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Naringenin - An Overview of Citrous Flavonoid

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Abstract: Citrus fruits are rich in naringenin, a naturally occurring flavanone that has been thoroughly investigated for its diverse biological and pharmacological properties. This narrative review addresses the chemical structure, natural sources, metabolism, and medicinal properties of naringenin, focusing particularly on its anti-inflammatory, antioxidant, antidiabetic, hepatoprotective, neuroprotective, and anticancer effects. Experimental research suggests that these effects are mediated via the control of several molecular pathways. However, naringenin's low water solubility and restricted bioavailability prevent it from being used therapeutically. Novel drug delivery technologies, particularly nanocarriers, and recent advancements in extraction procedures have demonstrated promise in circumventing these constraints and improving its pharmacological efficacy. All things considered, this review emphasizes naringenin's increasing significance as a bioactive phytochemical and its potential for further advancement as a medicinal agent.

Keywords: *Naringenin, Citrous Flavonoids, Bioavailability, Anti-Inflammatory, Cancer.*

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I. INTRODUCTION

Flavonoids are natural substances present in plants, herbs, and drinks, with a diverse array of more than 4,000 varieties. Naringenin (NRG), a specific type known as flavanones, was first identified in 1907 as a chalcone by Control and Tutin (1). Despite their ability to dissolve in alcohol and exist in various forms such as NRG or glycosidic forms, the low absorption of NRG by the body due to their limited water solubility has presented challenges in their practical use. To enhance the bioavailability of NRG, various initiatives have been undertaken. These include creating carriers for controlled release and aiming for targeted delivery to designated organs or tissues. Such measures are intended to boost effectiveness while reducing adverse effects. (2) These specialized carriers, which encapsulate plant compounds such as NRG or naringin, facilitate better water solubility, improved bioavailability, and increased therapeutic efficacy, thereby reducing the required drug dosage(3–5)

Flavonoids, which are phytochemicals derived from plants, account for the various colors of plant parts, including the yellow, orange, and red hues found in flowers. Over 4,000 flavonoids, including flavanols, flavones, flavanonols, flavanones, and isoflavones, have been documented in food plants and are regulated for inclusion in the human diet. (6) Flavonoids, found in fruits and vegetables, have several health benefits. (7) Flavonoid biosynthesis occurs through a combination of shikimic acid and acylpolymalonate metabolic pathways. A The starting compound is phenylpropane, a cinnamic acid derivative derived from shikimic acid, into which three acetate residues are incorporated, followed by ring closure. The chalcone structure serves as an intermediate for flavones, allowing for hydroxylation and reduction at various positions.

(8) Recent studies have demonstrated that in adults, a diet abundant in flavonoids leads to reductions in total cholesterol, low-density lipoproteins, and plasma triglycerides, along with a decrease in the occurrence of cardiovascular disease and osteoporosis. (6) Naringenin and hesperetin, which are natural flavonoids, are commonly found as aglycones and glycosides in certain edible fruits and vegetables. Grapefruit has the highest concentration of naringenin, which is utilized in cosmetics, perfumery, and a range of pharmaceutical products. Properties such as hypocholesterolemic, antiesterogenicity, hypolipidemy, hypertension, and anti- inflammatory effects have been recognized.

II. NARINGENIN

Naringenin is a polyphenol known as 4,5,7-trihydroxy-flavanone, which belongs to the subclass of 4 hydroxy flavanones and contains three hydroxyl groups. Its heterocyclic structure features a ketone oxygen at the fourth carbon and a chiral center at the second carbon, which contribute to its stereospecific profiles and various bioactivities. This tasteless and colorless flavanone is

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especially abundant in citrus fruits. The naringenin concentration is highest in grapefruit (43.5 mg/100 ml), followed by orange juice (2.13 mg/100 ml) and the lowest concentration found in lemon juice (0.38 mg/100 ml). (9,10) The synthesis of naringenin in various parts of the plant is influenced by multiple factors, including genetics, soil/environmental light conditions, germination stage, maturity, and storage conditions. (11)

Naringenin (molecular formula: C15H12O5) is the glycoside component of the naringin monomer, which possesses an interesting chemical structure. (12) It features a straightforward flavonoid structure comprising 15 carbon atoms and three rings, two of which are benzene rings that link the three carbon chains. (13) Naringenin, which has a molar mass of 272.3 and melts at 251.0 ◦C, is chemically designated as 4',5,7-trihydroxyflavone. (14) Naringenin, found in nature as a solid, is nearly insoluble in water but dissolves in organic solvents like ethanol, ether, dimethylformamide, and dimethylsulfoxide. Naringenin occurs mainly in citrus fruits such as lemons, oranges, blood oranges, grapes, and grapefruit, with research indicating that grapefruit peel may have the highest concentration of it. (15) The compound has been linked to a variety of advantageous effects. (16) In a study involving male Wistar rats on a high-cholesterol diet, for instance, naringenin administration significantly lowered the risk of renal failure. In a similar fashion, another study found that rats given naringenin exhibited a noteworthy decrease in hyperlipidemia and hepatic steatosis. (17) As per the findings of Yi Qiao Hua and colleagues, Naringenin led to a decrease in the expression levels of TNF-α and IL-6, drew macrophages to the site, and mitigated liver inflammation. (18) Moreover, it was demonstrated that bacteria such as Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus) are resistant to it. (19) Naringenin has also been shown to reduce tumor cell proliferation and migration in a dose-dependent manner in B16f10 and SK-MEL-28 (human melanoma cells) mice. (20) Moreover, naringenin diminished inflammation and hyperproliferation in the colons of Wistar rats to avert cancer development. (21) Mice with fatty liver were given naringenin (100 mg/kg/day), while a methionine-choline deficient (MCD) diet was used to induce inflammatory responses. (22) An in vitro study has demonstrated that naringenin, canrenol, apigenin, and lignocaine possess anti-cancer and antifibrotic properties. It also holds great therapeutic promise for treating diabetes. (23) Current investigations into naringenin center on its anti-inflammatory and anti-infective effects, especially regarding autoimmune inflammatory diseases and conditions resulting from specific viral and bacterial infections. Naringenin's low aqueous solubility (5.81%) poses a limitation for its clinical applicability and may be linked to an insufficient residence time of the drug at the absorption site. (24) Moreover, the substance's limited bioavailability might be connected to excessive first-pass elimination. (25,26) The enzymes naringenase and -L-rhamnosidase hydrolyze naringenin to produce prunine and rhamnose. Following the breakdown of prunine into "naringenin" by β-D-glucosidase, naringinase performs hydrolysis on "naringenin," which is then absorbed in the digestive tract. (27) Naringenin It is quickly absorbed from the digestive system, where it swiftly combines to create glucoside or thioglucoside and attaches to serum albumin. Serum albumin is subsequently delivered to vital organs including the kidneys, spleen, heart, liver, and brain, while its metabolites are eliminated through the biliary and urinary systems. (28) Advancements have been achieved in the extraction of naringenin in recent years. For example, the enzyme-assisted extraction method has a higher processing capacity and extraction efficiency and yields a purer final product than the conventional solvent extraction method. However, its operating process must consider additional influencing factors such as temperature, pH, and time. (29) The ultrasonic extraction method operates based on the unique physical characteristics of acoustic waves, which can lead to the rupture of plant cell walls or deformation of their tissues, facilitating the extraction of active compounds. While this approach diminishes the environmental impact and bolsters extraction efficiency, it is affected by ultrasonic attenuation factors and entails greater costs. (29) The ultrasound-assisted enzymatic approach (EVAE) harnesses the benefits of ultrasound and enzymes to minimize diffusion constraints at the enzyme-substrate interface and enhance reaction rates. However, it is complicated by greater operational challenges and higher costs. (30) Even though these extraction methods come with certain drawbacks, they aid in the extraction and purification of flavonoids like naringenin and further research on these substances.

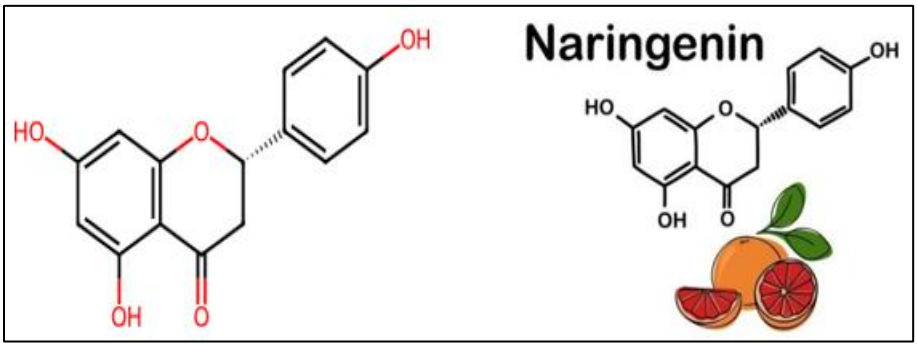

Fig 1: Structural Elucidation of Naringenin.

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➢ *Naringenin: Origin and Source*

Narrateren is found in brush as a grapefruit (115-384 mg/l 59) (31) and further listed in Bergamot, Cochena, Manone of mint, drugs, and beans. (32) To eighteen man's source was nobodybird, but the concentration is different from the picking, pickle and Environmental situation, e. g. , Citrus Aurantium (19. 7 µg / ml) Reticulated citrus (3383 3 µg / ml) Citrus Paradis (230. 0 µg / ml). (33) The solid tissue has higher concentration, while the fluid also contains a good amount of Sapanons. Naininine (Ninguentine-7-NeoHhenPoidosis) is the main spy lies in poor, oranges and a small sninina is also found in palate. Initially, Ninguenina was reported to be separated by the seeds of API, Grapefruit leaves. The skin of the tomato holds Naringenin-chalcone, which is converted to Naringenin when making ketchup. Naringenin exists as "Naringin," an inactive form that intestinal bacteria convert into "Naringenin." (34) The distribution of naringenin throughout various sections of the fruit relies on the levels of biosynthesis enzymes. As an illustration, in the peel of Solanum lycopersicum, the synthesis of chalcone and the expression of the flavanone 3-hydroxylase gene are at levels that exceed those of the chalcone isomer. This indicates that naringenin is accumulating in large quantities. (35)

Table 1: Therapeutic Potential of Naringenin in Various Metabolic Conditions.

Therapeutic	Diseases	Treatment	Targets and Effects	Experimental Model	Ref.
Anti- inflammatory	Arthritic Inflammation	5–20 mg/kg	Decreased expression of TNF-α and NF-kB mRNA. Elevated Nrf-2/HO-1s	In vivo, Wistar rats	(36)
	Cognitive effect-memory impairment	25–100 mg/kg	Reduced expression of caspase- 3, Bad, Bax, NF-kB, tumor necrosis factor-α, interleukin (IL)-6 and IL-1β	In vivo, neonatale Sprague-Dawley-Ratten	(37)
	Endometriosis	5–100 µM	Antiproliferative and proapoptotic effects (elevated Bax and Bak, activated MAPK, and inactivated PI3K). Depolarization of the potential across the mitochondrial membrane Activation of the proteins eIF2α, IRE1α, GADD153, and GRP78	In vitro, VK2/E6E7 vaginal mucosa-derived epithelial endometriosis cells and End1/E6E7 endocervix epithelial- derived endometriotic cells	(38)
	Endotoxaemia	10 mg/kg	Inhibition of TNF-α, IL-6, TLR4, inducible NO synthase (iNOS), cyclo-oxygenase-2 (COX2), NADPH oxidase-2 (NOX2), NF-kB, and mitogen-activated protein kinase (MAPK)	In vivo, Mäuse der Linie BALB/c Peritoneal macrophages acquired from the rats in vitro	(39)
	Hypertrophic scars (HS)	25–50 µM	Inhibition of hypertrophic scars. Downregulation of TNF-α , IL-1β, IL-6 and TGF-β1	In vivo, female KM mice	(40)
	Liver diseases	50 mg/kg	Oxidative stress is inhibited via the TGF-β pathway, and the trans-differentiation of hepatic stellate cells (HSC) is prevented. Induction of apoptosis, suppression of MAPK, TLR, VEGF, and TGF-β pathways, and alteration of lipid and cholesterol production.	In vivo	(41)

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	LPS-induced endotoxemia and Con A–induced Hepatitis	100 µM 50 mg/kg 10 mg/kg	Post-translational suppression of TNF- and IL-6 (without interfering with the TLR signaling cascade, cytokine mRNA stability, or protein translation)	In vitro, cell line RAW264.7 derived from murine macrophages In vivo, female C57BL/6 mice In vivo, female BALB/c mice	(42)
	Lung injury	50–100 mg/kg	Down-regulation of nuclear factor-κB, inducible NO synthase, tumor necrosis factor- α, caspase-3; elevation of heat shock protein 70	In vivo, rats	(43)
	Neuro inflammation-spinal cord injury	50–100 mg/kg	Repression of miR-223	In vivo, female Wistar rats	(44)
	Osteoarthritis	40 mg/kg	Lessening of pain behavior and enhancement of the tissue morphology. Inhibition of the expression of MMP-3 and the NF-kB pathway	In vivo, male Wistar rats	(45)
	Pain	16.7–150 mg/kg	Analgesic effect via the activation of the NO-cGMP– PKG-ATP-sensitive potassium channel pathway.Decreased recruitment of neutrophils,	In vivo, male Swiss mice	(46)
			oxidative stress in tissues, and production of cytokines (IL-33, TNF-α, and IL-1). Downregulation of the mRNA expression levels of gp91phox, cyclooxygenase (COX)-2, and preproendothelin-1. Increased expression of mRNA for nuclear factor (erythroid- derived 2)-like 2 (Nrf2), heme oxygenase (HO-1), and NF kB		
	Protective effect on renal failure	50 mg/Kg	Enhancement of kidney indicators. Reduced lipid profile and suppression of pro-oxidant and inflammation markers	In vivo, rats	(47)
Anti-oxidant	Skin damage-burns	25–100 mg/kg	Reduction of TNF-α, IL-1β, IL- 6, NO, PGE2, caspase-3, LTB4 and NF-kB levels as well as of the levels of PGE2 and caspase-3. Elevated activities of SOD, catalase, GPx, and GST	In vivo, male Wistar albino rats	(48)
`Anti-diabetic	Skin injury	Pemphigu s vulgaris (PV) serum treated HaCaT cell	Reduction of Dsg1, Dsg3, E- cadherin and ROS production; improvement of the decrease in mitochondrial membrane potential. Heightening of the activity of SOD, GSH-Px and TAC. Decreased of NOD2, RIPK2 and NF-kB p-p65,	In vitro, cell line HaCaT of human keratinocytes	(49)
	Diabetic Neuropathy	25–50 mg/kg	Mitigation of alterations in serum glucose, insulin, and pro- inflammatory cytokines (TNF- alpha, IL-1beta, and IL-6) induced by diabetes. Reduction of oxidative stress indicators. Reduction	Rats with streptozotocin-induced diabetes in vivo	(50)

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			of insulin growth factor and nerve growth factor		
	Diabetic Retinopathy	50 mg/kg	reduction of oxidative stress, apoptosis-regulating proteins (Bcl-2, Bax, and caspase-3), and neurotrophic factors (brain derived neurotrophic factor (BDNF), tropomyosin-related	Rats with streptozotocin-induced diabetes in vivo	(51)
			kinase B (TrkB), and synaptophysin)		
	Diabetes	0.05%	increased levels of insulin receptor substrate 1 (IRS 1) and glucose transporters (GLUTs 1, 3)	In vivo, streptozotocin-induced diabetic rats	(52)
	Vascular endothelial dysfunction	50–100 mg/kg	enhanced poor glucose tolerance, up SOD activity, decreased blood glucose, serum lipid, malonaldehyde, ICAM-1, and insulin resistance index values	In vivo, streptozotocin-induced diabetic rats	(53)
	Diabetic renal Impairment	5–10 mg/kg	Reduced amounts of malondialdehyde had an impact on the activity of the enzymes glutathione, catalase, and superoxide dismutase. decrease in TGF-β1, IL-1, and apoptotic activity	In vivo, streptozotocin-induced diabetic rats	(54)
Anti-cancer	Diabetes Complications	50 mg/kg	Reduced levels of lipid peroxidation in kidney and liver tissue	Alloxan- induced diabetes mice in vivo	(55)
	Breast cancer	250 µM	HER2-TK inhibition, pro- apoptotic, anti-proliferative, and anti-cancer activity	SKBR3 and MDA-MB-231 breast carcinoma cells in vitro	(56)
	Liver cancer	100–200 µM	Block in the G0/G1 and G2/M phases, p53 accumulation, nucleus damage-induced apoptosis, elevated Bax/Bcl-2 ratio, cytochrome C release, and caspase-3 sequential activation	Human hepatocellular carcinoma HepG2 cells in vitro	(57)
	Postmenopausa l breast cancer	Diets that are heavy in fat (HF), low in naringeni n (LN; 1% naringeni n), or high	Cell growth is inhibited, AMP- activated protein kinase phosphorylation is increased, Cyclin D1 expression is downregulated, and cell death is induced. Tumor growth was delayed in vivo, but the final tumor weight did not change.	E0771 mammary tumor cells in vitro. E0771 cells were implanted into ovariectomized	(58)

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		in naringeni n (HN; 3% naringeni n)		C57BL/6 mice in vivo.	
	Prostate cancer	5–50 µM	ROS generation, apoptotic induction, and inhibition of migration and proliferation. Increased Bax/Bcl-2 ratio and loss of mitochondrial membrane potential	PC3 and LNCaP prostate cancer cells in vitro	(59)
	Melanoma	25–100 µM	Antiproliferative action, a rise in the proportion of cells in the subG0/G1, S, and G2/M phases, and a fall in the G0/G1 phases	B16F10 melanoma cells in vitro	(60)
	Gliomas-brain Cancer	211 µM	Cytotoxicity	Human glioblastoma U-118 MG cells in vitro	(61)
	Breast cancer	200 mg/kg	reduced TGF-β1 production and intracellular TGF-β1 build-up. PKC activity and TGF-β1 trafficking from the trans-Golgi network are inhibited.	Breast cancer 4T1-Luc2 cells were injected into Balb/c mice in vivo.	(62)

III. INFLAMMATORY DISEASES

When there is illness or damage, macrophages release substances like cytokines, nitric oxide, and prostaglandins during inflammation. The generation of numerous such substances may lead to various inflammatory diseases, including long dies, stritis, he felt, stoun, and cancer.

(63) So, their check can be an important way to deal with many inflammatory diseases developed. Kumar and Abraham plans to make a special kind of nanopartics Nrg covered with pvp there is. (64,65) The safety and effects on the immune system of these nanoparticles were studied in male mice. It was found that they are safe and can be used for medical purposes. Their aim was to find out whether NRG can halt inflammation in mouse cells. In summary, the study demonstrated that the NRG nanoparticle could reduce bodily inflammation. It halted the production of proteins that facilitate communication and decreased the production of substances that trigger inflammation. Investigated the effect of energy stored in gelatin-covered PCL nanoparticles on human mesenchymal stem cells. (66) The small nrg particles helped reduce cell swelling. This means they can help protect the cells from damage when they do not receive enough oxygen and glucose (67,68) Their minor medicines can be useful to handle brain vascular accident and other brain intakes. Rajaman and others, was suggested to use a very small mixture of drug to keep the strong medicine and well. Them. Mix the things that use a highly pressed method. In a bunch of tests, scientists looked at how well the tiny medicine worked to reduce inflammation compared to regular medicine and NRG. They did tests in the lab and on animals. The NRG with less in it helped swelling go down more than the normal NRG and diclofenac sodium.

An ischemic stroke can cause inflammation throughout the body by allowing blood components into the brain. This occurs when the blood-brain barrier breaks down. In this case, substances such as NRG, that reduces the swelling, seems to help prevent brain and trouble- grade-grade accidents. (63) Ahmad and her team also performed on NRG blocked in PCL Nanoparticles Coquades with gelatin affects mesenchimal human cloth. The reduction in the inflammation signals suggests NRG nanoparticles are effective in protection cells from damage caused by the lack of oxygen and glucose. So his little medicines can be useful to be treated writing in the center and other during here were with in indmammazation. (66)

- *Naringenin's Anti-Inflammatory Properties*

Naringenin's anti-inflammatory and antioxidant effects were also assessed in thermally burned rats. (69) A study on macrophages infected with Chlamydia trachomatis, which can lead to acute cervicitis, pelvic inflammatory disease, or an asymptomatic chronic condition, showed that naringenin has anti-inflammatory effects. This is achieved through the down-regulation of various cytokines (TNF-α, IL-1β, IL-1α, IL-6, IL-10, IL-12p70) and chemokines (CCL4, CCL5, CXCL1, CXCL5 and CXCL10). (70,71) Naringenin was identified as an inhibitor of inflammation-induced neuronal cell death by reducing nitric oxide production and iNOS expression in glial cells, which are triggered by LPS/IFN-γ. Additionally, it prevented the phosphorylation of MAPK (p38 mitogen-activated protein kinase) and the activation of STAT-

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1 induced by LPS/IFN-γ. (72,73) Naringenin was also shown to be effective against trichloroethylene (TCE), a commonly used industrial solvent that impacts liver function, in human epidermal keratinocytes (HaCaT). TCE has been allotted to Ca2 + Interclarular production that always increases free radical and fragmentin the narring again all of the TCE-citotxic manner of TCE. (74)

➢ *Naringenin's Anticancer Properties*

Narringine was discovered Citotoxic in different cells of MDF-7 (Cancer MDA), MDA (MDA), HPPRI (WEPG2,, HEmBB (File Cancer), hella-tg (cancer cervical), pk-1 (cancer pancre). Extremely cytotoxic High for leukemia cells such as nalm-6, hl-60, jurk, and u937 has been noted to prompt in a dose-dependent manner in these cell lines. Additionally, the noting of noting, junk was also discovered inhibition the coughing in the cousten in the challenged tics of Sarom S-180. (75) Inhibit stimulated absorption of insulin in masf-7 cistells, leading to their growth and rapid spread. A study demonstrated that a brave of the brave in the braver in glucosa has been noted with 10 μm ninight. This inhibiting effect is caused by the dish's brake brake and hacks, as well as a swift-back. (76) Ningugen stops mutagenic alterations induced by the cell lines and stimulates fundamental repair of the DNA's excitation. The enzymes i., darnician, dna poliasasas β, and 8-Oxoguanin-add Glycosylase 2 engage with prostate cancer cells at a rate of three, functioning as stimulants for Asc repair. (77) Narringina also inhibits the metastasis of chest cancer by regulating the immunity of the host in cases of breast cancer. The cell proportion expressing IL-2 and IFN-γ has been significantly increased by oral administration of Ningenine. This test evaluates the effectiveness of surgical orders in patients with breast cancer. (78)

➢ *Diabetes*

NRG helps to reduce blood sugar levels by stopping the body from holding onto sugar from food. NRG anti-diabetic medicine makes insulin work better, lowers sugar in blood, and decreases swelling in fat. It also affects certain proteins and enzymes in the body that are involved in controlling blood sugar. In a later study, Maity and Chakraborty made small particles with a drug using a special method. (79) The NRG connection was about 70%, and the particles were measured to be around 129 nanometers. Moreover, if nanoparticles NRG - ad they help you by diabetes, compare to the use of Nrg in yourself. They tried to mice with diabetes caused by streptozatocin. (80) The circles found that nanopartic mice had lower levels of glifrobin glifrow, higher levels of stress, and cholesterol stress. This has not been observed in rats that have been treated with NRG FREE. Stay with body juice and as Well, the Pharmaceutical Outlet changed with terrific levels of corrosion. (81) Required Nanormulations will gradually pay the vitality of time. In living creatures, the diabetic mice seemed to be inferior blood sugar after receiving oral nrag nanoparichic. Also, tests in the tissue and blood they appear that small particles were in the mouth. Medicines caused a devastating impact in the body. (82)

IV. CONCLUSIONS

Naringenin, a naturally occurring flavanone, exhibits significant therapeutic potential, as demonstrated by extensive studies showing its antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, neuroprotective, and anticancer effects. Naringenin's wide range of biological activities and its natural occurrence in citrus fruits make it a promising candidate for use in pharmaceuticals and nutraceuticals. Despite the benefits of naringenin, its clinical application is constrained by its low water solubility, limited bioavailability following oral consumption, and considerable first-pass metabolism. The pharmacokinetic profile, therapeutic efficacy, and targeted delivery of the product have improved significantly due to recent advancements in extraction technologies and formulation strategies, especially nano-based delivery systems. These developments have also reduced potential side effects.

In conclusion, naringenin is a promising and versatile phytochemical with significant potential for developing new therapeutic interventions. Nevertheless, further research is required to standardize extraction techniques, improve delivery systems, and conduct meticulously designed clinical trials to assess its safety, efficacy, and dosage parameters in humans. To fully harness naringenin's translational and clinical potential, ongoing interdisciplinary collaboration that brings together pharmacology, nanotechnology, and clinical research will be essential.

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