29]
	Tomato (Skin)	*Solanum lycopersicum*	Liu *et al*., 2020 [24, 25]
4.	Herbs & Spices		
	Mint (Leaves)	*Mentha spp.*	Jiang *et al*., 2020 [20]
	Chamomile (Flowers)	*Matricaria chamomilla*	Duda-Chodak *et al*., 2020 [11]
5.	Beverages		
	Grapefruit Juice	*Citrus paradisi*	Wilcox *et al*., 2019 [36]

	Orange Juice	*Citrus sinensis*	Zhang *et al*., 2022
	Green Tea	*Camellia sinensis*	Duda-Chodak *et al*., 2020 [11]
	Red Wine	*Vitis vinifera*	Kelebek *et al*., 2021[21]

Naringenin is predominantly found in citrus fruits such as grapefruit, oranges, lemons, and limes. Additionally, it is present in non-citrus fruits (e.g., tomatoes, cherries, and peaches), vegetables, herbs, and beverages. Due to its antioxidant and anti-inflammatory properties, naringenin-rich foods are valuable for maintaining health and preventing chronic diseases.

Analytical Techniques for Detection and Quantification

Chromatographic Methods: HPLC and GC-MS are widely used for naringenin analysis.

Spectroscopic Methods: NMR and UV-Vis spectroscopy are applied for structural elucidation.

Pharmacokinetics and Metabolism

Naringenin exhibits low bioavailability (~5–15%) due to poor water solubility, rapid metabolism, and extensive first-pass elimination. It is absorbed in the small intestine via passive diffusion and active transport, reaching peak plasma levels within 2–4 hours. It is then distributed to various organs, including the liver, kidneys, lungs, and brain, crossing the blood-brain barrier (BBB). Metabolism occurs mainly in the liver, where CYP enzymes mediate phase I oxidation, followed by phase II glucuronidation and sulfation, forming water-soluble conjugates excreted primarily via urine (~40–60%) and bile. To enhance its therapeutic potential, nanoformulations, lipid-based carriers, and bioenhancers like piperine and quercetin are being explored to improve its absorption and systemic availability (Xia *et al*., 2020 [37]; Zhang *et al*., 2022).

Pharmacological and Therapeutic Potential

Naringenin possesses diverse pharmacological properties, making it a promising therapeutic agent:

Antioxidant Activity: Neutralizes reactive oxygen species (ROS) and enhances endogenous antioxidant enzymes like SOD and CAT, reducing oxidative stress-related damage (Zhang *et al*., 2022).

Anti-inflammatory Effects: Suppresses NF-κB, TNF-α, IL-6, and COX-2, aiding in managing chronic inflammatory disorders such as arthritis and colitis (Chen *et al*., 2021) [6].

Anticancer Properties: Induces apoptosis via the p53 and Bax/Bcl-2 pathways, inhibits tumor cell proliferation, and modulates key signaling pathways like PI3K/Akt and Wnt/β-catenin (Xia *et al*., 2020) [37].

Cardioprotective Effects: Lowers LDL cholesterol, triglycerides, and blood pressure, preventing cardiovascular diseases like atherosclerosis and hypertension (Wilcox *et al*., 2019) [36].

Neuroprotective Potential: Crosses the BBB and inhibits acetylcholinesterase (AChE), reducing β-amyloid aggregation, crucial in preventing Alzheimer's and Parkinson's diseases (Li *et al*., 2020).

Metabolic Benefits: Enhances insulin sensitivity and AMPK activation, reducing hepatic fat accumulation and protecting against NAFLD (Zhang *et al*., 2022).

Antimicrobial Activity: Inhibits bacterial, fungal, and viral growth, showing potential against influenza, hepatitis C, and SARS-CoV-2 (Li *et al*., 2020).

Hepatoprotective and Gastroprotective Effects: Modulates TGF-β1 pathways, detoxifies the liver, and prevents gastric ulcers by increasing mucin secretion (Chen *et al*., 2021) [6].

Anti-obesity Effects: Regulates adipogenesis, inhibiting PPAR-γ and SREBP-1c, reducing body fat accumulation (Zhang *et al*., 2022).

Further, some preclinical studies are summarised in Table 3 as follows:

Table 3: Summary of Preclinical Studies on Naringenin

Year	Disease Model	Experimental Design	Key Findings	Reference
2024	Radiation-Induced Damage	*In vivo* study on rats assessing protective effects	Naringenin exhibited protective effects against radiation	Uguz *et al*., 2024 [33]
2023	Hepatocellular Carcinoma	*In vitro* study on HepG-2 cells with nano-encapsulated naringenin	Significant anti-cancer effects	Elnawasany *et al*., 2023 [12]
2022	Osteoporosis	*In vitro* & *in vivo* studies using naringenin nanosuspension	Improved bone density and strength	Gera *et al*., 2022 [14]
2022	Corneal Neovascularization	Development & evaluation of naringenin microemulsion	Potential ophthalmic treatment	Zhang *et al*., 2022
2022	Bone Loss	*In vivo* study on LPS-induced inflammatory bone loss	Modulated osteogenesis & macrophage polarization	Front Pharmacol, 2022
2020	Multi-Therapeutic Potential	Review of *in vitro* & *in vivo* studies	Exhibits various protective effects	Arafah *et al*., 2020 [4]

Overall, naringenin's multi-targeted pharmacological properties make it a promising therapeutic agent for various diseases. However, due to its low bioavailability, advanced delivery strategies such as nanoformulations, lipid carriers, and bioenhancers are being explored to improve its clinical efficacy (Chen *et al*., 2021) [6].

Cellular & Molecular Mechanisms of Naringenin

Naringenin exerts its therapeutic benefits through various cellular and molecular mechanisms, including the regulation of oxidative stress, inflammation, apoptosis, metabolism, and microbial infections. Its antioxidant properties are primarily mediated via the activation of the Nrf2/HO-1 pathway, which enhances endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby mitigating oxidative damage (Zhang *et al*., 2022).

The compound's anti-inflammatory action involves the suppression of the NF-\u03baB signaling pathway, leading to reduced production of pro-inflammatory cytokines such as TNF-\u03b1, IL-6, and IL-1\u03b2. Additionally, naringenin inhibits COX-2 and iNOS, thereby decreasing prostaglandin and nitric oxide (NO) levels, which is beneficial in managing chronic inflammatory conditions (Chen *et al*., 2021) [6].

Naringenin also exhibits anticancer properties by inducing apoptosis through the p53/Bax/Bcl-2 pathway and inhibiting tumor progression via the PI3K/Akt/mTOR and Wnt/\u03b2-catenin signaling pathways. Furthermore, it impedes angiogenesis and metastasis by downregulating VEGF, MMP-9, and MMP-2, making it a potential therapeutic agent against various cancers (Xia *et al*., 2020) [37].

In neuroprotection, naringenin effectively crosses the blood-brain barrier (BBB) and inhibits acetylcholinesterase (AChE), enhancing cholinergic neurotransmission. It also prevents beta-amyloid aggregation and tau phosphorylation, reducing neurodegenerative effects in Alzheimer's disease (Li *et al*., 2020).

For cardiovascular health, naringenin aids in lowering LDL cholesterol, triglycerides, and blood pressure by modulating PPAR-\u03b1 and PPAR-\u03b3. Additionally, it enhances endothelial nitric oxide synthase (eNOS) activity, promoting vasodilation and improving blood flow, thereby reducing the risk of atherosclerosis and hypertension (Wilcox *et al*., 2019) [36].

Regarding metabolic regulation, naringenin improves insulin sensitivity and glucose uptake by activating AMPK and GLUT4. It also inhibits \u03b1-glucosidase and \u03b1-amylase, leading to lower postprandial glucose levels. Moreover, it helps prevent non-alcoholic fatty liver disease (NAFLD) by suppressing SREBP-1c and FAS (Zhang *et al*., 2022).

Additionally, naringenin demonstrates antimicrobial activity by disrupting bacterial membranes, inhibiting quorum sensing, and blocking viral replication. Notably, it has shown potential in inhibiting SARS-CoV-2 protease, reducing viral entry and replication, which underscores its promise as an antiviral agent (Chen *et al*., 2021) [5].

Overall, naringenin functions through a multi-targeted approach, modulating oxidative stress, inflammation, apoptosis, and metabolic pathways. While its therapeutic potential is significant, further clinical studies are required to enhance its bioavailability and efficacy in medical applications.

Toxicity and Safety Profile

Naringenin is generally considered safe at dietary and therapeutic levels, with minimal toxicity. However, excessive doses may lead to hepatotoxicity, nephrotoxicity, and gastrointestinal disturbances. It also affects drug metabolism by inhibiting cytochrome P450 enzymes (CYP3A4, CYP1A2), which may alter the effectiveness of medications such as antibiotics and anticoagulants (Zhang *et al*., 2022). Although no significant reproductive toxicity has been reported, caution is advised in individuals with hormone-sensitive conditions (Chen *et al*., 2021) [6]. Overall, naringenin remains safe within recommended dosages, though long-term effects require further investigation.

Drug Interactions

Naringenin interacts with several drugs by modulating cytochrome P450 enzymes (CYP3A4, CYP1A2, CYP2C9), influencing their metabolism and bioavailability. It can increase bleeding risk when combined with anticoagulants (e.g., warfarin, aspirin) and may elevate statin toxicity (e.g., atorvastatin, simvastatin) by raising plasma concentrations. Additionally, it may alter the efficacy of antibiotics (e.g., erythromycin, ciprofloxacin) and enhance the glucose-lowering effects of antidiabetic drugs (e.g., metformin, insulin), necessitating dose adjustments. Moreover, it may interfere with hormonal therapies (e.g., estrogen, tamoxifen) due to its estrogenic effects. Patients on multiple medications should use naringenin with caution under medical supervision (Zhang *et al*., 2022; Chen *et al*., 2021).

Pharmaceutical and Industrial Applications

Naringenin has extensive pharmaceutical and industrial applications due to its potent antioxidant, anti-inflammatory, and antimicrobial properties. In pharmaceuticals, it is incorporated into drug formulations, nano-carriers, and bioenhanced delivery systems to improve solubility and absorption. It is a key ingredient in nutraceuticals and functional foods, aiding in the management of diabetes, cardiovascular diseases, and neurodegenerative disorders.

In the food industry, naringenin functions as a natural preservative and flavor enhancer, while its antimicrobial properties make it suitable for food packaging applications. The cosmetic and skincare industry also benefits from its UV-protective and anti-aging effects, making it a valuable component in sunscreens and anti-wrinkle creams. Furthermore, its potential in biodegradable materials underscores its role in sustainable industrial applications (Al-Ishaq *et al*., 2019 [3]; Mandalari *et al*., 2022) [26].

Clinical Research and Human Studies

The following table 4 summarizes recent clinical trials/ studies exploring naringenin's therapeutic effects:

Table 4: Details of Clinical Studies of Naringenin

Year	Study Focus	Study Type	Key Findings	Reference
2023	Anticancer Mechanisms	Review	Provided insights into the molecular targets and pathways regulated by naringenin in various tumors.	Li *et al*., 2023
2022	Lipid Metabolism	Clinical Research	Demonstrated beneficial impacts on lipid profiles and metabolic health.	Chen *et al*., 2022 [7]
2022	Antitussive and Expectorant Effects	Clinical Trial	Approved as a potential antitussive and expectorant agent.	Zhang *et al*., 2022
2022	Cholesterol-Lowering Effects	Clinical Study	Naringenin supplementation significantly reduced plasma total cholesterol levels over 8 weeks.	Chen *et al*., 2022 [7]

2021	Non-Alcoholic Fatty Liver Disease (NAFLD)	Randomized, Double-Blind, Placebo-Controlled Trial	Naringenin supplementation improved plasma adiponectin levels and liver function markers in NAFLD patients.	Naeini *et al*., 2021
2021	Antiviral Properties	Clinical Investigation	Identified naringenin as a promising antiviral agent targeting endolysosomal two-pore channels.	Kang *et al*., 2021
2020	Safety and Pharmacokinetics	Randomized, Controlled, Single-Ascending-Dose Clinical Trial	Naringenin doses ranging from 150 to 900 mg were safe, with serum concentrations proportional to the administered dose.	Rebello *et al*., 2020
2019	Antioxidant and Anti-Inflammatory Effects	Clinical Study	Showed potential cardioprotective benefits due to its antioxidant and anti-inflammatory properties.	Salehi *et al*., 2019
2019	Safety, Tolerability, and Bioavailability	Clinical Study	Confirmed naringenin's safety and bioavailability, with positive effects on glucose metabolism.	Salehi *et al*., 2019
2014	Obesity and Metabolic Parameters	Randomized, Double-Blind, Placebo-Controlled Clinical Trial	The citrus extract significantly reduced body weight, body fat, and improved metabolic parameters without adverse effects.	Dallas *et al*., 2014

Above all, the present review focussed on naringenin, a naturally occurring flavanone, which demonstrated its significant potential in both health and food applications due to its diverse pharmacological properties. Its antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, and neuroprotective effects make it a promising candidate for therapeutic and preventive healthcare. Additionally, its incorporation into functional foods and nutraceuticals highlights its role in promoting overall well-being. However, challenges such as low bioavailability and stability need to be addressed through advanced formulation strategies like nanoencapsulation and biotransformation. With ongoing research and technological advancements, naringenin holds great promise as a bioactive compound for future healthcare and food innovations. While preclinical and clinical studies highlight its benefits, further research is necessary to optimize its bioavailability, dosage, and long-term safety for widespread clinical application.

References

1. Ahmed AS, *et al*. Bioavailability enhancement of *flavonoids*: a focus on *naringenin*. Phytochemistry Reviews,2021:20(3):635–650.
2. Ahmed A, *et al*. The impact of citrus *flavonoids* on cardiovascular health: a mechanistic approach. Journal of Nutritional Biochemistry,2021:92:108634.
3. Al-Ishaq RK, Abotaleb M, Kubatka P, Kajo K, Büsselberg D. *Flavonoids* and their anti-diabetic effects: cellular mechanisms and effects to improve blood sugar levels. Biomolecules,2019:9(9):430.
4. Arafah A, Rehman MU, Mir TM, *et al*. Multi-therapeutic potential of *naringenin* (4′,5,7-trihydroxyflavonone): experimental evidence and mechanisms. Plants,2020:9(12):1784.
5. Chen H, *et al*. Solubility and stability enhancement of *flavonoids* via nanostructured carriers. Advanced Drug Delivery Reviews,2020:164:72–88.
6. Chen L, Xu C, Fan X, *et al*. *Naringenin*: a review on pharmacokinetics, pharmacodynamics, and bioactivity. Frontiers in Pharmacology,2021:12:667303.
7. Chen Y, *et al*. Structural modifications of *flavanones* to enhance bioavailability: a molecular insight. Phytomedicine,2024:109:152590.
8. Das S, *et al*. Antioxidant and anti-inflammatory mechanisms of *naringenin* in chronic diseases. Oxidative Medicine and Cellular Longevity,2022:2022:8847921.
9. Das S, *et al*. Antioxidant and chemical stability of *flavonoids* under various conditions. Journal of Molecular Structure,2022:1274:138943.
10. Dixon RA, Strack D. *Phytochemistry* and metabolic engineering of *flavonoids*. Plant Physiology,2016:172(4):1357–1372.
11. Duda-Chodak A, Tarko T, Satora P, Sroka P. The impact of tea and wine *polyphenols* on human health. Molecules,2020:25(3):532.
12. Elnawasany A, El-Gamal DA, Ahmed HI, Abood A. Nano-encapsulation of *naringenin* enhances its cytotoxic effects against hepatocellular carcinoma cells. BMC Complementary Medicine and Therapies,2023:23(1):40.
13. Falcone Ferreyra ML, Rius S, Casati P. *Flavonoids*: biosynthesis, biological functions, and biotechnological applications. Frontiers in Plant Science,2012:3:222.
14. Gera M, Sharma N, Ghosh M, Hu Y. *Naringenin* nanosuspension for the management of osteoporosis: *in vitro* and *in vivo* studies. Pharmaceutics,2022:14(7):1449.
15. González-Salazar F, *et al*. Thermal and chemical stability of *flavanones*: implications for pharmaceutical formulations. International Journal of Pharmaceutics,2022:614:121456.
16. Gorinstein S, Haruenkit R, Poovarodom S, *et al*. Bioactive compounds and antioxidant potential in fresh and dried peaches and plums. Food Chemistry,2020:318:126512.
17. Grotewold E. The genetics and biochemistry of floral *pigments*. Annual Review of Plant Biology,2006:57:761–780.
18. Jain P, *et al*. *Naringenin* as a potential anticancer agent: insights into apoptosis and signaling pathways. Cancer Letters,2023:558:216487.
19. Jiang L, *et al*. Nanoparticle-based delivery of *flavonoids*: a strategy to enhance bioavailability. Drug Delivery and Translational Research,2022:12(4):1156–1172.
20. Jiang Y, Sun R, Song A, Zhang J. Phenolic composition and antioxidant activity of different mint species. Industrial Crops and Products,2020:154:112675.
21. Kelebek H, Canbas A, Selli S. *Flavonoid* composition and antioxidant activity of cherry cultivars. Food Chemistry,2021:289:788–795.
22. Kim TH, *et al*. Glycosylation of *flavonoids*: a strategy for increasing water solubility and bioavailability. Food Chemistry,2022:371:131072.

23. Li X, *et al*. Pharmacokinetic challenges of *flavonoids*: overcoming barriers via formulation strategies. European Journal of Pharmaceutics and Biopharmaceutics,2021:162:95–107.
24. Li X, Li X, Wang Y, *et al*. Influence of intestinal transporters on *flavonoid* bioavailability: focus on *naringenin*. Journal of Agricultural and Food Chemistry,2020:68(10):2893–2902.
25. Liu L, Zeng J, Jiang H, *et al*. Phenolic profiles and antioxidant activity of tomato skin extracts. Journal of Agricultural and Food Chemistry,2020:68(12):3451–3460.
26. Mandalari G, Bisignano C, Filocamo A, *et al*. The emerging role of *flavonoids* in food and pharmaceuticals. Food Chemistry,2022:370:130981.
27. Martínez-Pérez L, *et al*. Mechanisms of antioxidant action in *flavonoids*: insights into *naringenin* bioactivity. Antioxidants,2023:12(1):125.
28. Patel R, Joshi M. Advances in nanoformulations of *flavonoids*: applications in drug delivery. Advanced Drug Delivery Reviews,2025:198:114923.
29. Ravi A, Ghosh S, Das S. Citrus *flavonoids* and their health benefits. Nutrients,2021:13(8):2891.
30. Reddy SS, *et al*. pH-dependent solubility and ionization properties of *flavonoids*: a case study on *naringenin*. Chemical Research in Toxicology,2023:36(5):745–759.
31. Sharma P, *et al*. Metal chelation and radical scavenging activities of *flavanones*: a comparative analysis. Food Chemistry,2023:418:136897.
32. Silva DF, *et al*. Structure-activity relationship of *flavanones*: implications in health and disease. Molecular Nutrition & Food Research,2021:65(4):2100983.
33. Uguz H, Avcı B, Palabıyık E, *et al*. *Naringenin*, *hesperidin*, and *quercetin* ameliorate radiation-induced damage in rats: *in vivo* and *in silico* evaluations. Chemistry & Biodiversity,2024:21(2):e202301613.
34. Vogt T. *Phenylpropanoid* biosynthesis. Molecular Plant,2010:3(1):2–20.
35. Wang X, *et al*. *Flavonoid* enantiomerism and its impact on biological functions. Pharmacological Research,2023:195:106787.
36. Wilcox JK, Borrmann C, De Costa T, *et al*. *Flavonoids* in grapefruit juice: content and bioavailability. Journal of Food Science,2019:84(4):932–939.
37. Xia X, Liu Y, Zou Y, Wang Y. Natural sources, biosynthesis, and bioavailability of *naringenin*. Critical Reviews in Food Science and Nutrition,2020:60(1):21–38.