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Review

A Review on Pharmacological and Analytical Aspects of Naringenin

Kanika Patel[1], Gireesh Kumar Singh[2], and Dinesh Kumar Patel [2]

ABSTRACT Flavonoids are a widely distributed group of phytochemicals having benzo-pyrone nucleus, and more than 4,000 different flavonoids have been described and categorized into flavonols, flavones, flavanones, isoflavones, catechins and anthocyanidins. Flavonoids occurs naturally in fruits, vegetables, nuts, and beverages such as coffee, tea, and red wine, as well as in medical herbs. Flavonoids are responsible for the different colors of plant parts and are important constituents of the human diet. Flavanoids have different pharmacological activities, such as antioxidant, anti-allergic, antibacterial, anti-inflammatory, antimutagenic and anticancer activity. Naringenin belongs to the flavanones and is mainly found in fruits (grapefruit and oranges) and vegetables. Pharmacologically, it has anticancer, antimutagenic, anti-inflammatory, antioxidant, antiproliferative and antiatherogenic activities. Naringenin is used for the treatments of osteoporosis, cancer and cardiovascular diseases, and showed lipid-lowering and insulin-like properties. In the present review, detailed pharmacological and analytical aspects of naringenin have been presented, which revealed the impressive pharmacological profile and the possible usefulness in the treatment of different types of diseases in the future. The information provided in this communication will act as an important source for development of effective medicines for the treatment of various disorders.

KEYWORDS analytical techniques, flavonoids, naringenin, pharmacological activity, phytoconstituents

Plants have been used by human being since antiquity for diverse purposes such as food and medicine. Many of the currently available drugs have been derived from natural sources. More than 25% of the drugs prescribed worldwide are derived from plants, and 121 such active phytoconstituents are used for different disorders.[1,2] A large number of African and Asian populations depend on traditional medicines for their primary healthcare. About 2–3 decades ago, most of the drugs were of herbal origin.[3] The term flavonoid is derived from the Latin word "*flavus*", meaning yellow. It is a plant secondary product that has characteristics in red, blue, and purple pigments in plant tissues. Apart from their physiological roles in the plants, flavonoids are important components of the human diet, even though they are not considered as nutrients. Flvonoidal compounds share the same basic skeleton, the flavan-nucleus, consisting of two aromatic rings with six carbon atoms (ring A and B) interconnected by a hetero cycle including three carbon atoms (ring C).[4-8] Flavonoids are plant-derived phytochemicals responsible for the different colors of plant parts like shades of yellow, orange and red in flowers. More than 4,000 flavonoids, such as flavonols, flavones, flavanols, flavanonols, flavanones, and isoflavones have been reported in the edible plants and are consumed regularly in the human diet.[9] Flavonoids, found in fruits and vegetables, have various health benefits.[10] The biosynthesis of flavonoids occurs via the combination of shikimic acid and acylpolymalonate metabolic pathways. A starting compound is phenylpropane, a cinnamic acid derivative derived from shikimic acid, in which three acetate residues are incorporated followed by ring closure. The chalcone structure is an intermediate to the flavone structures, which might be hydroxylated and reduced at different positions.[11] Recent evidences have indicated that an adult human diet rich in flavonoids leads to a decrease of total cholesterol, low-density lipoproteins, and triglycerides in plasma, as well as a reduced incidence of cardiovascular diseases and osteoporosis.[9] Among naturally occurring flavonoids, naringenin and hesperetin are very common in some edible fruits and vegetables as aglycons and glycosides. Naringenin is most abundant in grapefruit and are used in perfumery, cosmetic and in different pharmaceutical formulations. It has been reported for the hypocholesterolemic, antiestrogenic, hypolipidemic, antihypertensive, and antiflammatory activities.[12]

1. G.L.A Institute of Pharmaceutical Research, Mathura, India; 2. Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005, India
Correspondence to: Dr. Dinesh Kumar Patel, Tel: 91-9919192440, E-mail: dkpatel.rs.phe@itbhu.ac.in
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Importance of Flavonoids

Plants produce a vast array of natural products including phenolic compounds, which are responsible for the major organoleptic characteristics of plant-derived foods and beverages. They play an important role in the color and taste properties of fruits and vegetables.[13,14] Flavonoids, a group of phytochemicals, have diverse beneficial biochemical and pharmacological properties, mainly presented in foods of plant origin, such as fruits, vegetables, tea, wine, seeds, herbs, spices, and whole grains.[15] Flavonoids are biological pigments responsible for the colors from red to blue in flowers, fruit and leaves.[16] Flavonoids are composed of two aromatic rings linked through three carbon atoms that form an oxygenated heterocycle. Variations on the basic structure of flavonoids yield different classes of flavonoidal compounds (Appendix 1).[17] Flavonoids are a widely distributed group of polyphenolic compounds characterized by a common benzo-pyrone structure. Over 4,000 different flavonoids have been described and categorized into flavonols, flavones, flavanones, isoflavones, catechins, and anthocyanidins (Appendixes 1 and 2). The daily Western intake of mixed flavonoids has been estimated to be in the range of 0.5 to 1 g/day.[18] Diverse biochemical properties of flavonoids including naringin, hesperidin, diosmin, and rutin have provoked interest in biology and medicinal chemistry. These compounds have exhibited a broad range of biological and pharmacological activities, such as antioxidant, anti-allergic, antibacterial, anti-inflammatory, antimutagenic and anticancer effects.[19] Flavonoids represent one of the most prevalent classes of compounds in vegetables, nuts, fruits and beverages, as well as in medical herbs (e.g., *Silybum marianum*, *Alpina officinarum*, *Hypericum perforatum*). The large number of compounds arises from the various combinations of multiple hydroxyl and methoxyl group substituents on the basic flavonoid skeleton.[20] Traditionally, human consumption of flavonoids has occurred through the ingestion of fruits, vegetables, legumes, and plant-derived products such as tea, wine, cocoa, coffee, and fermented foods.[21] Flavonoids are important effective constituents of some medicines, especially of Chinese herbal medicines, and showed a wide range of therapeutic activities against cancers, tumors, acquired immunodeficiency syndrome, allergies, etc.[22-24] In addition to their antioxidant properties, flavonoids have been reported to exhibit antiviral, antibacterial, anti-inflammatory, vasodilatory, anticancer, and anti-ischemic activity. Moreover, they are also able to inhibit lipid peroxidation and platelet aggregation, and increase capillary permeability and fragility.[6] Rich dietary sources of flavonoids are soybean (isoflavones), citrus (flavanones), tea, apple and cocoa (flavanols), celery (flavones), onions (flavonols) and berries (anthocyanins).[8] In Asian countries, especially in China, most of the medicinal plants used to prevent or cure diseases are rich in flavonoid content. Molecular mechanisms of the therapeutic effect of flavonoids have also been investigated in many studies. Furthermore, higher intake of total flavonoids was significantly associated with lower risk of non-Hodgkin's lymphoma and their putative anticarcinogenic activities.[23,24]

Importance of Naringenin

Naringenin (5,7,4'-trihydroxyflavanone, Figure 1) belongs to the class of flavonoids called the flavanones. The flavanones are abundant in citrus fruits such as grapefruits (*Citrus paradisi*) and oranges (*Citrus sinensis*). The role of naringenin and the related citrus flavanone hesperetin in the treatment of disease has received considerable attention, with particular interest as anticancer and antiatherogenic compounds.[25] Naringenin is associated with beneficial effects in osteoporosis, cancer and cardiovascular diseases.[9] It has anticancer, antimutagenic, anti-inflammatory, and antiatherogenic activities. Naringenin was recently shown to reduce the accumulation of collagen fibers in dimethylnitrosamine-induced liver injury in rats and exhibit antifibrogenic effects.[26] Naringenin is found to be more abundant in citrus fruits and tomatoes and is reported to have antiproliferative effects in different cancer cell lines, including colon, breast, and uterus cancer cell lines.[9,27] It also showed both lipid-lowering and insulin-like properties. In cholesterol-fed rats, naringenin lowered plasma cholesterol by inhibiting hepatic cholesterol synthesis and esterification.[28]

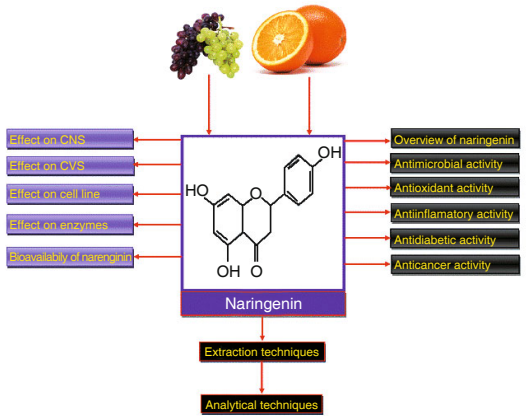

Figure 1. Chemical Structure and Overview of Naringenin

Pharmacological Activity of Flavonoids

In nature, flavonoids are involved in a wide range of functions, such as providing pigmentation for flowers,

fruits and seeds, attracting pollinators and seed dispersers, protecting against ultraviolet light, providing plant defence against pathogenic micro organisms, functioning in plant fertility and germination of pollen, and acting as signal molecules in plant microbe interactions.[8,29] Several epidemiological studies suggest the positive effects of flavonoids on human health. Flavonoids are best known for their antioxidant activities along with some other biological effects like effect on intracellular signaling pathways.[17] Various types of nutrients and non-nutrients, including flavonoids, have been shown to inhibit or prevent chemical carcinogenesis in animal models. Flavonoids have been reported to have a wide range of biochemical effects including metal chelation, free radical scavenging, inhibition of enzymes, inhibition of cellular proliferation and induction of apoptosis. Various flavonoids are effective chemopreventive agents against 7,12-dimethylbenz(a) anthracene (DMBA)2-induced mammary cancer in rodents as well as other chemically induced models of carcinogenesis.[30] Recently, much attention has been paid to different flavonoid derivatives as antioxidants, and dietary intake of these natural compounds has a significant effect on preventing a variety of diseases. Most of the flavonoids are very potent antioxidants because they can chelate metal ions, scavenge oxygen free radicals, and prevent the oxidation of low-density lipoprotein.[31]

Pharmacological Activities of Naringenin

Antimicrobial Activity of Naringenin

Antimicrobial activity of Naringenin against pathogenic bacteria, such as L. *monocytogenes*, *E*. *coli* O157:H7 and *S*. *aureus* was investigated. From the data, it was found that there was no antimicrobial activity at the tested concentration against these microorganisms.[32] Naringenin was screened for its capacity to reduce the production of quorum sensing (QS)-controlled factors in the opportunistic pathogen *Pseudomonas aeruginosa* (strain PAO1). Results showed that naringenin dramatically reduced the production of acylhomoserine lactones N-(3-oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) and N-butanoyl-L-homoserine lactone (C4-HSL), which is produced by the lasI and rhlI genes respectively.[33] Antifilarial activity of some flavonoids, including naringin, against the human lymphatic filarial parasite *Brugia malayi*, was investigated by using an *in vitro* motilities assay with adult worms and microfilaria. Results showed that naringenin and flavone have activities against *Brugia malayi*, which may provide a lead for design and development of new antifilarial.[34] In another study, effect of naringenin on *Salmonella Typhimurium* LT2 was investigated. Naringenin was found to be active against this microorganism with specifically repressed 24 genes in the *Salmonella* pathogenicity island 1 and down-regulated 17 genes involved in flagellar and motility.[35]

Antioxidant Activity of Naringenin

For the determination of antioxidant activity of naringenin, effect of naringenin plus vitamins C and E on Cd-induced oxidative hepatotoxicity in Wistar rats was investigated. From the results, it was found that combined administration of naringenin plus vitamins C and E are more beneficial in the treatment of Cd-hepatotoxicity than naringenin treatment alone.[36] Interactions of individual phenolic compounds, in cluding naringenin with others, were analyzed for their antioxidant capacity in order to know the potential antagonistic, additive or synergistic interactions. From the result, it was found that different combinations showed some synergistic effect compared to alone.[37] Effects of silymarin and naringenin in counteracting arsenic-induced hepatic oxidative stress in the male Wistar rats were investigated. Increased silymarin or naringenin administration reduced glutathione (GSH) levels, and was found to be beneficial in both the recovery of altered superoxide dismutase (SOD) and catalase activity and significantly reducing blood and tissue arsenic concentration.[38] Several flavonoids including naringenin were studied *in vitro* for their efficacy against ONOO(-) or hemoglobin/$NaNO_2$/H_2O_2-mediated nitrative/oxidative damage to human plasma proteins. Results showed that, these flavonoids inhibited ONOO(-)-induced protein oxidation dose-dependently while no effect was observed on hemoglobin/$NaNO_2$ $NaNO_2$/H_2O_2-triggered protein oxidation, which may contribute to their protective effect partly through inhibiting protein nitration.[39] Antioxidant capacity and radical scavenging activity of naringin and its aglycone were investigated *in vitro*. The results showed that naringenin exhibited higher antioxidant capacity and hydroxyl and superoxide radical scavenger efficiency than naringin. Additionally, naringenin showed a greater effectiveness in protecting against oxidative damage to lipids in a dose-dependent manner.[40]

Anti-inflammatory Activity of Naringenin

Anti-inflammatory effects of some bitter compounds including naringenin were tested in primary mouse splenocytes in the absence or presence of lipopolysaccharide (LPS). Naringenin treatments showed the strongest anti-inflammatory activity among all the selected compounds.[41] Anti-inflammatory effects of naringenin on LPS-stimulated RAW 274.6 macrophages and BV2 microglia were investigated. Moreover, the suppressive

effects of naringenin and vitamin C on LPS-induced nitrite production were also investigated. The results showed that macrophages could maintain cell viability at higher naringenin concentrations and were more easily activated by LPS in comparison to microglia. Under LPS stimulation in both cell types, naringenin inhibited nitrite production and inducible nitric oxide synthase and cyclooxygenase-2 expression in a dose-dependent manner.[42]

Antidiabetic Activity of Naringenin

For the determination of the interaction of some flavonoids including naringenin with glucose uptake both in the basal state and after insulin stimulation, Murine 3T3-L1 adipocytes and isolated mature human adipocytes were taken in the present investigation. From the results, it was found that naringenin improved glucose transport from plasma to cells, which could be beneficial for the diabetic patients.[43] Effect of naringenin on the levels of DNA damage in the blood, liver and kidney cells in diabetic mice were investigated. Naringenin treatment showed significant increases in the body weight, the hematological and immunological parameters of blood, as well as leading to 100% survival of diabetic mice.[44] In another study, effects of naringenin on skeletal muscle glucose uptake were investigated. Naringenin stimulated glucose uptake in L6 myotubes in a dose and time dependent manner through glucose transporter type 4 (GLUT4) glucose transporters.[45] Effect of naringenin on adipocyte functions including adipocytokine production was investigated. Naringenin chalcone promoted gene expression and protein secretion of adiponectin from 3T3-L1 adipocytes. These results indicate that naringenin improved adipocyte metabolic functions and exerts insulin-sensitizing effects by activating an adiponectin-related pathway.[46] In another study, naringenin inhibited tumor necrosis factor α (TNF-α)-stimulated free fatty acids (FFA) secretion from mouse adipocytes and blocked the TNF-α-induced activation of the nuclear factor kappa B (NF-κB) and extracellular signal–regulated kinase (ERK) pathways. These findings showed that naringenin may directly inhibit TNF-α-stimulated FFA secretion, which may be useful for ameliorating FFA-induced insulin resistance.[47]

Anticancer Activity of Naringenin

To get better anticancer compound from natural resources, derivative of naringenin was prepared and subjected for anticancer effects on non-small-cell lung cancer (NSCLC) cell lines NCI-H460, A549, and NCI-H1299. Naringenin derivative N101-43 was found to induce apoptosis via up-regulation of Fas/FasL expression, activation of caspase cascades, and inhibition of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) survival signaling pathways in the tested cells.[48] Effect of anticancer activity of naringenin on a breast cancer resection model (metastases) was investigated. Result showed that orally administered naringenin could inhibit the outgrowth of metastases after surgery via regulating host immunity.[49] Naringenin, isolated from *Salvia leriifolia* was subjected for cytotoxic activity against a panel of human cancer cell lines. Results showed that naringenin had strong cytotoxic activity compared to vinblastine in the C32, LNCaP, and COR-L23 cell lines.[50] For the determination of the anticancer activity of naringenin, docking study was performed. Results showed that naringenin have highest affinity towards mutant H Ras. Further naringenin effectively inhibited the function of mutant H-Ras P21 protein, which in turn arrests the process of cell growth and proliferation of the cancer cell.[51] Effect of naringenin in fostering apoptosis in cerebrally implanted C6 glioma cells rat model was investigated. Results showed that supplementation of naringenin to experimental animals' modulated Bcl-2/Bax ratio, up-regulation of caspase-3 and 9 and the expression of Cx43.[52]

Effect of naringenin in TNF-related apoptosis-inducing ligand (TRAIL) induced apoptosis in TRAIL-resistant NSCLC A549 cells was investigated. Result showed that it had no detectable inhibitory effects on cell proliferation of normal lung fibroblast cells. DR5 proteins were up-regulated and knockdown of DR5 expression by siRNA attenuated naringenin plus TRAIL-induced apoptosis. Furthermore, co-treatment with naringenin and TRAIL resulted in reduction of the clonogenic capacity of A549 cells, and surviving clones could be re-sensitized for repeated TRAIL treatment.[53] Effect of naringenin toxicity on whole mouse cultured embryos and their ability to protect embryos against hydroxyurea-induced insult were evaluated. Naringenin produced significant reduction of developmental and growth parameters compared to the control group. Embryos exposed to the concurrent administration of naringenin with hydroxyurea were significantly protected from growth and developmental retardation, and abnormalities induced by hydroxyurea.[54] Effects of four citrus flavonoids and one limonoid mixture containing naringenin on chemically induced colon cancer in rats were investigated. Naringenin increased apoptosis of luminal surface colonocytes compared to the control diet. The ability of dietary naringenin to reduce high multiplicity aberrant crypt foci (HMACF), lower proliferation and increase apoptosis may contribute toward colon cancer prevention.[55] In another study, human myeloid leukemia HL-60 cells treated with naringenin with or without caspase

inhibitors initiated the caspase cascade through an intrinsic apoptotic pathway.[56] Effect of naringenin for their cytotoxic and apoptogenic effects in human acute lymphoblastic leukemia MT-4 cells was tested. The naringenin-treated cells showed different cell cycle profiles with accumulation in G2/M phase.[57] In another study, naringenin was used as a positive control to examine the cytotoxicity of geranylated flavanones isolated from the fruits of *Paulownia tomentosa* and *Morus alba* against the selected human cancer cell lines and normal human fibroblasts.[58]

Effect of Naringenin on Central Nervous System

Mouse behavioral models of depression were used for the determination of the neuropharmacological mechanism of the dietary flavonoid including naringenin. Naringenin significantly decreased the immobility time after acute treatment in the mouse tail suspension test, but not in the forced swimming test, without producing locomotor alteration in the open-field test. These data demonstrated that naringenin possessed potent antidepressant-like property via the central serotonergic and norepinephrine systems.[59]

Effect of Naringenin on Cardiovascular System

In vivo antihypertensive and *in vitro* functional vasorelaxant mechanism of naringenin in rats were investigated. Vasorelaxant effect of naringenin was shifted to the right when endothelium-intact aortic rings were pre-incubated with l-NG-nitro-arginine methyl ester (l-NAME) and oxadiazolo[4,3-a]quinoxalin-1-one (ODQ). Furthermore, naringenin (NG) relaxant curves were displaced to the right in the presence of tetraethylammonium and 2-aminopyridine on endothelium-denuded aortic rings.[60]

Effect of Naringenin on Cell Lines

Effects of flavonoids including naringenin on matrix metalloproteinase-13 induction were examined in the human chondrocyte cell line SW1353. From the result it was found that naringenin did not showed significant activity.[61] Effect of naringenin on β-naphthoflavone (β-NF)-induced cytochrome P450 1A1 (CYP1A1) expression in mouse hepatocytes in primary culture was investigated. Naringenin induced CYP1A1 mRNA expression, flavone was especially found more effective than β-NF.[62] Effects of flavonoids including naringenin were tested for their ability to inhibit quorum sensing using Vibrio harveyi reporter assay. Result showed that it altered the expression of genes encoding Type Ⅲ Secretion System (TTSS) genes in Vibrio harveyi.[63]

Effect of Naringenin on Enzymes

Geraniol 10-hydroxylase, a cytochrome P450 monooxygenase catalyzed 3'-hydroxylation of naringenin to eriodictyol. From the experimental study, it was found that the catalytic activity of CrG10H was approximately 10 times more efficient with geraniol than with naringenin.[64] In another study, the activity of key enzymes of ammonium assimilation in cell-free extracts of soybean rhizobia characterized with different effectiveness in symbiosis was investigated. The nonspecific flavonoid naringenin has not stimulated glutamine synthetase (GS)-activity of the highly efficient rhizobia, but has stimulated the activity of glutamate dehydrogenase.[65] Prostaglandin E2 has a central role in inflammation and both cyclooxygenase-2 (COX-2) and prostaglandin E synthases are critical enzymes in its synthesis. Naringenin effectively inhibited LPS-induced prostaglandin E2 production.[66] In another study, five thousand mutants of Herbaspirillum seropedicae SmR1, carrying random insertions of transposon pTnMod-OGmKmlacZ, were screened for differential expression of LacZ in the presence of naringenin.[67] Trans-flavonoids including naringenin have been reported as mammalian α-amylase inhibitors, a property which could be useful in the management of postprandial hyperglycemia in diabetes and related disorders.[68] Protective effects of several phenolic antioxidants, including naringenin, against the DNA-damaging effect of idarubicin originating from its P450 reductase-catalyzed bioactivation was also investigated in another study.[69]

Clinical Effects of Naringenin

Low bioavailability of naringenin has been a major drawback in optimally obtaining its beneficial effects. Using differentiated and polarized Caco-2 human intestinal epithelial cell lines to study the transport mechanism of naringenin, it was found that low bioavailability of naringenin is due to absorption by passive diffusion and ATP-dependent transport, mediated by multidrug resistance associated protein (MRP)1 substrate.[70] However, complexation of naringenin with hydroxypropoyl-β-cyclodextrin (HP beta CD) is a viable option for the oral delivery of naringenin as a therapeutic entity with enhanced bioavailability and application in the treatment of dyslipidemia, diabetes, and hepatitis C virus (HCV) infection.[71] In another study, it was again proved that absorption rate of naringenin can be increased by using aglycones rather than the naturally occurring glycosides.[72] In order to explore the methods to increase the bioavailability besides complexing with polymers, it was observed that cooked food containing naringenin show better bioavailability of naringenin.[73] Naringenin has been shown to bind with human serum albumin[74] and undergoes

extensive first pass metabolism.[75] Pharmacokinetic study of naringenin after its oral and intravenous administration has revealed that sulfates and glucuronides are the major metabolite products and possibly responsible for most of the bioactivities.[18,76] Using radiolabeled molecules, it was found that naringenin is widely distributed in brain, lungs and heart tissue, which may be inferred as its beneficial effects may extend to various organs of the body.[77] Using solid dispersion method, calcium alginate-chitosan beads of naringenin having intra-gastric floating property was prepared, which showed sustained release of naringenin.[78] Effects of naringenin on the pharmacokinetics of doxorubicin in rats were investigated. The plasma concentration, biliary and urinary clearance, and tissue distribution of doxorubicin were not altered by pre-treatment with naringenin.[79] Food-drug interactions are increasingly recognized as important clinical events, which may change significantly the bioavailability of orally administrated drugs.[80] The precipitation kinetics of naringenin in pure water as well as in micellar solutions of Tween 80 was investigated in another study.[81] Encapsulation of citral in emulsions and the addition of naringenin could greatly enhance citral's chemical stability during storage.[82] The most important compounds of grapefruit juice considered to be involved in the pharmacokinetic interaction are naringenin.[83] Naringenin can be metabolized as the forms of glucuronidation, sulfation and naringenin can also be metabolized as the forms of methylation with hydroxylation and glucuronidation with hydroxylation *in vivo* after administration.[84]

Extraction and Isolation Techniques of Naringenin

For the isolation of the naringenin, different extraction and isolation techniques have been used so far by using different solvent systems. Naringenin was isolated and identified in the ethanol (EtOH) extract of the aerial parts of Lippia salviaefolia Cham.[85] A simple extraction procedure and high-performance liquid chromatography (HPLC) method was developed to analyze the major and minor components of *Cicer arietinum* L. and *Pisum sativum* L. Naringenin with other compounds were found to be present in the tested samples.[86] Naringenin was isolated using silica gel, Sephadex LH-20 chromatography from aerial part of *Aremisia lavandulaefolia* with other components.[87] A stereospecific HPLC method that could separate two enantiomers (R/S epimer) of naringenin in bottom base has been developed and validated in another study.[88] Using naringenin as a sample, two continuous extraction techniques, intermittent counter-current extraction and dual flow counter-current chromatography were developed and their advantages and disadvantages were identified, in terms of loading and throughput using the GUESSmix (GUESSmix is comprised of 21 natural products of varying polarity, molecular weight, and functional groups).[89] The HPLC enantioselective separation of (R/S)-naringenin, a chiral flavonoid found in several fruits juices has been performed on both analytical and (semi)-preparative scale using an amylose derived Chiralpak AD chiral stationary phase.[90] Five flavonoid including naringenin from *Drynaria fortunei* were isolated in another study.[91] Using various chromatographic methods, three flavonoids including naringenin were isolated from the pollen of *Typha angustata*.[92]

Capillary electrophoresis as a chiral additive for the separation of flavanones and flavanone-7-O-glycosides including naringenin was investigated.[93] Repeated silica gel column chromatography leads to the isolation of naringenin from *Lignum Dalbergiae Odoriferae*.[94] Naringenin with other compound were extracted from the leaves and rhizomes of two varieties of *Zingiber officinale* at three different growth points (8, 12 and 16 weeks after planting).[95] Twelve compounds including naringenin were isolated from the seeds of *Aplinia katsumadai* on repeated column chromatography on silica gel and Sephadex LH-20.[96] A phytochemical investigation of the poisonous *Elaeodendron croceum* leaves guided by cytotoxicity against Vero cells led to the isolation of five known compounds including naringenin.[97] Flavonoids such as naringenin with other compounds were isolated from *Euphorbia* and *Pycnanthus* species.[98] The phytochemcal profiles of *Cudrania cochinchinensis* leaf, twig, stem and root were compared by HPLC analysis. Naringenin was also isolated from *Cudrania cochinchinensis* in the present study.[99] Nine compounds including naringenin were isolated using silica gel, reverse phase C18 (RP-C18) silica gel column chromatography and preparative HPLC from root of *Berchemia lineata*.[100]

Analytical Techniques of Naringenin

The above metioned properties of naringenin explained the intense interest towards plant flavonoid research, thus there is the need of development of the appropriate analytical methods for the determination of this unique phytochemical in the different samples that are suitable to serve various researches in the fields of biological sciences. From the analytical point of view, the qualitative analysis of flavonoidal compound is not an easy task since the estimated number of flavonoids varies between 4,000 and 8,000, and all flavonoids are structurally related molecules.

Naringenins are important constituents of different systems of medicines especially of Chinese herbal medicines. Several analytical techniques, such as HPLC, capillary zone electrophoresis, chemiluminescence (CL), ultra-high-pressure liquid chromatography (UHPLC), capillary micellar electrokinetic chromatography, gas chromatography-flame ion detection (GC-FID), enzyme-linked immunosorbent assays (ELISAs), solid-phase extraction HPLC method, nano-liquid chromatography, radioimmunoassay, capillary electrochromatography, capillary zone electrophoresis, gas chromatography-mass spectrometry (GC-MS), and mass spectrometry have all been used for the determination of naringenin in the different samples.

Eight polyphenols including naringenin have been identified by HPLC method in the *Withania somnifera*.[101] A fast and reliable method based on an UHPLC, coupled with photodiode-array detection and a linear ion trap high-resolution mass spectrometer, has been developed for the identification of bioactive constituents including naringenin in the whole plant of *Sarcandra glabra* and its related four preparations.[102] HPLC identification of phenolic compounds from the extracts of flowers of *Helichrysum plicatum* indicated the presence of naringenin with some other compounds.[103] A simple and fast ultra-high-performance liquid chromatography method was developed for the identification and quantification of the naringenin with other compounds in the samples.[104] A comparative analysis of *Cuban red propolis* (CRP), *Brazilian red propolis* (BRP), and *Dalbergia ecastophyllum exudates* (DEE) by HPLC with diode-array detection and tandem mass spectrometry were performed. Naringenin was found to be present in the CRP, BRP and DEE samples.[105] A new liquid chromatography-tandem mass spectrometry method has been developed and validated for the determination of five flavonoids including naringenin in rat plasma using sulfamethalazole as internal standard.[106] Naringenin and some other compounds were detected in the acetonitrile and hydrochloric acid (5:1) solvent extract of *Lentinus lepideus*.[107] An ultra-performance liquid chromatography-photodiode array detector-quadrupole time-of-flight mass spectrometry method was established to analyze the aqueous extract in *Fructus Aurantii* and the constituents absorbed into blood. Six parent compounds including naringenin glucuronide and four metabolites were identified in rat plasma.[108] Naringenin and its metabolites in rat urine and feces after intragastric administration of alcohol extract of *Exocarpium Citri Grandis* were identified in another study.[109] Analysis of banana sap using HPLC-electrospray ionization-mass spectrometry indicated the presence of phenolics including naringenin glycosides.[110]

A method of capillary micellar electrokinetic chromatography with a diode array detector was developed for the simultaneous determination of seven active ingredients including naringenin in *Scutellaria barbata* D. Don and its ointment.[111] A capillary electrophoresis with electrochemical detection method was developed for the simultaneous determination of flavonoids including naringenin.[112] Phytochemical investigation of the polar extracts of the aerial parts of *Origanum dictamnus* afforded 15 secondary metabolites including naringenin.[113] Bioactive polyphenols including naringenin and naringin were detected in Quercus infusions by HPLC methods.[114] Determination of different flavonoids including naringenin in unifloral honeys by HPLC coupled with coulometric electrode array detection (CEAD) has been performed. Quercetin, naringenin, hesperetin, luteolin, kaempferol, isorhamnetin, and galangin were detected in the unifloral honeys in this method.[115] Data regarding the different analytical techniques of naringenin have been presented in the Appendix 3.

Conclusion

In the present review, article authors have presented a detailed pharmacological and analytical aspect of naringenin. Collected information showed that naringenin has various impressive pharmacological activities including antioxidant, antimicrobial, anti-inflammatory and anticancer activity. Thus, there is a vital need for further research in this phytochemical to explore their medicinal importance. The information provided in the present manuscript will act as an important source for development of effective medicines for the treatment of various disorders. On the basis of plethora of knowledge available about naringenin, we may conclude that particular flavanoid has huge potential for the development of diverse therapeutic agents. Emphasis should be given to increase productivity of naringenin, and there is still scope in advancement of techniques for the extraction of higher contents of naringenin and reduction of its cost. For the production of the high level of naringenin, tissue culture techniques could be used in the future. More investigation should be performed regarding general health beneficial property of naringenin, including its uses as nutraceutical and food supplement. As there is very less data available in regrads to its safety and optimum dose level, more study should be performed to determine the safety profile prior to its uses in the human. Dose level should be optimized for naringenin to get better pharmacological activity through toxicity study in the future. Preclinical and clinical study should be performed to explore the different pharmacological

potential of naringenin in curing various diseases. Different types of advanced analytical techniques should be developed for the determination of naringenin in plant extract as well as in biological system for its standardization. The preclinical data available with naringenin should be translated into clinical trials for the development of novel therapeutic agents having potential for the treatment of various disorders.

Conflict of Interest

The authors report no conflict of interest.

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