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A Systematic Review on: Dietary Flavonoids and Their Formulation Approaches

Jitendra Kumar[1], Lata Gupta[1], Dr. Meenakshi Gupta[2]

[1]School of Pharmaceutical Sciences C.S.J.M.U Kanpur
[2]Senior Assistant Professor School of Pharmaceutical Sciences C.S.J.M.U Kanpur

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ABSTRACT

Dietary flavonoids play an important role in the prevention of diseases related to oxidativestress in living systems and also it is a group of bioactive compounds that include flavone, flavonols, flavanol, flavanone, isoflavone, anthocyanidin, and chalcones.These are phenolic compounds found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. These natural products are well-known for their health-promoting properties due to their anti-oxidant, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties.Flavonoids have limited bioavailability and consequently low plasma concentrations.Flavonoids are now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. For pharmaceutical purpose cost effective bulk production of different type of flavonoids has been made possible with the help of microbial technology. In the present review, attempts have been made to discuss about the flavonoids, its biological activities, Approaches use to enhance the bioavailability of flavonoids (Quercetin, Rutin, Kaempferol and Naringenin).

Keywords: Flavonoids,Reactive Oxygen Species (ROS), Anti-inflammatory activity, Antiviral activity, Bioavailability, Cyclodextrin, Liposome, NLC_s (Nanostructured Lipid Carrier), Self Emulsifying Drug Delivery System (SEDDS)

1. INTRODUCTION OF FLAVONOIDS

Flavonoids are secondary metabolites with varied polyphenol structures that are found in the plant kingdom. Fruits, vegetables, grains, barks, roots, stems, and flowers all contain phenolic chemical [1, 2]. They have a diverse spectrum of structures and influence the properties of plant-based meals and drinks. Flavonoids found in nature have been identified in over 5000 different plants. Flavones, Flavonols, Flavanones, Isoflavones, Chalcones, and Anthocyanins are the six subgroups of flavonoid. They are linked to plant physiology. Flavonoids impact plant hormone trafficking. They play a role in photosensitization, photosynthesis, and plant physiological survival[3]. Flavonoid molecules of various architectures can affect the biological process of agitator and cell systems in humans, revealing antioxidant, antiviral, anti-inflammatory, antibacterial, and anti-allergic properties[4].Table:1 show the various class of flavonoids;

Table 1 Class of flavonoids and its source

S.no.	Flavonoid subclass	Example of compounds	Food source	Reference
1	Flavonols	Kaempferol, myricetin quercetin, and tamarixetin	Onion, red wine, kale, olive oil, broccoli apples, cherries, berries, and grapefruit and tea	5
2	Flavones	Chrysin, Rutin, luteolin, apigenin, and glucosidestangeretin	Fruit skins, red wine, buckwheat, red pepper, tomato skin, Parsley, Thyme	6-9
3	Flavonones	Naringin, taxifolin, naringenin, and hesperidin	Citrus fruits, grapefruits, lemons, and oranges	10-11

4	Flavanol	Catechin, epicatechin, epigallocatechin, glausan-3- epicatechin, proanthocyanidins	Apple, tea	5
5	Anthocyanidins	Apigenidin, delphinidin, cyaniding, pelargonidin, malvidin	Cherries, raspberry, strawberry, and Grapes	5,7
6	Isoflavones	Daidzein, Genistein	Soya beans, Legumes	12,13

1.1 Flavonols

Flavonoids containing a ketone group and hydroxyl group are known as flavonols. The plant pigments proanthocyanins abundantly present in a wide variety of fruits and veggies are made up of these building units. The most abundant antioxidants are kaempferol, quercetin, myricetin, and fisetin is researched flavonols. Flavonols are rich in onions, broccoli, cabbage, tomatoes, apples, grapes, and berries. Flavonols can also be found in tea and red wine, in addition to fruits and vegetables. Flavonols utilization has been linked to a various health benefit, including antioxidant capacity as well as a reduced risk of vascular disorder.Unlike flavones, flavonols feature a hydroxyl group on the third carbon ring that can be glycosylated. Flavonols have a wide range of methylation and hydroxylation patterns, and because of the various glycosylation patterns, they are the most common and largest category of flavonoids in fruits and vegetables.. Many plant meals, for example, include quercetin,kaempferol[14].

1.2Flavones

Flavones are a type of flavonoid that is one of the most important subclasses. It found as glucosides in leafs, fruits, and flowers. Celery, parsley, red peppers, chamomile, mint, and gingko biloba all are the examples of flavones. In citrus fruits peels, the polymethoxylated flavones tageretin, nobiletin, and sinensetin are widely available [15].

1.3Flavanones

Flavanones are another important class of compounds that can be found in citrus fruits including oranges, lemons, and grapes. This group of flavonoids includes hesperitin, naringenin, and eriodictyol. Because of their free radical scavenging characteristics, flavanones have been linked to a variety of health benefits. Citrus juice and peel have a bitter taste due to these chemicals. Citrus flavonoids have pharmacological effects that include antioxidant, anti-inflammatory, blood lipid reducing, and cholesterol decreasing.Flavanones, also known as dihydroflavones, have a saturated C ring; thus, unlike flavones, the double bond between positions 2 and 3 is saturated, and this is the only structural difference between the two flavonoids subgroups. [16].

1.4 Isoflavonoids

Isoflavonoids are a vast and separate subclass of flavonoids. Isoflavonoids are predominantly found in oilseeds and some other leguminous plants, and their spread in the plant kingdom is restricted. Microbes have also been reported to contain isoflavonoids.[17].They are also identified to have an important role as materials for the synthesis of phytoalexins during plant-microbe interactions..[18,19]Isoflavonoids also have tremendous disease-prevention potential. They have estrogenic action in several animal models, isoflavones such as genistein and daidzein are commonly regarded as phytoestrogens.Researcher examined the role of genistein in inducing hormonal and metabolic changes, which can affect a variety of disease pathways. [20]

1.5 Anthocyanins

Anthocyanins give colour to plants, flowers, and fruits. cyanidin, delphinidin, malvidin, pelargonidin, and peonidin have been the most investigated anthocyanins. Cranberry, black currants, red grape, merlot grapes, raspberry, strawberries, blueberry, bilberries, and blackberries, among many other fruits, have them predominantly in their outer cell layers. Because of their durability and medical benefits, these chemicals can be used in a variety of dietary purposes [21].

1.6 Chalcones

The flavonoids known as chalcones are a subclass of flavonoid. The absence of the basic flavonoid skeletan's 'ring C' distinguishes them. As a result, open-chain flavonoid isreferred as chalcones. Phloridzin, arbutin, phloretin, and chalconaringenin are just a few examples of chalcones. Tomatoes, pears, strawberries, bearberries, and some wheat products all contain significant amounts of chalcones. Because of their numerous nutritional and biological benefits, chalcones and their derivatives have received a lot of attention.[22-23]

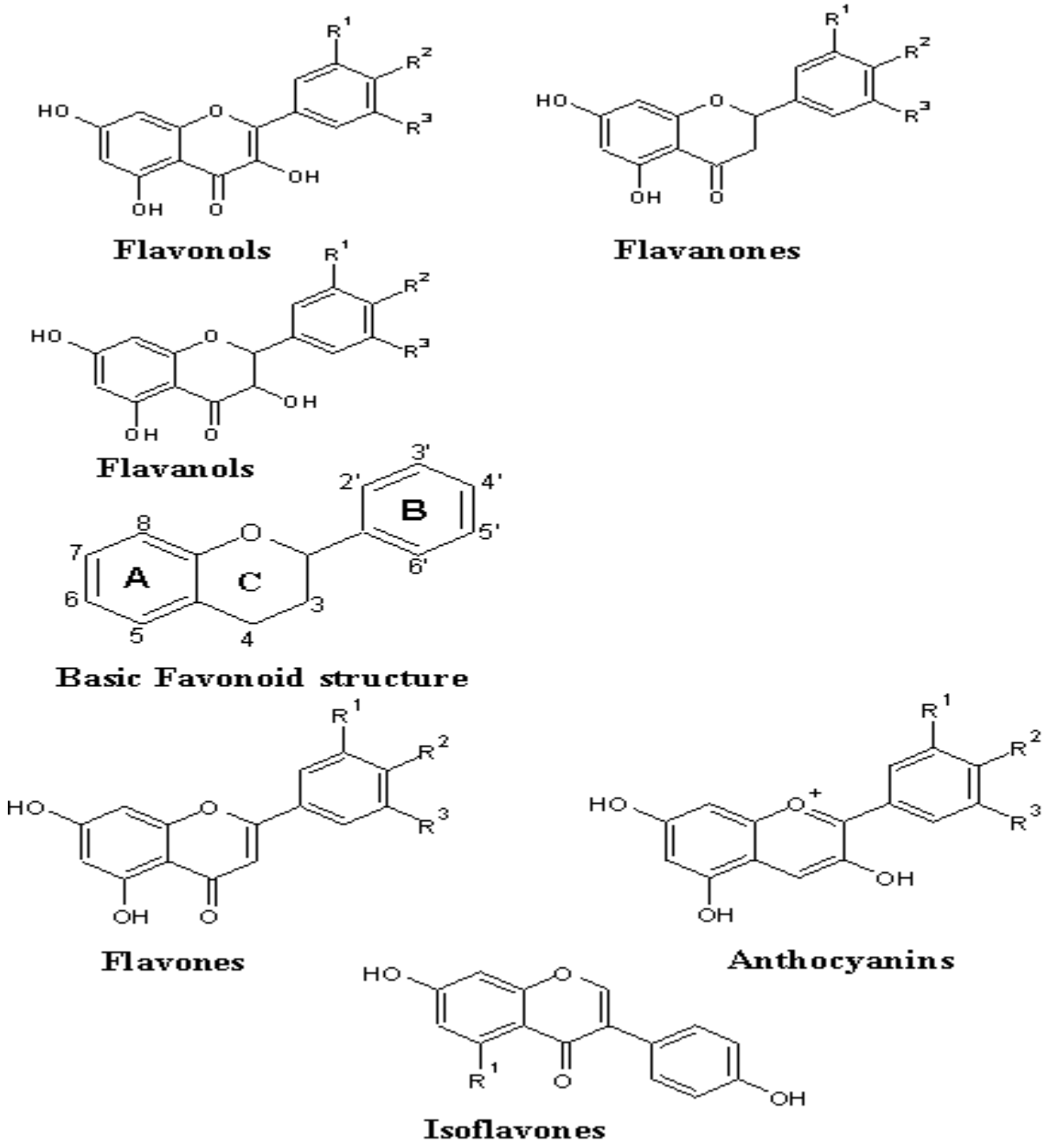


Figure: 1 Basic structures of the flavonoids

2.Quercetin (QC)

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is the most prevalent naturally occurring flavonoid and has received a lot of interest as a possible anticancer drug[24,25]. Quercetin is a well-known antioxidant that protects against damage create by oxidative stress andcaused by free radicals or reactive oxidative species (ROS)[26,27]. It has a yellow colour and is completely dispersible in lipids and alcohol; however, in cold water it is insoluble and springily soluble in hot water. It obtained from Latin word "quercetum," that convey or mean "oak forest," [28]. It also possesses a wide number of anticancer effects,and various research's have proposed that it is potent as a cancer-prevention agent [29-32].Platelet aggregation, capillary permeability, and lipid peroxidation have all been demonstrated to be inhibited by this compound as well as improve mitochondrial biogenesis [33, 34].Takamura K*et al* used quercetin to bind copper to create the first liposomal copper-quercetin formulations which improve apparent solubility of quercetin at least 100 folds which is suitable for intravenous administration [35].

Figure: 2 Source of Quercetin

2.1 Biological activity of quercetin

2.1.1 Antioxidant Activity

Health related benefits of quercetins have been related to its antioxidant activity.Magar, R.T *et al* discovered that altering quercetin structure diminishes its antioxidant activity, with the overall activity being as follows: quercetin > tamarixetin > isorhamnetin > quercetin-3-O-glucuronide > isorhamnetin-3-O-glucoside > quercetin-3, 5, 7, 3', 4'-pentamethylether > quercetin-3, 4'-di-glucoside [36].Methylated derivatives of quercetin (e.g., isorhamnetin and tamarixetin) are more potent for inhibiting lipid peroxidation than quercetin as reported by Boots A.W *et al* [37].Quercetin is used to suppress or constrained the growth of malignancies by modifying oxidative stress elements and antioxidant enzymes. In a rat study, researchers tested histology or oxidative stress indicators such decreases glutathione, hydrogen peroxide (H_2O_2) and lipid peroxidation (LPO to see antioxidant activity. [38]. Several studies revealed that quercetin reduces acryl amide-induced oxidative damage, radiation-induced brain damage in rats, neurodegenerative illnesses, cadmium fluoride-induced oxidative stress and nerve destruction in diabetic rats' retinas[39].It inhibits oxidants and strengthens the body's antioxidant protections, reducing oxidative stress caused due to the development of nicotine-induced oxygen radical in the treatment of disorders like nicotine dependency [40]. *In vivo* investigations have revealed that it also shows hepatoprotective property against tertiary butyl hydrogen peroxide-induced acute liver failure. By suppressing or removing free radicals and raising the amounts of endogenous antioxidants, it efficiently defends cells from genetic fatal and radiation-induced damage [41].

2.1.2 Antiviral Activity

Quercetin has also been discovered to have antiviral properties. The antiviral activity of quercetin was observed as opposed to anti-Japanese encephalitis virus , which causes the mosquito-borne illness known as Japanese encephalitis as well as against dengue virus type2[42]. QC also suppress hepatitis C virus and influenza A virus[43].

2.1.3 Anti-inflammatory activity

QC also possesses anti-inflammatory activity. *In vivo* investigation found that when combination of quercetinwith polysorbate 80 administered orally, it reduce the paw edoema[44]. Due to its less absorption throughout the skin surface, quercetin has been described ineffective/fruitless against topical inflammation. However, a penta-methyl-ether derivative of it has been reported as an anti-inflammatory agent through skin [45]. Quercetin has been shown to suppress inflammatory mediators such as reactive C-protein when given to cultivated hepatocyte cell line [46]. Intraperitoneal injection of quercetin improved insulin sensitivity in mice, and this followed by a decrease in inflammation, which are related to the insulin resistance [47].

2.1.4 Antimicrobial Activity

Quercetin is an antibacterial agent[48]. Furthermore, in the presence of Lucas, chitosan activated by quercetin shows exceptional antibacterial effect against bacteria such as *E. coli*, *Listeria monocytogenes*. Furthermore, because of its ability to block D-Ala-D-Ala ligation, quercetin acts as a bacteriostatic agent[49]. Because of its bacteriostatic properties, quercetin is an excellent candidate for antibacterial medication development [50].

2.1.5 Anticancer Activity

Quercetin possessesto be a strong anticancer agent because it have radical scavenging properties and help to prevent cancer caused by oxidative stress [51]. Quercetin chemoprotective activity against tumor cell lines via apoptosis and metastasis makes it a promising contender as a possible anticancer drug [52]. Its conjunction with intratumoral doxorubicin injection has been shown to improve immune responses in case of breast tumor development [53]. However, quercetin was shown to decrease angiogenesis in tamoxifen-resistant breast cancer cells in an *In Vitro* investigation belonging to human Michigan Cancer Foundation-7 cells [54]. Figure: 3 demonstrate the biological activity of quercetin.

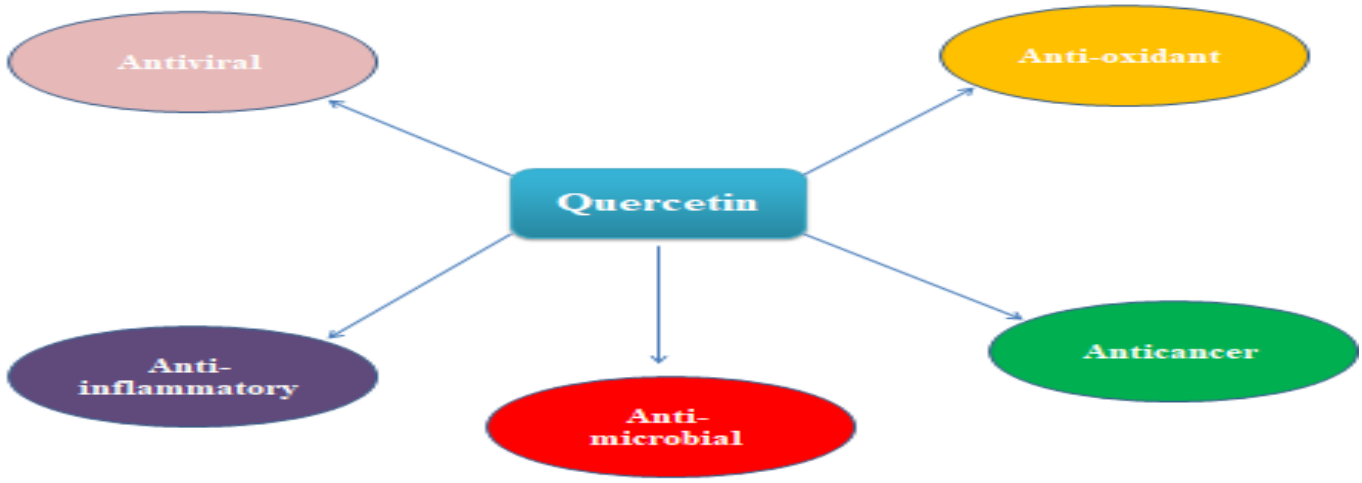


Figure: 3 Biological activity of Quercetin

2.2 Bioavailability and Pharmacokinetics of Quercetin

Quercetin has low oral bioavailability due to macronutrient absorption[55]. Glycosides, which are consumed in the form of quercetin, are produced during chewing and absorption. The activity of β-glycosidase enzymes converts quercetin glycosides into aglycone in colon before they are soak up by enterocytes [56]. It is a lipophilic molecule, therefore it anticipated that it may penetrate the intestinal membranes by simple diffusion, and theoretically, this absorption shows better result than its glycoside versions which reaches to the intestines without Foods degradation[57]. One probable explanation is that quercetin glycosides are hydrolyzed as they are transformed to aglycone byβ-glycosidase enzymes. The majority of these enzymes are absorbed when they are detected in the small intestine [58].Figure:4 Show the reason of low bioavailability of quercetin.

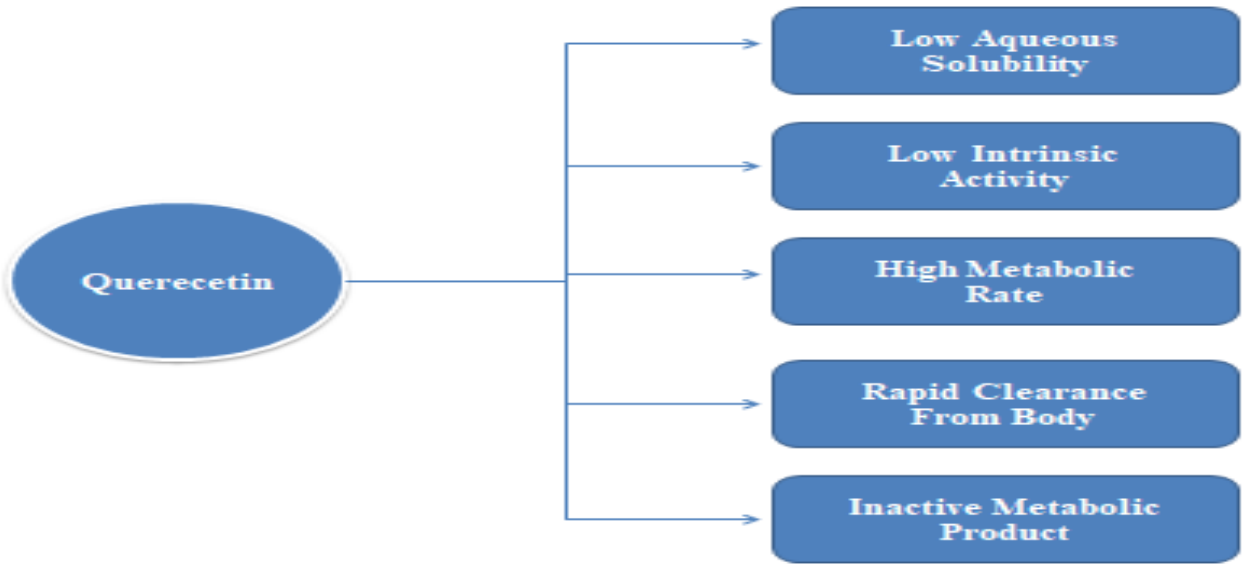


Figure: 4 Low bioavailability reason of quercetin

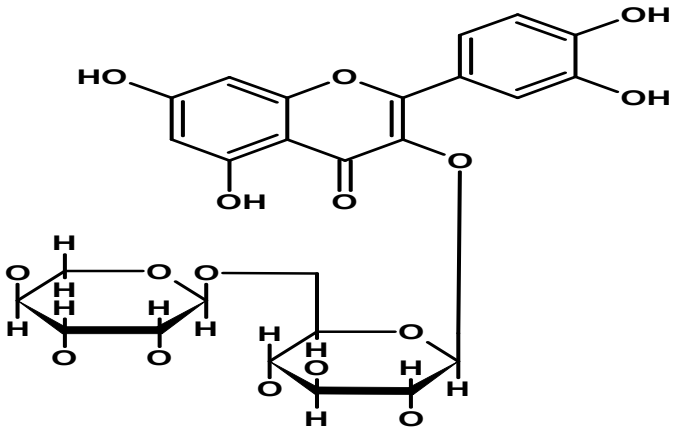
3. Rutin

Rutin gets its name from the Ruta graveolens plant (common Rue), which is composed of rutin in its aerial portions and it is also known as vitamin P [59]. In the Plant Kingdom, it is extensively dispersed. They can be found in a variety of vegetable sources (fruits,roots, flowers, seeds or wine)[60]. It is soluble in organic solvents including pyridine, methanol, and ethanol since it is a lipophilic component [61]. It has a variety of pharmacological activityand commonly used as an antifungal, anti-allergic and antimicrobial. On the other hand,It has demonstrated its broad-spectrum pharmacological potential in the treatment of many chronic diseases including cancer, hypertension, hypercholesterolemia and diabetes [62]. Table: 2enlists the plant species as source of rutin.

Figure: 5 Source of Rutin

Table: 2 Different species of plant and their parts used for isolation of Rutin

S.No.	Plant Species	Common Name	Parts Used	References
1.	Capparis spinosa, C. sicula and C. orientalis	Capers	Flower buds	[63]
2.	Fagopyrum esculentum Moench	Buckwheat	Whole grain flour	[64]
3.	Asparagus officinalis	Sparrow grass	Asparagus spears (stem)	[65]
4.	Ribes nigrum, Rhus chirindensis, Ribes rubrum	Berries	Fruits	[66]
5.	Rubus occidentalis	Black raspberry	Fruits	[67]
6.	Olea europaea L	Olive	Fruits	[68]



Rutin

3.1 Biological activity of Rutin

3.1.1Prevention of neuroinflammation

Rutin has property that it can protect the brain against ischemia. Due to the disconcerting of p53 expression and lipid peroxidation, rutin administration resulted in a reduction in 'ischemic neuronal apoptosis' and increase in 'endogenous antioxidant defensive enzymes.'[69]. Javed, H*et al* reported that sporadic dementia of Alzheimer's type, 'neuroinflammation' was reduced [70].

3.1.2 Sedative activity

In mice, rutin's CNS and behavioral activities were tested using a hole board, loco motor activity tests and thiopental-induced sleeping period. When it administered intraperitoneally had a depressive effect on the CNS. Rutin's showsdepressive action on CNS which to be improbable owing to GABAA receptor involvement, according to research [71].

3.1.3 Anticonvulsant activity

Rutin also possess anticonvulsant properties and appears to be shield guard for epilepsy patients, since it doesn't interfere with the activity of any antiepileptic drugs or cause any side effects [72].

3.1.4 Antidepressant activity

The 'antidepressant like activity' of rutin extracted from *Schinus molle* plant which were investigated using a forced swimming test and Tail suspension test.the immobility time was reduced in the tail suspension test. The loco motor activity remained unchanged. Antidepressant-like action is achieved by increasing the accessibility of serotonin and noradrenaline in synaptic cleft [73].

3.1.5 Anti-arthritic activity

Rutin showed a significant reduction in Fanconi anemia and Rheumatoid arthritis by suppressing 'oxygen radical overproduction,' [74].Rutin inhibited the acute and chronic phases of inflammation in an adjuvant arthritis rat model. In the chronic phage of inflammation, it was the highly active [75]. It is used for the treatment of septic arthritis which is caused by Candida albicans because it has antifungal and anti-arthritic potential [76]. Rutin also reduced inflammatory and catabolic cartilage markers in osteoarthritic lesions in Hartley guinea pigs in an independent investigation [77].

3.1.6 Anti-inflammatory activity

Rutin's show anti-inflammatory properties because it inhibit the key enzymes which involved in inflammation and/or cell signaling pathways, such as Lipoxygenase (LOX) and cyclooxygenase (COX), protein kinase C (PKC), and phosphoinositide 3-kinase (PI 3-kinase), all of which are involved in the producing inflammatory mediators like leukotriene and prostaglandins[78-79].Rutin was found to decrease PLA2 activity in human synovial fluid, which is the first enzyme in the arachidonic acid cascade [80].

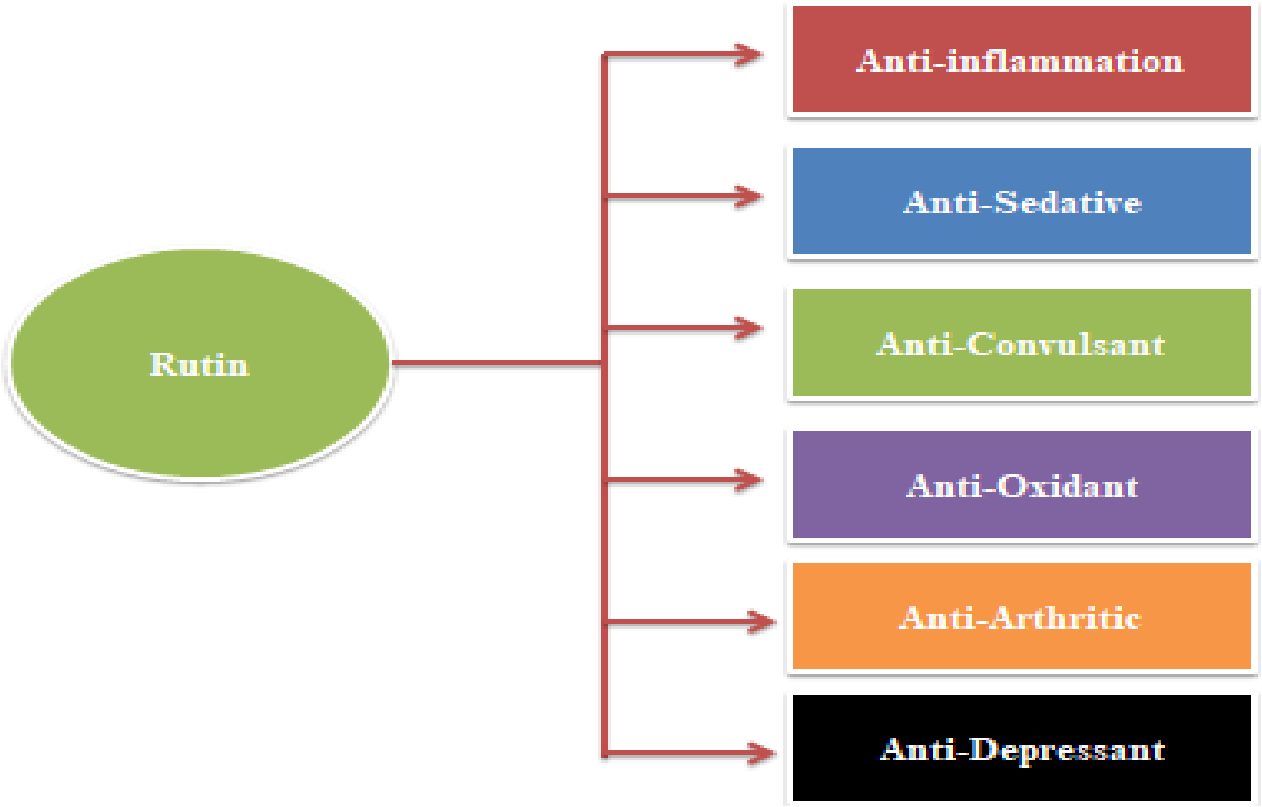


Figure: 6 Biological activities of Rutin

Role of rutin in various condition	Mode of action	Reference
Antioxidant effect	• Free radical segregation • Transition metal chelation	**[81-82]**
Anti-inflammatory effect	• Eicosanoid production • COX, lipoxygenase, and PLA2 inhibited.	**[83-84]**
Anticancer effect	• Cell growth is slowed, • reactive oxygen species (ROS) are removed, • StopDNA damageand mutations.	**[85-86]**
Antidiabetic effect	• Insulin release from Langerhans is improved • PPARγ expression is increased.	**[87-89]**
Antihypertensive	• Suppression of ACE and inhibition of the NO/guanylatecyclase pathway	**[90]**

Table 3: Mechanism of rutin in different disease

3.2 Bioavailability of rutin

Rutin's solubility In aqueous medium rutin solubility is very low which is one of its biggest drawbacks [91]. This is the primary cause of its low bioavailability. Particle reduction to the submicron range and rutin complexation with Cyclodextrins and variety of metals are methods for increasing rutin bioavailability.

4. KAEMPFEROL

Kaempferol have antioxidant, anticancer, anti-inflammatory, cardio protective, neuroprotective, and antidiabetic potential [92].They are extensively found in plants and are frequent ingredients in fruits, vegetables, and even drinks. Some epidemiological studies discovered a link between the utilization of flavonoids-rich foods and a lower risk of cancer and cardiovascular disease [93, 94]. According to epidemiological research, a high consumption of kaempferol is linked to a lower risk of cancer in several organs, including the skin, colon, ovary, pancreas,liver, stomach, and bladder [95, 96].The intake of kaempferol and its application in cancer therapy is garnering a lot of interest in the scientific community. Cancer prevention is mostly accomplished by inducing apoptosis, which inhibits cancer cell growth [97, 98].Fig:7 show the sources of the kaempferol.

Figure 7 Sources of kaempferol

4.1 Biological Activity of Kaempferol

4.1.1 Antioxidant Activity

Cells require oxygen for oxidative phosphorylation, a mitochondrial mechanism that generates energy (oxphos). [99].When a molecule of oxygen(O_2) gains just one electron and form superoxide anion (O_{2}–), this very highly reactive oxygen species (ROS) obtain 3 more electrons and 4 protons to obtain Water molecules; this process imply various responses and produces other reactive oxygen species such as hydroxyl radical, hydrogen peroxide , and peroxynitrite. The regulated generation of reactive oxygen species has a crucial physiological activity [100]. The term "oxidative stress" has been used to describe a condition in which the body's been indicate that it plays a key role in the pathogenesis of cancer, heart disease, atherosclerosis, and hypertension are all conditions that can lead to death [101].*In vivo* antioxidant properties of extract of Ginkgo biloba including kaempferol and quercetin derived product has also been observed [102]. Kaempferol has been discovered to be an effective superoxide scavenger with IC_{50} of 0.5M.[103].When a kaempferol derivative-containing extract of Capparis spinosa was administered topically to healthy human volunteers, it demonstrated strong antioxidant activity [104]. Injecting *Crassocephalum crepidioides* extract containing kaempferol glycosides intraperitoneally had a substantial anti-oxidative effect and protected galactosamine and lipopolysaccharide induced hepatotoxicity[105].

4.1.2 Anti-inflammatory Activity

Inflammation is a natural reaction to tissue injury generated by a microbial pathogen infection, chemical irritation, or trauma. The inflammatory response is influenced by the stimulation and movement of leukocytes to the site of injury, as well as the producing the growth factors, reactive oxygen, cytokines and nitrogen species. Immune surveillance, effective healing, and regeneration following damage all need inflammatory activities [106,107]. on the other hand,Chronic inflammation happens when acute inflammation is not cured, and it has a negative impact on a variety of illnesses,

including atherosclerosis, asthma,cancer, and several neurological diseases including Alzheimer's and Parkinson's disease[108]. *In vitro* and *In vivo* studies have demonstrated that kaempferol and kaempferol glycosides have anti-inflammatory effect [109]. By contributing in the synthesis of prostaglandins, leukotriene's and the creation of reactive species, the enzymes lipoxygenases (LOX),cyclooxygenases (COX), and inducible nitric oxide synthase (iNOS) are known to play essential roles in inflammation. Kaempferol has been revealed to suppress COX-, LOX-, or iNOS in several studies [110,111]. It can lower ROS levels in the cells [112]. *In vitro*/*In vivo*investigations have found that kaempferol has anti-inflammatory effect and have identified different pathways that may be involved [113].

4.1.3 Antimicrobial Activity

Antimicrobial activities of kaempferol and its glycosides identified from plants used in traditional medicament. Kaempferol, its glycosides version and plants containing kaempferol have been shown to have antibacterial, antiprotozoal,antiviral, antifungal properties in several studies [114]. This flavonols has been shown to have antibacterial action *In vivo*. Four weeks after orally inoculating *M.gerbils* with *H. pylori*, researchers found that taking kaempferol twice a day for ten days greatly reduced the amount of *Helicobacter pylori* colonies in gerbils stomachs [115]. Oral injection of kaempferol-7-O-methyl-3-sulphate enhanced the duration of mice infected or contaminated with *Klebsiella pneumoniae*. Antibiotics (e.g. rifampicin, methicillin,vancomycin, clindamycin, erythromycin) can also work in tandem with kaempferol and its glycosides to combat antibiotic-resistant bacteria [116].

4.1.4 Anticancer Activity

Addition of kaempferol-rich nourishment may lower the chance of acquiring variety forms of cancer, including lung cancer, pancreatic cancer, gastric cancer, and ovarian cancer [117,118]. A most widely recognized hypothesis of carcinogenesis (the somatic mutation theory of cancer) holds that DNA mutations cause cancers [119]. Several studies have suggested that modest levels of kaempferol may save DNA from harmness caused by certain carcinogens [120]. It is commonly believed that the development of a malignant tumour necessitates acquisition of numerous characteristics (known as cancer hallmarks), such as apoptosis resistance, enhanced angiogenesis, and the ability to invade and metastasize [121]. Tumor cells must gain apoptosis resistance in order to become a cancer and kaempferol has been shown to trigger apoptosis [122].

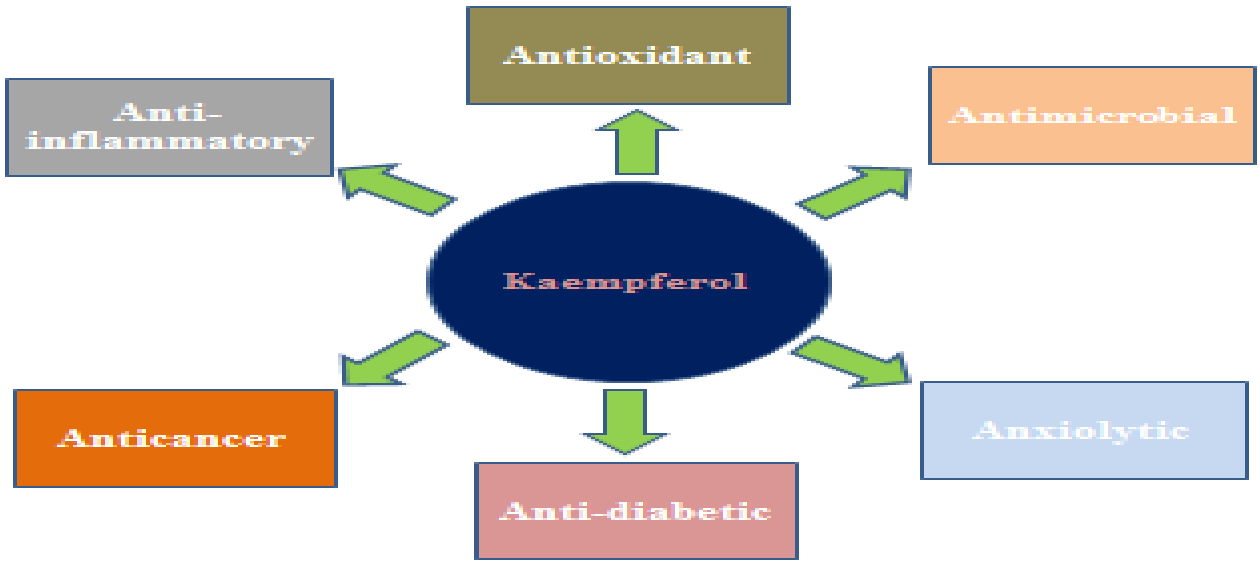


Figure: 8 Biological Activities of Kaempferol

4.2 Bioavailability of Kaempferol

Kaempferol's lipophilicity makes passive diffusion easier, but research suggests that it can also be absorbed through facilitated diffusion or active transport. Intestinal conjugation enzymes can metabolize it in the small intestine [123]. Kaempferol and its glycoside version are extensively metabolized by the colon micro flora, just like other flavonoids. [124].Radket et al [125] studied the plasma concentrations of different flavonoids in 48 normal women and discovered that

the average daily intake of kaempferol is 4.7 mg, with a mean plasma concentration of 10.7 nM. To enhance the therapeutic benefits of kaempferol, its limited oral bioavailability and high metabolism in humans should be addressed (e.g., by employing different routes and modes of administration).Several studies have determined that kaempferol's oral bioavailability is in the nano or microgram per ml level, yet it nevertheless has a wide range of therapeutic benefits and is used to treat a variety of diseases. As a result, it's reasonable to believe that kaempferol is therapeutically effective in low dosages. [126].

5. NARINGENIN

Naringenin, also known as 5 7-trihydroxyflavanone, is one of the most significant flavonoids and have lots of biological potential.[127]It is aglycone of naringin, which is known as the bitter constituent of citrus fruits[128] It's found in a wide range of fruits and green vegetables, including grapefruit, bergamot,lemon, oranges, and tomatoes[129].Naringenin has a nearly 5.81 percent oral bioavailability rate, and it is absorbed in the gastrointestinal tract via both passive diffusion and active transport [130]. Because of its multiple health benefits, this can be utilized in a variety of pharmaceutical formulations to enhance human health. [131].Naringenin have low bioavailability is the major drawback of it.Some formulations, such as naringenin-loaded nanoparticles, have been come about to overcome it.[132].

Figure: 9 Source of Naringenin

5.1 Biological activity of naringenin

5.1.1 Anticancer activity

Naringenin has been shown to inhibit cell proliferation in a variety of cancer cell lines. In activated B-cells, naringenin has been reported to prevent bladder cancer cell migration by suppressing matrix metalloproteinase (MMP-2), decreasing AKT activity (protein kinase B), and blocking nuclear translocation of nuclear factor ƙ-light chain enhancer [133]. It inhibits the development of human hepatocellular carcinoma (HepG2 cells) by inhibiting cell proliferation and inducing apoptosis (cell death) via activating the caspase-3 enzyme[134]. Recently, researchers discovered that combining naringenin with tamoxifen at lower concentrations was more efficient than either molecule alone in inhibiting cell growth and viability in breast cancer cells (MCF-7) [135]. In transglutaminase-induced differentiation of human prostate cancer cells, alpha-tocopherol and naringenin exhibit synergistic effects[136]. Naringenin also improved doxorubicin's anti-tumor effect by regulating drug efflux pathways selectively. As a result, it could be an effective complement to chemotherapeutic agents in the therapy of cancer progression[137]. When compared to free naringenin, naringenin-loaded nanoparticles demonstrated more significant anti-lipid peroxidative antiproliferative activities and antioxidant capability against 7, 12- dimethyl Benz(a)anthracene produced experimental oral carcinogenesis, confirming its chemo preventative value [138].

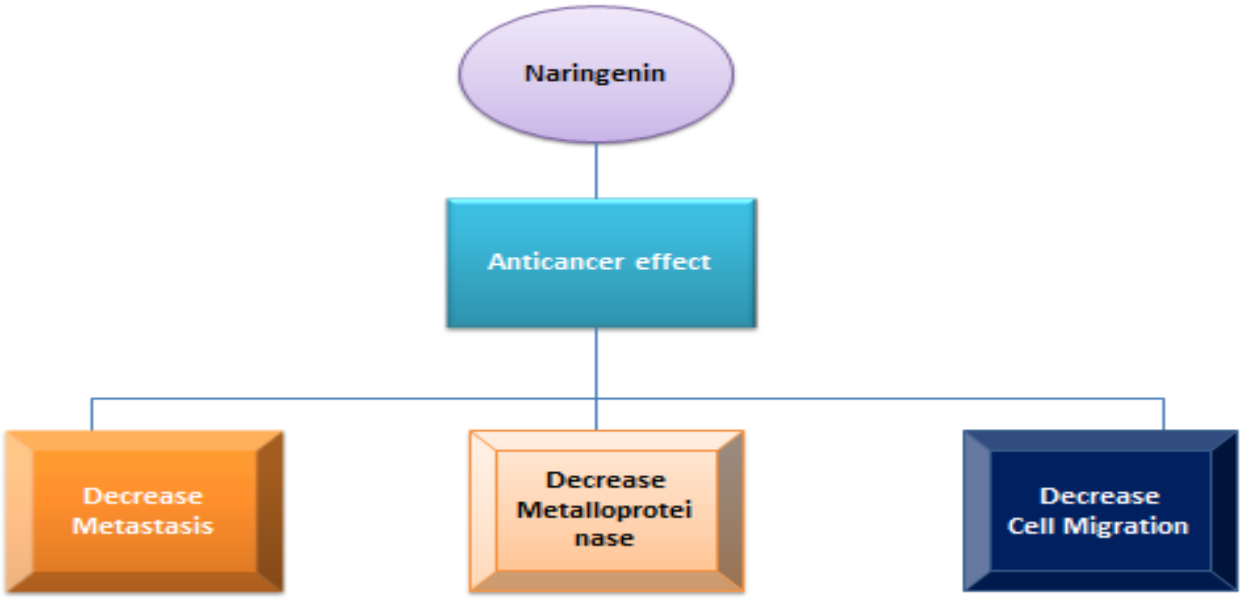


Figure 10 Anticancer activity of Naringenin

5.1.2 Neuroprotective Activities

The capability of naringenin to minimize oxidative stress and maintain the integrity of mitochondrial membranes [139]. Naringenin was discovered to protect against ischemic brain damage by reducing neuroinflammation caused by the nuclear factor ƙ-light-chain-enhancer of activated B cells (NF-ƙB) protein [140].The shielding effect of naringenin on dementia caused by an intracerebroventricular injection of streptozotocin demonstrated that naringenin therapy improved Alzheimer's disease recovery in the early stages. [141]. In a recent research's, the protective properties of naringenin against iron-induced brain neurotoxicity were discovered to be linked to oxidative stress [142]. Naringenin has also been discovered to serve as an antidepressant by stimulating the signalling of the brain-derived neurotropic factor (BDNF) [143].

5.1.3 Anti-Inflammatory Activities

Naringenin has been found to have anti-inflammatory potential, protecting variety of human and animal parts and organs from inflammation-related diseases and pathogenesis.[144,145]. It has been discovered to safeguard for the liver from oxidative stress by stimulating the nuclear translocation of nuclear factor erythroid 2 (NFE2)-related factor 2 and inhibiting the TNF-α pathway, resulting in anti-inflammatory action in liver tissue[146]. It has also shown analgesic effects in rats by reducing neuropathic pain and suppressing neuroinflammation [147]. Naringenin reduces the production of interferon-γ by activated CD4 (+) T lymphocytes, which decreases the development of atopic dermatitis-like skin lesions [148]. It also protects against neuroinflammatory damage by inhibiting inflammatory signals in glial cells [149]. By inhibiting Toll-like receptor 4/NF-kB signalling, it protects against experimental colitis [150].

5.1.4 Anti-Obesity effect

Naringenin and other citrus polyphenols have been shown to reduce body weight, fat storage, and development of hyperlipidemia and hyperglycemia by increasing the transcriptional activity of enzymes which involve in the β -oxidation pathway [151]. Naringenin also inhibits adipocyte differentiation, which is linked to obesity, by blocking insulin-stimulated glucose absorption and affecting mature fat cell activity in a dose-dependent way. Furthermore, in mature murine and human adipocytes, naringenin reduced adiponectin protein expression [152].

5.1.5 Anti-oxidant effect

Naringenin had a stronger antioxidant capacity as well as the ability to scavenge hydroxyl and superoxide radicals. The efficacy of inhibiting the enzyme xanthine oxidase was reduced by glycosylation, and the aglycone might operate as a more potent chelator of metallic ions than the glycoside. In addition, naringenin was found to be more efficient in protecting

lipids from oxidative damage in a dose-dependent way. The flavanone was shown to be efficient at preventing DNA damage [153].

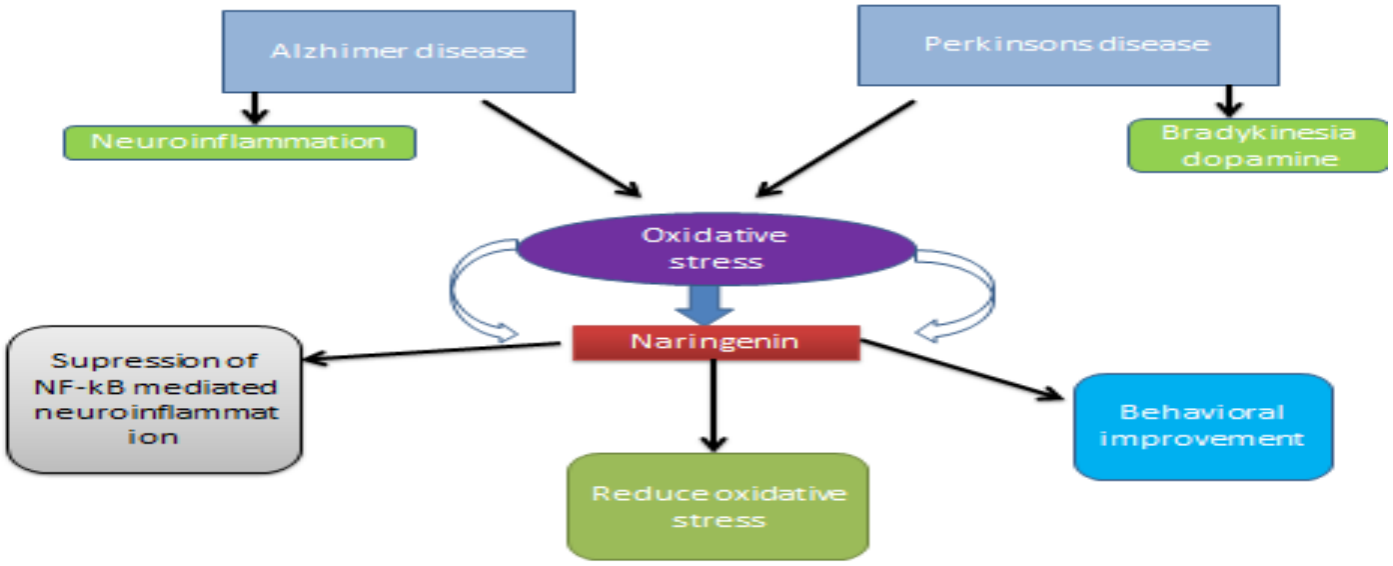


Figure 11 Activity of Naringenin

5.1.6 Gastro-intestinal activity

Pre-treatment with naringenin reduced the severeness of colitis and resulted in lower levels of proinflammatory mediators in the colon mucosa (inducible NO synthase (iNOS), intercellular adhesion molecule-1 (ICAM-1), cyclo-oxygenase-2 (Cox2), TNF-α monocyte chemoattractant protein-1 (MCP-1), and IL-6 mRNA) [154].

5.1.7 Anti-HCV agent

Naringenin has also been offered as a potential therapeutic drug for the treatment of hepatitis C virus infection. Indeed, at a concentration lower than the lethal value in primary humanhepatocytes, this has been shown to lower HCV release by 80% in infectedcells[155]

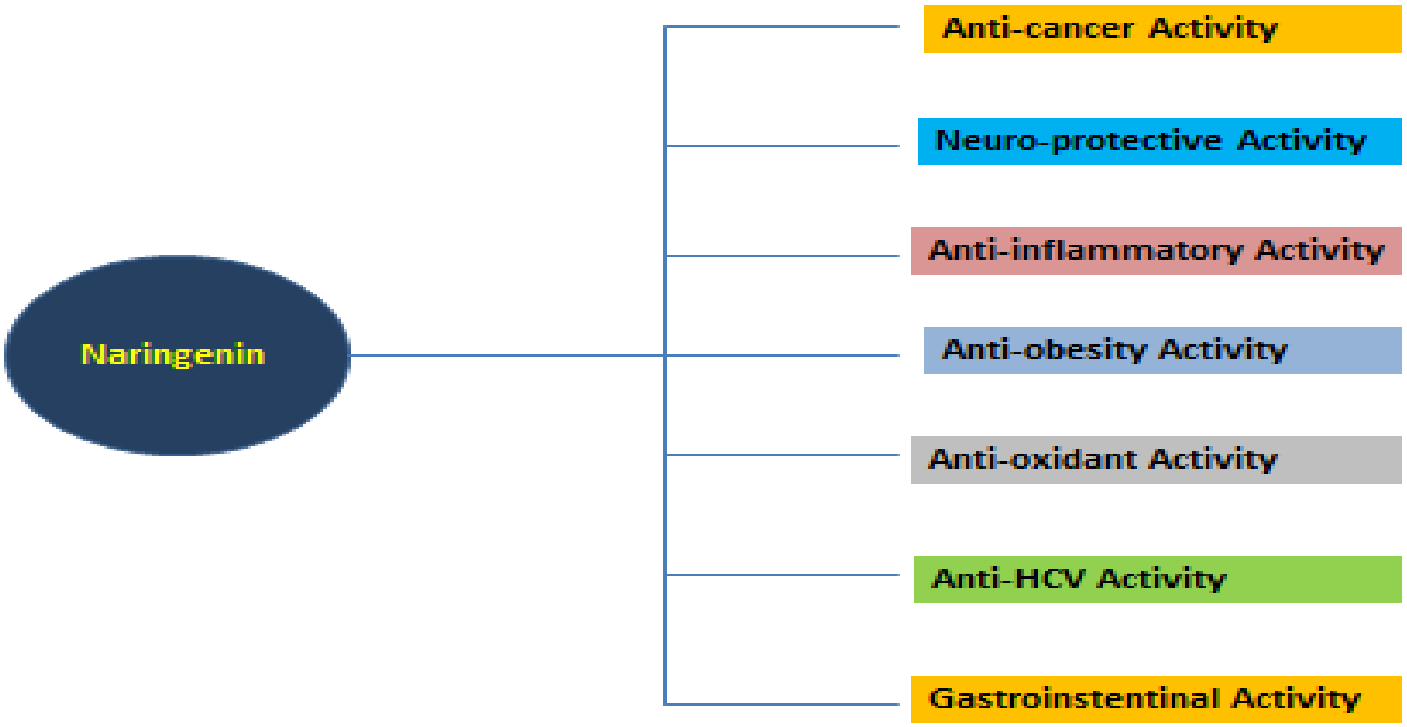


Figure: 12 Biological Activities of Naringenin

5.2 Bioavailability of Naringenin

The bioavailability of flavones following a single consumption of 400 to 760 mL of orange or grape juice were investigated by Erlund *et al* [156]. The obtained plasma concentrations were rather high (up to 4 mg/L or 15 mol/L), which is not surprising given the high amount of the chemicals in citrus fruits and drinks. Flavanone plasma half-life were rather short (1-2 h). Furthermore, naringenin renal clearance seems to be dose-dependent. After drinking 0.5 or 1 litres of orange juice, plasma levels were found to be similar [157].

6. APPROACHES USE FOR ENHANCEMENT OF BIOAVAILABILITY OF FLAVONOIDS

6.1 Complexation with cyclodextrin

Cyclodextrin molecules due to torus-shaped structure effectively form inclusion complexes with a various variety of molecules to promote bioavailability by improving drug water solubility and stability [158].*Kale et al.* synthesized solid inclusion complexes of quercetin (QC) and cyclodextrin,furtherreported the increase in the solubility and dissolution rate after complexation of quercetin (QC) cyclodextrin which was more effective in suppressing cell proliferation in human erythroleukemia and cervical cancer cells. The complex formulation showed dramatically better anti-cancer activity at low concentrations when using cyclodextrin carriers, indicating that dose reduction without understanding therapeutic efficacy is possible[159].For improving the solubility and stability of rutin ,Sri K.V. *etal* reported encapsulation with variety of cyclodextrin substituents[160].Eunae Cho *etal*(2014) reported that the aqueous solubility of the kaempferol increased after the complex formation with β-cyclodextrin.[161].By complexing naringenin with β-cyclodextrin, Maria Shulman et al increased it solubility 400-fold and its transport across a Caco-2 model of the gut epithelium by 11-fold. The results demonstrate that combining naringenin with Hydroxypropoyl-β-cyclodextrin (HPβCD) is a promising approach for delivering naringenin as a therapeutic agent for the treatment of dyslipidemia, HCV infection, and diabetes[162].

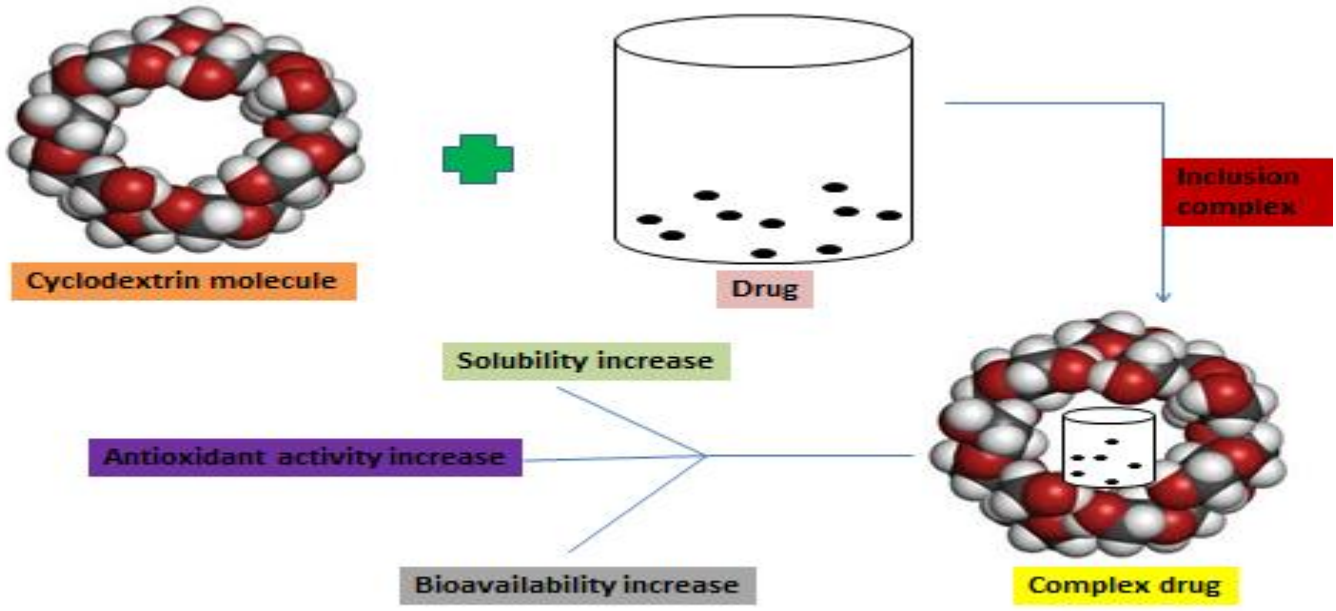


Figure: 13Complex formation of drug with cyclodextrin molecule

6.2 Phytosome/Phospholipid complex

Phytosomes are amphiphilic molecule complexes in which bioactive molecules (mostly polyphenolics) bind to phospholipids, particularly phosphatidylcholine that form supramolecular adducts with a defined stoichiometry.The superiority of phytosomes over other formulations is that they improve gastrointestinal absorption after oral administration by increasing the rate and extent of bioactive solubilization in aqueous intestinal fluids and enhancing the ability to cross lipid-rich bio membranes, resulting in higher plasma levels and reduced kinetic elimination that increased systemic bioavailability [163,164].The water/n-octanol solubility of rutin were improvein the complex, which enhanced the delivery of weakly soluble rutin[165].Further, complex of Quercetin with phospholipid were developed to improve its aqueous solubility for better absorption via the gastrointestinal tract [166]. The water solubility of Quercetin wereimproved by 12

folds (from 3.44 µg/ mL to 36.81 µg/ mL) in the prepared complex.When compared to pure kaempferol, Darshan R. Telange et al modified phospholipid complex demonstrated an increase in oral bioavailability as evidenced by enhancements in key pharmacokinetic parameters.[167].Kexia Zhang*et al* (2015) modify the solubility and bioavailability of Kaempferol by optimizing kaempferol-phospholipid complex, Complex formulation showed higher solubility and dissolution rate than Kaempferol, indicating a significant incensement in hydrophilicity [168].To improve the bioavailability and prolong its duration in body system, Ajay Semalty *et al* made its phospholipid complex by a simple and reproducible method. In the presence of dichloromethane, naringenin binds to phosphatidylcholine in an equimolar ratio. In the prepared compound, naringenin's water solubility increased from 43.83 to 79.31 g/mL. Naringenin's phospholipid complex might be useful for increasing bioavailability [169].

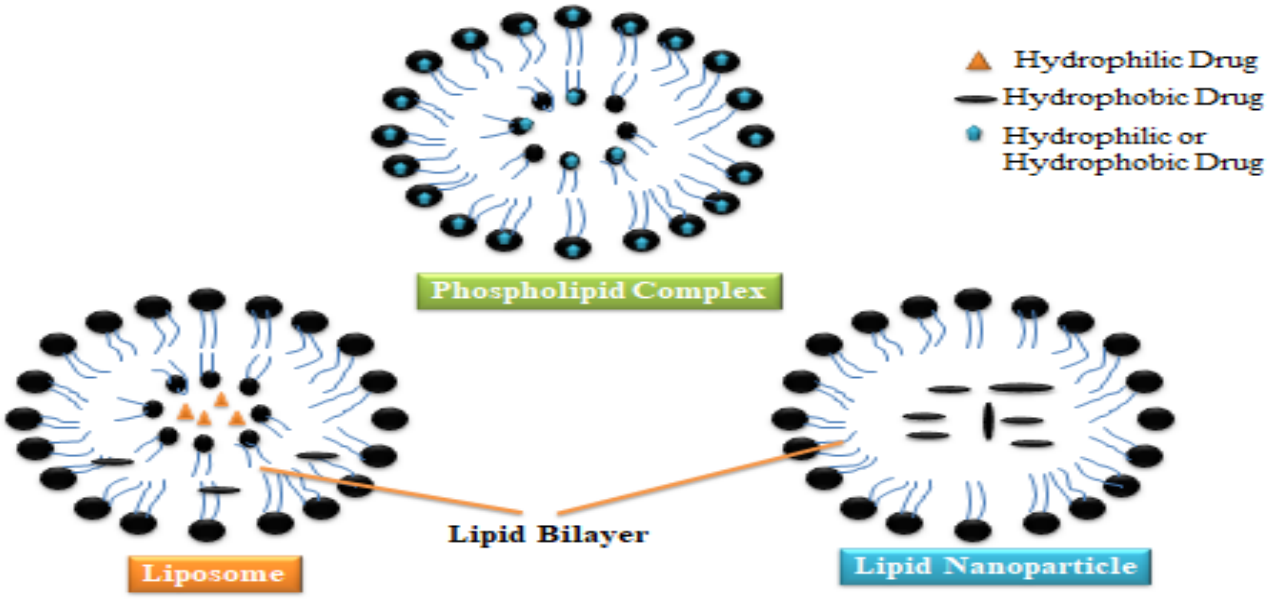


Figure:14 Various type of drug loaded liposome and lipid formulation

6.3 Nanostructured lipid carriers

NLCs (nanostructured lipid carriers) are lipid-based Nano carriers that can be used to encapsulate a variety of bioactive compounds. They are made up of both solid and liquid lipids and have a higher loading capacity, are easier to manufacture, and have a more controlled release profile than solid lipid nanoparticles.[170]. Babazadeh et al (2016) making food grade NLCs for the encapsulation of rutin with the objective to creating new functional foods.[171] Encapsulation of QC in LNC was reported by Barras et al. that showed 100 folds increase in its apparent aqueous solubility. [172] According the results, it seems most Bioavailability of Quercetin probable that QC is arranged at this LNC interface between the oil phase and the hydrophilic polyethylene glycol moieties of the surfactant. In addition, colloidal suspensions proved to be stable in term of encapsulation for at least 10 weeks and QC was not oxidized.In MDA-MB 468 breast cancerous cells, Toofan Aghazadeh et al explored the influence of Kaempferol loaded in nanostructured lipid carriers in promoting cytotoxicity, efficacy, and paclitaxel-dependent apoptosis. The findings suggest that incorporating Kempferol into NLCs as an anti-cancer adjuvant is a potent tool that could be a valuable delivery system for improving the effect of chemotherapy agents on breast cancer cells[173].The characterizations, trans epithelial transport, intestinal permeability, and inhibitory activity of a naringenin loaded nanostructured lipid carrier on nonalcoholic fatty liver disease (NAFLD) induced by methionine choline shortage were investigated. The inhibitory activity of naringenin on NAFLD(nonalcoholic fatty liver disease) were significantly boosted by NLC formulation, which boosted drug release rate, trans epithelial transport, and intestinal absorption, as well as oral bioavailability and liver naringenin distribution[174].

6.4 Micro emulsion

Micro emulsions (ME) are liquid solutions with an oil phase, surfactants and a water phase that are optically isotropic and thermodynamically durable/stable [175].ME has many advantages, including Nano metric size, transparency, low viscosity, ease of preparation, high solubilization capacity, and resistance to drug degradation, hydrolysis, and oxidation[176].It was looked into the possibility of using a W/O ME as a topical carrier mode for the antioxidant Quercetin (QC) [177].The W/O

ME enhances the penetration of QC into the stratum corneum and epidermis plus dermis in vitro at different time intervals (3, 6, 9, and 12 hours) after application, as well as in vivo at 6 hours after application. According to the research, using this optimized formulation for up to two days didn't cause skin irritation. In W/O ME containing QC, UVB irradiation-induced glutathione exhaustion and met alloproteinase secretion/activity were significantly reduced.Another ME formulation with oil, surfactant and cosurfactant were investigated[178]. The solubility of QC in this formulation increased when compared to the solubility of QC in water. Another study found that the rutin has low permeability across the blood brain barrier (BBB) which tends to its low therapeutic index. Sagar Kishore Savale make the rutin loaded micro emulsion for intranasal delivery which considered as promising channel for its targeting to CNS to treatment of the brain cancers[179].A naringenin micro emulsion developed by researcher for inhibiting corneal neovascularization (CNV). The results showed that naringenin micro emulsion released more drugs and permeated more corneal permeability than naringenin suspension[180].

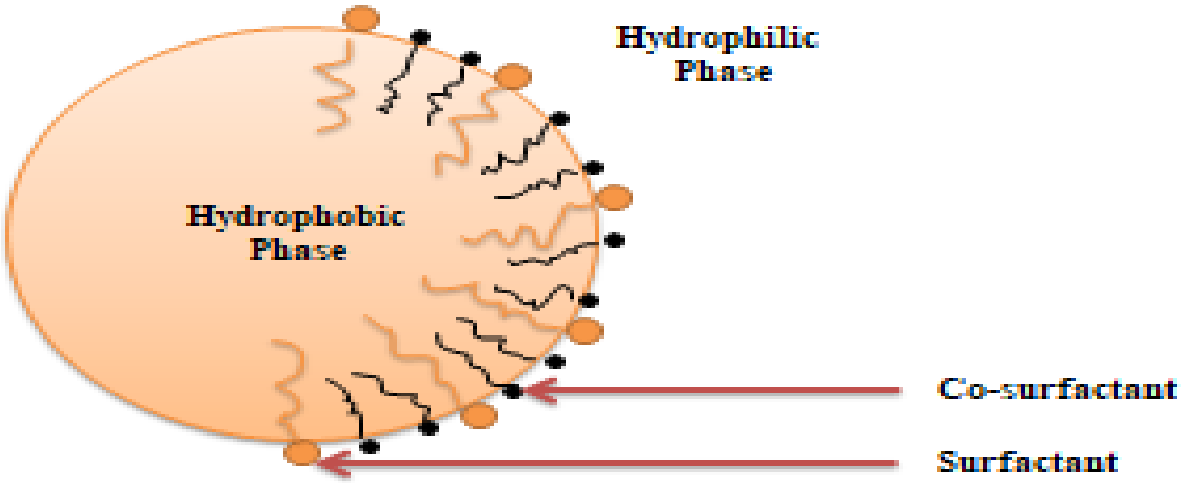


Figure: 15 Structure of micro emulsion

6.5 SEDDS(Self Emulsifying Drug Delivery System)

Self-emulsifying drug delivery system (SEDDS) produces nano-emulsions called SNEDDS. Regardless of preparation method, they are heterogeneous dispersions of two immiscible liquids (oil-in-water [O/W] or water-in-oil [W/O]) with a mean droplet size in the Nano metric scale (usually 20–200 nm). This is especially true for medications that increase solubility[181].The SEDDS produce SMEDDS, which are microemulsions. It forms an optically transparent emulsion and is thermodynamically stable. The key distinction between micro-emulsions and conventional emulsions is the particle size of the droplets. The size of common emulsion droplets range from 0.2 to 10 meter, while the size of micro-emulsion droplets set up by the SMEDDS is typically between 2 and 100 nm. Because of the tiny particle size, the surface area for absorption and distributions is substantially bigger than that of a solid dosage form, and it may simply penetrate and be absorbed, bioavailability is improved by the formulation of SMEDDS [182].Self-micro-emulsifying drug delivery systems (SMEDDS) using Moringa oleifera extract are being developed by Namfa Sermkaew and ThipapunPlyduang. found flavonoids in *M. oleifera* leaf extract include kaempferol and quercetin. Within 15 minutes, SMEDDS may improve the solubility of kaempferol and quercetin[183].In order to improve quercetin oral bioavailability, a self-nanoemulsifying drug delivery system containing quercetin was created to generate oil-in-water Nano emulsions in situ. ThanhHuyen Tran *et al.* reported that the increased the solubility approx 2 to 3 folds when compared with the quercetin control suspension[184].According to Shrestha Sharma et al. Rutin SNEDDS might be a useful technique for increasing rutin's oral bioavailability and effectiveness, and thereby decreasing oxidative stress in neurodegenerative diseases like Parkinson's disorder[185].Quercetin and its glycosides (hyperin, isoquercitrin) were found in persimmon leaf extract, along with kaempferol and its glycosides (astragalin). When compared to commercial tablets, SNEDDS considerably improved the oral bioavailability of quercetin and kaempferol in beagle dogs In vivo [186].Further enhance in drug release and bioavailability as contrast to drug suspension from SNEDDS formulation may be attributed to the Nano sized droplets and modify the solubility of naringenin in the SNEDDS. Plasma concentration profile of Naringenin for SNEDDS exhibited a great development of drug absorption than the drug suspension [187].

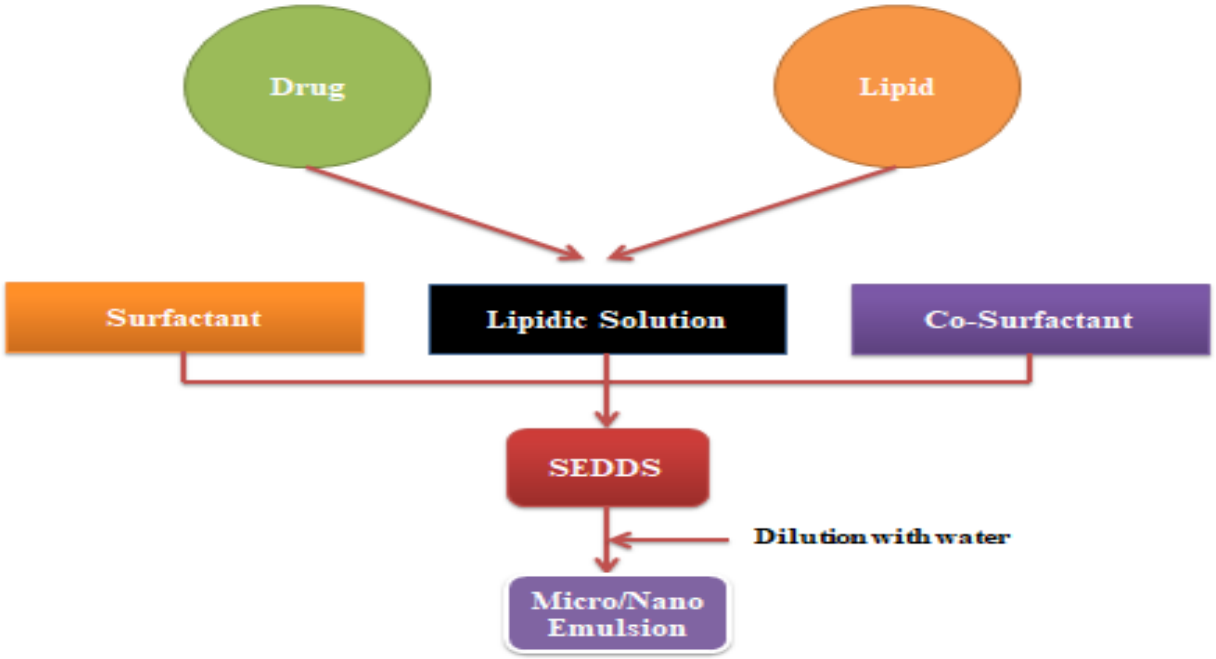


Figure: 16General strategy of formulating Self Emulsifying Drug Delivery System

6.6 Liposome

It is microscopic vesicles made up of one or more lipid bilayer spheres separated by water or an aqueous buffer compartment. They are used as carriers for improving drug solubility, bioavailability, stability, and targeting due to their biphasic features, diversity in design, and composition[188].Water-soluble medications can be carried in the central core, lipid-soluble drugs in the membrane, and peptides and small proteins at the lipid-aqueous interface[189].The miscellaneous design-response surface technique was used to improve quercetin-loaded liposomal formulations, and it was discovered that the quercetin-loaded liposomal formulations achieve sustained drug release in wound regions [190].*In vivo*, researches developed a liposomal QC to prevent bleomycin-induced lung fibrosis. Liposomal QC reduced total cell and macrophage counts in broncho alveolar lavage fluid [191].Ghosh et al [192] used liposome-entrapped QC to test its therapeutic effectiveness in rat hepatocytes and brain cells for arsenic toxicity-mediated oxidative damage. Liposomal QC was shown to be the most effective in completely preventing arsenite-induced antioxidant depletion in the liver and brain of rats.When compared to the traditional medicine, Aparajita Varshneya and Padmini Ravikumar created rutin trihydrate liposomal gel for topical delivery and discovered that the liposomal gel displayed longer drug release and anti-elastase action[193].Yuanwen Wang prepared a naringenin-loaded liposome for oral administration and found that the liposomal formulation considerably increased naringenin solubility and oral bioavailability[194].Further researcher produced a new phytochemical-based deformable liposomal formulation suspended in an aqueous gel for the controlled release of naringenin, indicating that deformable liposomes may be useful in enhancing medication penetration across dermal cells[195].In the term of kaempferol Researchers created a KPLC formulation (kaempferol liposomal complex) and discovered that it increased kaempferol oral bioavailability[196].

6.7 Nanocrystal

Nanocrystals, which have been reported for addressing physicochemical and therapeutic concerns, are one of the new platforms for synthesizing flavonoids. Drug Nanocrystals are colloidal dispersion systems with a submicron active component stabilized by polymers or surfactants. Nanocrystals can be crystalline, amorphous, or partly amorphous, depending on the manufacturing procedure, and are available as capsules, powders, and tablets. Because of the enhanced curvature available for medium to remain in touch with drug crystals, Nanocrystals improve flavonoids bioavailability by reducing particle size and increasing dissolving rate[197].N G Sahoo et al observed that synthesizingNanocrystals using high-pressure homogenization increased the solubility rate of a weakly water-soluble medicine, quercetin, and that the dissolution rate of the drug Nanocrystals was substantially greater than the pure drug at pH 6.8 and 1.2. The quercetin Nanocrystals have more antioxidant and reducing power than the regular quercetin[198].Rachmat Mauludin *et al.* created an oral rutin Nanocrystal formulation that improves the dissolving behavior of the rutin Nanocrystal-loaded tablet, resulting in improved bioavailability of the poorly soluble rutin in the body[199].

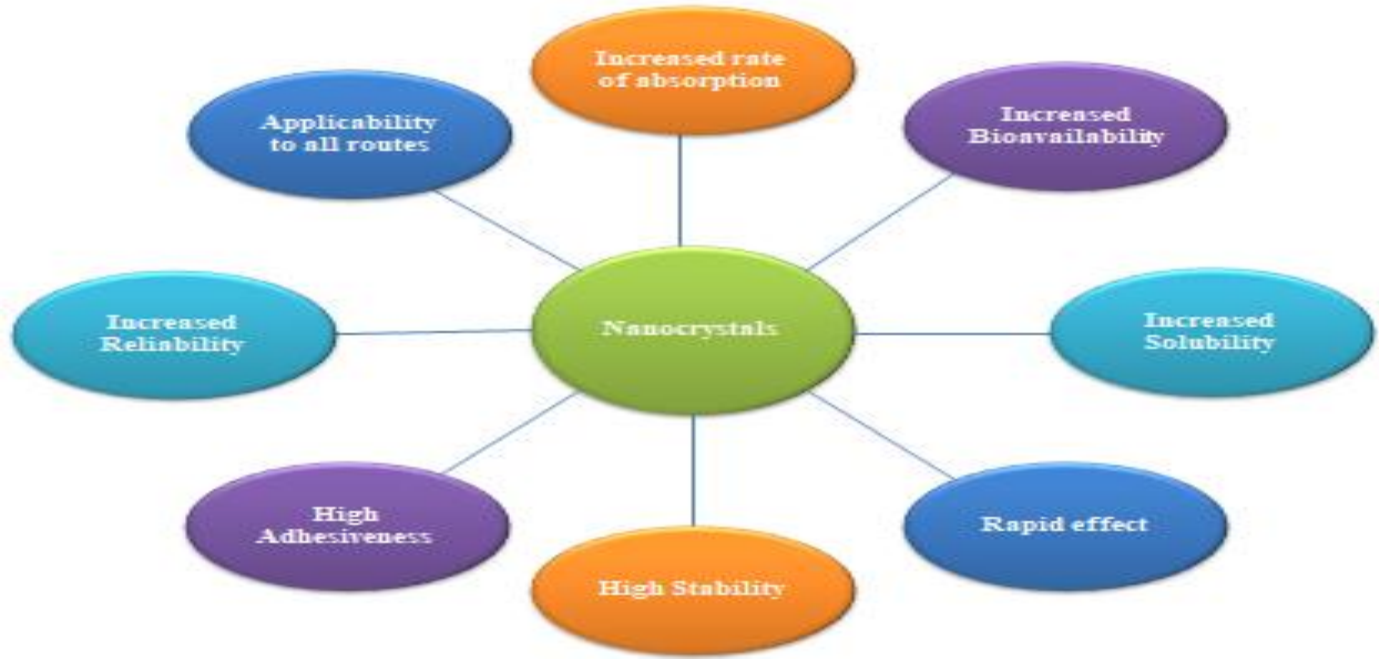


Figure: 17 Advantages of Nanocrystals

CONCLUSION

This review summarize the flavonoids are one of the most studied phytochemicals due to their diverse health benefit. It is widely dispersed in the green leafy fruits and vegetables. Itdemonstrates several biological activity such as anti-bacterial, anti-inflammatory, anti-cancer etc. Low bioavailability of flavonoids required to be increase for full exploitation of their therapeutic benefit in prevention and used in the treatment of diseases. For increasing the oral bioavailability of poorly water soluble flavonoids many formulation approaches such as carrier complex with cyclodextrin, Liposome Formulation, SEDDS (Self Emulsifying Drug Delivery System), Nanocrystal approaches, Micro emulsion approaches have been developed to circumvent the issue of low bioavailability of active flavonoids by enhancing their solubility and dissolution rate, increasing their mucosal permeation.

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