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REVIEW ARTICLE

Potential of Naringin, Hesperidin and Rutin: Phytochemical and Biological Benefits

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Abstract

This review provides an overview of the recent biological and phytochemical advancements of the compounds such as naringin, hesperidin and rutin, which are bioactive flavonoids mainly present in citrus fruits with substantial therapeutic potential. Naringin possesses beneficial properties such as antioxidant, antitumor, antiviral and many more discussed in the article. Studies have indicated that naringin aids in slowing the progression of cancer in different regions of the body. Its anticancer effects are so extensive that it can change how cells interact and transmit signals, decrease the production of specific proteins such as cytokines and growth factors and also impede the proliferation of cancer cells. Hesperidin has demonstrated notable anticancer and neuroprotective potential. Rutin is widely recognised or known for its venotonic, anti-thrombotic, anti-inflammatory and anticancer properties. This review offers in-depth analysis and details of their constituents and their industrial applications.

Key words: Flavonoids; Cytokines; Signal transduction; Neuroprotective agents; Hesperidin; Rutin, Naringin.

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Introduction

The reason for choosing naringin, hesperidin and rutin for this review article is:

- Rich abundance in citrus fruits: These three flavonoids are naturally abundant in citrus fruits, making them accessible for extensive study of their health benefits.
- Strong antioxidant properties: it has been found that they are powerful antioxidants which have been found to help combat oxidative stress, a major factor in the development of chronic diseases.
- Multifunctional therapeutic potential: Naringin is well known for its anti-inflammatory, anti-cancer and lipid-lowering effects. Hesperidin, has been found to exhibit cardiovascular, anti-inflammatory and neuroprotective benefits. Rutin has been found to promote vascular health and has anti-diabetic properties and it aids in wound healing.
- Safe and natural: As plant-derived compounds, these three are considered safe for consumption and offer a natural alternative to synthetic drugs.

Naringin is a natural flavonoid which is found in grapes, citrus fruits and also in traditional Chinese medicine. The four steps involved in isolation or extraction of naringin from plants are mainly extraction, identification, isolation and purification.[1] The process uses methods like microwave-assisted extraction (MAE), high-performance liquid chromatography (HPLC) with a photodiode array and mass spectrometry. Its detection is mainly done by using HPLC or ul-

tra-performance liquid chromatography (UHPLC) combined with mass spectrometry (MS) or photodiode array (PAD) detectors. It possesses a number of therapeutic benefits, such as reducing inflammation, preventing cell death, reducing oxidative stress, treating ulcers, fighting tumours, fighting viruses and helping with muscle fibre repair. Clinical trials have indicated that it as an effective cough suppressant and expectorant. Its potent anti-inflammatory properties can be used to manage various inflammatory pathologies in different organs and the respiratory system.[2]

Another flavonoid discussed, hesperidin is present in citrus fruits, mainly in oranges and their juices, which constitutes about 90 % of the flavonoids. In the human body, it is converted or metabolised into hesperidin by gut bacteria.[3] It possesses various beneficial therapeutic properties, including anti-inflammatory and can positively influence various pathophysiological conditions, such as insulin resistance, non-alcoholic fatty liver disease, metabolic syndrome and cardiovascular diseases (CVDs).[4] Factors like its bioavailability and absorption can affect its efficacy. Extensive research has demonstrated that it can ameliorate cardiovascular disease risk factors such as insulin resistance, high blood sugar, blood pressure, cholesterol levels and inflammation, based on both *in-vitro* and *in vivo* studies.[5]

Rutin is a flavonoid that was first found in plant *Ruta graveolens*, commonly known as rue. It is also referred to as vitamin P, rutoside, or quercetin-3-O-rutinoside.[6] It possesses anti-inflammatory, antidiabetic, heart-protective, liver-protective, anticancer and brain-protective properties. Researchers have evaluated various methods for extracting rutin from plants and exotic fruits, which are cultivated based on the geographical conditions of each region. Several techniques, such as spray drying, nanoemulsions and liposome entrapment, have been explored to improve its stability and solubility.[7]

Hesperidin

Hesperidin, which belongs to the group of bioflavonoids, is a major waste product of citrus farming and is also cheap. Hesperidin's absence from food may lead to unusual leakage of fluids in capillaries and pain sensations in the hands and feet, making one weak or causing leg cramps during the night. Studies have reported on several medicinal effects of it, as well as its aglycone hesperidin. Hesperidin can be found in abundance in some plant species including, *Agathosma serratifolia* (Curtis), *Citrus aurantium* (L). Generally, it has been observed that hesperidin remains stable at temperatures lower than 75 ºC without oxygen and prefers either neutral or acidic environment. The presence of heavy metals (Cu^{2+}, Fe^{3+}) and exposure to intense light may accelerate the degradation process of hesperidin.[8]

Occurrence

Hesperidin is gathered in significant quantities from orange zest. *Citrus aurantium* L, *C sinensis* and other species belonging to the Citrus genus (family *Rutaceae*).[9] It is primarily found in highest concentration within immature fruits while its levels increase during storage. The allocation and amount of it within various tissues of developed orange fruit have been determined using a radioimmunoassay. In seeds, there was an increase in hesperidin content after germination, signifying that the compound was produced in greater amount during seedling development, partly stimulated by light. Hesperidin may exist as needle-like crystalline aggregates or sphero-crystalline aggregates inside cells.[10] Di Mauro et al illustrated an innovative technique for extracting it from the citrus peel by-product, by utilising a styrene-divinylbenzene scaffold to adsorb dilute hesperidin extracts.

Phytochemistry

In mentioning hesperidin, it is found that hesperitin or methyl eriodictyol acts as the attached aglycone, whereas a disaccharide, rutinose, forms the part of its structure; hence, it can be regarded as 7-rutinoside of it. The disaccharide unit consists of one molecule of rhamnose and one of glucose therefore there are two possible isomers ie, either rutinose or neo-hesperidose.[11] Hesperetin (C16H14O6) is, in terms of chemistry, 3, 5, 7-trihydroxy-4-methoxyflavanone. Hence, it is accurate to say that hesperitin is 3, 5, 7-trihydroxy-4 methoxyflavanone-7- (6--L-rhamnopyranosyl--D-glucopyranosides thus -7-rutinosides as well as O-hesperidin (C16H16O7) whose proper formulae would become given below G'[1] – aldehyde plus ketone hydrocarbons per acid plus hydroxyls and finally any alkaloid; second type with other classes mostly found as tartrates salts except one lyatropism ie hesperidin on hydrolysis led to the formation of phloroglucinol and

hesperetenic acid. While it yields one mole each of hesperetin, D-glucose and L-rhamnose during acid hydrolysis.[12] Hydrolysis using either diluted sulphuric acid or sulphuric acid dissolved in ethylene glycol yields an optically active mixture of O- and O-hesperetin, which can be separated through fractional crystallisation. The relationship between structure of disaccharide and the taste of its substance is very interesting. While rutinosides do not have any taste, neo-hesperidosides are extremely bitter. Hesperidin itself is characterised as being a flavonoid rutinoside that lacks any bitterness. The grapefruit contains mainly these bitter neo-hesperidosides while oranges and lemons are rich in non-bitter rutinosides.[13] The chemical structure of hesperetin and rutinosides can be seen in Figure 1(a) and Figure 1(b).

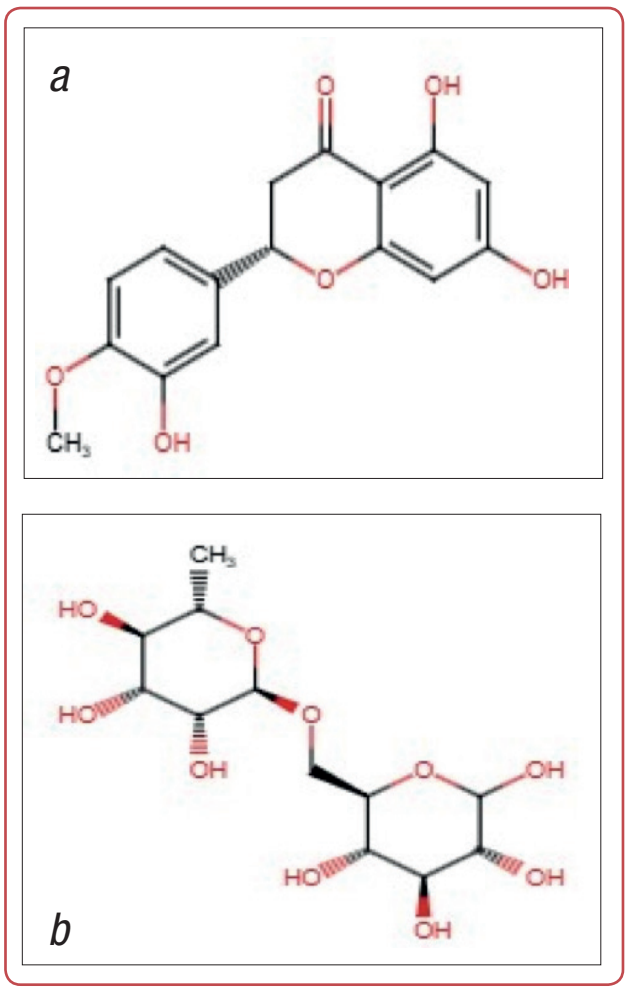

Figure 1: Chemical structure of (a) hisperetin; (b) rutinosides

Pharmacological actions

It is utilised as an adjunct in the treatment programmes and protocols of the supportive environment as shown in (Figure 2).

Antiepileptic effects

The antiepileptic activity of hesperidin has been researched. In pentylene-tetrazole-pretreated Laca mice, hesperidin reversed mitochondrial, biochemical and behavioural alterations. Restoration of reduced glutathione, superoxide dismutase and catalase levels were also seen.[14] In a different experiment conducted by the same group, it was revealed that hesperidin, when combined with l-arginine (100 mg/kg) or l-NG-nitro-arginine methyl ester (10 mg/kg) produced significant neuroprotective effects.[15]

Sedative effect

The overall sedative effect was potentiated by the co-administration of alprazolam, bromazepam, midazolam and flunitrazepam with hesperidin. It played a vital role in CNS depression through its specific inhibition of the phosphorylation of ERK 1/2 (extracellular signal-regulated kinases), which represents one of the main elements responsible for this phenomenon.[16] This also plays a crucial role in opioid receptors' mediation of such an effect, since naltrexone and norbinaltorphimine reversed the related sedative action of hesperidin.[17]

Anti-Parkinson disease effect

In aged mice, Parkinson disease-like symptoms developed after intra-cerebro-ventricular injection of 6-hydroxydopamine. There was an improvement in behavioural and biochemical parameters in the animals after treatment for 28 days. Treatment with hesperidin prevented memory impairment, depressive-like behaviour and restored depleted levels of glutathione and catalase in the aged mouse *striatum*.[18] It has also been shown that hesperidin is effective at alleviating episodes of oxidative stress through binding to and blocking sulfonylurea receptor 1 (SUR1) possibly thus reverting cerebrovascular accident in animals.[19] Administration of hesperidin resulted to reduced formation of reactive oxygen species (ROS) down regulation of BAX cytochrome c as well as caspases 3 and 9 levels with elevation of reduced glutathione concentrations. It exhibited anti-apoptotic action (against rotenone induced oxidative stress) by up regulating Bcl-2. There was an independent study whereby MPTP induced Parkinson disease in mice and hesperidin treatment appreciably protected 'microglial activation' reduced inflammatory cytokines release such as TNFα, IL6, IL4 and IL10 in *striatum/substantia nigra,* respectively.[20] In the brain, such a result helped to safeguard the *striatum* and the

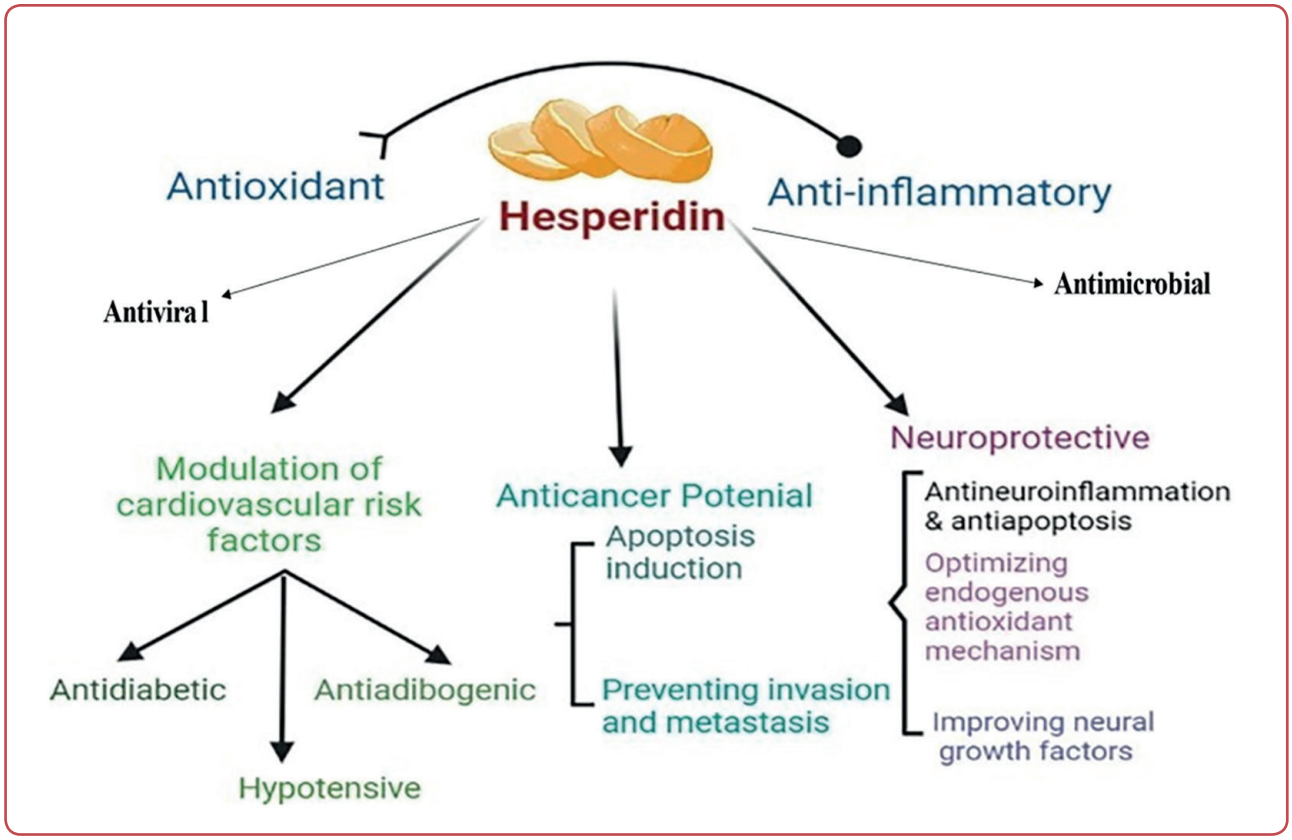

Figure 2: *Pharmacological actions of hesperidin*

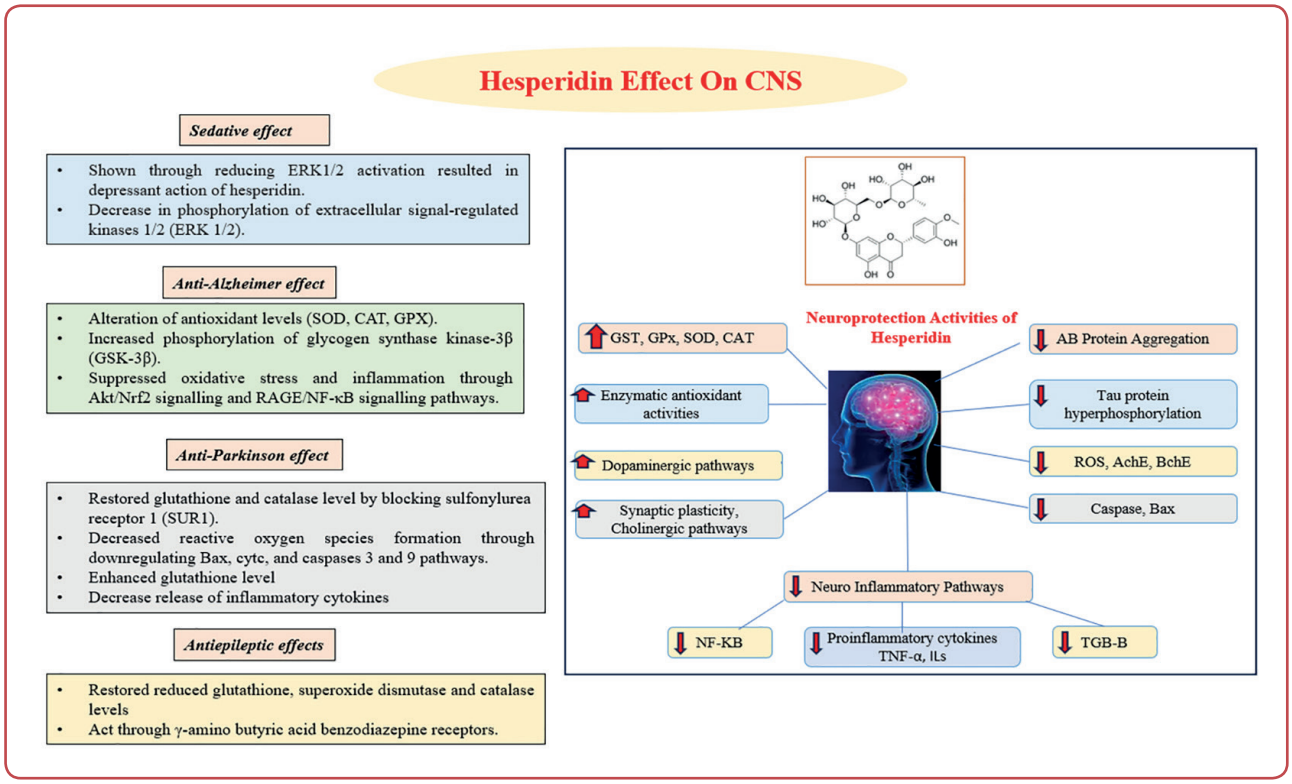

Figure 3: *Illustrating effect of hesperidin on central nervous system (CNS)*

SOD: superoxide dismutase; CAT: catalase; GPX: glutathione peroxidase; GST: glutathione S-transferase; TNF: tumour necrosis factor; IL: interleukin; NF-KB: nuclear factor kappa B; TGB-B: transforming growth factor beta; ROS: reactive oxygen species; AChE: acetylcholinesterase; BchE: butyrylcholinesterase;

substantia nigra region. Hesperidin also showed anti-Parkinson action (Figure 3) in a Drosophila model.[21]

Anti-Alzheimer's disease effect

In aluminium chloride treated animals, hesperidin administration (oral) decreased brain acetyl-cholinesterase activity, aluminium concentrations and other secreted molecules in the brain. Behavioural experiments indicated better spontaneous motor and exploratory performances in "open field test" with improved performance on Morris maze as compared to control rats. Such data obtained through histological examination of brain further confirmed a protective role of hesperidin on brain tissues. It was suggested that due to chelation of aluminium this compound exhibits such protective effect.[22-24] Another study considered hesperidin's impact on glucose utilisation impairment induced by Aβ, the results of which show improvement in Aβ-induced inhibition of autophagy in neurons.[25-27] In addition, hesperidin was able to elevate levels of brain-derived neurotrophic factor, which contributed to an antidepressant effect in mice subjected to chronic mild stress. Research indicated that hesperidin offered a protective benefit against cognitive decline caused by ischemia-induced brain damage.[28]

Antimicrobial activity

In-vitro, several plant and animal microbes have been shown to be susceptible to the anti-infective and anti-replicative activities of flavonoids, such as hesperidin and hesperetin among others. Hesperidin and flavonoids have inhibited the growth of Helicobacter pylori in *in-vitro* analyses. H. pylori cause chronic gastritis progress into gastric cancer.[29-31]

Antiviral

Reportedly, Wacker and Eilmes conducted two studies in which they found hesperidin to have antiviral activity against vesicular stomatitis virus at various concentrations in cell cultures. The fact that hyaluronidase could negate its antiviral activity indicated that its action was on account of the effect of this substance on antihyaluronidase. Furthermore, the authors also reported the efficacy of hesperidin towards influenza virus.[31, 32] In another study recently conducted, it was discovered that hesperidin has a minor effect against *Herpes simplex* virus. According to Middleto, some flavonoids including hesperidin were found to be antiviral agents against *Herpes simplex* type I, parainfluenza 3, poliovirus type I and respiratory syncytial virus (RSV) when tested in tissue cell monolayers. Among other flavonoids, Mucsi and Pragai demonstrated that there was an inhibitory influence of hesperidin on human *Herpes simplex* virus type I together with said *Herpes simplex* virus type I.[33] Among the flavonoids examined, a linear correlation was seen between their viral inhibition and cyclic AMP production in cells. In addition, quercetin and hesperetin also possess antireplicative actions (that is they can inhibit virus multiplication after a certain time post infection) when taken during cell stimulation. However, hesperetin did not show any effect against HIV virus as pseudorabies virus, *Herpes simplex* virus[34] and rhinovirus. In a recent study flavonoids were checked for their ability to inhibit rotavirus infections which mainly cause sporadic diarrhoea in infants and young children; these researches revealed that hesperidine has a strong anti-rotavirus action. The assumption by researchers before this newfound fact was that the rutinose moiety is crucial in avoiding entry of a rotavirus into the cells. *C aurantium* fruit containing large amounts of hesperitin along with neohesperidin has also been found effective against rotaviruses.[35, 36]

Industrial utility

Innovative formulations of hesperidin for anticancer, antimicrobial and neuroprotective effects.

Anticancer effects

As reported the anticancer mechanisms of hesperidin that were found to be remarkable included modulation of cell cycle arrest, angiogenesis, apoptosis, DNA repair mechanisms. In order for hesperidin to reach its therapeutic target via an effective delivery system, there was a need for overcoming its poor solubility and bioavailability.[37, 38] In study, chitosan functionalised Fe_3O_4 NPs were used to encapsulate hesperidin extracted from orange peel. In addition to significant antioxidant activity, this nano formulation was more toxic against MCF-7 breast cancer cells than chitosan-coated magnetite nanoparticles.[39] Doxorubicin (a chemotherapy drug) that was combined with apigenin and hesperidin enhanced its antitumor efficiency on MCF7 cells which specifically target the breasts. The values of MCF-7 cell viability after treatment using apigenin-doxorubicin and hesperidin-doxorubicin were found to be 15.35 % and 19.93 % respectively. This was in

comparison with apigenin alone that had a value of 49.02 % whilst doxorubicin recorded a much higher. It was evident from that these agents caused severe oxidative damage of DNA exhibiting main anticancer mechanism.[40] In order to decrease the cardiotoxicity associated with imatinibmesylate among mice afflicted by solid Ehrlich carcinoma, PLGA nanoparticles loaded with both hesperidin and imatinibmesylate were used during the combined treatment available in this study. The combined therapy using polymeric nanoparticles showed remarkable reductions on tumour volume, MDR 1 gene expression levels as well as certain haematological/cardiac markers, when compared to monotherapy using imatinibmesylate.[41]

Anti-neuroinflammatory and neuroprotective effects

Neurodegenerative diseases advancement was totally attributed to the inflammatory process. Hesperidin has been identified to be neuroprotective in different models of CNS disorders and shows both antioxidant and anti-inflammatory activities.[42] In hippocampus hesperidin decreases 5-HT and IL-β levels while BDNF and NE concentrations are increased. Furthermore; Nrf2/Glo-1/ARE pathway might also activate antidepressant effects of this metabolite.[42] Motor dysfunction resulting from spinal cord injury has its cause in secondary degeneration as caused by inflammation cells spilling into tissue due to mechanical injury. Hesperidin improved in rats the neuro-pathological degeneration associated with motor dysfunction due to SCI. In this way, then this flavanaglycone worked mainly through an antioxidant and anti-inflammatory mechanism.[43] The main cells participating in neuroinflammation included activated microglia astrocytes. The disease affects with auto-reactive T-cell retorting myelin proteins some patients resulting in multiple sclerosis (MS) which is a widespread CNS inflammatory disorder. As known, hespiridine diminishes neuro-inflammation and enhances immune consequences of multiple sclerosis. In female mouse model, 21 days treatment with hesperidin lead to increased levels of fork-head box P3 but lowered levels of retinoid-related orphan receptor gamma t factor expression.[44] The chief side effects of cisplatin which is a frequently used anticancer medicine include neurotoxicity, ototoxicity, liver toxicity and kidney damage.[45] This drug may result in histopathological damage in the sciatic nerve and changes in electromyography.[46]

Antimicrobial effects

Antimicrobial effects are needed to fight bacterial infections caused by MDR bacteria. The requirements include the availability of new biocompatible antibacterial agents with diverse functions.[47] It was found in an study that the antibacterial activity of hesperidin was lower than that of hesperetin and hesperidin glucoside.[48] Components such as plants, bacteria and fungi together with lichen can be utilised as reducing and stabilising agents.[49] The NPs at 66.7 µg/mL minimum inhibitory concentration (MIC) destroyed *E coli* cell wall because it produced reactive oxygen species which led to the excretion of bacterial macromolecules through their membranes.[50]

Knowledge of the antimicrobial properties of hesperidin microemulsion against various bacteria was carried out in a single research work including *Escherichia coli* and *Pseudomonas aeruginosa*. The findings revealed that hesperidin micromotion exhibited considerable antimicrobials against those examined separately on bacterial strains with an MIC range between 128-8 µg/mL. In conclusion, the unique method of forming hesperidin microemulsion might act as a natural chemopreventive agent or therapeutic measure for all bacterial infections.[51]

In one other study it was found that hesperidin had an inhibitory action on *Herpes simplex* virus type 1 due to lower levels intracellularly cAMP (cyclic adenosine monophosphate). *In vitro* studies suggested that hesperidin significantly reduced virus replication in cultures infected with HSV -1 viruses too.[52] Hesperidin can also be used as an inexpensive but effective inhibitor of NS3 protease, which Wang et al revealed in their research.[29] Hesperidin has been found to inactivate KSHV post infection whereby it reduced viral protein expression and slowed down viral multiplication.[53-56] For instance, Wu et al found that hesperidin was able to block ACE2 receptor binding domain binding with ACE2 domain itself.[57]

Hesperidin was not only known for its antibacterial and antiviral properties but also antifungal ones. One study looked into how citrus flavonoid hesperidin's aglycone whereby hesperetin affected *Candida albicans*, one of the most common fungal pathogens found in humans. The results demonstrated that when present at MIC, 0.165 mg/mL concentration level, hesperetin inhibited growth rate of *C albicans* completely. Researchers

proposed that hesperetin is potentially an alternative to traditional antifungal agents for the management of fungal infections.[58] As indicated by the *in-vitro* study, hesperidin decreased radial expansion of *Penicillium digitatum* by 38 %.[59] For instance, hesperidin significantly reduced growth of Aspergillus *parasiticus* and *Aspergillus flavus* at 0.8 mM by up to 38 % and 25 %, respectively.[60]

Naringin

Asahina and Inubuse were the first to identify and characterise the chemical structure and molecular formula of naringin in 1928. They discovered that naringin consists of a disaccharide derivative substituted at position 7 by a 2-O-(alpha-L-rhamnopyranosyl)-beta-D-glucopyranosyl moiety through a glycosidic bond.[61] The molecular structure of naringin is illustrated in Figure 4, with increasing temperature, both naringin and its aglycone equivalent, naringenin, demonstrates enhanced solubility in various solvents.[62, 63] Notably, naringin complexes exhibit solubility in water that is 15 times greater than that of free naringin at 37 ± 0.1 °C. However, degradation of naringin initiates at temperatures exceeding 100 °C or in the presence of light.[64, 65] Naringin exhibits unique chemical properties owing to its flavonoid glycoside structure, while its physical properties influence its solubility, stability and bioavailability. Understanding these characteristics is essential for harnessing the potential benefits of naringin in various applications, from food technology to therapeutic interventions.[66] The chemical structure of naringin is shown in Figure 4(a).

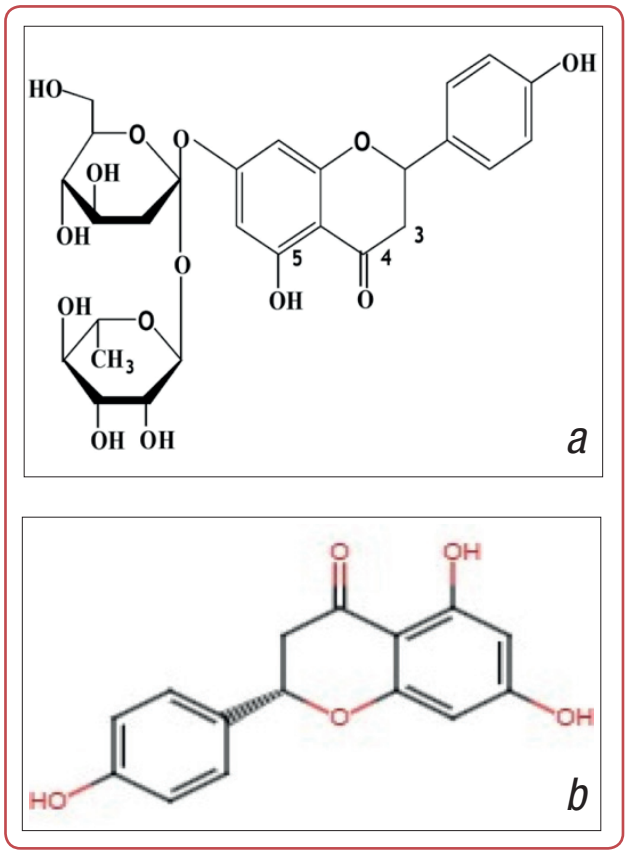

Figure 4: Chemical structures of: (a) narginin; (b) naringenin

Occurrence

Plants harbour a diverse array of flavonoids, compounds renowned for their wide distribution and significant biological roles. Citrus fruits, commonly utilised in research due to their high naringin content, offer a rich dietary source of flavonoids.[67] Predominantly located in the peel of grapefruit, lime and related variants, naringin serves multifaceted functions and finds extensive applications in food, cosmetics and medicine. Initially identified by DeVry in 1857, naringin's distribution within citrus fruits varies, with higher concentrations typically found in the pith, peel and membrane compared to the seeds and juice. For instance, grapefruit seeds contain approximately 200 µg/mL of naringin, whereas grapefruit peel exhibits levels as high as 2300 µg/mL.[68] Similarly, pummelo boasts significant naringin concentrations, with peel concentrations reaching 3910 µg/mL, substantially higher than those found in the juice (220 µg/mL). Lime, on the other hand, exhibits relatively low naringin levels, with the skin containing the highest concentration (517.2 µg/mL) compared to the juice (98 µg/mL) and seeds (29.2 µg/mL) (Figure 5). Furthermore, studies delineating the distribution of naringin in *Citrus aurantiifolia* reveal significant concentrations in the skin. In sour orange, naringin content is reported at 47.1 µg/mL, with varying concentrations across different floral components. Beyond naringin, citrus fruits also harbour phenolic compounds, such as tannins, which are renowned for their astringent properties, indicative of the rich phytochemical diversity inherent in these fruits.[69] The localisa-

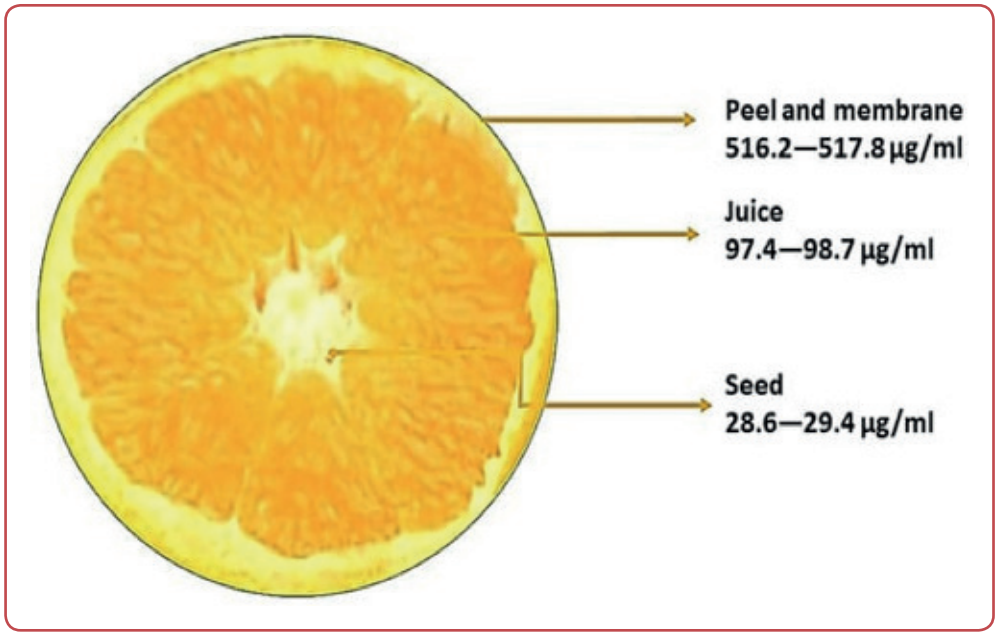

Figure 5: The localisation of naringin in Citrus aurantiifolia

tion of naringin in *Citrus aurantiifolia* is shown in Figure 5.

Phytochemistry

Naringin, a glycoside with a molecular weight of 580.54 g/mol (C27H32O14), is composed of neohesperidose and naringenin, featuring a flavonoid backbone, two phenolic rings and a pyran ring. It undergoes hydrolysis by α-L-rhamnosidase in naringinase, yielding rhamnose and prunin (trihydroxyflavonone-7-glucoside).[1] Prunin then be further hydrolysed into glucose and naringenin (4'-5,7'-trihydroxyflavonone) by the β-D-glucosidase component of naringinase. Naringin is integral to plant phytochemistry due to its involvement in various intra-plant interactions, biosynthetic pathways and potential bioactivities.[70] Functioning as a secondary metabolite, it contributes to pivotal roles such as plant defence mechanisms against pathogens, UV radiation shielding and modulation of pigmentation processes. Its bioactive properties encompass a wide spectrum, including antioxidant, anti-inflammatory and cardioprotective effects. These physiological responses are primarily attributed to its capacity to scavenge ROS, modulate signalling pathways related to inflammation, suppress proliferation of cancer cells and mitigate cardiovascular risks.[71] Moreover, naringin's metabolism within the human body leads to the formation of naringenin, its glycone counterpart, which also exhibits notable health-promoting attributes. This metabolic conversion underscores the dual significance of naringin in both plant physiology and human health, highlighting its potential applications in pharmacology and medicine.[72]

The biological and pharmacological effects of naringin (NRG) have been widely investigated. NRG's health benefits can mostly be attributed to the similarity in chemical composition with flavonoids and natural carbohydrates connected to both aromatic rings- a feature that has endowed it with specific physicochemical, physiological and chemical properties necessary for diverse functionalities. The recent studies have confirmed that naringin had therapeutic actions through regulation of various proteins and enzymatic expressions. The structure of naringenin can be seen in Figure 4(b).

Pharmacology

The primary pharmacological actions of naringin include its potent antioxidant activity, wherein it effectively scavenges free radicals and mitigates oxidative stress, thereby shielding cells and tissues from damage instigated by ROS. This antioxidative attribute holds significant implications for a spectrum of health conditions, encompassing cardiovascular diseases and cancer. Moreover, naringin exhibits notable anti-inflammatory effects through intricate modulation of inflammatory mediators and signalling pathways.[73, 74] Furthermore, compelling evidence

suggests that naringin harbours anti-hyperlipidaemic properties, thereby ameliorating dyslipidaemia by effectively reducing levels of cholesterol and triglycerides within the bloodstream. Its mechanism entails the inhibition of dietary cholesterol absorption within the intestinal milieu, coupled with the facilitation of lipid breakdown processes. This dual modulatory effect ultimately culminates in the enhancement of lipid profiles and concomitant mitigation of the risk associated with cardiovascular disease progression.[75]

Anticancer effects

Research has indicated its ability to inhibit various malignancies by modulating multiple cellular signalling pathways[76] have shown that naringin can suppress malignant cell growth, induce apoptosis, arrest the cell cycle and regulate oxidative stress, inflammatory processes and angiogenesis.[77, 78] It also inhibits cell proliferation and expansion in U937 and THP-1 leukaemia cells.[79, 80] In human cervical cancer cells (SiHa), naringin exhibited significant suppression of cell growth and induced apoptosis, indicating its potential for cervical cancer treatment.[81-83]

Antidiabetic effects

Naringin has been demonstrated to enhance insulin sensitivity, thereby improving insulin action and glucose uptake by cells. Insulin resistance is a significant factor contributing to the development of type 2 diabetes and naringin's ability to enhance insulin sensitivity can aid in overall glycaemic control and blood sugar regulation.[84]

Naringin may inhibit certain enzymes involved in carbohydrate metabolism, including glucosidase, which converts complex carbohydrates into simple sugars. By blocking this enzyme, naringin can lower postprandial glucose levels, slowing down carbohydrate digestion and absorption. However, it is important to note that naringin should not be used as a standalone treatment for diabetes but rather as a complementary strategy alongside traditional treatment methods such as a healthy diet, regular exercise and prescribed medications.[85, 86]

Anti-inflammatory effects

Naringin has long been recognised for their anti-inflammatory properties. Inflammation is categorised into acute and chronic types. Acute inflammation occurs in response to immediate injuries, initiating the healing process by recruiting inflammatory cells to the site of injury. Conversely, chronic inflammation persists even in the absence of external threats, leading to prolonged tissue damage and diseases like rheumatoid arthritis.[87, 88]

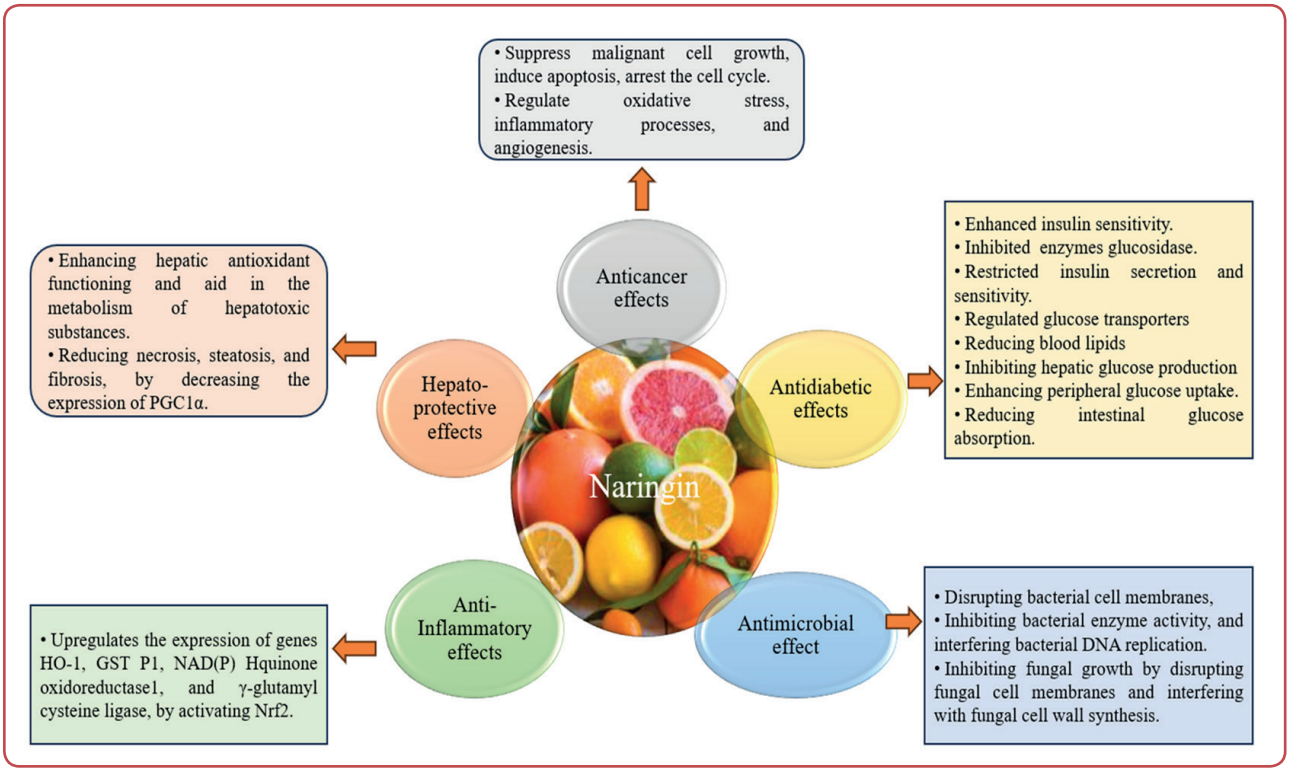

Figure 6: Pharmacological potential of naringin

Furthermore, a traditional Chinese medicine formulation known as "painopowder," containing naringin, neohesperidin, paeoniflorin and platycodin-D, has demonstrated significant anti-inflammatory effects, with naringin playing a prominent role among the four ingredients.[89] An illustration of pharmacological potential of naringin can be seen in (Figure 6).

Hepatoprotective effects

Hepatoprotection refers to the ability of a chemical compound to inhibit liver toxicity. Naringin has been suggested to enhance the hepatic antioxidant system's functioning and aid in the metabolism of hepatotoxic substances.[90, 91]

Antimicrobial effect

Naringin, a flavonoid compound found abundantly in citrus fruits, has garnered attention for its potential antimicrobial properties. Research indicates that naringin exhibits activity against various microorganisms, including bacteria, fungi and viruses[92] demonstrated that naringin possesses antibacterial effects against both Gram-positive and Gram-negative bacteria.[90]

Industrial utility

Food industry

The utilisation of naringin microspheres in yogurt has shown promising results in effectively reducing whey precipitation and slowing down pH drop. A recent study indicated that the incorporation of naringin-encapsulated microspheres could potentially extend the shelf life of yogurt as a bioactive product, presenting a novel approach to functional yogurt.[90, 93-97]

Pharmaceutical industry

Treatment with a naringin ointment formulation led to a significant reduction in wound area and epithelisation phase duration, accompanied by a notable increase in wound contraction velocity. The formulation of naringin ointment modulates collagen-1 expression, thereby promoting angiogenesis and facilitating wound healing. This effect is achieved through the down-regulation of inflammatory markers (such as ILs, NF-κB and TNF-α), apoptotic factors (such as pol-γ and Bax) and growth factors (such as TGF-β and VEGF).[98, 99]

Livestock sector

The past studies have shown that naringin can considerably lower the number of protozoa and methanogens in the rumen which leads to reduced methane production without causing any negative impacts on ruminal fermentation variables. Additionally, the use of daily diets with hesperidin and naringin has been successful in improving milk oxidative stability without affecting its chemical composition, coagulation ability or fat content in any way.[100, 101]

Moreover, taking hesperidin and naringin leads to a significant increase in the antioxidant capacity of breast and thigh meat from broiler chicks. Consequently, it appears that these bioflavonoids might gain entry through phospholipid membranes of the cells constituting tissues in poultry muscles. Indeed, these finding states that slower rate of lipid oxidation can extend shelf life thereby benefiting both consumers and poultry industry alike. In addition to this role, hesperidin and naringin are known to help preserve meat saving from any adverse consequences on avian growth or flesh quality thus are good additives for chicken feeds.[102]

Cosmetic industry

Anticancer, anti-inflammatory, antimicrobial activity, anti-oxidative, anti-aging etc are some of the benefits of naringin.[103] Studies show that when naringin is put into sunscreen formulations, it can reduce toxicity risks posed by other sunscreen components such as TiO_2 depending on its antioxidant capability. Furthermore, naringin neutralises free radicals that are produced by UV radiation and photocatalytic actions similar to those seen in ZnO and TiO_2 decreasing chances of toxicity.[104] Natural essential oils from plants like eucalyptus oil, lavender oil and peppermint oil have also been known to be good sources of antioxidants and antibacterial agents which can act as environmental friendly substitutes to synthetic antioxidants and preservatives used in cosmetics.[105] In addition there are microemulsions loaded with naringin having oils from eucalyptus or lavender whose results have shown comparable if not better than the best results when compared against artificially made ones. Moreover, they are more stable with higher release profile than any form without naringin in their components. The usage of micro emulsions containing essential oils in skin care formulations offers advantages such as better release and skin absorption of active ingredients, enhanced stability and other environmental-friendly alternatives to synthetic antioxidants.[106]

Total antioxidant scavenging activity

Naringin is a type of total antioxidant scavenging activity that indicates its ability to remove or neutralise different types of radicals and ROS in biological systems.[107] This compound, which is primarily found in citrus fruits, has powerful antioxidant properties because it can donate electrons or hydrogen atoms addressing the unstable radicals thus preventing cell or tissue death through oxidation. Studies show that naringin's antioxidant capabilities can occur via different mechanisms such as scavenging highly active free radicals like superoxide radical anion, hydroxyl radical and lipid peroxidation radical. This flavonoid also enhances the performance of some endogenous antioxidants such as superoxide dismutase, catalase and glutathione peroxidase. Due to its total antioxidant scavenging ability, naringin can be used in the medical industry, cosmetics, foods among other fields where diseases are generated because of oxidative stress or their product stability depends on it. In addition to battling oxidative stressors that lead to cellular aging together with degeneration, drug resistance tumour cell growth may be prevented by it thus providing therapeutic and dietary advantages (Figure 7).[108-113]

Clinical translation and challenges for its therapeutic application

The principal reason why naringin has not yet been authorised for clinical use either independently or when mixed with other bioactive elements is that the powerful *in vivo* metabolism of flavonoids hindered its therapeutic effectiveness. Though it has proven as a useful agent in the prevention and treatment of various diseases, its use has remained limited so far.[114, 115] Naringin's low solubility is another factor contributing to its crossing of the intestinal walls slowly.[116]

Flavonoids such as naringin have low oral bioavailability (8.8 %) and poor dissolution rates with limited solubility led to reduced drug effectiveness.[116] Moreover, it has been an acid-sensitive drug that could easily be broken down within the intestinal tract by endogenous ß-glucosidases produced through microbiota present in the gut.[117]

Most of its exploitation happened through oral administration although it did not absorb well in the intestines. Unlike other orally active substances absorbed quickly upon entry through the mouth, it's gastro-intestinal absorption was rath-

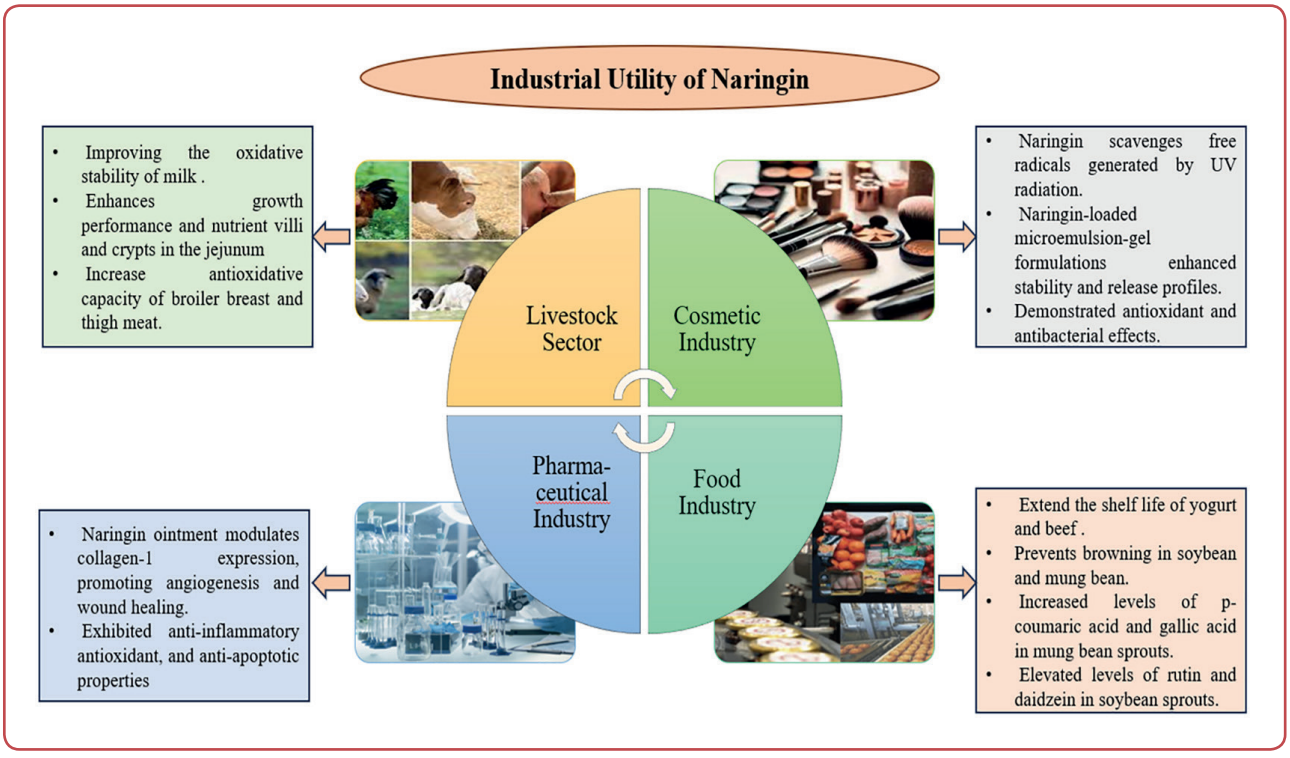

Figure 7: Industrial utilisation of naringin

er slow and unpredictable. In addition, flavonoid bioavailability and related clinical effectiveness depend significantly on gut microbes present.[118]

At present, various attempts have been directed towards addressing some of the limitations associated with its for use in clinical situations. *In-vitro* methods have been used to modify solubility and dissolution rates of flavonoids in order to improve their bioavailability and absorption while preventing their degradation by gut microbes, especially through encapsulation of nano-particles or micro-particles.[118, 119] It also underwent degradation upon administration into the bloodstream. In the blood, its presence is often unstable, becoming oxidised once it enters the serum or liver where β-glucosidases act on it.[120] As such, naringin's connection with bovine serum albumin happens quickly in physiological conditions which characterise its pharmacokinetics and therefore leads to higher rates of excretion thus affecting its bioavailability.[121] A number of different approaches were usually aimed at enhancing both the bioavailability as well as biological activity of natural substances with medicinal properties.

It's important to note that these were just some examples that reflected ongoing efforts in the field of pharmaceuticals targeting existing gaps through innovative designs targeting rare diseases clinically considered hard-to-treat such as in clinical applications intended for treatment such like cancers. *In-vitro* research including studies aimed at quite improving towards the enhancement of solubility and dissolution rates concerning flavonoids has been much focused on the use of encapsulation techniques involving microscopic particles or even nanometre-sized ones so as to avoid their degradation by intestinal bacteria.[122, 123] When given intravenously (iv), it can also degrade while circulating in blood. As such it is generally not stable within the system thereby oxidising quite easily within serum besides liver where it is broken down by β-glycosidase.[119] This therefore means that bovine serum albumin immediately forms complexes with it only under normal body conditions that ascertain its movement in the body hence promoting its excretion thereby determining its bioavailability through this mechanism.[120] The enhancement of bioavailability and bioactivity of active compounds for medicinal purposes is always executed using different techniques.

Such strategies comprise innovations in drug delivery mechanisms utilising nano-technology, pharmaceutical technology, colloids etc, changing chemical structure of drug targets, or employing certain bio enhancers and inhibiting the intestinal cell transporters among others.

The advancement of micro or nano formulations is considered one of the most potent research avenues for over- coming drug biopharmaceutics and physicochemical limitations in treating various pathologies. There are many micro-and nano-delivery systems that increase bioavailability and pharmacokinetics properties of it, hence preventing the degradation as well as random inter-actions when staying in circulation for long.[121, 122]
Such systems can have a sustained drug release profile after the right modifications with exact targeting mechanisms on inputted elements boosting their accumulation at defined sites. Thus, it is possible to improve bioavailability of it by linking it on suit-able micro or nano transporter.[123]

Naringin nano-formulations

There has been significant increase in the studies that are aimed at combining it with different types of nanocarriers for improvement of its bioactivity in a variety of biological set ups. The structures that are used in this case include liposomes, micelles, nanocrystals, solid lipid nanoparticles (SLNs), scaffolds and nanostructured lipid carriers. Some systems have been shown to have many merits over pure it in various pharmacological applications as indicated by literature reviewed although there is little information about how such nanoparticles containing it behave within an organism's body. Below are recent nano formulations designed for delivery of it via different routes.[123]

Liposomes

Liposome's have been considered as the most examined medicinal formulations because they can hold almost any kind of drug or other substances for therapeutic use due their ability to comprise drugs and other compounds possessing hydrophobic, hydrophilic and amphiphilic properties. Depending on how they are prepared, the size of these colloidal vesicles apprehended varies from twenty nanometres to several microns. As systemic delivery mechanisms, they are employed in

practically all sorts of liquid, solid and semi-solid preparations, thus finding applications in oral, intramuscular, subcutaneous, ocular as well as intravenous administration methods.

But a small number of liposomal systems have shown good results in transporting NRG for therapeutic purposes. Among them are Pleguezuelos-Villa et al who formulated ultra-deformable liposomes loaded with it aimed at treating skin inflammation. They have been recognised as very effective nanosystems for improving the cutaneous delivery of herbal extracts because their deformability and elasticity properties are determined by the mixture of surfactant and phospholipids which disrupts the organisation of lipid bilayers thereby increasing deformability.[124]

In the recent work by Mohanty et al, they suggested therapeutic potential of NRG and other nutraceutical-containing liposomes (isothiocyanates) that have anti-inflammatory activities like RA.[125] Two combinations were studied under various acute and chronic inflammation models *in vivo*; these were liposomes containing naringin plus sulforaphane (SFN) as well as those involving NRG plus phenethyl isothiocyanate (PEITC). Their study was conducted using DSPE-020CN, which is an analogue of DSPE-PEG2000 but with a methoxy group (-OCH_3) instead an amino one (-NH_2) on its polyethylene glycol (PEG) chain. The aim of this modification was to alter the surface characteristics of liposomes and thereby prolong blood circulation time within the formulation such that the sites of inflammation would experience more accumulation as a result of ELVIS mechanism (extra due to pull out from vessel causing reaction by inflammatory cells).

The different formulations obtained had low mean particles sizes ranging between 140.5 nm and 165.6 nm and were monodisperse with PDI ranging between 0.062 – 0.248 having highly negative charges at their surfaces (-47.3 mV to -53.3 mV). According to the authors, for the encapsulation of diverse compounds, liposomes made from DPPC/Chol/DSPE-020CN in a ratio of 15:4:1 were more effective thus these systems were employed *in vivo* as carriers loaded with different combinations of liposomal forms. The outcomes of the aforementioned experiments revealed that these formulations are effective in both short- and long-term inflammation cases in rats. In comparison to NRG + SFN, NRG + PEITC liposomes are more potent due to their slower rates of release as per *in-vitro* studies conducted by the authors. The release of PEITC and NRG lasts for 6 hours; hence they will stay longer in the body than SFN, which has a discharge time of 3 hours only. In their conclusion, it was emphasised that both types of liposomal formulations were able to decrease levels of proinflammatory cytokines significantly while enhancing those of anti-inflammatory cytokines besides reducing subcutaneous egg albumin induced oedema and carrageenan induced swelling, increasing C-reactive protein (CRP), normalising serum rheumatoid factor (RF), aiding in reducing some oxidative stress markers like glutathione (GSH), superoxide dismutase (SOD) or serum catalase, as well as limiting acute joint destruction with less granulocyte infiltration.[126]

NRG-laden liposomes were designed as one of the possible therapies against pulmonary fibrosis through inhalation. Accordingly, Kotta et al synthesised the liposomes using phosphatidylcholine, which is an endogenous pulmonary surfactant-mimicking lipid, for aerosol administration.

The most hopeful arrivals were those that were realised in the *in vivo* model of pulmonary fibrosis induced by bleomycin. The treatment with liposomal naringin lowered the number of inflammatory cells in bronchoalveolar lavages, lactate dehydrogenase (LDH) activity, total protein accumulation and oxidative stress markers. Moreover, histological analysis of lung tissues showed great improvement in the histopathological alterations and reduction in collagen deposition. Hence the authors suggest these lipid-based nanoparticles loaded with NRG as a possible alternative for managing pulmonary fibrosis because they produce effects similar to those induced by naringin [127] on this pathology in addition to forming a liposomal system that reduces accessibility to deep alveoli for enhanced therapeutic efficacy. Thus, the application of such constructions can go beyond other lung diseases as well.

According to Zheng et al, naringin loaded liposomes were modified with the trans activator of transcription (TAT) peptide and arginine-glycine-aspartate (RGD) tripeptides to enhance osteogenic properties of NRG.[128] The TAT peptide, which belongs to the family of short peptides known as cell penetrating peptides (CPPs), originates from human immunodeficiency virus (HIV) transcription protein and is mainly used as ligands facilitating intracellular uptake.[129] RGD

peptides serve as specific ligands for integrin transmembrane receptors that play significant roles in the regulation of intercellular communication and cell-extracellular microenvironment interactions.[130] To obtain NRG-loaded liposomes, a film hydration technique followed by using filters with 400 nm, 200 nm, 100 nm and 80 nm pore sizes was employed; then they were kept at 4 °C. Subsequently, TAT and RGD peptides were conjugated by pre-activating carboxylic functionality on the NGR-liposomes through 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC). As mentioned, the results show 160.70 nm as average particle size, - 20.77 mV negative zeta potential and 6.82 % low entrapment efficiency. TAT-RGD-NRG-liposomes underwent dialysis method which yielded NRG release to be 38.1 ± 1.8 % at 12 hours and 63.9 ± 2.2 % at 36 hours, respectively. According to published *in-vitro* assays, TAT-RGD- NRG liposomes were more effective than other agents in human dental pulp stem cells (hDPSCs) administration without causing any cytotoxicity. Also, a formulated compound had a stronger effect on cellular proliferation along with osteogenic differentiation as demonstrated by higher levels of alkaline phosphatase (ALP) expression and increased gene expression associated with bone formation as well as greater degree of mineralisation within hDPSCs.

Some reports have also proposed new generations of liposomes such as ethosomes, proposomes and phytosomes for transdermal and topical administration of naringin. The success of these newer liposomal generations as delivery systems is mainly due to their elastic structures and deformability that facilitate skin penetration for drugs. Ethosomes loaded with NRG were developed by Gollavilli et al to improve its skin retention and penetration properties. This suggests that NRG could be used for its antioxidant and photoprotective properties.[105] Ethosomes are liposomes which contain cosurfactant molecules made up of ethanol that can be inserted into bilayers closer to the polar heads of phospholipids making them less rigid than other types of liposomes.[131] Furthermore, it enables them to become more elastic and malleable since ethanol acts by modifying SC's conformation thus affecting lipid organisation in order to reduce SC fluidity thereby allowing bigger amount of the encapsulated drug penetrate into deeper levels of the skin. Thereafter, NRG-loaded ethosomes were prepared, optimised and finally incorporated into sunscreen creams containing nano-ZnO and -TiO_2 as photocising agents. The mechanical dispersion procedure allowed us to acquire ethosomes with superior particle size and EE. Permeation profiles of skin indicated that ethosomal formulation had a greater permeation of NRG than NRG suspension and creams. Moreover, when comparing ethosomes with suspended naringin, the former exhibited greater skin retention (403.44 ± 15.33 μg/cm^2) than the latter (202.81 ± 9.45 μg/cm^2). This formulation also confirmed the antioxidant activity of encapsulated NRG, which was lower than the standard curcumin and NRG suspension probably due to slow naringin release from ethosomes. In addition, SC4 was optimally formulated as sun protection cream having good SPF values and low permeation rate compared to other ethosome formulations with minimum absorption into human skin tissues. The authors argue that this is because ethosomes are incorporated into sunscreen creams for their stability. The use of NRG-loaded ethosomes in topical applications has never been reported before.

For enhanced wound healing, various authors created NRG loaded proposomes (liposomes based on propylene glycol (PG)) to fight the action of free radicals on injuries' healing routes.[132] Indeed, free radicals (ROS) are primary issues that have a central impact on healing process, while NRG has been shown to have properties that can block such negative responses within the cells caused by these substances.

Broadly speaking, proposomes serve for epidermis, dermis and transdermal delivery of skin medications as well as for other therapeutic uses with different lipid and PG contents.[133, 134] Just like in ethosomes where ethanol is mixed in order to stabilise both drugs and formulations; this technique has resulted in improved skin penetration and drug deposition as a result. In this case, for best results as far as tissue regeneration is concerned; the authors loaded topically applied gel using naringin proposomes on Carbopol 974 polymer base. Besides being prepared using hot micro-emulsion technique; NRG loaded gel was characterised then assessed both *in vivo* and *ex-vivo* with respect to various wound healing properties. The surface charge is negative net (-79.46 mV to -97.30 mV), thus contributing towards the stability of their formulation.

Polymeric micelles

Spherical nanometer-sized micelles are often

formed during the self-assembly of different amphiphilic molecules. They can enhance the pharmacokinetics and distribution of drugs in tissues, thus improving their bioavailability; they also provide a prolonged and regulated release of substances, maintain the physical and chemical stability of encapsulated molecules, in addition to allowing intravenous administration.[135]

A strategy to enhance naringin's antiulcer and anticancer activity was the design of NRG loaded polymeric micelles by Mohamed et al.[136] It is fascinating that Pluronic polymers can form micelles in water with hydrophobic polypropylene oxide (PPO) core and in function, they have been studied for their potential to overcome multidrug resistance (MDR) against many anticancer agents. Micelles produced with highest polymer content (NRG-PF68 1:50) had maximum EE value, average diameter below 100 nm, narrow size distribution and good stability which makes them suitable drug release systems. Based on the anticancer effects of the formulation, *in-vitro* cytotoxicity studies show that encapsulating NRG in Pluronic micelles made from PF68 considerably increases its cytotoxicity against various cell lines tested, with Caco-2 cells being the most sensitive. It even had better activity than the reference anticancer cisplatin. In comparison to free NRG, *in vivo* anti-tumour activity tests conducted on Ehrlich ascites carcinoma (EAC)-bearing mice also indicated greater tumour growth inhibition in patients treated using this micellar naringin formulation. The authors suggest that increased in vitro toxicities associated with naringin have been caused by its micelles made from Pluronic polymers which facilitate drug penetration into and retention within cancer cells and perhaps prevent drug efflux pumps or P-glycoprotein activities via Pluronics. The authors have also described comparative advantages of micellar NRG over free antiulcer naringin ethanol-induced ulceration in a rat model. The micellar formulation, compared to the positive control group significantly reduces mucosal damage, lowers gastric levels of malondialdehyde (MDA) and expression of alpha tumour necrosis factor (TNF), caspase-3 and promotes increase in GSH as well as SOD.[137, 138]

Lavrador et al created NRG-loaded polymeric micelles intended to regulate stem cells' osteogenic differentiation.[123] Naringin is thought to be one of the most effective plant medicines for promoting proliferation and maturation of osteoprogenitor cells into osteoblasts while at the same time inhibiting osteoclasts. The polymeric micelles were produced through a Michael-type addition reaction involving hydrophilic methoxy-poly (ethylene glycol)-maleimide (mPEG-MAL) and hydrophobic thiol-poly (l-lactide) (PLAS-H). Consequently, NRG was assembled together with copolymer on nanoscale level. These naringin micelles possess high EE along with an appropriate size (84.48 ± 2.44 nm), which is suitable for potential parenteral application to bone tissue, negative surface charge and controlled release profile for NRG over time. The stability studies indicated that they remain stable for up to two weeks even in deionised water or buffer phosphate saline solution (pH = 7.4) at a temperature of 4 °C. Results from *in-vitro* analyses illustrated that micelles like these can be absorbed into human adipose-derived stem cells (hASCs) leading to their migration towards lysosomes or endosomes. They also showed that NRG further enhances its pro-osteogenic abilities when the micellar system is internalised. In particular, compared with non-encapsulated naringin administration, micellar NRG stimulates osteopontin expression more intensely, increases ALP accreditations significantly and increases matrix mineralisation in these cells.[139, 140]

Lipid nanoparticles

Lipid nanoparticles (LNPs) refer to the tiny-sized structures formed of lipids that are commonly used as carriers for various therapeutic agents ranging from small molecules to the products of biotechnology. The fundamental reason for this is that they can be produced easily, are safe and have biocompatible formulations. Solid lipid nanoparticles (SLPs) [140, 141] could also be categorised as nanostructured lipid carriers (NLCs) which are referred to as second-generation lipid nanoparticles.[132, 134] An NLC integrated with naringin was formulated by Zhu et al, where liquid lipids like coix seed oil (CSO) were employed which is a potential formulation in the fight against hepatocellular carcinoma (HCC).[142] This means that CSO can enhance loading efficiency of NRG and hence synergistically combine two anti-cancer agents.

In-vitro release tests at pH 5 and 7.4 indicate that CSO derived NLCs release NRG faster compared to traditional lipid based NLCs like oleic acid and neo decanoate triglycerides; however, CSO NLCs can release naringin for up to 36 hours under control conditions. The assessment by CCK-8 staining for viable cells and Annexin V-PE assay

kit to measure apoptosis shows that the formulation with NRG and CSO has more antiproliferative effect on HepG2 cells as well as greater potentiality of inducing apoptosis than other tested formulations. Furthermore, this combination was more effective in inhibiting tumour growth in xenograft model than any single agent (RLX), whose study was carried out by Alhalmi et al, indicating increased spleen weight and superior concentrations of IL6 or 10 above normal levels within serum collected from mice which had been treated only with RLX. These findings lead the authors to suggest that their lipid-based formulation could be useful for co administration of two different anticancer drugs. In an attempt to develop an alternative formulation for breast cancer therapy, Alhalmi et al also prepared and optimised NLCs for the co-delivery of NRG and an oestrogen receptor modulator (raloxifene hydrochloride (RLX)).[143]

The hot homogenisation-sonication approach led to dual nano-structuring of Compritol 888 ATO and oleic acid and this resulted in optimised near spherical nanoparticles (137.12 nm) which had a size close distribution (0.266), positive zeta potential and high EE for both components. However, the authors did not provide any information regarding antitumor actions of their optimised formulations, but previously conducted research indicated that obtained NLCs are capable to release two drugs at a controlled rate for 24 hours (pH 6.8 buffer) with an initial burst release; thus, enhancing the *ex-vivo* intestinal permeability profiles of NRG and RLX against NRG/RLX suspension and showing improved antioxidant activity *in-vitro* (2,2-Diphenyl-1-picrylhydrazyl) DPPH). It can therefore be inferred that there is a synergistic antioxidant effect caused by this interaction. Further, it confirms that this formulation is safe and its lyophilised form has a good stability and integrity for three months. The same authors earlier reported similar results when they carried out research on NLCs optimised solely for loading NRG where sustained release profiles were examined as well as increased intestinal permeation capacity *ex-vivo* compared to NRG suspension indicating possibilities of inventing enhancing oral bioavailability of naringin.[144]

Rutin

Rutin, classified as a flavonoid glycoside, emerges as a complex molecule distinguished by its unique chemical structure, which underlies its diverse biological activities. Positioned centrally within this structure is a flavonol scaffold, presenting a tricyclic arrangement characterised by two aromatic rings interconnected through a heterocyclic pyran ring recognised as the C ring (Figure 8). This foundational arrangement hosts pivotal functional groups vital for its biochemical interactions, encompassing a ketone group (C4 carbonyl) alongside hydroxyl groups (OH) situated at positions 3, 5 and 7, thereby conferring essential reactivity and fostering the potential for hydrogen bonding. Rutin's glycoside nature stems from the attachment of a glycosidic moiety

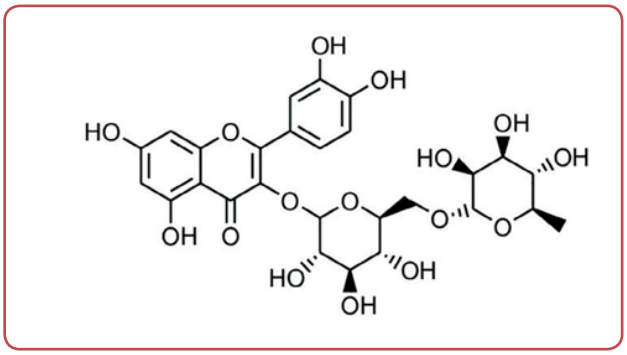

Figure 8: Chemical structure of rutin

to its flavonol core. This sugar component consists of two integral units: rhamnose and glucose. Rhamnose, an emblematic deoxyhexose sugar, establishes linkage to the flavonol core at the C3 position through a glycosidic bond. This inclusion of rhamnose not only induces alterations in rutin's physicochemical attributes but also orchestrates modulations in its biological functionalities, potentially influencing its dynamics related to absorption, distribution, metabolism and excretion within biological milieus. Additionally, a glucose unit is affixed to the rhamnose moiety, engendering a distinctive disaccharide entity. This adjunct glucose unit assumes a pivotal role in shaping both the structural integrity and functional repertoire of rutin. The glycosidic linkage between rhamnose and glucose confers stability upon the rutin molecule, thereby exerting discernible effects on its solubility, bioavailability and interactions with cellular receptors or enzymes.[145] The amalgamation of the flavonol core and the appended sugar residues imparts

a robust antioxidant profile to rutin, characterised by its adeptness in scavenging free radicals and mitigating damage incurred from oxidative stress. Beyond its antioxidant prowess, rutin demonstrates notable anti-inflammatory attributes, adept at modulating a plethora of signalling cascades intricately involved in inflammatory processes. Such structural intricacy, coupled with its multifaceted biological activities, has catalysed substantial interest within the realms of pharmaceutical and nutraceutical research, with envisaged applications spanning the prophylaxis and therapeutic interventions against a gamut of maladies, encompassing cardiovascular disorders, oncological afflictions and neurodegenerative conditions.

In summation, the chemical constitution of rutin embodies a flavonol core embellished with rhamnose and glucose sugar moieties, endowing it with a spectrum of biological functions and therapeutic potentials. Comprehensive comprehension of its intricate architecture and molecular interplays is indispensable for harnessing its salutary effects across realms of health and disease.[146]

Occurrence

Rutin, a notable flavonoid glycoside, exhibits widespread distribution across the plant kingdom and is prevalent in an extensive array of botanical reservoirs. Its presence is evident in numerous plant species, encompassing but not restricted to buckwheat, citrus fruits, apples, cherries, berries, tea and select vegetables like asparagus and onions. This pervasive occurrence underscores rutin's pivotal role as a natural constituent within various dietary staples and herbal formulations.[147] Buckwheat (*Fagopyrum esculentum*) emerges as a significant repository of rutin, notably abundant in glycosidic form, prominently within its seeds and foliage. The ample presence of rutin in buckwheat renders it a subject of interest for extraction endeavours, driven by its perceived health benefits and its integration into traditional medicinal practices as well as contemporary pharmacological applications. Similarly, citrus fruits, renowned for their richness in bioactive compounds, serve as another substantial reservoir of rutin. Varieties such as oranges, lemons, grapefruits and others house notable quantities of rutin within their peel, pulp and juice, accentuating the health-promoting potential associated with their regular consumption and derivative products.[148] Furthermore, rutin extends its prevalence to various berries like cranberries, elderberries and mulberries, thereby augmenting their antioxidant repertoire and potential health contributions. Noteworthy concentrations of rutin are also discernible in apples, particularly concentrated within their peel, amplifying its prevalence among commonly consumed fruits.[148] Beyond the realm of fruits and vegetables, rutin finds expression in tea leaves, particularly in green tea variants, bolstering the antioxidant capacity and purported health benefits attributed to tea consumption. This ubiquitous presence underscores the accessibility of rutin through dietary channels, thereby accentuating its potential impact on human health and well-being. In essence, the widespread distribution of rutin across diverse botanical sources underscores its stature as a bioactive compound endowed with potential health-promoting attributes. Its integration within commonplace foods and herbal remedies highlights its relevance within both traditional and contemporary paradigms of wellness and disease management.[149]

Phytochemistry

Rutin, as a flavonoid glycoside, presents a complex phytochemical profile characterised by its intricate chemical structure and diverse biological functions. Belonging to the flavonol subclass, rutin features a flavonoid core composed of two aromatic rings fused to a heterocyclic pyran ring (Figure 8) adorned with hydroxyl (OH) groups at positions 3, 5 and 7, alongside a ketone group (C4 carbonyl), which imparts significant antioxidant and anti-inflammatory properties.[150] The glycosidic character of rutin arises from the attachment of sugar moieties to its flavonoid core. Specifically, rhamnose, a deoxyhexose sugar, predominantly links to the C3 position of the flavonol core via a glycosidic bond. Additionally, a glucose unit forms an adjunct linkage with rhamnose, resulting in the formation of a disaccharide entity. These sugar residues exert considerable influence on rutin's physicochemical attributes, thereby influencing its solubility, bioavailability and interactions within biological matrices. Rutin's phytochemical profile extends beyond its structural components to encompass a spectrum of secondary metabolites, including other flavonoids, phenolic acids and terpenoids. These bioactive compounds often collaborate synergistically with rutin, amplifying its antioxidant, anti-inflammatory and potentially anticancer ef-

fects, thereby augmenting its therapeutic versatility across various disease contexts.[151, 152]

Pharmacology

Rutin exhibits robust intrinsic activity, yielding the most potent inotropic responses among various flavonoids (Figure 9). Its efficacy extends to demonstrating antiulcer activity and exerting regenerative and hepatoprotective effects in experimental cirrhosis, alongside venorutin. Both rutin and quercetin have found utility as integral constituents in pharmaceutical formulations targeting capillary fragility and phlebosclerosis. Explorations into the pharmacological potential of flavonoids and esters of phenolic acids have unveiled their antibacterial, antifungal and antiviral properties. Notably, rutin exhibits activity against *Bacillus anthracis*, *Parainfluenza* and *Influenza* virus.[153] Antioxidant compounds, crucial for health preservation, function by neutralising free radicals arising from various biological sources, initiating degenerative diseases by oxidising vital biomolecules such as nucleic acids, proteins, lipids and DNA. Phenolic acids, polyphenols and flavonoids are recognised for their antioxidant prowess, with rutin emerging as an effective inhibitor of iron-ion-dependent lipid peroxidation, primarily through chelation of iron ions. Rutin's chelating mechanism demonstrates superior efficacy compared to quercetin in thwarting lipid peroxidation induced by iron ions.[154]

Anticancer effects

Rutin has been identified as a modulator of apoptosis in cancer cells, with further research needed to compare its anticancer efficacy and mechanisms to other natural agents like curcumin, zerumbone and thymoquinone.[155]

Industrial application

Food industry

In the food industry context, phenolic compounds are studied to standardise the transformation processes that prevent degradation of the compound, replace chemical additives or enhance nutritional value of food and design bioactive packs. However, even though many health benefits of rutin were known to by people, it was not widely used in the food industry because watery environment changes its physicochemical characteristics therefore resulting in a sour and bitter flavour, which is typical of flavonoids. Furthermore, as rutin tends to break during cooking, its disintegration makes it impossible to utilise it when preparing some meals.[156]

A cooking method has been adopted to determine rutin content in food, among other methods. The rutin content in asparagus cooked at temperature ranging from 80 to 90 °C was evaluated; it was observed that there was no significant loss of the rutin compounds when temperatures were below 90 °C and for a period of thirteen minutes.

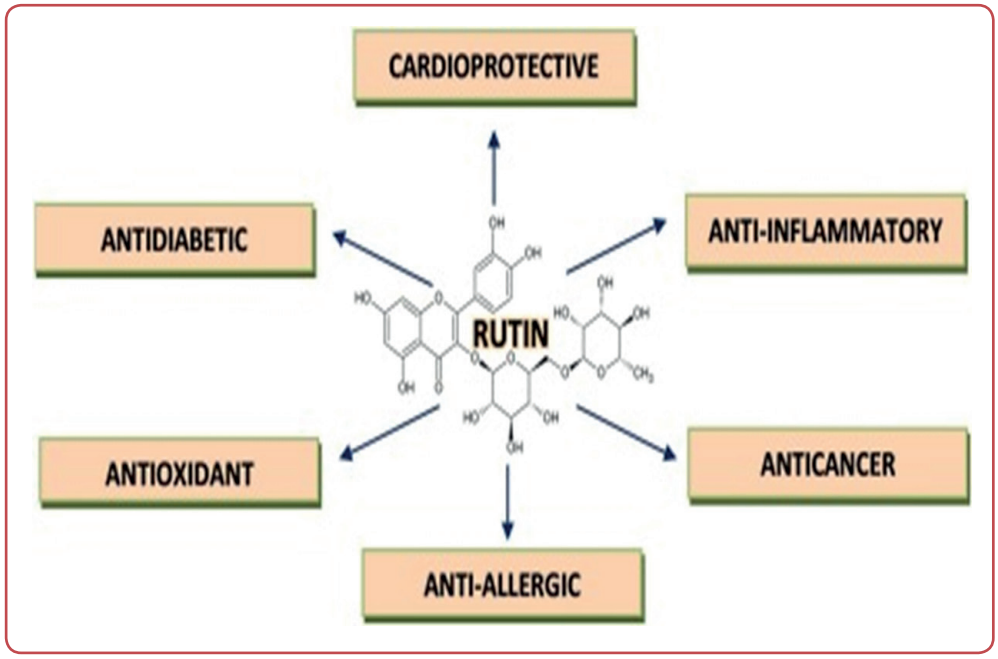

Figure 9: Rutin intrinsic activity

An experiment was conducted to determine the conditions that resulted in the maximum retention of rutin in dough made from buckwheat, with the aim of inactivating enzymes that would degrade the compound during thermal treatment, leading to a bitter taste.[157]

In similar research, buckwheat paste was prepared and it showed that samples that contained hydrothermally treated paste at 70 °C for fifty minutes had much more "rutin" than the standard paste at 0.27 g/100 g during cooking, therefore resulted in less stickiness and anodal viscoelastic properties compared to other kinds of pastes.[158]

Rutin and its plant extracts were studied to check their ability to prevent the food from spoiling. Thirty percent of the phenolic compounds were combined to form one of the commercial antioxidants used in the formulation of sausages. Among other things, concentrations of malondialdehyde, which is an indicator for oxidative stability, were found to be low even after forty-five days. The use of buckwheat husk extract, rich in rutin, increased free radical scavenging activity, measured using 2,2-diphenyl-1-picrylhydrazyl and improved Fe(II) ion chelation over a period of one hundred and eighty days.[159]

Active packaging

Rutin can be encapsulated in liposomes for controlled release, demonstrated by low polydispersity index, high encapsulation efficiency, favourable Z potential values and antioxidant properties.[160]

Furthermore, the edible bioactive films made from corn starch contained zein and rutin nanoparticles. The nanoparticles containing 10 % w/v of rutin had the best antioxidant characteristics. However, beyond 10 % of rutin concentration, the modulus of elasticity for starch films increased as tensile strength also increased. It was also found that films incorporated with both zein and rutin nanoparticles exhibited lower moisture permeability as well as decreased water solubility compared to their counterparts lacking these nanomaterials. Rutin was slowly released from these films within a few hours when present at concentrations ranging from 27.1 % to 36.9 %.[161]

Food fortification

Rutin and quercetin were added to a spreadable cheese formulation at levels of 0.5 g/100 g and their retention studies were carried out at different melting times and temperatures for quercetin and rutin, as well as for total phenolic content and antioxidant capacity (80 and 90 °C for 1.5 and 10-mins correctly). The research determined that there is a significant decrease in these two flavonoids which affects the antioxidant capacity. Rutin is more influenced by melting temperature than that of quercetin. In order to encapsulate rutin into milk, orange juice and apple juice; food-grade nanostructured lipid carriers were developed. Surfactants consist of cocoa butter with oleic acid in the oily phase. The most effective ratio was found to be 10 % rutin to 10 % lipid. Pasteurization (30 minutes at 65 °C) and sterilisation (15 minutes at 121 °C) were used for the food models, while the final product was not significantly affected by the fortification process. Over time, particle size, pH value as well as turbidity status were evaluated in their stability; moreover, properties of enriched foods did not change at all.[162, 163]

Cosmetic applications

The recent interest of researchers in natural materials with photoprotective potential and antioxidant activity stems from their combined benefits that they bring along with them to the traditional sunscreen compositions. The experiment conducted on the clinical safety of a product, antioxidant ability and sun protection factor (SPF) of the two forms of sunscreens containing 0.1 % and 3 % w/w rutin was evaluated in this research. It was observed that 3 % rutin preparation has an ability to raise the SPF very high, up to about 70 %. Thus, it is effective and safe for use in suntan agents. Again, this formulation was found to promote removal by 40 % increase in free radicals compared to those lacking rutin.[164]

Researchers have looked at how rutin affects disruptions or lysis of cutaneous fibroblast membranes that are induced by UV rays. They cultured fibroblasts for 12 hours before exposing them to UVA and UVB radiation for 24 hours. The lipidomic analysis revealed that rutin decreased levels of phosphatidylethanolamine and phosphatidylcholine while inhibiting the dispholipaseupregulation, thereby stopping production of reactive oxygen species as well. Moreover, GSH-Px, vitamin E and vitamin C levels were preserved during this period, thereby suggesting its potential use as a sunscreen against solar radiation.[165]

The researchers assessed the probable advantages of dermo-cosmetic products containing rutin based on their UVA absorption as well as their ability to

eliminate ROS. Various formulations underwent four tests: antioxidant actions, photoprotective effectiveness *in-vitro*, photostability and skin tolerance tests *in vivo*. The outcomes revealed that human skin is well-comparable with it adsorbent potential due to excessiveness of 75 % removal activity than common UVB filters. Despite post-irradiation photodegradation did not prevent by rutin, however significant wavelengths' increment was observed especially in UVA range demonstrating photoprotective benefit.[166]

As an element in a more extensive research project, the antioxidant capability and potential sunlight shielding of gelatin nanoparticles loaded with rutin were examined. Rutin encapsulated particles were found to have a 74 % higher antioxidant capacity than unconstrained solution. In addition, there was a 48 % increase in SPF. In addition, tests were conducted on compatibility with human skin and the results indicated that gelatin nanoparticles loaded with rutin are potential effective photo-protective agents that are also biocompatible and possess additional antioxidant merits.[167-169]

Conclusion

In conclusion, the comprehensive review of hesperidin, naringin and rutin highlights their multifaceted therapeutic potential and diverse applications across various industries. As a flavonoid compound abundant in citrus fruits, they showcase robust antioxidant properties, effectively neutralising free radicals and reactive oxygen species within biological systems. Moreover, studies elucidate their ability to modulate the activity of endogenous antioxidant enzymes, further enhancing its antioxidative capacity. Beyond their antioxidant prowess, they demonstrate promising anti-inflammatory and anti-cancer properties. These attributes make them versatile candidates for medicinal interventions; skincare formulations and functional food products aimed at promoting health and well-being. Furthermore, naringin's and rutin's role in enhancing the stability of sunscreen formulations and their potential to mitigate the toxicity risks associated with certain sunscreen ingredients underscore its relevance in skincare applications. Additionally, their incorporation into microemulsions and other delivery systems offers improved stability, enhanced release profiles and environmentally friendly alternatives to synthetic antioxidants in skincare formulations. Overall, the review underscores hesperidin, naringin and rutin significance in combating oxidative stress, supporting wound healing, protecting against liver damage. As research continues to unveil its therapeutic mechanisms and explore new applications, they stand as poised as a valuable natural compound with immense potential for improving human health and enhancing product quality across diverse industries.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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