Phytochemical Properties, Extraction, and Pharmacological Benefits of Naringin

Subjects: Food Science & Technology

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Naringin is a nutritional flavanone glycoside that has been shown to be effective in the treatment of a few chronic disorders associated with ageing. Citrus fruits contain a common flavone glycoside that has specific pharmacological and biological properties. Naringin, a flavone glycoside with a range of intriguing characteristics, is abundant in citrus fruits. Naringin has been shown to have a variety of biological, medicinal, and pharmacological effects. Naringin is hydrolyzed into rhamnose and prunin by the naringinase, which also possesses l-rhamnosidase activity. D-glucosidase subsequently catalyzes the hydrolysis of prunin into glucose and naringenin. Naringin is known for having anti-inflammatory, antioxidant, and tumor-fighting effects. Numerous test animals and cell lines have been used to correlate naringin exposure to asthma, hyperlipidemia, diabetes, cancer, hyperthyroidism, and osteoporosis.

naringin flavonoid extraction bioactive potential pharmaceutical

1. Introduction

Numerous phytochemicals, such as flavonoids (such as hesperidin and naringin), limonoids (such as limonin and nomilin), carotenoids (such as beta-carotene and lutein), and vitamin C are abundant in citrus fruits. Citrus fruits' vivid colors, distinctive flavors, and distinctive scents are all influenced by these phytochemicals. Citrus fruits include a variety of phytochemicals that have many health advantages [1]. They have antioxidant capabilities that assist the body in fighting off dangerous free radicals and guarding against oxidative stress and cellular damage. Citrus phytochemicals have also been associated with anti-inflammatory effects, which can help reduce the risk of chronic diseases like cardiovascular disease and certain types of cancer. Citrus fruit polyphenols have also been linked to stronger immune systems, better cardiovascular health, and potential anti-diabetic effects. According to some research, these substances may assist with healthy weight management, lowering cholesterol levels, and lowering blood pressure. Citrus fruits include a wide variety of phytochemicals that are essential for overall health and wellbeing, thus including them in the diet is crucial. Beyond what can be achieved by a single vitamin, these chemicals act synergistically to promote health. Regular citrus fruit consumption can support optimal health and lower the risk of chronic diseases by promoting a balanced and nutrient-rich diet [2].

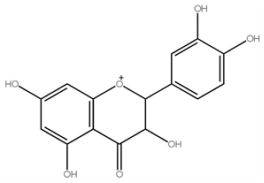
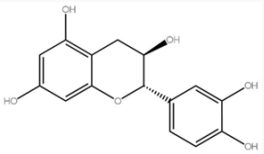
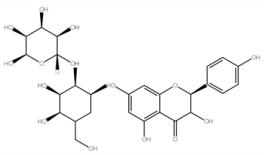
2. Chemical Composition of Naringin

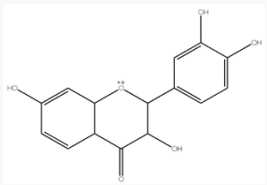
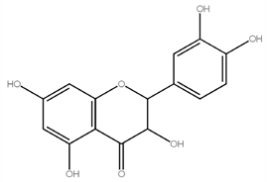
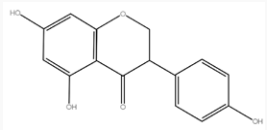
The flavonoid substance naringin is mostly present in grapefruits and other citrus fruits. In chemical terms, it is a glycoside made up of the disaccharide neohesperidose and the flavone naringenin. The chemical structure of naringin consists of a flavonoid backbone, two phenolic rings, and a heterocyclic pyran ring. Its molecular weight per mole is 580.54 g and its chemical formula is $C_{27}H_{32}O_{14}$. Pharmaceutical and nutraceutical research is interested in naringin because of its bitter taste and its variety of biological qualities, such as antioxidant, anti-inflammatory, anticancer, and cardioprotective properties [1].

2.1. Significance of Flavonoids

In plants, animals, and microbes, flavonoids have a variety of biological effects. Long known to be synthesized at specific locations in plants, flavonoids are also important for the color and scent of flowers, the ability of fruits to draw pollinators and, as a result, fruit dispersion, the germination of seeds and spores, and the development and growth of seedlings. Plants are protected from various biotic and abiotic challenges by flavonoids, which also serve as special UV filters, allopathic substances, signal molecules, phytoalexins, antimicrobial defensive components, and detoxifying agents. Flavonoids have protective effects against frost drought resistance and hardiness, and they may serve to help plants adapt to heat and tolerate freezing temperatures. There are six types of flavonoids [3]. The major classes of flavonoids, their examples, chemical structures, and main dietary sources are listed in **Table 1**.

Table 1. The major classes of flavonoids, examples, chemical structures, and main dietary sources.

Flavonoids	Examples	Chemical Structure with Molar Mass (g/mol)	Food Sources	Reference
Anthocyanin	Cyanidin, pelargonidin, peonidin	 Cyanidin (287.24)	*Solanum melongena, Rubus fruticosus, Ribes nigrum, Vaccinium sect. Cyanococcus*	[4][5]
Flavan-3-ol	Catechin, epicatechin, epigallocatechin	 Catechin (290.26)	Green tea, Chocolate, *Phaseolus vulgaris* L., *Prunus avium*	[5]
Flavanones	Hesperidin, Naringin, Eriodictyol	 Naringin (580.54)	Orange juice, grapefruit juice, lemon juice	

Flavonoids	Examples	Chemical Structure with Molar Mass (g/mol)	Food Sources	Reference
Flavanones	Apigenin, luteolin	 Apigenin (270.05)	*Petroselinum crispum, Apium graveolens, Capsicum annuum*	[6]
Flavonols	Quercetin, kaempferol, myricetin	 Quercetin (302.23)	*Allium cepa, Malus domestica, Brassica oleracea* var. *sabellica, Allium porrum*	[7]
Isoflavones	Genistein, daidzein, glycitein	 Genistein (270.24)	Soyflour, soymilk, *Glycine max.*	[8][9]

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The two primary groups of phenolic chemicals present in citrus fruits are flavonoids and phenolic acids. Citrus flavonoids have been proven to have anti-cancer, anti-inflammatory, anti-aging, anti-bacterial, hepatoprotective, and cardiovascular protective effects, according to several studies. The primary class of phytochemicals found in citrus fruits, particularly in the pulp, peels, and seeds, are called flavonoids. Flavones, flavanones, and flavonols are the three main categories of citrus flavonoids. **Table 2** depicts the classification of citrus flavonoids isolated in citrus species, major fruit sources, C-ring structures, and substitution patterns [10].

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Table 2. Flavonoids isolated in citrus sp. their structure, molecular weight, fruit sources, C-ring structure and substitution pattern (FLA: flavanone FLO: flavone FOL: flavonol).

Flavonoid	Molecular Weight	C-Ring Structure	Fruit Sources	Substitution Pattern	Reference
Naringin	580.541 g/mol	FLA FLA	*Citrus paradisi* *Citrus aurantium*	5,4′-OH 7-O-Neo	[11][12]
Neoeriocitrin	596.5 g/mol	FLA	*Citrus aurantium*	5,3′,4′-OH 7-O-Neo	[7][11]
Diosmin	608.54 g/mol	FLO	*Citrus sinensis* *Citrus limonia*	5,3′-OH 4′-OMe 7-O-Rut	[10]
Hesperidin	610.1898 g/mol	FLA	*Citrus sinensis*	5,3′-OH, 4′-OMe	[13]

Flavonoid	Molecular Weight	C-Ring Structure	Fruit Sources	Substitution Pattern	Reference
				7-O-Rut	
Rutin	610.517 g/mol	FOL	*Citrus limonia*	5,7,3′,4′-OH 3-O-Rut	[13][14]
Naringenin	272.257 g/mol	FLA	*Citrus paradisi*	5,7,4′-OH	[15][16]
Hesperetin	302.27 g/mol	FLA	*Citrus sinensis*	5,7,3′-OH 4′-OMe	[12][17]
Kaempferol	286.23 g/mol	FOL	*Citrus paradisi*	5,7,3,4′-OH	[11]
Quercetin	302.236 g/mol	FOL	*Citrus limonia*	5,7,3,3′,4′-OH	[13]
Tangeretin	372.37 g/mol	FLO	*Citrus aurantium* *Citrus paradisi* *Citrus limonia*	5,6,7,8,4′-OMe	[18]
Luteolin	286.24 g/mol	FLO	*Citrus limonia* *Citrus aurantium*	5,7,3′,4′-OH	[19]

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2.2. Structure of Naringin

Asahina and Inubuse identified and characterized the chemical structure and molecular formula of naringin in 1928. A 2-O-(alpha-L-rhamnopyranosyl)-beta-D-glucopyranosyl moiety is substituted at position 7 of the disaccharide derivative naringin by an alpha-L-rhamnopyranosyl group via a glycosidic bond. The melting point of naringin is 83 °C at a solubility of 1 mg/mL at 40 °C and the molecular weight of naringin is 580.5 g/mol [20]. The molecular structure of naringin is shown in **Figure 1**. With a rise in temperature, naringin and naringenin, its aglycon equivalent, become more soluble in various solvents. In the order of methanol, ethyl acetate, n-butanol, isopropanol, petroleum ether, and hexane, naringin was soluble in the six solvents [15]. Naringin complexes are 15 times more soluble in water at 37 ± 0.1 °C than free naringin. It starts to degrade at temperatures above 100 °C or when light is present [16]. The presence of a carboxylic group is suggested by the wide, strong -OH stretching absorption from 3300 per cm to 2500 per cm. Alcohols and phenols are represented by the strong and wide hydrogen-bonded O-H stretching bands centered at 3300 cm^{-1} and 3400 cm^{-1} [6]. The C=C stretching bands for aromatic hydrocarbons appear outside the typical region where C=C emerges for alkenes (1650 cm^{-1}) between 1600 and 1450 cm^{-1}. These peaks only group with naringin when researching flavonoid cyclodextrin inclusion complexes; it was discovered that the characteristic peaks for aromatic rings and phenols in naringin at 1519 cm^{-1} and 1361 cm^{-1} had disappeared. The amount of naringin measured and the correlation coefficient (r) for sensory bitterness was 0.97IBU [21].

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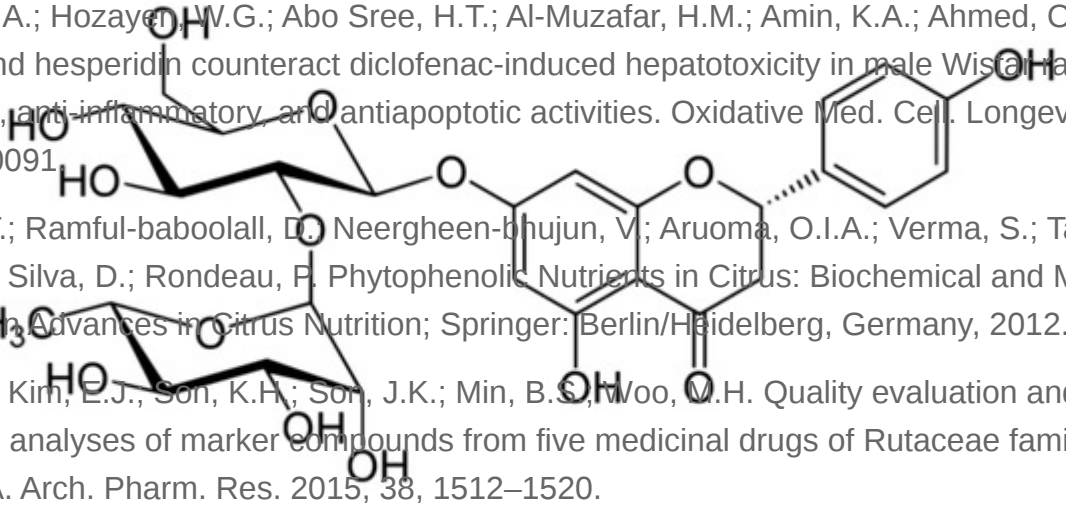

Figure 1. Molecular structure of naringin.

3. Sources of Naringin

Plants contain a variety of flavonoids, which are widely dispersed and have significant biological functions. Since the quantity of naringin is comparatively higher at the immature stage, citrus fruits are typically used in studies to determine the amount of naringin in fruits [22]. Citrus fruits provide a large number of flavonoids in the diet. Naringin is mostly found in the peel of grapefruit, lime, and their variations; it has several biological functions and is frequently used in food, cosmetics, and medicine. Naringin is a glycoside flavanone seen in grapes and citrus fruits. Naringin was first discovered by DeVry in 1857 [23]. It has been reported that the pith contains a higher quantity of naringin in grapefruit, followed by the peel with the membrane, the seeds, and the juice [24]. The amount of naringin in the seeds of grapefruit is 200 µg/mL and 2300 µg/mL is found in the peel of grapefruit [25]. Pummelo has plenty of naringin in it. Compared to the juice, the quantity of naringin was higher in the peel; the naringin content of the juice of pummelo is 220 µg/mL and in the peel it is 3910 µg/mL. The amount of naringin in lime is very low when compared with pummelo. In both species, a high amount of naringin content is present in the skin of the fruits. The amount of naringin found in skin, juice, and seed is 517.2 µg/mL, 98 µg/mL, and 29.2 µg/mL, respectively [26]. The distribution of naringin based on the calculations of grapes studied in *Citrus aurantiifolia* is shown in **Figure 2**. Naringin content in sour orange is 47.1 µg/mL. In sour orange flower, the amount of naringin in the receptacle, petal, and stigma is 1.3444 µg/mL, 9.036 µg/mL, and 2.554 µg/mL, respectively [27]. Phenol is a chemical compound with a hydroxyl group attached to an aromatic ring. Tannin is a type of phenol compound found in plants, known for its astringent properties. Naringin is a flavonoid compound found in citrus fruits that exhibits antioxidant and anti-inflammatory effects.

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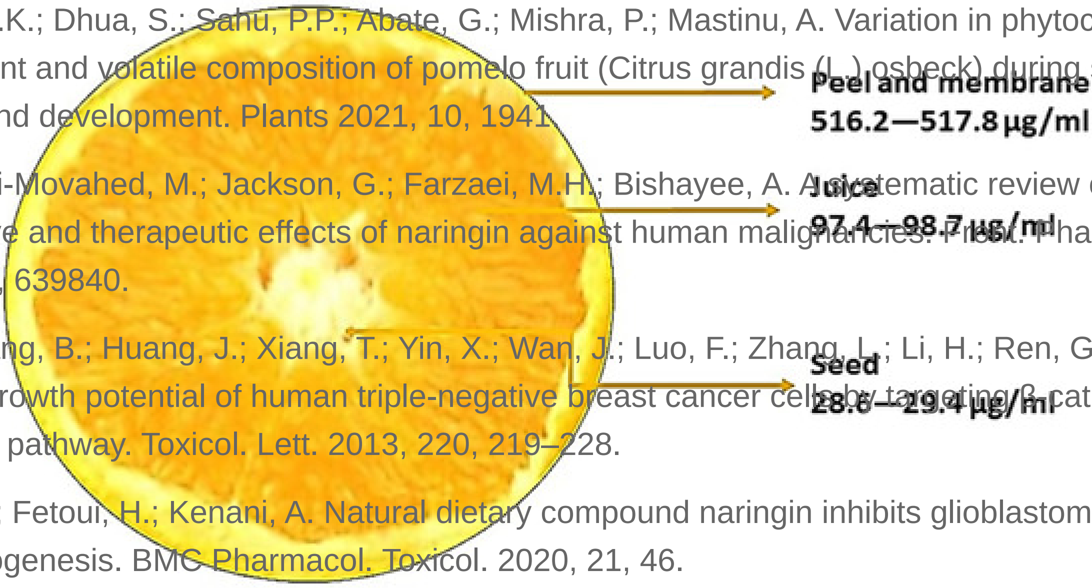

Figure 2. The distribution of naringin in *Citrus aurantiifolia*.

4. Extraction of Naringin

The citrus peel contains significant levels of the flavanones neohesperidin, hesperidin, naringin, and narirutin as well as polymethoxylated flavones tangeretin, sinensetin, and nobiletin. Flavonols, glycosylated flavones, and hydrocinnamic acid are present in very minor amounts [28]. There are three main steps for naringin isolation from fruits including extraction, separation, and purification [10]. Only after utilizing the proper extraction process can flavonoids be isolated, recognized, and classified. The amount of naringin in fruit is determined by numerous factors which include the harvesting time of the fruit, the section of fruit utilized, and whether the peel is a source of naringin. The most prevalent method of extraction is conventional solvent extraction [29]. The various non-traditional techniques include high hydrostatic pressure extraction [30], ultrasound assisted extraction [31], microwave assisted extraction [32], and subcritical [33] and supercritical [34] extraction. The first step in the process involves pre-treating or preparing the sample, during which centrifugation, filtration, drying, and other techniques may be performed. Naringin is extracted, isolated, and purified from various plant materials in the second stage. Naringin is extracted utilizing techniques like soxhlet, maceration, water infusion, microwave extraction, ultrasound extraction, supercritical fluid extraction, auto-hydrolysis, and solid micro-phase extraction, etc. in this step, as given in **Figure 3**. The final phase often involves the identification, quantification, and recovery of flavonoid components using chromatography techniques on the purified and extracted extracts.

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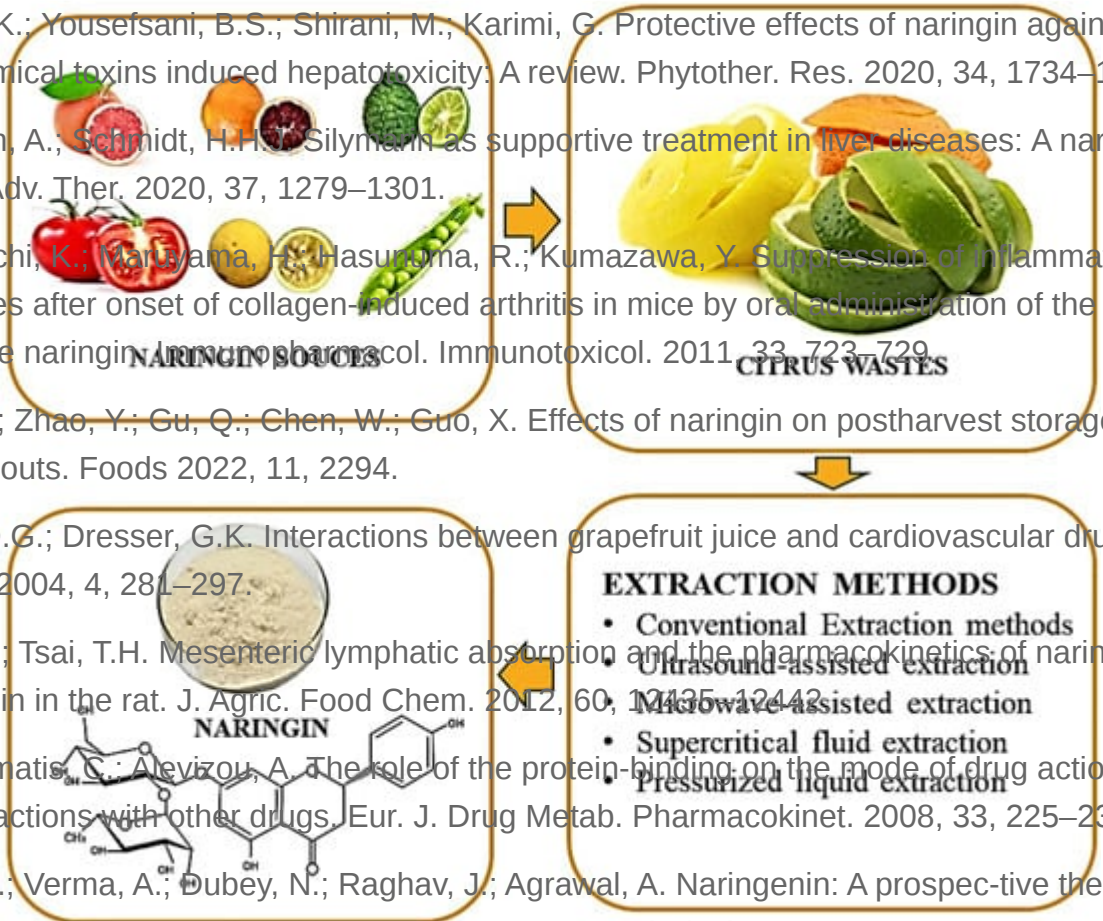

Figure 3. Extraction of naringin using different techniques.

5. Possible Health Benefit

Since ancient times, citrus fruits have been utilized as natural herbal treatments in traditional medicine. Citrus peel has been utilized in traditional Chinese medicine to enhance digestion, minimize gastric gas, bloating, and clear congestion [7]. Clinical and epidemiologic research states that eating citrus fruits lowers the risk of lifestyle-related disorders like cancer, cardiovascular disease, diabetes (type-2), and osteoporosis [34]. Naringin has been shown to have anticancer, antiapoptotic, cholesterol-lowering, antiatherogenic, and metal binding capabilities, as well as antioxidant qualities, as shown in **Figure 4**. Naringin is also said to enhance medication absorption and metabolism [35][36][37].

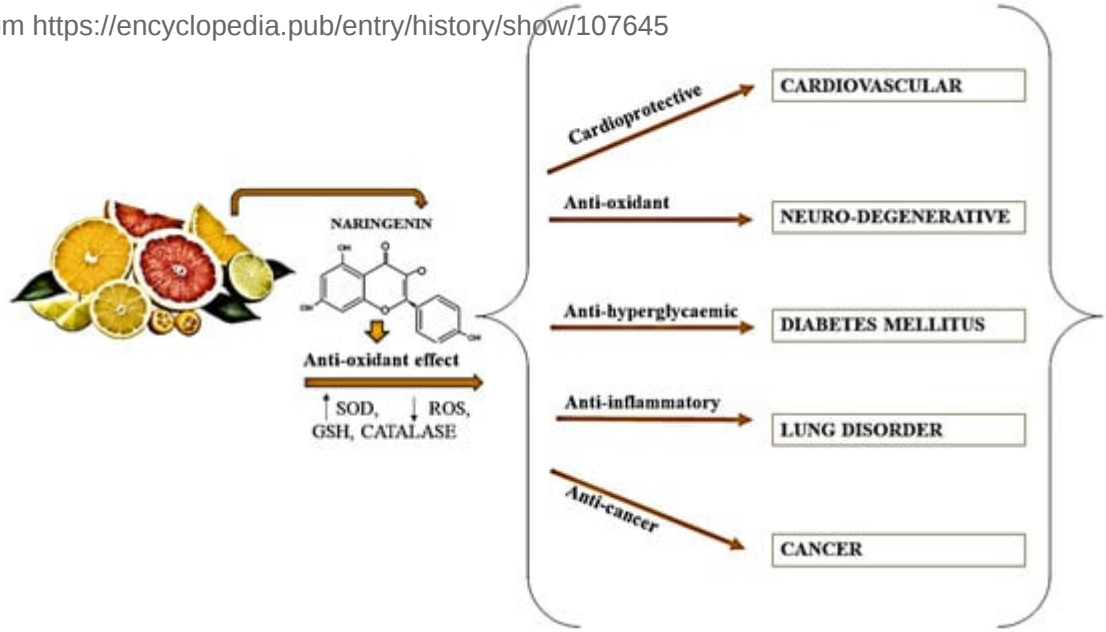

Figure 4. Potential health benefits of naringin; SOD: superoxide dismutase, ROS: Reactive oxygen species, GSH: γ-l-glutamyl-l-cysteinyl-glycine (glutathione).

5.1. Anticancer Properties of Naringin

Naringin has been reported to inhibit many malignancies through the regulation of various cellular signaling cascades, including the inhibition of malignant cell growth, the induction of apoptosis and also the arresting of the cell cycle and the regulation of oxidative stress, inflammatory processes, and angiogenesis [38]. It was discovered that naringin at concentrations of 250–2000 M promoted cell apoptosis in cervical cancer cells (SiHa) in a dose-dependent way. This impact of naringin is thought to have contributed to the suppression of cell growth as well and also increase in apoptosis [10].

Naringin in the concentrations of 1 M, 5 M, and 10 M has reduced cell mortality caused by rotenone in human neuroblastoma cells (SH-SY5Y). In 4, 6-diamidino-2-phenylindol (DAPI) staining and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) tests, naringin prevents condensation of chromatin and breakage of DNA strand production by rotenone [39]. Naringin also decreases rotenone-induced phosphorylation of the mitogene-activated kinase (MAPK) family members p38 and Jun NH2-terminal protein kinase (JNK) [40]. According to one study, naringin inhibits the growth of cells, and apoptosis was induced in K562, HL-60, and Kasumi-1 human myeloid leukemia cells in a concentration- and time-dependent manner by downregulating Mcl-1 expression and activating the caspase and PARP pathways. In U937 and THP-1 human leukemia cells, naringin therapy increased cell death and lowered cell cervical proliferation and expansion [41].

Breast cancer is a term that refers to various types of cancers. A vast variety of individualized treatments for breast cancer have recently been offered, all of which have been shown to be effective [42]. Chemotherapy and cancer chemoprevention are both carried out with natural products containing bioactive chemicals. In MCF-7 cell lines, naringin treatment reduced proliferation and growth while also increasing apoptosis. In canine mammary cancer

cells (CMT-U27), naringin oxime treatment decreased cell proliferation and viability [40]. Cervical cancer is the second most common cancer in women around the globe and continues to be difficult. At a dose of 750 M, naringin displayed a 50% suppression of SiHa human cervical cancer cells.

5.2. Antidiabetic Properties of Naringin

It has been demonstrated that naringin enhances insulin sensitivity. Naringin has shown that it can improve insulin action and cell uptake of glucose. Insulin resistance is a major contributor to the onset of type 2 diabetes. This can enhance overall glycemic control and help control blood sugar levels. Insulin moves sugars from the bloodstream into cells, where they are used or stored as energy [43]. Diabetes is when the body does not produce enough insulin or cannot utilize the insulin it makes efficiently [18]. Diabetes is divided into two types. Type 1 Diabetes is a condition that is autoimmune. Cells in the pancreas, which make insulin, are attacked and destroyed by the immune system and what generates this attack remains an enigma. Approximately 10% of diabetics have this type of diabetes [21].

Naringin is a powerful biomolecule that has the potential to help people with diabetes and its consequences [44]. Naringin restricts the secretion and sensitivity of insulin, PPAR, glucose transporters, blood lipids, hepatic glucose production, peripheral glucose uptake, intestinal glucose absorption, biosynthesis of cholesterol, oxidative stress, and inflammation [45]. Inflammatory cytokines are elevated and insulin resistance and hyperglycemia are generated by a high-fat diet. Naringin's hypoglycemic impact has been thoroughly documented. Vitamin C (50 mg/kg) with naringin co-treatment improved insulin concentration and oxidative stress reduction in rats with streptozotocin-induced diabetes [18].

5.3. Anti-Inflammatory Properties of Naringin

The process by which the body's white blood cells and the substances they make protect against bacterial and viral illness is known as inflammation. Flavanone-rich plants, such as naringin, hesperidin, and neohesperidin, have long been known to have anti-inflammatory properties [17]. Inflammation is divided into two types. Acute inflammation is the body's reaction to a quick injury, such as cutting your finger. Your body sends inflammatory cells to the wound to help it heal. The healing process begins with these cells [46]. Chronic inflammation occurs when your body sends inflammatory cells even when there is no external threat.

The anti-inflammatory process controlled by nuclear factor-erythroid 2–related factor 2 (Nrf2) regulates cellular antioxidant synthesis and thus plays a very important role in preventing various degenerative illnesses [47]. In 3-nitropropionic acid-induced rats, naringin upregulates the expression of mRNA in HO-1, GST P1, NAD(P)H:quinone oxidoreductase 1, and g-glutamylcysteine ligase; this is followed by activating Nrf2 and the reduced expression of proinflammatory mediators like TNF-a, cyclooxygenase-2, and inducible NO synthase [48]. Naringin did not inhibit cell proliferation, but it did inhibit RANTES (regulated upon activation of normal T-cell expressed and secreted) production in a human epidermal keratinocytes cell line (HaCaT cells) by restricting nuclear translocation of NF-JB [49].

5.4. Hepatoprotective Properties of Naringin

The capability of a chemical compound to inhibit liver toxicity is known as hepatoprotection [50]. Naringin is suggested to enhance the functioning of the hepatic antioxidant system as well as the metabolism of hepatotoxic substances [51]. Naringin exhibits protection against naturally occurring genotoxins in food, like PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine) and other cooked food mutagens, by lessening PHIP induced genotoxicity in human liver segments at a concentration of 1000 M [48]. Naringin (0.05–0.125 g/L) increased ethanol and lipid metabolism in rats, alleviating the adverse effects of ethanol consumption. It also reduced necrosis, steatosis, and fibrosis in rat models of alcoholic liver disease, as demonstrated by reduced expression of PGC1α (Peroxisome proliferator-activated receptor-gamma coactivator) or Sirt1; it is an enzyme involved in regulating energy metabolism in response to calorie restrictions at a dosage of 100 mg/day [52].

5.5. Pharmacokinetics of Naringin

Studies were conducted with help of rats to understand the pharmacokinetic properties of naringin. The study of the absorption, distribution, metabolism, and excretion of drugs is known as pharmacokinetics [53]. Proton-coupled active transport and passive diffusion are used to absorb flavanone aglycones into the enterocytes. The low molecular weight, high lipophilicity, and slightly acidic character of aglycones cause passive diffusion. Once within the cells, naringin is expected to go through phase I metabolism, such as oxidation or demethylation by cytochrome P450 monooxygenases, then passing to phase II metabolism, such as sulfation, glucuronidation, or methylation, in intestinal cells or liver cells [54][55]. Naringin is rapidly absorbed in the blood, with the initial concentration peaking at 15 min and the second peaking at 3 h after naringin monomer oral administration; 480 min later, it is undetectable [56]. The affinity of these food chemicals for serum albumin, the primary transport protein, coincides with their tissue distribution and elimination.

In terms of tissue distribution, the liver had the largest quantities of flavanone conjugates after repeated or single dose flavanone treatment in rats. By partially undergoing breakage of the bacterial ring and then the three bridges of carbon to dihydrochalcone moiety, naringin is eliminated by the kidneys into the urine and by the liver into bile According to Fuhr and Kummert's findings (1995). Urine excretion ranges from 5 to 57 percent of total intake. Sulfates were the most common naringenin type detected in the tissues of rats. Only the liver and kidney had glucuronide concentrations that could be measured [57]. The average Cmax of naringin in portal plasma was 18.83.8 min (determined by the concentration reached at tmax in portal plasma), whereas the absorption ratios of naringin in portal plasma and lymph fluid were approximately 95.9 and 4.1, respectively, after naringin administration via a duodenal cannula (600 and 1000 mg/kg). This suggests that naringin is absorbed largely by portal blood rather than mesenteric lymph fluid and that it is excreted primarily by bile, with just a tiny quantity entering systemic circulation following hepatic metabolism [58].

6. Application of Naringin

6.1. In Cosmetic Industry

The flavonoid naringin has anti-cancer, anti-oxidative, anti-aging, antibacterial, anti-inflammatory, cholesterol-lowering, and free radical scavenging properties [59]. Studies show that naringin reduces the risk of toxicity caused by other sunscreen ingredients like TiO_2 when it is added to sunscreen formulations because of its antioxidant activity. It also scavenges free radicals produced by UV radiation and by the photocatalytic activity of ZnO and TiO_2, which further lowers the risk of toxicity [60].

6.2. Pharmaceutical Application

The area of the wound and the length of the epithelization phase significantly decreased during treatment with naringin ointment formulation, whilst the velocity of wound contraction dramatically increased. Naringin ointment formulation modulates collagen-1 expression to promote angiogenesis, which in turn promotes wound healing. This is accomplished by down-regulating the expression of inflammatory (ILs, NF-Jb, and TNF-a), apoptotic (pol-g and Bax), and growth factor (TGF-b and VEGF) genes [61].

6.3. In Livestock Sector

Naringin and quercetin reduce protozoa and methanogen populations in the rumen and suppress methane production without negatively affecting the parameters of ruminal fermentation. Daily diets containing hesperidin and naringin have proved successful in enhancing milk's oxidative stability while having no negative impacts on the substance's chemical compositions, coagulation abilities, or fatty acid profile [62].

6.4. Food Industry

The use of naringin microspheres in yogurt demonstrated their ability to effectively reduce whey precipitation and to slow pH drop. According to a study, naringin-encapsulated microspheres could extend the shelf life of this bioactive product and offer a fresh concept for functional yogurt [63]. Hesperidin, naringin, and coumarins have been found to inhibit xanthine oxidase, which directly reduces cellular free radical production. When compared to dietary citrus pulp and control diets, feeding dietary citrus pulp prolonged the shelf life of beef during retail display by increasing antioxidant activity, lowering coliforms, and reducing lipid and protein oxidation [64]. Naringin's incorporation caused significant UV blocking, plasticizing, and antioxidant and antibacterial effects. The biological oxygen demand (BOD) in saltwater was used to test the biodegradability of these films, showing excellent disintegration under these circumstances [65].