Review Article

Naringin: Biosynthesis and Pharmaceutical Applications

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Naringin is a plant flavonoid of huge medicinal importance. It is synthesized by the phenylpropanoid pathway via seven enzyme catalysed steps from phenylalanine to prunin. The genes encoding the enzymes of phenylpropanoid pathway have been cloned and characterized. Naringin has been known to possess antioxidant, antiinflammatory and antitumer potential. Exposure to naringin *in vivo* and *in vitro* in several test animals and cell lines has been reported to demonstrate activities that could treat asthma, hyperlipidaemia, diabetes, tumour, hyperthyroidism and osteoclastogenesis. Based on the reported research of naringin on test animals, naringin could be regarded as an efficient natural remedy for the treatment of human metabolic disorders. However, detailed exploration of naringin exposure on humans needs to be studied.

Key words: Naringin, phenylpropanoid pathway, medical applications, health, nutrition

Naringin is a plant flavonoid of great human value. Flavonoids are ubiquitous polyphenolic secondary metabolites isolated from vascular plants[1]. They have a general structure of 15-carbon skeleton that contains two phenyl rings A, B and a heterocyclic ring C[2]. Flavonols are the most important flavonoids participating in the stress responses of plants[3]. Approximately 8000 flavonoids have been identified from various citrus fruits, vegetables and beverages[4]. They behave as chemical messengers, pollinator attractants and stress regulatory elements of plants[5]. Flavonoids also exhibit human health promoting abilities like antioxidant and free radical scavenging potential[6]. They act as antiviral, antibacterial, antiinflammatory, vasodilatory, anticancer and antiischemic agents[7-12]. Flavonoids can undergo various metabolic transformations such as methylation and sulfation to change their structures and hence their biological activities[13].

ACCUMULATION OF FLAVONOIDS

The biosynthesis and accumulation of flavonoids is site-specific. Flavonoids are localized in the nucleus, vacuole, cell wall, cell membrane and cytoplasm of the plant cells[14-16]. Further, the site specificity of flavonoids in plants is related to their typical physiological, biochemical or morphological traits. The alfalfa seeds have been reported to possess quercetin, luteolin and 7,4′-dihydroxyflavone flavonoids. The stem and roots, however accumulated isoflavonoids, medicarpin 3-O-glucoside-6-O-malonate, formononetin 7-O-glucoside-6″-O-malonate and coumestrol glycosides[14]. The *Betula pendula* and *B. resinifera* plants originating from Finland, Germany and Alaska have also been reported to accumulate flavonoids, condensed tannins and hydroxycinnamic acid only in the leaves on exposure of UV-B radiations. However, the plants belonging to Alaska showed highest flavonoid accumulation[15]. Likewise, various forms of soluble flavonoids are predominantly present in grape seeds, white clover and fruit berries. A detailed description of accumulation and transport of distinct flavonoids of grapevine has already been extensively discussed[16-18]. Hence, flavonoids are ubiquitous but site specific in nature.

NARINGIN

Naringin is an important water soluble flavonoid isolated from the citrus fruits[19]. It has a molecular weight of 580.4 g/mol and molecular formula is $C_{27}H_{23}O_{14}$ (fig. 1). It has antioxidant potential and plays an important role in the development of leaves, flowers,

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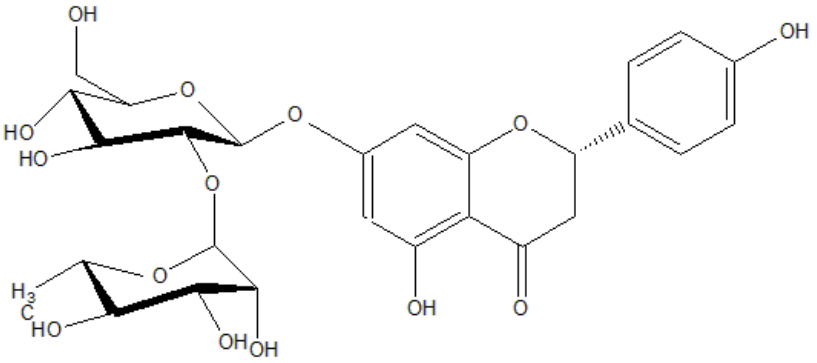

Fig. 1: Molecular structure of naringin
Naringin has a molecular weight of 580.4 g/mol and a molecular formula of $C_{27}H_{23}O_{14}$. It is a water soluble antioxidant compound

buds and fruits of plants. It has further induces bitterness to the fruits as in grape fruit. However, the bitterness can be reduced upon reduction by the enzyme naringinase[20].

Naringin biosynthesis via phenylpropanoid pathway:

The phenylpropanoid pathway begins with phenylalanine, an end product of shikimate pathway. The phenylpropanoid pathway gives rise to a diversity of end products ranging from flavonoids, tannins and lignins[21]. The description of phenylpropanoid pathway is discussed hereafter.

The first 7 enzyme catalysed steps of phenylproponoid biosynthesis pathway leads to naringin synthesis (fig. 2). The first step catalyses the conversion of phenylalanine into cinnamic acid by enzyme phenylalanine ammonia-lyase (PAL). Phenylalanine is deaminated to cinnamic acid and ammonia. In the second step, cinnamate 4-hydroxylase (C4H) catalyses conversion of cinnamic acid into p-coumarate. p-Coumarate is later metabolised into p-coumaroyl CoA via enzyme 4-coumarate CoA-ligase (4CL)[22]. The pathway up to p-coumaroyl CoA synthesis is general phenylpropanoid pathway. Subsequently, the pathway diversifies into isoflavonoids, stilbenes, proanthocyanidins, flavonols and anthocyanins[23]. The enzymes chalcone synthase (CHS) and chalcone isomerase (CHI) catalyse the division of phenylpropanoids into flavonoid biosynthesis. Further, uridine diphosphoglucose-flavanone 7-O-glucotransferase (UF7GT) mediated catalysis generates a group of diverse metabolites[23].

CHARACTERIZATION OF ENZYMES INVOLVED IN NARINGIN BIOSYNTHESIS

Phenylalanine ammonia-lyase (*PAL*):

The *PAL* gene encoding enzyme has been isolated from a wide range of plant species. In *Epimedium*, *EsPAL* was reported to significantly regulate the metabolite flux of phenylpropanoid pathway for the biosynthesis of various metabolites including icariin, epimedin A, B and C[24]. *SsPAL1* from ornamental plant *Coleus*, *Solenostemon scutellarioides* was characterized to be stress responsive because of the presence of cis-acting elements[25]. The *PAL* gene has also isolated and sequenced from three Buckwheat species, *Fagopyrum tataricum*, *F. esculentum* and *F. dibotrys*[26]. A biotic stress responsive 2145 bp long *HbPAL* has also been characterized from rubber[27]. Similarly, *PAL* has been reported to be cloned and characterized from various plants including *Salix*, *Capsicum*, *Musa acuminate* and rice[28-31]. Like higher eukaryotes, 2114 bp long *TcPAL* has also been characterized from yeast *Trichosporon cutaneum*[32]. Hyun *et al*. describes various *PAL* genes isolated and characterized from plants and fungi[33].

Cinnamic acid 4-hydroxylase (*C4H*):

C4H belongs to the P450 monooxygenase super family localized in the endoplasmic reticulum of plants[34]. It is involved in the detoxification of herbicides as well as pesticides[35]. Most recently, *BnGC4H* gene has been characterized from ramie (*Boehmeria nivea*) to be strongly expressed in mature xylem suggesting its role in lignin biosynthesis[36]. Likewise, abiotic stress responsive *GbC4H* isolated from *Ginkgo biloba* was characterized to possess recognition sites for stress responsive transcription factors GT-1, WRKY transcription factor and myeloblastosis family transcription factor/Myc[37]. Recently, *PaC4H*, *MpC4H1* and *MpC4H2* showing catalytic activity towards trans-cinnamic acid have been isolated from bryophytes, *Plagiochasma appendiculatum* and *Marchantia paleacea*, respectively[38]. Abiotic stress inducible *C4H* genes have also been characterized from tea and sweet potato[39,40]. Similarly, *C4H* gene

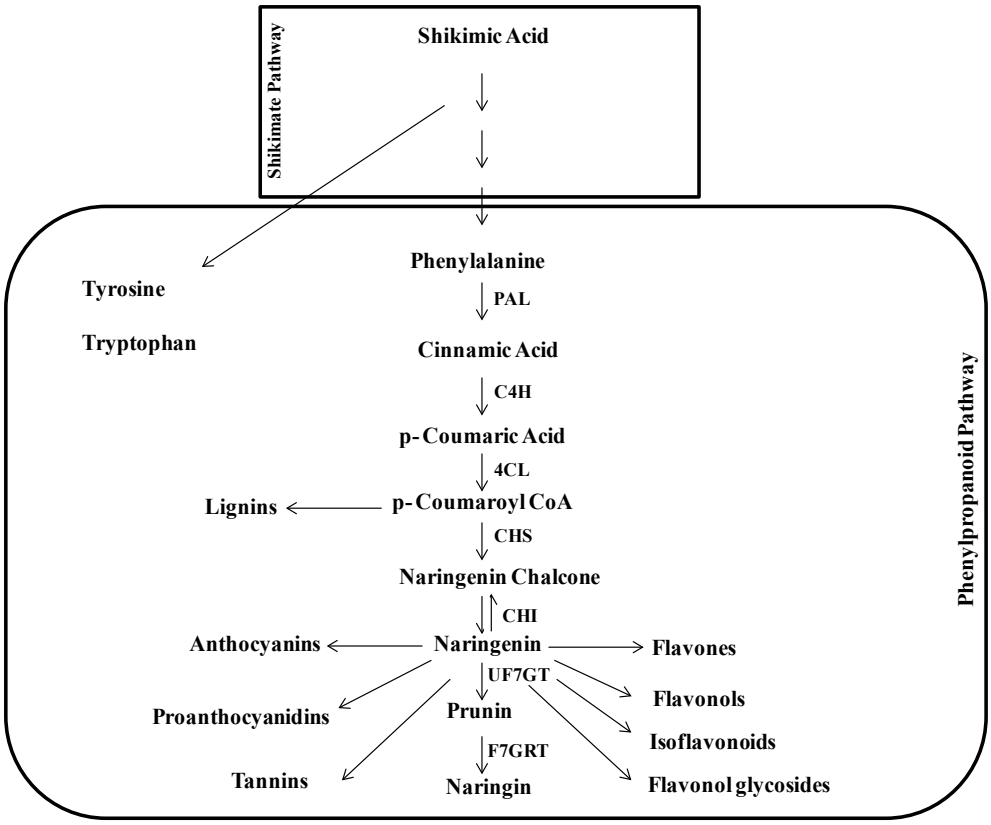

Fig. 2: Brief overview of phenylpropanoid biosynthesis pathway

The shikimate pathway leads to the synthesis of phenylalanine that acts as starting molecule of the phenylpropanoid biosynthesis pathway. Phenylalanine is metabolized into naringin via 7 enzyme-catalysed steps. The enzymes abbreviated as *PAL, C4H, 4CL, CHS, CHI, UF7GT* and *F7GRT* stands for phenylalanine ammonia lyase, cinnamate-4 hydroxylase, 4-coumaroyl: CoA-ligase, chalcone synthase, chalcone isomerase, uridine diphosphoglucose-flavanone 7-O-glucosyltransferase and flavanone 7-O-glucoside 2-O-beta-L-rhamnosyltransferase, respectively

has been isolated and characterized from several plant species[41,42].

4-coumaroyl: CoA-ligase (*4CL*):

The *4CL* mediated catalysis is the last crucial step of phenylpropanoid metabolism[22]. The *4CL* gene has been characterized from various plants[43,44]. The cytosol specific putative four *4CL* genes has been reported from *Peucedanum praeruptorum*, out of which only *Pp4CL1* showed root specific catalytic activity for p-coumaric acid[45]. A *4CL* homolog *Pa4CL1* from liverwort *Plagiochasma appendiculatum* was characterized to possess 4-coumaroyl: CoA-ligase activity in *E. coli*[46]. The *4CL* isoform homologues *4CL1-4CL4* characterized from *Arabidopsis thaliana* showed phylogenetic closeness but distinct functionality. The *4CL1* showed significant role in lignin biosynthesis while *4CL3* was responsible for flavonoids biosynthesis[47].

Chalcone synthase (*CHS*):

CHS is the first regulatory enzyme as it diverts phenylpropanoid to diverse flavonoid biosynthesis[48]. Five stress responsive *MaCHS* genes isolated from cytoplasmic fractions of mulberry has revealed the abundant accumulation of *MaCHS1*, *MaCHS2* in fruits, *MaCHS3*, *MaCHS5* in old leaves and *MaCHS4* in root bark[48]. Likewise, environmental stress responsive *NtCHS* genes has also been characterized from vegetative and floral tissues of tobacco[49,50]. The *MdCHS* isolated from apple was validated for polyketide synthase activity leading to the synthesis of phloretin, naringenin chalcone, and pinocembrin chalcone[48]. The functional validation of *SoCHS* isolated from *Syringa oblate* in tobacco has identified it as flavonoid metabolism regulator[51]. Several reports of *CHS* characterization from plants have been documented[52,53].

Chalcone isomerase (*CHI*):

CHI importantly regulates the intramolecular stereospecific cyclization of chalcones into (S)-flavanones. The characterization of *CHI* from various plant species has been reported[54,55]. The

DaCHI1 isolated from *Deschampsia antarctica* has shown enhanced substrate specificity for naringenin chalcone than isoliquiritigenin. The multi-substrate acting potential of *DaCHI1* facilitated flavonoids production during oxidative stress and environmental variability[56]. The *CHI* gene isolated from Chinese water chest nut was characterized for maximum activity at 45° and pH 7.5 in presence of Ca^{2+} and Cu^{2+}[57]. The characterization of *SlCHI1* from wild tomato has revealed a probable metabolic link with terpenoid biosynthesis[58]. Similarly, snapdragon *AmCHI1* was characterized to regulate the metabolite flux of flavonoids biosynthesis towards aurone and non-aurone flavonoids[59,60].

Uridine diphosphate-sugar dependent glycosyltransferases (*UGTs*):

Flavonoids constitute a variety of aglycone and glycone derivatives catalysed by *UGTs*. The *UGTs* either code for flavonoid glucosyltransferase and/or rhamnosyltransferase in support of phenylpropanoid pathway[61]. The metabolic conversion of naringenin to naringin occurs via two *UGTs* catalysed steps. The involved probable *UGTs* are Uridine diphosphoglucose-flavanone 7-O-glucosyltransferase (*UF7GT*) and flavanone 7-O-glucoside 2-O-beta-L-rhamnosyltransferase (*F7GRT*). Recently, *UGT* flavonoid glycosyltranserase (*UFGT*) isolated from sweet orange was characterized for flavonoid 7-O-glucosyltransferase and 7-O-rhamnosyltransferase activities to metabolize substrates including naringenin, hesperetin, kaempferol and quercetin[62]. Likewise, *UFGTs* from *Freesia hybrida* and *Crocus sativus* were characterized for 3GT activity in *A. thaliana*[63,64].

THERAPEUTIC POTENTIAL OF NARINGIN

Naringin appeared to possess diverse activities such as antioxidant, antiinflammatory, anticancer and antiapoptotic[65]. Its pharmacological effects have been well validated through *in vitro* and *in vivo* animal studies. However, its effect on human health is still unknown[66]. The various therapeutic applications of naringin are described hereafter (Table 1).

Effect of naringin on ischemic reperfusion injury of animals:

Ischemia is a common means of inducing mortality to animals. Ischemia followed by reperfusion and presence of oxygen-derived free radicals known as reactive oxygen species (ROS) leads to animal mortality. Hence, nutritional and pharmaceutical-based therapies are investigated to regulate the free radical mediated damage[67]. Naringin has been reported to effectively regulate the ischemic reperfusion mediated neurological alteration in the cortex, striatum and hippocampus brain regions of male Wistar rats on exposure of 50 and 100 mg/kg dosage by enhancing their ROS scavenging potential[68]. Naringin was documented to cross blood-brain barrier and scavenge peroxynitrite-induced mitophagy in human neural SH-SY5Y cells[69]. The antioxidant potential of naringin alleviated the ischemic reperfusion-induced renal damage at 400 mg/kg exposure[70]. Likewise, protective effect of naringin against mesenteric ischemia in rats at exposure of 80 mg/kg dose was reported[71]. Isoproterenol-mediated myocardial ischemia symptomized by reduced activity of mitochondrial antioxidant enzymes was alleviated on pre-naringin treatment[72,73]. Similarly, 400 mg/kg naringin regulated the skeletal muscle ischemia/damage of male Sprague Dawley rats[74].

Naringin and cancer cells:

The antitumor potential of naringin in animal cells including human cell lines has been documented. Naringin inhibited the β-catenin signalling pathway of human derived triple-negative (ER-/PR-/HER2-) breast cancer (TNBC) cells and arrested the cell proliferation in the G1 phase of cell cycle followed by cellular apoptosis[75]. Likewise, naringin activated Ras/Raf/ERK pathways for enhanced p21WAF1 expression to arrest proliferation and induce apoptosis of human bladder carcinoma 5637 cell line[76]. *In vivo* intraperitoneal administration of naringin reduced TNF-α and IL-6 accumulation to inhibit the tumorous growth in rats bearing walker 256 carcinosarcoma[77]. Ganglioside-mediated anticancer potential of naringin has also been reported. Naringin inhibited glycosidase NEU3 to enhance GM3 gangliosides that inhibited proliferation of HeLa and A549 cell lines[78]. Likewise, naringin regulated the proliferation of HepG2 hepatocellular carcinoma cell line[79]. Further, naringin-based synthetic ruthenium complex showed anticancer potential against A549 human cell line without any toxicity on dermal fibroblasts[80].

Effects of naringin on metabolic syndrome:

Collective occurrence of genetic and environment-induced physiological, biochemical and metabolic variations designates metabolic syndrome. These are generally associated with glucose intolerance, insulin resistance, increased blood pressure, atherogenic

TABLE 1: MEDICINAL APPLICATIONS OF NARINGIN

Medical condition	Animal exposed	Mode of delivery	Observed Alteration	Reference
Ischemic reperfusion	Male Wistar rats	Intraperitoneal administration for seven days	Improved neurobehavioral alterations, debilitating oxidative damage	[69]
	Rats	Administered as suspension in physiological saline	Renopotective effect	[71]
	Rats	Intraperitoneal infusion	Lowered oxidative stress markers and injury score	[72]
	Male Sprague Dawley rats	Oral administration	Lowered GSH-Px level, decreased SOD and CAT activity of muscles, higher plasma level of CK	[75]
Cancer cells	Male Wistar rats	Intraperitoneal administration	Inhibited tumor growth, increased survival rate and reduced TNF-α and IL-6 levels	[78]
	Rats bearing walker 256 carcinosarcoma	Intraperitoneal administration	Inhibited tumor growth and reduced levels of TNF-α and IL-6, enhanced survival rate of rats	[78]
	HeLa, A549 cancer cell lines	Exposed to cells in mixture with DMSO	Suppressed growth of cell lines and NEU3 glycosidase degrading GM3 ganglioside. Increased GM3 ganglioside. Downregulation of Epidermal Growth Factor Receptor and extracellular signal-regulated kinases phosphorylation	[79]
Metabolic syndrome	High fat diet fed Rats	Oral administration	Normalised systolic blood pressure and improved vascular dysfunction and ventricular diastolic dysfunction	[92]
	Rats	Orally using an intragastric tube	Decreased total ester and free cholesterol level, TG, FFA in serum and heart. Reduced alteration of serum lipoprotein and lipid metabolic enzymes.	[73]
	Male Wistar rats	Intubation to stomach	Improved plasma lipid level and increased plasma antioxidant activity	[94]
	Rats	Oral administration	No change in apolipoprotein A-1 level, lowered apolipoprotein B, increase in erythrocyte superoxide dismutase and catalase activity	[90]
	Rabbits	Oral administration	Exhibit hepatic lipid droplets, cardiac adipocytes infiltered and damage in endothelial lining in aortic wall	[84]
	Mice	Oral administration	Lowered plasma total cholesterol level and hepatic HMG-CoA reductase activity	[93]
Hyperthyroidism	Rats	Oral administration	Antithyroid and antioxidative activity	[123]
	Cholesterol and 25-OH-cholesterol-treated HepG2 cells, TNF-α-treated human umbilical vein endothelial cells (HUVECs)	Not mentioned in study	Regulation of nuclear factor kappa-b (NF-κB) and ERK signalling pathways, regulate the cholesterol level and inflammatory responses	[87]
	Rats	Cell cultured with naringin	Regulated hyperthyroidism by free radical scavenging potential	[123]
Asthma	Ovalbumin induced asthmatic mice	Oral administration	Level of interleukin-4, INF gamma, T-bet, GATA binding protein 3, Th1 and Th2 levels back to normal, progression of asthma significantly inhibited	[98]
	Sprague-Dawley rats exposed to cigarette smoke	Intragastrical administration	Inhibited the infiltration of inflammatory cells, expansion of alveolar space and thickening of bronchial walls	[99]
Osteoclastogenesis, bone resorption, osteolysis	Mice	Oral administration	Increased femoral bone mineral density on distal and middle portions, suppression of osteoclast formation	[103]
	Murine osteoblastic MC3T3-E1 cells	Cell cultured with naringin	Promote osteoprotegerin secretion *in vitro* by osteoblasts and suppress bone loss	[105]
	Bone marrow stromal cells	Cell cultured with naringin	Upregulated osteogenesis related genes, increased alkaline phosphatase activity and accumulation of calcium in cell cultures. Accumulation of Notch1 protein during osteogenesis	[107]

dyslipidaemia and inflammation[81]. The 25 % of the total world's adult population is suffering from metabolic syndrome. Increased diet, lesser physical activity, sedentary lifestyle and enhanced body mass index leads to enhanced occurrence of metabolic syndrome[81,82]. The potential of naringin to regulate metabolic disorders have been documented[72,83].

Signal transduction-mediated regulation:

Naringin alleviated diet-induced metabolic syndrome in C57BL/6 mice fed on fat-rich diet[84]. Activation of AMP activated protein kinase and insulin receptor substrate 1 blocked the activation of MAPKs pathways to improved lipogenesis and insulin resistance (fig. 3)[84]. Naringin reportedly, regulated insulin resistance, β-cell dysfunction, dyslipidaemia, liver and kidney damage by upregulating the PPARγ and heat shock proteins HSP-27 and HSP-72[85]. The potential of naringin to alter inflammatory cytokines expression and cholesterol metabolism via nuclear factor kappa-b (NF-κB) and ERK signalling pathway regulation was responsible for cholesterol reduction in 25-OH-cholesterol-treated HepG2 and TNF-α-treated human umbilical vein endothelial cells[86]. Similarly, naringin-mediated downregulation of chemokine C-X3-C motif ligand 1 (CX3CL1) and reduced ROS production was responsible for the antihyperglycemic potential of naringin[87]. Likewise, naringin-mediated regulation of heme oxygenase 1 via NF-κB and AMPK regulation was responsible for its antiinflammatory response during sepsis[88].

Regulation of diabetes, cardiovascular dysfunction and obesity:

The ability of naringin to regulate glucose, fatty acid and cholesterol metabolism was responsible for its antidiabetic potential towards hyperglycaemic and extremely obese C57BL/KsJ mice as shown in fig. 4[89]. Naringin reportedly, enhanced the expression of angiopoietin-1 and collagen-1 promoting angiogenesis and inhibited apoptosis in the foot ulcers of diabetic rats[90]. Likewise, naringin normalized cardiovascular dysfunction including systolic blood pressure and ventricular diastolic dysfunction of male Wistar rats fed on high carbohydrate and fat diet[91].

Regulation of hyperlipidaemia:

The hypocholesterolemic potential of naringin contributes for its response against hyperlipidaemia. Naringin reduced the activity of acyl-coenzyme A, cholesterol acyltransferase and enhanced the activity of hepatic 3-hydroxy-3-methylglutaryl CoA reductase regulating the levels of low density lipoproteins, cholesterol and hepatic lipids, thus retarding aortic endothelium damage[83]. Likewise, naringin inhibited hepatic 3-hydroxy-3-methylglutaryl CoA reductase to regulate cholesterol accumulation of LDL receptor knockout LDLR-KO mice[92]. Likewise, rats fed with cholesterol were documented to maintain the plasma lipid levels and increase the plasma antioxidant activity on naringin exposure[93]. Further, naringin significantly showed antiplatelet effect on hyperlipidemic rabbits due to inhibition of P-selectin and platelet factor 4 accumulations[94]. Likewise, HIV-1 nucleotide reverse transcriptase inhibitor-based hyperlipidaemia, apoptosis and oxidative stress of Wistar rats was potentially alleviated by naringin[95].

Naringin and immunity:

Awassi male lambs pre-treated with antigen phytohemagglutinin (PHA) exposed to naringin showed accumulation of increased titres of antibody against PHA antigen compared to non-treated lambs. Further, the activity of antioxidant enzymes and weight of naringin-treated lambs was increased. Hence, naringin has enhanced the immune responses of lambs in addition to improvement in the other evaluation parameters[96].

Antiasthmatic effect of naringin:

Naringin significantly inhibited the ovalbumin-induced asthma by normalizing the levels of interleukin-4, INF gamma, T-bet, GATA binding protein 3 and cytokine Th1, Th2[97]. The infiltration of inflammatory cells, expansion of alveolar space and thickening of bronchial walls induced by cigarette smoke was inhibited on naringin exposure[98]. Naringin, likewise regulated the pathological state of lungs, reduced interleukins and decreased lung airway hyper-responsiveness in guinea pigs[97].

Promotion of bone formation and maintenance:

Naringin potentially induces osteoblast differentiation and bone formation by inhibiting HMG-CoA reductase inhibitor[99]. Bone grafting with naringin-collagen matrix has shown significant formation of new bones in the defects[100]. Naringin enhanced protein accumulation, bone cell and alkaline phosphatase activity in *in vitro* culture of UMR 106 osteoblasts[101]. Naringin reportedly, suppressed osteoclast formation

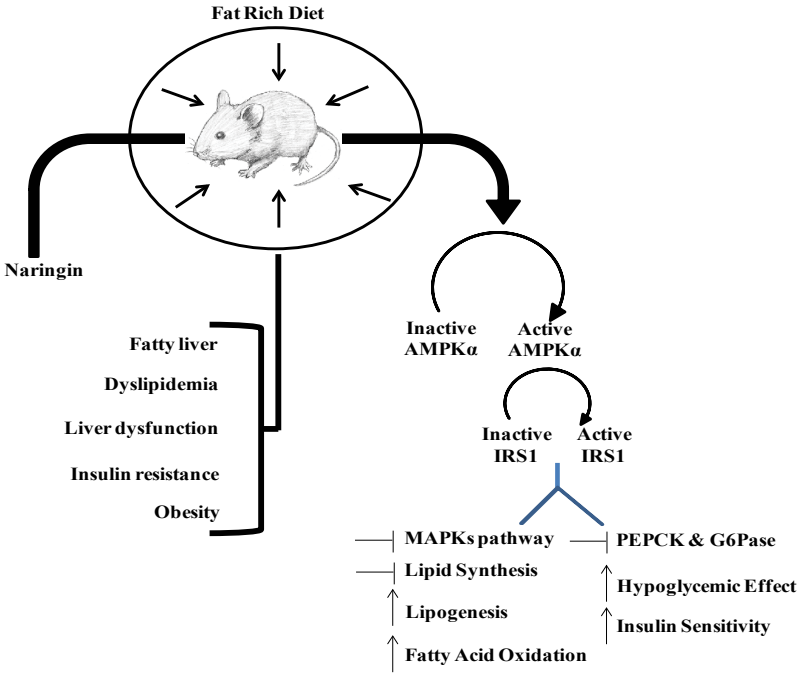

Fig. 3: Regulatory effect of naringin on metabolic syndrome
Mice fed with fat-rich diet showed metabolic syndrome characterised by fatty liver, dyslipidemia, liver dysfunction, insulin resistance and obesity. Naringin phosphorylated the AMP activated protein kinase (AMPKα) and insulin receptor substrate 1 (IRS1). Their activation led to inhibition of MAPK pathway and lipid biosynthesis. Simulatneously, the fatty acid oxidation, lipogenesis and insulin sensitivity was increased. Collectively, these alterations led to conteraction of metabolic syndrome, (↑) upregulation, (┤) inhibition

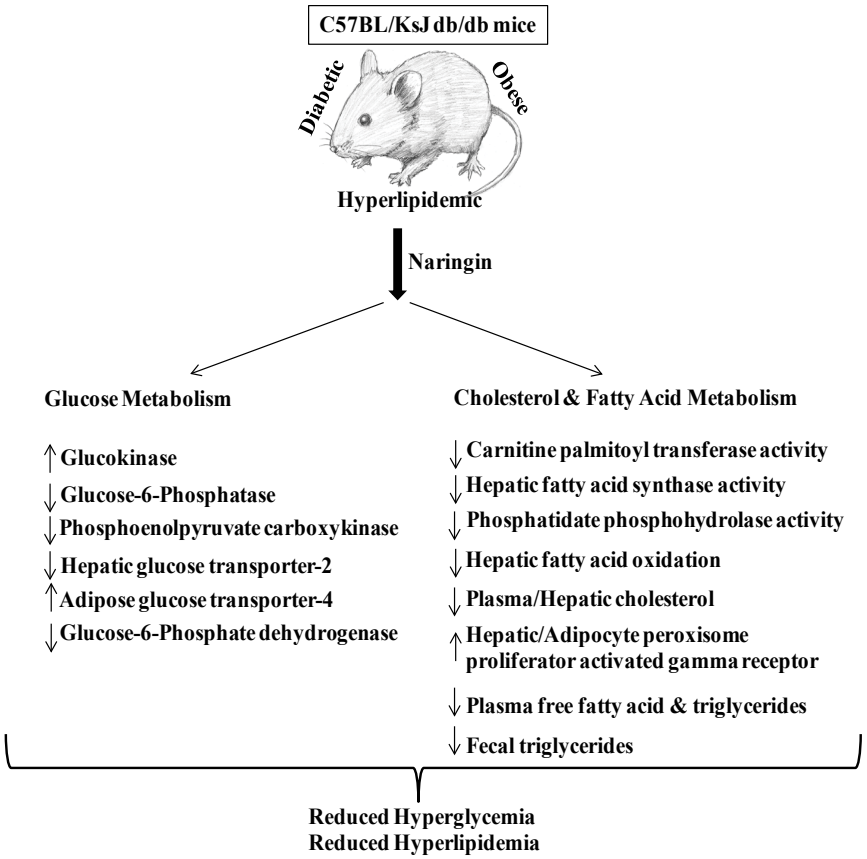

Fig. 4: Regulatory mechanism of naringin on diabetes
Naringin exposure variously affected the enzymes of lipid metabolism and glucose-regulating enzyme and reduced hyperglycemia and hyperlipidemia, (↑) upregulation, (↓) downregulation

and increased the femoral bone mineral density in mice[102]. Likewise, inhibition of bone resorption on naringin exposure has been documented[103,104]. Naringin-mediated regulation of NF-κB, ERK (fig. 5) and notch signalling pathway was responsible for its osteogenic activity[105,106].

Regulation of neurodegenerative disorders:

The potential of naringin to regulate neurodegenerative disorders has been revealed[107-110]. Naringin reportedly upregulated brain-derived neurotrophic and vascular endothelial growth factor followed by inhibition of neural apoptosis to alleviate spinal cord injury[108]. Role of naringin on the prevention of Parkinson's disease has also been documented[109]. Further, naringin enhanced glia-derived neurotrophic factor and suppressed TNF-α to regulate the symptoms of Parkinson disease in rat models[110].

Alleviation of metal and chemical compound-induced toxicity:

Naringin significantly alleviates metal as well as chemical compound-induced toxicity. Naringin stimulated the antioxidant system to counteract nickel-induced nephrotoxicity and hepatotoxicity[111,112]. The concomitant exposure of naringin with mercuric chloride potentially chelated the metal ions to ameliorate induced toxicity[113]. Likewise, toxicity induced by metallic chlorides and arsenites were reportedly alleviated on naringin exposure[114-116]. Neuroprotective potential of naringin to suppress insecticide deltamethrin-induced toxicity has also been reported[117]. Similarly, alleviation of cardiotoxicity, neurotoxicity and renal-hepatic toxicity induced by doxorubicin, bleomycin, acetaminophen and methotrexate on naringin exposure are reported[118-122].

Antithyroid potential:

Hyperthyroidism induced by L-thyroxine (L-T4) in rats has been documented to be regulated by the exposure of naringin[122]. The free radical scavenging potential of flavonoids, naringin, rutin and hesperidin regulated hyperthyroidism without any risk of hepatotoxicity[123].

Hence in view of the reports documenting the multifarious medicinal applications of naringin,

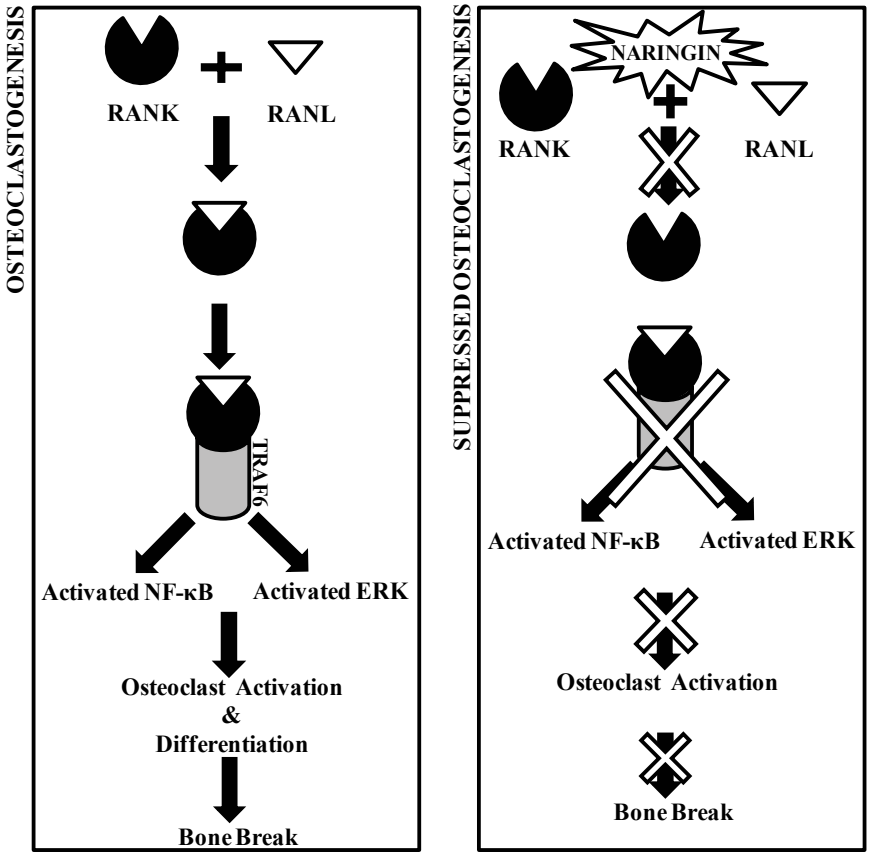

Fig. 5: Regulatory effect of naringin on bone resoprtion
Osteoclast activation leads to bone resorption leading to bone breakage. Binding of RANK with RANL leads to activation of NF-κB and ERK and promotes osteoclast formation. Naringin exposure inhibits the binding of RANK with RANL thus, inhibiting the downstream activations and counteracting the osteoclast formation

naringin containing food products can be recommended as a probable supplementation to the existing treatments for various disorders as well as maintain human health. Naringin could be used as a natural therapeutic supplement along the treatment line to alleviate several medical disorders and alterations. Studies have reported the underlying mechanism of naringin action on animal cell lines. However, detailed understanding of molecular and biochemical aspects of naringin exposure can extrapolate its medicinal applications on humans as well. Further, better understanding of the phenylpropanoid pathway will reveal the scope of synthesis and regulation of naringin *in vitro* as well as *in vivo*.

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Conflicts of interest:

The authors declare no conflict of interest.

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