CHAPTER 2

Chapter-2. Literature review

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CHAPTER 2

Literature review:

Flavonoids are found abundantly throughout the plant kingdom, they belong to the category of polyphenolic compounds. Flavonoids exist as glycosides and the glycosidic linkage is located at seventh or third positions and the sugar moiety can be D-glucose, glucorhamnose, L-rhamnose, galactose or arabinose. The aglycone part of flavonoid is a condensed ring system consists of three rings A and B condensed together and C ring is attached as a substituent at ring B. The structure of the three rings is listed below.

- Ring A - Benzene ring
- Ring B – Six member ring attached to a phenyl ring at 2-γ position phenyl ring
- Ring C - As a substituent.

Benzene ring is condensed with either α-pyrone (flavonols and flavonones) or its dihydro derivative (flavanols and flavanones). When substituted with benzenoid substituent at second position it forms flavonoids and when substituted at third position it forms isoflavonoids. Flavonols have similar structure like flavonones they differ only by the presence of hydroxyl group at 3-position and double bonds at C2-C3 position.
The structures of flavonoidal compounds and other naturally found fused ring systems are presented in fig. No.2.1 and 2.2 respectively.

**Fig.2.1: Basic structures of flavonoidal compounds**

**Fig.2.2: Structures of basic nucleus of flavonoidal compounds**

A large number of bio flavonoids have been presented in table 2.1. All the flavonoids usually have anti-oxidant activity; this is due
to the presence of the phenolic ring which easily donates electron to the free radical and still can form a stable free radical due to the resonance of the phenyl ring. Flavonoids were found to possess a lot of pharmacological activity and are discussed in the later part of this chapter.

Table 2.1: Nomenclature of sub class of flavonoids based on position of their substituents

<table>
<thead>
<tr>
<th>Class</th>
<th>Compounds</th>
<th>Substituents</th>
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<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Flavones</td>
<td>Apigenin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Flavone</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Luteolin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Chrysin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Baicalein</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Nobiletin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Wogonin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Oryxilin A</td>
<td>H</td>
</tr>
<tr>
<td>Flavanols</td>
<td>Epicatechin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>ECG1</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>EGCG2</td>
<td>H</td>
</tr>
<tr>
<td>Flavanones</td>
<td>Naringenin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Taxifolin</td>
<td>OH</td>
</tr>
<tr>
<td></td>
<td>Morusin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Vexibinol</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Hesperidin</td>
<td>H</td>
</tr>
<tr>
<td>Flavonols</td>
<td>Kaempferol</td>
<td>OH</td>
</tr>
<tr>
<td></td>
<td>Galangin</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Morin</td>
<td>OH</td>
</tr>
<tr>
<td></td>
<td>Myricetin</td>
<td>OH</td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>OH</td>
</tr>
<tr>
<td></td>
<td>Fisetin</td>
<td>H</td>
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</table>
Quercitrin: ORh OH OH OH OH H
Isoflavones:
Daidzein: H H OH H OH H
Genistein: H OH OH H OH H
Anthocyanidin:
Cyanidin: OH OH OH OH H
Pelargonidin: OH OH OH H OH H
Chalcones:
Xanthohum: H H H H OH H 2=OH

2.1. Pharmacological Profile of Hesperidin

Leandro C. Souza and co-workers (2013) investigated hesperidin for antidepressant-like activity in mice using the forced swimming test (FST) and the tail suspension test (TST) and suggested that hesperidin possesses strong interaction with the serotonergic 5-HT1A receptors and produces antidepressant-like activity\textsuperscript{30}.

Suarez J et al.,(1998) worked on the antioxidant properties of hesperidin and its analog neohesperidin dihydrochalcone and concluded that hesperidin analog has proven to have better antioxidant activity and inhibit lipid peroxidation activity\textsuperscript{31}.

Kannampalli Pradeep and co-workers (2008) have studied the hepatoprotective and antioxidant effect of hesperidin against γ-irradiation induced oxidative damage in the liver of rats. They have concluded that oral administration of hesperidin offers a protective effect against hepatocellular damage through its membrane stabilizing ability\textsuperscript{32}.

Masaki Yamamoto et al.,(2008) have studied the hypotensive effect of G-hesperidin against spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats (WKYs). The report of their study concluded that regular administration of G-hesperidin to
spontaneously hypertensive rats reduces oxidative stress by interfering in the expression of nicotinamide adenine dinucleotide phosphate oxidase in vasculature, which leads to amelioration of endothelial dysfunction and hypertension\textsuperscript{33}.

Cecilia Martíneza et al.,(2009) have administered hesperidin and neo hesperidin (a structural analog of hesperidin) intraperitoneally in sedative dose and demonstrated that these flavonoids induce sedative like effect by lowering the levels of \textit{p}ERK1/2 in CNS\textsuperscript{34}.

Fernández,S.Pet al., (2005) have studied the synergistic interaction between hesperidin and diazepam. They concluded that administration of hesperidin with benzodiazepines may reduce the therapeutic dose level\textsuperscript{35}.

Mariel Mardera and co-workers (2003) have first isolated hesperidin and 6-methyl apigenin from Valeriana wallichii and reported that 6-methyl apigenin enhanced the sleep enhancing property of hesperidin\textsuperscript{36}.

Emim et al., (1994) performed anti-inflammatory activity of hesperidin and reported that hesperidin possess mild anti-inflammatory activity\textsuperscript{37}.

Jung UJ and co-workers (2004) have performed hypoglycemic effects of hesperidin and naringin. The study concluded that these flavonoids prevent progression of hyperglycemia by reducing hepatic gluconeogenesis and enhancing hepatic glycolysis and glycogen concentration\textsuperscript{38}. 
Wilmsen PK and co-workers (2005) demonstrated antioxidant activity of hesperidin by reducing the level of free radical DPPH with similar effect to that of trolox, a positive control and also reduces the level of catalase and superoxide dismutase whereby it provides strong cellular antioxidant activity.\textsuperscript{39}

Scarborough (1940) reported that hesperidin is active against increasing capillary resistance and can be used in the treatment of purpura, and syphilis.\textsuperscript{40} Later, beiler and martin proved that the above said activity is due to hyaluronidase inhibitory effect.\textsuperscript{41}

Korthuis and Gute, (1999) proved that diosmin and hesperidin (9:1) prevents ischaemia / reperfusion induced leukocyte adhesion in skeletal muscles generalized in the ischemic region.\textsuperscript{42}

Son et al., (1991) reported anti-hypercholesterolaemic activity of hesperidin in CCl\textsubscript{4}-induced hypercholesterolaemic rats.\textsuperscript{43} Monforte et al., (1995) have proved that hesperidin lowers cholesterol, low density lipoproteins (LDL), total lipids and triglyceride levels significantly in normo-lipidaemic rats and in diet- or Triton-induced dyslipidaemic rats and also increases high density lipoprotein (HDL) levels.\textsuperscript{44}

Bok et al., (1999) performed a study on tangerine peel extract and a mixture of hesperidin and naringin. The study proved that peel extract and the mixture of flavonoids lowers plasma and hepatic cholesterol levels, and hepatic triglycerides compared with control. They also found a reduction in the excretion of faecal neutral sterols, plasma and hepatic activities of HMGCoA reductase and acyl CoA: cholesterol transferase.\textsuperscript{45}
The methanolic extracts of the stems of Prunus davidiana Fr. (Rosaceae), containing hesperetin-5-glucoside and other flavonoids, was found to exert antihyperlipidaemic effects and can be used for the treatment of hyperlipidaemia. The author found that intraperitoneal administration of hesperetin-5-glucoside to high fat diet rats significantly reduce total cholesterol level compared with the control group and has no effect on the serum triglyceride level 46.

In another study, Monforte et al., (1995) demonstrated the antilipaemic activity of hesperidin in normal rats and in hypercholesterolaemic induced rats. He stated that increased hepatic cholesterol catabolism may be the reason for the antilipaemic activity of hesperidin44. Kawaguchi et al., (1997) also confirmed the above statement by identifying the lipase inhibitory effect of hesperidin in porcine pancreas and from Pseudomonas47.

Oral administration of hesperidin in rats have shown significant antihypertensive and diuretic effects at 200 mg/kg body weight, this increase in diuresis may be ascribed for this hypotensive effect 48 and other mechanisms which supported the above statement is the influence of hesperidin on various enzymes like lipoxygenase, cyclooxygenase and protein kinase which has effect of lowering erythrocytic adhesion, platelet aggregation. Likewise they are also potent inhibitors of cyclic-AMP which may be the cause for the observed diuretic effect49.

in their study proved that hesperidin acts synergistically through its antioxidant free radical scavenger activity and inhibition of eicosanoid synthesis to have potent activity against inflammatory disorders and anti-oedematous actions\textsuperscript{51}. Crespo \textit{et al.}, (1999) and co-workers have performed anti-inflammatory effect of hesperidin using trinitrobenzenesulphonic acid (TNBS) model of rat colitis and found that Pre-treatment of rats with hesperidin decreased colonic damage in comparison with TNBS control rats. He concluded that reduction in colonic myeloperoxidase activity may be the possible mechanism for intestinal anti-inflammatory activity of hesperidin. In addition to this Jean and Bodinier co-workers proposed that antioxidant property of hesperidin may be the possible mechanism for its anti-inflammatory activity in colitis rats\textsuperscript{52}.

Beiler and Martin (1947) synthesized derivatives of hesperidin and evaluated for hyaluronidase inhibitor activity\textsuperscript{41}. The reports of the study stated that the sulphonated and phosphorylated hesperidins are potent when compared with hesperidin, whereas its acetylated derivative is slightly more potent when compared to the parent molecule\textsuperscript{36}.

Many \textit{in-vitro} studies have proved that hesperidin has mild to potent inhibitory activities on enzyme’s like human acrosin (a sperm enzyme), aldol reductase (lens), alkaline phosphatase, alpha-glycosidase\textsuperscript{36} but it has no inhibitory activity on xanthine oxidase, and reverse transcriptase, \textit{in-vitro}\textsuperscript{53}. In another study made by kuppusamy \textit{et al.}, (1992) showed that hesperetin inhibits lipolysis
induced by epinephrine, in a dose dependent manner but does not inhibit phosphodiesterase\textsuperscript{54}. Hesperidin alone and in combination with diosmin (1:9), showed prostaglandins inhibitory activity when tested against sponge-induced granuloma in rats\textsuperscript{55}.

Bae \textit{et al.}\textsuperscript{,}(1999) in a study proved that hesperidin is active against \textit{Helicobacter pylori}. \textit{In-vitro} study on agar plates by Islam and Ahsan showed that hesperidin is inactive against \textit{Bacillus subtilis}, \textit{Staphylococcus aureus}, \textit{Streptococcus hemolyticus}, \textit{Escherichia coli}, \textit{Klebsiella species}, \textit{Pseudomonas aeruginosa}, \textit{Salmonella typhi}, \textit{Shigella dysenteriae}, \textit{Shigella flexneri} and \textit{Vibrio cholera}\textsuperscript{56,57}.

Hesperidin showed potent antifungal activity against \textit{Botrytis cinerea}, \textit{Trichoderma glaucum} and \textit{Aspergillus fumigatus} and found to be inactive against \textit{Aspergillus niger}, \textit{Trichoderma species}, \textit{Candida albicans} and \textit{Saccharomyces cerevisiae}\textsuperscript{58}.

A study was conducted on N-butyl-N-(4-hydroxybutyl) nitrosamine-induced carcinogenesis on male mouse urinary bladder. After inducing cancer they administered hesperidin and diosmin in combination for a period of 8 weeks during the initiation phase and the results shown that the above compounds have inhibited carcinogenesis. Anti-cancer activity of hesperidin was proved in 4-nitroquinoline-1-oxideinduced oral carcinogenesis at a concentration of 500 ppm/kg body weight. Hesperidin decreased polyamine levels in tongue tissue, the number of lesions and cell proliferation activities\textsuperscript{59}. In another study hesperidin showed chemo preventive activity against
azoxymethane induced rat colon carcinogenesis by suppressing cell proliferation\textsuperscript{58}.

In a study conducted by Berkarda et al.,(1998) hesperidin did not inhibit 7,12-dimethylbenz anthracene where as it inhibited 12-O-tetra decanoyl-13-phorbol acetate (TPA) induced tumour which clearly suggest that it is a good chemo preventive agent\textsuperscript{60}. Hesperidin has also shown protective effect against TPA induced hyperplasia in the dorsal skin of CD-1 mouse \textsuperscript{61}.

Hesperetin was investigated for its mutagenic activity along with other flavonoids and their derivatives using \textit{Salmonella typhimurium} mutants which reveals base pair substitutions and frame shift mutagens. The results suggested that these flavonoids and their derivatives do not have any mutagenic activity\textsuperscript{62}. Later study conducted by Choi et al.,(1994) proved the anti-mutagenicity of naringin, hesperidin, nobiletin and tangeritin\textsuperscript{63} and another study conducted by Calomme et al.,(1996) proved weak antimutagenic effect on \textit{Salmonella typhimurium} against benz(α)pyrene-induced mutations\textsuperscript{64}. Tanaka et al.,(1997) has also reported antimutagenic effect of hesperidin in N-methyl-N-amylnitrosamine-induced tumorigenesis in rats\textsuperscript{59}.

When hesperidin and hesperetin were tested for mutagenicity and the result showed that both require metabolic activation in microsomal activation system for inducing mutagenicity\textsuperscript{63}. Anti-mutagenic effect of hesperetin was demonstrated against aflatoxin B1 in \textit{S. typhimurium} and the result showed more than 70% inhibition
rate in existence of a mammalian metabolic activation system. Among all the dietary flavonoids, hesperidin and hesperetin were found to possess potent inhibitory activity against 3-methyl colanthrene induced neoplastic transformation in C3H 10T1/2 murine fibroblasts.

When hesperidin pretreated rats were administered thrombogenic diet, it enhanced the lifetime of rats by 16–71 days but did not have any effect on rats provided with an atherogenic diet. Friese necker et al., (1995) performed an assay on capillary venules, after ischaemia reperfusion in guinea pigs following intragastric administration of hesperidin and diosmin. The result clearly showed the reduction in leukocyte adhesion to the endothelium, this indicates the anti-ischemic effect of hesperidin. Further it was confirmed in another study made on hamster by Bouskela and Donyo, the study showed a significant reduction of ADP induced platelet aggregation and increased platelet disaggregation was seen in hesperidin and diosmin administered rats. Binding of fibrinogen to ADP induced platelets was decreased significantly.

A study demonstrated that hesperidin causes electron transfer along with proton transfer reaction there by reduces superoxide free radical invitro and hydroperoxide present in liver homogenate using chemiluminescence method. Bouskela et al., (1997) in a study proved the synergetic effect of hesperidin and diosmin combination as antioxidant. Many researches have proved that hesperidin has moderate antioxidant and free radical scavenging activity in
comparison to other flavonoids. Limasset et al., (1993) proved that hesperidin does not have the ability to inhibit the generation of singlet oxygen species released from neutrophils\textsuperscript{73}.

A study was conducted by Kim and Cho to evaluate the immune modulatory activity of hesperidin and reported that hesperidin reduces the production of bacterial alpha amylase antibody production which clearly indicates immunomodulatory activity of hesperidin\textsuperscript{74}. Immunomodulatory activity on various other models reported that hesperidin develops the immunological memory. Kawaguchi et al., (1999) evaluate immunomodulating activity on hesperidin by performing colony stimulating factor (CSF) inducing activity and reported that hesperidin showed concentration dependent CSF inducing activity\textsuperscript{47}.

Kim and co-workers (1990) demonstrated the anti-anaphylactic activity of hesperidin in red blood cells of sheep. Where it prevented mast cell induced cutaneous anaphylaxis\textsuperscript{75}. Allam G and co-workers (2013) have performed \textit{in-vitro} and \textit{in-vivo} examination on hesperidin’s effect on adult worms of \textit{Schistosoma mansoni} and report showed 100\% mortality rate at 200μg/ml concentration \textit{in-vitro} and \textit{in-vivo} result showed a decent deduction in the production of eggs and number of worms decreased less than 56\%, the IgG levels increased significantly, this clearly indicates that hesperidin has good schistosomicidal activity\textsuperscript{76}. 
2.3 Pharmacological profile of Naringin

Naringin is a bioflavonoid isolated from the peel of grape fruit. Naringin comes under the category of flavonoid glycoside. It consists of naringenin as aglycone part and glycan part consists of rhamnoglucoside attached to the naringenin at seventh position of A ring.

\[
\text{MW:580.53, Formula: C}_{27}\text{H}_{32}\text{O}_{14}
\]

IUPAC name : (2S)-7-[(2S,3S,5S)-4,5-dihydroxy-6-(hydroxymethyl)-3-[(3R,4S,6S)-3,4,5-trihydroxy-6-methyl-tetrahydropyran-2-yl]oxy-tetrahydropyran-2-yl]oxy-5-hydroxy-2-(4-hydroxyphenyl)chroman-4-one.

Naringin, a bitter principle of grapefruit was first isolated by Kesterson, J. W, and R.Hendrickson in the year 1953\textsuperscript{77}. Later in the year 1966 Paul L. Davis has found an efficient way of isolating naringin using soxhlet extractor. In this study the isolation procedure using soxhlet extractor and normal conventional extraction procedure using ethanol as solvent was compared and reported that soxhlet extraction has maximum naringin content that the conventional extraction procedure and optimized the extraction procedure\textsuperscript{78}. 
Ng TB and co-workers (1996) studied the antimicrobial activity of coumarins, flavonoids and polysaccharo peptides and reported that coumarins did not possess antibacterial activity, and in flavonoids only rutin, naringin and baicalin showed mild activity against *P. Aeroginosa* at 128mg/l concentration\(^79\).

Seon-Min Jeon and co-workers (2001) have compared the antioxidative effect of naringin with lovastatin in highly cholesterol fed rabbits. The study concluded that lovastatin has potent lipid peroxide inhibitory effect than naringin\(^80\).

The lipid-lowering effect and antioxidant capacity of naringin was proved by U.J Jung and his co-workers (2003) in high-cholesterol diet fed animals. In this study the author reported that significant reduction of cholesterol and low-density lipoprotein cholesterol concentrations is mainly due to the effect of naringin. It reduced the apolipoprotein B and increased the catalase and erythrocyte superoxide dismutase activity\(^81\). In another study, Hye-Jin Kim and co-workers have investigated the lipid lowering and antioxidant capacity of naringin. They concluded that naringin inhibits hepatic HMG-CoA reductase and increases hepatic antioxidant enzymes and thereby decreases the oxidative stress in a hyper-cholesterolemic mice\(^82\).

Cytotoxic and apoptosis effect of naringin was investigated on mouse leukemia P388 cells treated with Cytosine arabinoside (1-β-d-arabinofuranosylcytosine; Ara-C) and reported naringin prevent the apoptosis triggered by Ara-C induced oxidative stress\(^83\).
Devinder Singh and co-workers (2004) worked on glycerol-induced myoglobinuric acute renal failure and evaluated the potency of naringin in rats. The result suggested that naringin has good antioxidant activity and also enhances the activity of cellular antioxidants and thereby reduces the risk of myoglobinuric acute renal failure\textsuperscript{84}.

A study was performed on Hep2 cells to identify the protective effect of naringin against iron induced toxicity to cells. The result of the study proved that administration of naringin as supplement in iron induced genomic insult may compensate the oxidative stress\textsuperscript{85}.

Seon-Min Jeon and co-workers (2004) have proved the hypo-cholesterolemic activity of naringin. In this study naringin reduced the hepatic 3-hydroxy-3-methylglutaryl CoA reductase and acyl-CoA:cholesterol acyl transferase activities while considerably increasing HDL-C/total-C ratio in comparision with the control group\textsuperscript{86}.

Ganesh Chandra Jagetia and co-workers (2005) have demonstrated that naringin has the ability to decrease lipid peroxidation and to increase antioxidant enzyme activity\textsuperscript{87}.

M. Rajadurai and co-workers (2006) investigated the cardio protective effect of naringin in isoproterenol (ISO)-induced rats and concluded that naringin has a potent cardio protective activity against oxidative stress induced myocardial infarction\textsuperscript{88}.

Isabel A. (2008) validated HPLC method for simultaneous determination of naringin and naringenin using C18 reversed phase column, flow rate 1 mL/ min. Linearity range of naringin and
naringenin was found to be 55–95 μg / mL and 10–60 μg / mL. LOD and LOQ of naringin and naringenin was found to be 2.83, 8.57 and 1.11, 3.37 μg / mL, respectively.89

In another study anti-inflammatory activity of naringin and naringenin was proved on 7% dextran sodium sulphate (DSS) induced colitis rats90.

Hae-Jae and co-workers (2009) have proved the rotenone-I inhibitory effect of naringin in rotenone induced cell death found in human neuroblastoma SH-SY5Y cells91.

Leelavinothan Pari and co-workers (2011) proved the hepato protective activity of naringin in nickel sulfate induced liver toxicity in rats. Naringin showed the increase in antioxidant enzyme activity and reduced lipid peroxidation which clearly demonstrates that naringin not only protects but also decreases the toxicity induced by nickel sulfate to rat liver92.

Saleh A and co-workers (2011) explored the chromosomal instability of naringin in somatic and germinal cells of diabetic rats. The results of the study showed that naringin prevented the chromosomal instability in diabetic induced rats, thus it was concluded that it could be used to reduce genotoxicity in diabetic patients and by using it in therapy may avoid secondary malignancy normally seen in diabetic patients93.

Celiz G (2011) studies the antimicrobial activity of naringin (NAR) and NAR derivatives against L. monocytogenes, E coli O157:H7 and S. aureus. The result showed that prunin-6″-O-acyl esters of
naringin showed promising antibacterial activity against gram positive bacteria but naringin has no effect up to 0.25 m mol$^{-1}$. The authors concluded that suitable changes in structure of naringin and their derivatives can enhance the antimicrobial activity$^{94}$.

Kulasekaran G (2011) has demonstrated the neuroprotective role of naringin in 3-nitropropionic acid (3-NP)-induced neurodegeneration. His study concluded that naringin activates the nuclear factor-erythroid 2-related factor-2 (Nrf2) and increases the production and activity of antioxidant enzymes thereby inhibiting the anti-inflammatory responses and cytotoxic effect of 3-NP. In relation to previous study the author has further studied the anti-apoptotic activity of naringin by inducing neurogeneration on Wistar rats using 3-NP. He found that apart from increasing the activity of oxidative enzymes it also restores the ATPase in striatum thereby it avoids neurogeneration$^{95}$.

Gaurav Swarnkar and co-workers (2012) have performed differentiation study of isosakuranetin, naringenin, phloretin, poncirin and naringenin-6-C-glucoside (NCG) on osteoblast cultures harvested from mouse calvaria and reported that naringenin-6-C-glucoside (NCG) is very potent derivative that activates osteoblast ERs and leads to osteogenic effect; it has also shown good oral bioavailability$^{96}$.

Prabu Thangavel and co-workers (2012) have studied the protective effect of naringin on liver in N-Nitrosodiethylamine (DEN) induced rat. The study concluded that naringin has protective effect on oxidative stress induced carcinogenesis$^{97}$.
Yu-Long Luo and co-workers (2012) have performed a study to examine the effect of naringin in the airway hyper responsiveness (AHR) and airway inflammation of guinea pigs exposed to cigarette smoke for 8 weeks. The result showed that administration of naringin significantly reduced the cough and airway hyper responsiveness by decreasing the levels of myeloperoxidase (MPO) activity in both bronchoalveolar lavage fluid (BALF) and lung tissue. It also reduced the levels of tumor necrosis factor-α (TNF-α), leukotriene B4 (LTB4) and interleukin-8 (IL-8) in BALF. The study clearly suggests that naringin possesses anti-tussive, anti-expectorant, anti-inflammatory activity and reduces the sensitivity towards the airway hyper responsiveness. This proves that naringin is a potential drug in the treatment of acute bronchitis.\(^{(98)}\)

D. Wang and co-workers (2012) characterized the effect of naringin on Alzheimer’s disease (AD) induced by amyloid-β (Aβ) protein using three-month-old APPswe/PSΔE9 transgenic mice. The mice showed good improvement in learning, locomotor activity. The authors have found reduction in scattered senile plaques, and amelioration and also significant increase in, GSK-3β phosphorylation. This proves the beneficial effect of naringin and can be used in the treatment of Alzheimer’s disease.\(^{(99)}\)

Md. Ashraful Alam and co-workers (2013) studied the effect of naringin in diet-induced obese rats. The result showed that naringin decreased the elevated systolic blood pressure to normal and showed good relief from vascular dysfunction and ventricular diastolic
dysfunction. They suggested these positive effects of naringin may be facilitated by decrease in inflammatory cell infiltration, reduced oxidative stress and lowered plasma lipid concentrations in rats\textsuperscript{100}.

H. Li and coworker have worked on \textit{in-vitro} and \textit{in-vivo} models on TNBC cell lines to explore anticancer activity of naringin. They proved that naringin can be used as potential supplement in treatment and prevention of breast cancer\textsuperscript{101}.

The past literature survey clearly states that hesperidin and naringin possess variety of pharmacological activity like immune modulatory, anti-allergic, analgesic, anti-depressant activity, sedative effect, anti-inflammatory, anti-oestrogenic, anti-carcinogenic, anti-spasmolytic, anti-hyaluronidase, anti-oxidant activity, anti-schistosomicidal activity, anti-anaphylactic activity etc. All the studies confirmed their activity but most of the study suggested that these compounds are very effective in the preventive stage rather than in curing stage. This is due to the lack of potency of these molecules. So in the present investigation author used the above mentioned molecules as a lead moiety to synthesize various derivatives. All the synthesized derivatives were subjected for pharmacological evaluation. The author also investigated that the introduction of functional groups increases or decreases the pharmacological activity.