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Review Article
Reconsidering a Citrus Flavonoid Naringin as a Promising Nutritional Supplement and its Beneficial Health Applications in Humans, Animals and Poultry

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Abstract

Flavonoids are ubiquitous plant metabolites, constitute an important group of natural compounds with various biologic activities and have been the subject of great interest for scientific research. Citrus flavonoids have been established as an important sub-class of flavonoids. Naringin is a prime example that is a natural flavanone glycoside, found mainly in grapefruits, grapes, tomatoes and citrus fruits as well. Citrus flavanones like naringin play an important role as anti-inflammatory, anti-oxidant, anti-apoptotic, antidepressant, hypolipidemic, immunoregulatory, hepatoprotective, wound healing, anti-diabetic and antihyperglycemic agent. It constitutes a major category of nature-derived bioactive compounds, has potent anti-oxidant and anti-inflammatory effects that render it as a promising dietary supplement in animal and poultry feeds. The use of these natural anti-oxidants can also play a vital role to extend the shelf life and increase the consumers' acceptability for meat and meat products. Both *in vivo* and *in vitro* studies have recognized the worth of naringenin several preclinical models of neurodegenerative disorders, cardiovascular diseases, osteoporosis, atherosclerosis, rheumatological disorders and diabetes mellitus. Moreover, it plays a chief role in lowering cholesterol, triglycerides and improvements in immune functions and anti-oxidant status, as reported in human and different animal model studies. This flavonoid has faced limited research and usage in the poultry production industry, although it has many promising biological effects. So this review paper aims to compile the important biologic activities of this compound in order to promote more studies pertaining to this citrus flavonoid, which could be used as a natural feed additive to improve health and meat quality and its potential to lower medicinal cost in animal and poultry industry.

Key words: Biological effect, citrus flavonoids, feed additive, naringin, poultry animal

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INTRODUCTION

Currently, synthetic growth promoters (antibiotics) are being extensively used in the poultry industry to achieve better growth and production performance as well as to treat many disorders[1,2]. However, the health of human beings has been affected because the addition of antibiotics at subtherapeutic doses in poultry diet may affect the response of the community to the drugs. In addition, microbial resistance against many antibiotics is becoming alarmingly evident[3]. Therefore, the use of antibiotics as growth promoters in animal and poultry feeds has been banned in Europe since January, 2006[3]. In the study of Toghyni *et al.*[4], it was demonstrated that bioactive plants could be used as additives in poultry feed to stimulate the appetite and feed intake with increased secretion of digestive enzymes. Additionally, as an antimicrobial drug, the additives may also stimulate the immune system. Medicinal herbs and their extracts are used in poultry as feed additives or mixed in drinking water. To this date, a plethora of studies have been conducted using different herbal medicinal plants and their products, either in extract or powder form and have been reported to have achieved positive effects on poultry performance and health[5-7].

Poultry nutritionists are seeking natural alternatives to be used as feed additives in poultry diet to improve productive performance[8,9]. The flavonoid compounds derived from the plant have been reported for entailing numerous properties such as anti-inflammatory, hypolipidemic, anti-oxidant, antiviral, antimicrobial, hepatoprotective and immunomodulatory. Presently, there is research interest to use plant-derived flavonoid including flavonols, flavones, isoflavones, flavanones, flavonoid and anthocyanins due to their multidimensional properties and immense availability[10,11]. Citrus plants are excellent source of flavonoids: nobiletin, hesperidin, narirutin, naringenin and naringin. These citrus flavonoids were envisaged to have an invaluable anti-inflammatory and anti-oxidant activities *in vivo* and *in vitro*[12]. Naringin is also well known among them, it is a flavanone glycoside that is formed from the flavanone naringenin and the disaccharide neohesperidose. It is one of the key active components of, *Citrus aurantium* L, *Citrus medica* L and Chinese herbal medicines known as Drynaria fortunei (Kunze)[13,14]. It also exists in citrus fruits[15] and gives a bitter taste to citrus juices[16]. Naringin and its colonic metabolite, known as naringenin, have demonstrated strong anti-inflammatory, anti-oxidant and cardioprotective effects, including the lowering of blood cholesterol and glucose levels and better insulin signaling[17].

In the study of Alam *et al.*[18], it was revealed that the dietary inclusion of naringin at 100 mg kg^{-1} daily lowered plasma fatty acids level, improved liver mitochondrial dysfunction and glucose intolerance, it had also improved the structure and function of both the liver and the heart without having any detrimental effect on total body weight. In another study, naringin 40 mg kg^{-1} efficiently inhibited dipeptidyl peptidase-4 *in vivo* and lowered blood sugar level in rat[19]. Naringin can prevent the development of hyperglycaemia by enhancing hepatic glycolysis and lowering hepatic gluconeogenesis[20]. As described by Da Silva *et al.*[21] the naringin had significantly reduced cholesterol-LDL, total cholesterol and triglycerides levels in chickens. In another study, Goliomytis *et al.*[22] found that use of naringin at 0.75 or 1.5 g kg^{-1} could positively achieve meat anti-oxidant properties without having any adverse effects on production index and meat quality attributes, hence it could be considered as an important feed additives for human and poultry industry. A growing body of scientific evidences have reported that naringin, has many biological effects like strong anti-oxidant, anti-inflammatory and cardioprotective effects, including reducing of blood cholesterol and glucose, wound healing, anti-diabetic and antihyperglycemic. However, limited research has been reported to use naringin in the broiler production industry. Therefore, the current review paper was aimed to gather all the scientific information available in the literature to unravel the underlying mechanism regarding the biologic activities of this compound so that it will promote researchers to conduct more studies pertaining to this citrus flavonoid, which could be used as a natural feed additive to improve health and meat quality, as a result of its strong anti-oxidant effect and its potential to lower medicinal cost in the poultry industry.

Chemical structure of naringin: The naringin (molecular formula: C27H32O14) is a flavanone glycoside that mainly exists in grape fruits (Fig. 1) and the molecular weight is 580.4 g mol^{-1}. Two units of rhamnose are found attached to its aglycone part, naringenin at the 7-carbon position[23].

Sources of naringin: The contents of naringin in different citrus fruits species are shown in Fig. 2[24-27].

Metabolism and absorption of naringin: Naringin gives the distinct bitter taste in grapefruit juice. This flavonoid can be enzymatically hydrolyzed by enzyme naringinase with expressed activity in α-L-rhamnosidase and β-d-glucosidase into rhamnose and pruning (one-third bitterness ratio to naringin), which can be further hydrolyzed into glucose and

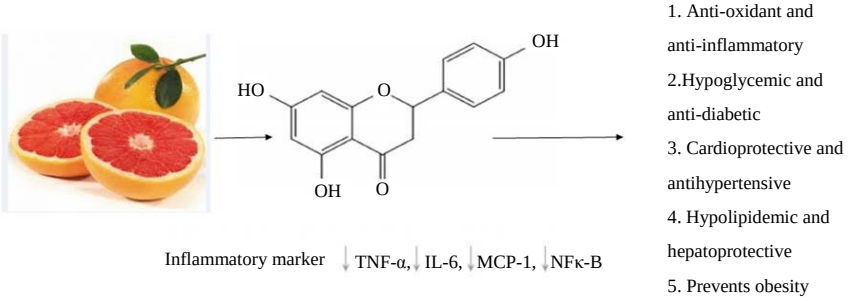

Fig. 1: Chemical structure and overall beneficial effects of naringin

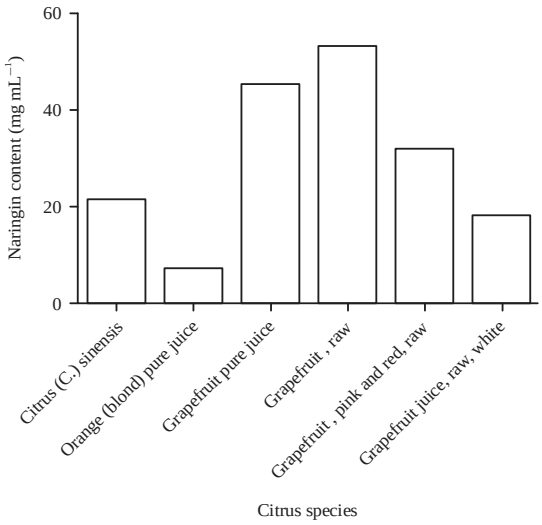

Fig. 2: Naringin contents found in different species of citrus fruits/juice

tasteless naringenin (Fig. 3). This biologically transformed naringin product may be used as a pharmacological agent and could be potentially useful as an anti-atherosclerosis, anticancer with many anti-atherogenic effects, such as vasodilator and antithrombotic. Naringins are strong anti-oxidants and are moderately soluble in water[20,28]. In the gut, microorganisms break down the naringin to its aglycone form, naringenin, which is then absorbed from the intestine[29].

Overall biologic activities of naringin: Most potential beneficial properties of flavanones have been based on *in vivo* animal models, which may be relevant in the elucidation of the mechanisms regarding the effective compounds in citrus. Nevertheless, few some studies have been carried out on citrus bioflavonoids and/or various citrus fruits for their possible applications in poultry.

Naringin studies in animal

Hepatoprotective effect of naringin: The hepatoprotective impact of naringin has been described by several investigators[30,31]. Supplementation of naringin had significantly decreased the higher plasma activities of transaminase in cadmium (naringin at 50 mg kg^{-1}) and nickel (naringin at 80 mg kg^{-1} b.wt.) induced hepatotoxicity in rats animals[32]. Besides, naringenin significantly decreased the lipid peroxidation and restored the activities of anti-oxidant indices like glutathione peroxidase (GPx), glutathione S-transferase (GST) and catalase in the liver[31]. A fructose feeding is a main cause of oxidative stress and non-alcoholic fatty liver disorders. Dietary naringin inclusion had also enhanced the nitrosative and oxidative stress in the livers of fructose-supplemented rats[32]. The strong hepatoprotective ability of this flavonoid in a high fat supplemented animal model was partly mediated by triggering the AMPK (adenosine monophosphate-activated protein kinase) pathway, which could significantly reinstate the anti-oxidant enzymes and bar the inflammation[33]. It was found that naringin has the ability to prevent the upsurge in hepatic biomarkers of enzyme activities such as ALP, ALT and AST and also decreased the hepatic fibrosis and lipid deposition in the high-fat-diet and high-carbohydrate-fed, in obese rats[13].

Anti-inflammatory effect of naringin: It has reported that the plant derived flavonoids have strong anti-inflammatory compounds[34]. There is growing body of scientific evidences that citrus flavonoid naringin shows anti-inflammatory effect in an air-pouch animal model of inflammation in which this bioflavonoid regulated the inflammatory cell infiltration and higher concentrations of TNF-α[35]. In some other studies, naringin ameliorated a high-glucose-induced augmentation of NF-κB expression[36,37]. The anti-inflammatory mechanism and the Nrf2 (Nuclear factor-erythroid 2–related factor 2) mediated the regulation of cellular anti-oxidants

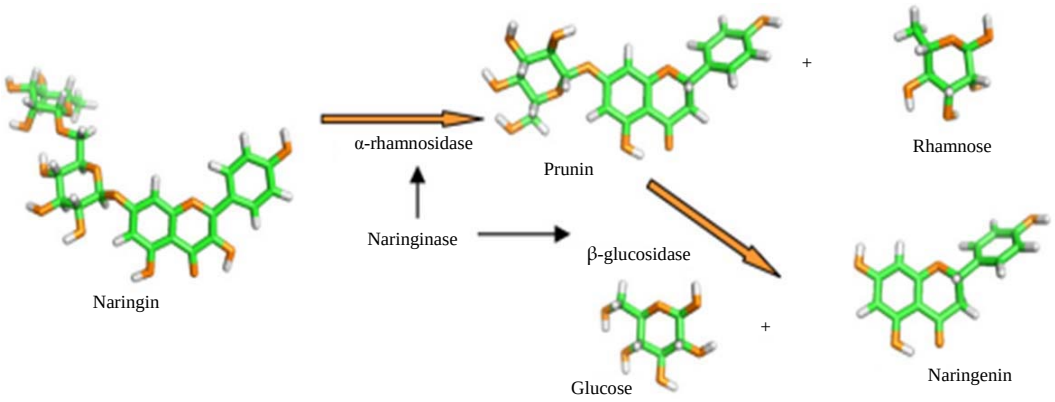

Fig. 3: Enzymatic break down of naringin into, naringenin, rhamnose, prunin and glucose by naringinase containing-l-rhamnosidase and d-glucosidase activities

accumulation, plays a key role against chronic degenerative disorders. Current published evidences indicated that naringin up regulates NAD(P)H: quinone oxidoreductase 1, Gstp1, HO1 and glutamate-cysteine ligase mRNA expression followed by the stimulation of Nrf2 and depressed the expression of pro-inflammatory mediators like inducible nitric oxide synthase, cyclooxygenase-2 and TNF-α, in 3-nitropropionic acid-induced rat animal model[38]. Apart from most effective anti-oxidants, bioflavonoids possess immunostimulatory and anti-inflammatory properties[39,40].

Anti-oxidant effect of naringin: The anti-oxidant mediators are essential for avian feed as they reduce lipid peroxidation and enhance the nutritional value and organoleptic sensory properties of chicken meat and eggs, thus they can extend shelf life[41]. Citrus fruit extracts have substantial quantities of bioflavonoids and show a strong scavenging activity against free radicals and ROS[42]. Both naringin and naringenin are strong free radical scavengers and have the potential as lipid peroxidation inhibitors. Both hydroxyl and superoxide radicals are scavenged by these compounds (flavanones) *in vitro*[43]. Naringin was reported to dramatically stop the xanthine oxidase activity in *in vitro* experiments[43]. In addition, it exhibited robust anti-oxidant properties in various *in vivo* disease models. A protecting effect of naringin was perceived in diabetic laboratory animals, dietary uptake of naringin had significantly alleviated anti-oxidant enzymes including catalase, GPx and SOD in diabetic rats[44,45]. It also dramatically increased the status of anti-oxidant enzymes in cholesterol-diet-fed rabbits[44]. Dietary inclusion of naringin decreased the hydroperoxides and MDA in the heart and circulation of isoproterenol-induced rats[45].

Hyperglycemia and anti-diabetes effect of naringin: The hypoglycemic (blood sugar lowering) activities of naringin are well summarized in Table 1. In another research in rats, that had combined naringin treatment and vitamin C (30 and 50 mg kg^{-1}, respectively) had significantly alleviated streptozotocin (STZ)-induced diabetes by increasing insulin level and had altered oxidative stress[45]. Variation of hepatic glucose regulating enzyme activities (e.g., phosphoenolpyruvate carboxykinase and glucose-6-phosphatase) also has a vital role in the glucose lowering impact of naringin in murine model of diabetes[20]. In another mice study, naringin supplementation at the rate of 200 mg kg^{-1} of diet improved insulin resistance and glucose intolerance in animal model of high fat diet[33].

Naringin and its aglycone naringenin are two well-known citrus flavonoid compounds with promising anti-diabetic effects. Many hitherto studies have reported the potent anti-diabetic effects of naringin, both *in vitro* and *in vivo*[46,47]. Naringin has also been found to regulate the plasma fatty acids in hypercholesterolemic animals offered a high fat diet. In hypercholesterolemic individuals, daily ingestion of naringin decreased the biosynthesis of hepatic cholesterol and plasma low-density lipoprotein (LDL)-cholesterol[48]. These scientific findings support the notion that naringin may play a strong role in preventing diabetes. In summary, it is speculated that, naringin is a most effective biomolecule that plays a vital role in treating diabetes related disorders and its complications. Moreover, naringin has shown marked modulatory effects on insulin sensitivity and secretion, hepatic glucose production, PPARγ, glucose transporters, blood lipids, peripheral glucose uptake, cholesterol biosynthesis, intestinal glucose absorption,

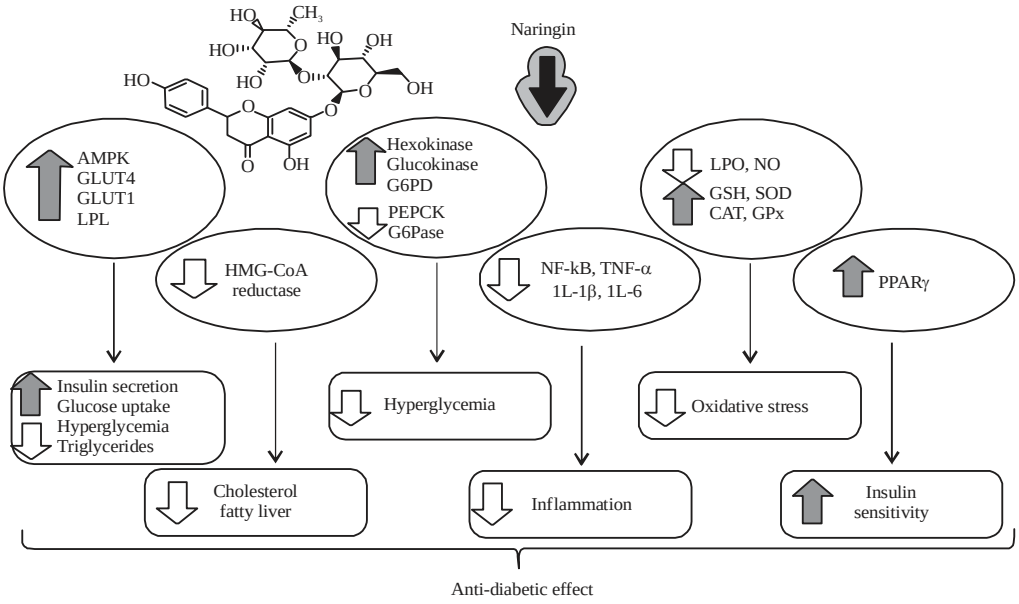

Fig. 4: Flow diagram presenting the anti-diabetic mechanism of naringin

GLUT: Glucose transporter, G6Pase: Glucose 6-phosphatase, AMPK: 5' adenosine monophosphate activated protein kinase, LPL: Lipoprotein lipase, PEPCK: Phosphoenolpyruvate carboxykinase, G6PD: Glucose-6-phosphate dehydrogenase, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme, TNF-α: Tumor necrosis factor alpha, PPARγ: Peroxisome proliferator activated receptor gamma, NF-κB: Nuclear factor-kappa B, LPO: Lipid peroxidation, IL: Interleukin, SOD: Superoxide dismutase, GSH: Glutathione, NO: Nitric oxide, GPx: Glutathione peroxidase, CAT: Catalase

oxidative stress and inflammation as well[49] (summarized mechanistic pathways are depicted in Fig. 4).

Hyperlipidemia effect of naringin: Hyperlipidemia is an important indicator of obesity and its associated metabolic disorders. The bioflavonoids derived from plant sources are known to decrease higher levels of plasma lipids[50,51]. Naringin supplementation had significantly decreased plasma lipids in *in vivo* models of obesity and hyperlipidemia. In addition, dietary naringin markedly decreased higher plasma fatty acid concentrations in high-fat-diet-fed rat's animal model[18,33,51,52] (Table 2) and also decreased plasma lipids in high-cholesterol-diet-fed rats[53]. The cholesterol-reducing impact of naringin was found in LDL receptor (LDLR) knockout murine model[51]. Also, a lipid-modifying impact of naringenin was observed in rats. In a clinical trial, the dietary uptake of naringin (0.4 g capsule/day) had significantly decreased the circulatory total and LDL-cholesterol levels, whereas plasma HDL-cholesterol and triglycerides levels remained unaffected in hypercholesterolemic human individuals[48].

Hypertension effect of naringin: Supplementation of dietary naringin was documented to ameliorate hypertension in obese murine model fed carbohydrate-rich/fat-rich-diets[54,55] and also in stroke-prone hypertensive rats as well. It should also be noted that naringin had markedly increased the production of nitric oxide in urine and enhanced the acetylcholine mediated endothelium function[54,55]. A similar vasodilatory effect was also shown in overweight rats fed carbohydrate-rich/fat-rich diets[18] as shown in Table 3.

Wound healing effect of naringin: Bioflavonoids are one of the most ubiquitous groups of naturally occurring anti-oxidants and act as vital inhibitors of lipid deterioration in the citrus membrane[56,57]. Moreover, bioflavonoids are well documented to improve the wound healing process as they have anti-inflammatory, antimicrobial, anti-oxidant and many astringent properties[57]. The mode of action of naringin in the wound healing process is probably due to its' radical scavenging and anti-oxidant effects. Naringin treatment markedly reduced wound position and therefore improved the degree of wound position contraction probably due to its anti-inflammatory potential. In the study of Kandhare *et al.*[58], who found that naringin has wound healing effect via the down-regulation of inflammatory expression (viz., TNF-α, NF-κB, IL-1β, IL-6, IL-8) and apoptotic (pol-gand Bax) mediators and it also up regulation of growth factors expression

Table 1: Effects of naringin on diabetes and insulin resistance in animal studies[34,35]

Naringin dose	Models	Experimental outcome
15 and 30 mg kg^{-1} b.wt.	STZ-induced diabetic rats	Lowered activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase in kidney and liver
15 and 30 mg kg^{-1} b.wt.	STZ-induced diabetic rats	Improved activities of hexokinase and reduced activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase in liver and kidney
200 mg kg^{-1} diet	C57BL/KsJ-db/dbmice	Improved glycogen concentration and significantly improved activities of both hexokinase and hepatic glucokinase, whereas, reduced activities of hepatic phosphoenolpyruvate carboxykinase and glucose-6-phosphatase

Table 2: Effects of naringin in hyperlipidemia in animal studies

Naringin dose	Models	Experimental outcomes
0.02 g/100 g	Cholesterol-fed LDLR-knockout mice	Decreased the liver HMG-CoA reductase activities and increased the excretion of fecal sterol
0.2 g kg^{-1} of diet	C57BL/6 mice fed high-fat-diets	Suppressed the fatty acids (FA) synthesis and increased FA oxidation, while upregulated AMPK
0.003, 0.006 and 0.012% supplemented feed for 6 weeks	Male Long-Evans hooded rats	Lowered hepatic and plasma concentrations of total cholesterol and triglycerides (TGs), also increased expression of UCP-2, PPARa and CPT-1
100 mg kg^{-1} day	Wister rats fed high-fat/high-carbohydrate diets	Reduced the NEFAs, TGs and total cholesterol. Preserved hepatic mitochondrial respiration

Table 3: Summarized studies shown the effect of naringin on hypertension[18]

Naringin dose	Models	Experimental outcomes
0.02 g/100 g	Cholesterol-fed LDLR-knockout mice	Hepatic HMG-CoA reductase activities were decreased and increased the defecation of fecal sterol
0.5 L/day of sweetie juice that contains 677 mg L^{-1} naringin	Patients with stage I hypertension	Significant beneficial effect was observed in decreasing diastolic blood pressure
250, 500 and 1000 mg kg^{-1} diet	Stroke-prone hypertensive rats	Reduced the blood pressure, possibly by improving bioavailability of NO_2
100 mg kg^{-1} b.wt./day	High-carbohydrate/high-fat-fed Wister rats	Lowered blood pressure and better endothelial dysfunction, possibly by increasing bioavailability of NO

including TGF-b and VEGF, thus improving gene expression of collagen-1 to induce angiogenesis thereby leading to wound healing (Fig. 5).

Beneficial health applications as nutritional supplements and feed additive: There is a growing body of scientific findings that indicate the improved production and meat quality in different animal models through dietary supplementation with flavonoids[59,60]. Naringin is a well-known among them, as a naturally occurring flavonoid that is abundant in grapefruits. Naringin, flavonoids are also ubiquitously found in citrus fruits, they have exhibited health promoting properties such as, anti-oxidant and modulation of lipid metabolism. In addition, increased anti-oxidant capacity and favorable fatty acid profile that are desirable properties for the broiler production industry[60]. In another study naringin had positively affected the meat's anti-oxidant properties without entailing any negative effects on growth and meat quality, also it has been reported that it could be considered as a valuable feed additives both for the consumer and poultry industry[22] and thus in future the bioflavonoids could be used as a potential alternative for anti-oxidant herbs/ plants and synthetic feed additives for the production of healthier chicken meat in poultry industry[61]. Some other poultry workers have used the citrus pulp in broilers, instead of using the extracted polyphenols. They have reported significant effects on health and meat quality and concluded that these effects could be attributed to higher flavonoid contents like naringin[62]. Hitherto, little work has been done regarding the use of the flavonoid naringin in the poultry industry even though it has many invaluable effects. Flow diagram demonstrating the role of citrus flavonoids (naringin) in modulation of poultry immune system has shown in Fig. 6.

Naringin studies in human

Obesity: Jung *et al.*[48] suggested that naringin can play an essential role in plasma cholesterol lowering as well as regulation of the anti-oxidant capacity in hypercholesterolemic subjects. Supplementation of naringin was reported to reduce plasma cholesterol by about 14% and LDL concentration by about 17%. Meanwhile, plasma HDL and triglyceride concentrations were not affected. Alam *et al.*[63] theorized that naringenin addition at levels of 0.003, 0.006 and 0.012% of the diet for 6 a period of weeks reduced triglyceride and adiposity contents in rats parametrial adipose tissue[52]. Naringenin supplemented diets statistically increased CPT-1 (carnitine palmitoyltransferase 1), PPARa and the expression of UCP-2 (uncoupling protein 2) in liver, that may

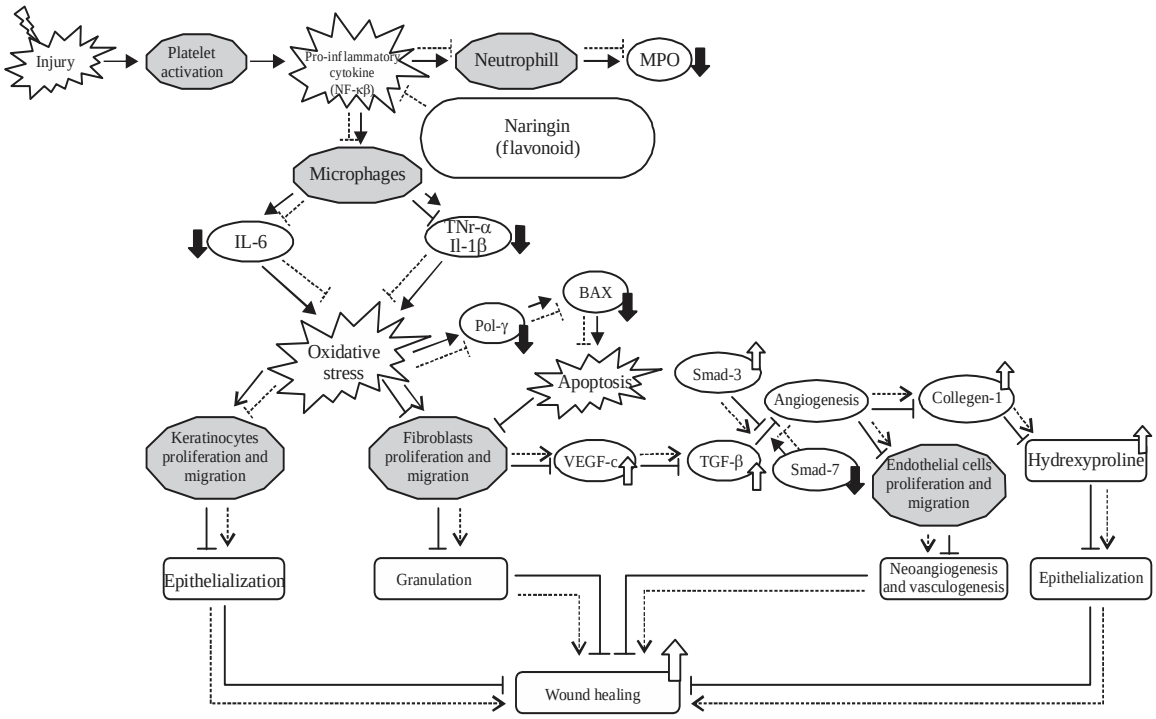

Fig. 5: Molecular mechanisms by which naringin facilitates rapid wound healing

Naringin may reduce the elevated oxidative stress and modulates the expression of growth factors such as VEGF-C, inflammatory mediators like IL-1β, TNF-α and IL-6 and apoptotic mediators (BAX and pol-γ) thereby up-regulated collagen-1 expression, which facilitates rapid wound healing (Dotted lines indicate the proposed mechanism of naringin in wound healing whereas black lines designates the delayed wound healing process)

be responsible for depression of adiposity in rats. It was reported that naringenin enhanced gene expression and the secretion of adiponectin protein from 3T3-L1 adipocytes[64]. The use of naringenin could be beneficial for inflammatory changes alleviation in the adipose tissue. Studies assured that MCP-1 which is derived from the adipose tissue is a key factor for activating the infiltration of macrophage into the adipose tissue[65].

Hypertension: The supplementation of naringin was observed to enhance hypertension in a high carbohydrate/high fat ration fed rats[18], in addition to stroke-prone hypertensive rats[55]. Furthermore, naringin statistically elevated NO production in the urine as well as enhancing the function of acetylcholine mediated endothelium with the use of aortic thoracic ring preparations through the production of NO[55]. Similar vasodilation impact was noticed in high carbohydrate/high fat ration fed rats[66] in addition to streptozotocin-induced diabetic rats[66]. Channels of calcium-dependent potassium are essential regulators for vascular relaxation. Studies showed that naringin induce large conductance calcium+ activated potassium+currents in rat tail artery myocytes in concentration-dependent manner[67]. Migration as well as proliferation of VSMCs (vascular smooth muscle cells) are the essential events in pathogenesis of hypertension and atherosclerosis. Using naringin caused an inhibition for TNF-α activated VSMC migration and proliferation[68].

Inflammation: The metabolic syndrome, diabetes and obesity are associated with the inflammatory responses. Inflammatory processes are known by inflammatory cells infiltration (mast cells and macrophages, in general) in inflamed tissues/organ, particularly in the adipose tissue[69,70]. Various adipocytokines like TNF- α, IL-6 and leptin are secreted by the adipose tissue which is considered as endocrine organ[71]. Many reports suggested that concentrations of inflammatory cytokine are higher in the individuals who are suffering from obesity and metabolic syndrome[72,73]. The TNF-α is the highly-known as inflammatory cytokine from the released cytokines in obesity. It could be found in blood plasma of individuals suffering obesity. The TNF-α is also important for insulin resistance[74] and damage of beta-cell in the pancreas islets[75].

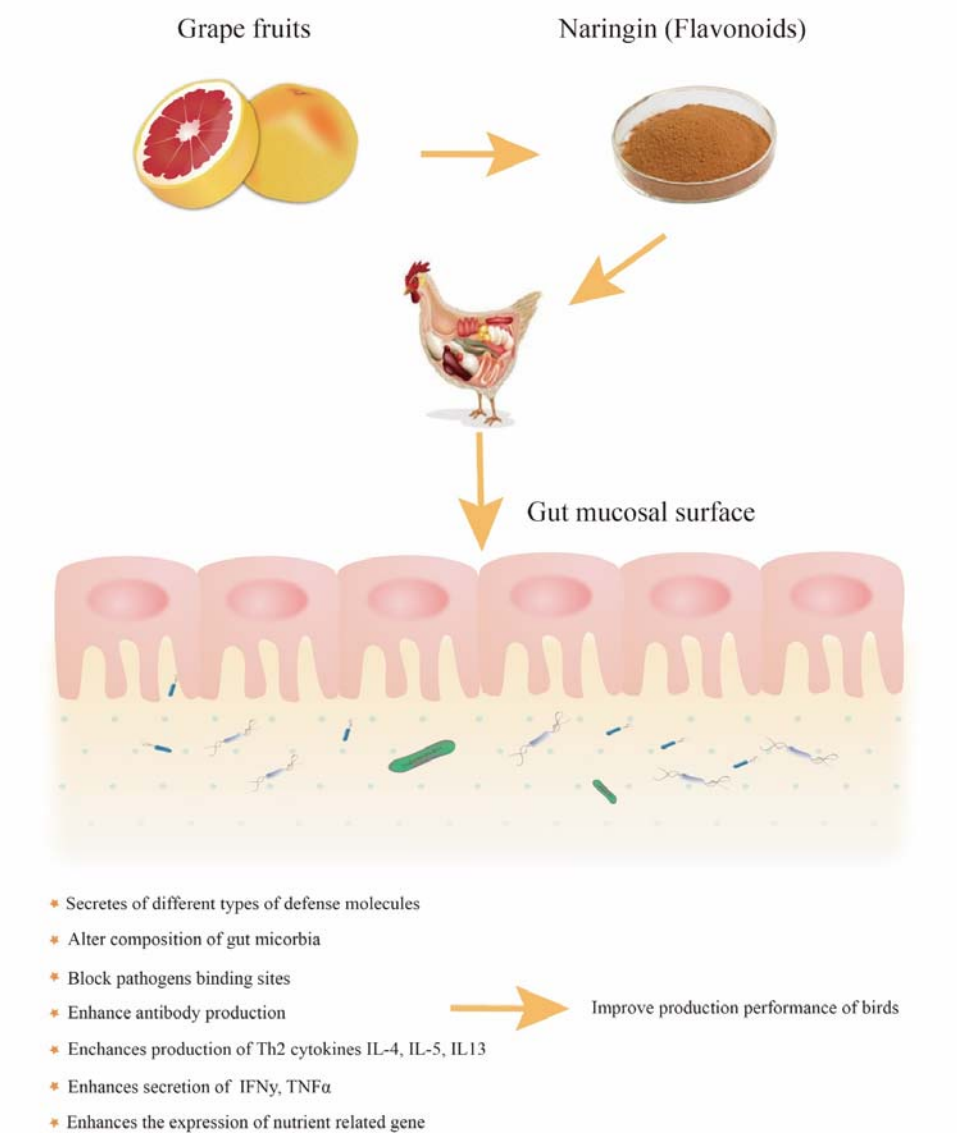

Fig. 6: Flow diagram illustrating the role of naringin in immune modulation of poultry birds

CONCLUSION

Naringin is a major flavanone glycoside which is mainly found in grapefruits and citrus family. It had been reported to possess different promising pharmacological characteristics such as: anti-inflammatory, antimicrobial, antimutagenic, anti-oxidant, cholesterol lowering, hepatoprotective, cardioprotective, antiatherogenic, antiulcer and neuroprotective effects. It could boost humoral and mucosal immunity in animal and poultry. In addition, naringin could be considered as a natural anti-oxidant agent due to being a strong scavenger of free radicals and preventing lipid peroxidation. After having compiled the scientific literature, it is evident that naringin is a cheap natural and safe supplement that could be used with a commercial level in animal and poultry nutrition to replace the synthetic growth promoters and an immune system booster, therefore lower veterinary costs whilst improving the growth and welfare of livestock and poultry.

SIGNIFICANCE STATEMENT

- Citrus flavanones such as naringin play a key role as anti-oxidant, anti-apoptotic, anti-inflammatory, antidepressant, hypolipidemic, immunoregulatory, hepatoprotective, wound healing and anti-diabetic agent

- Naringin also plays a critical role in lowering triglycerides, cholesterol and improvements in immune functions and anti-oxidant status
- Naringin could be considered as a natural anti-oxidant due to being a strong scavenger of free radicals and preventing lipid peroxidation

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