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FLAVONOIDS AMALGAMATED IN NANOTECHNOLOGY: A NEW ERA OF NANOMEDICINE

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ABSTRACT

Flavonoids are a class of naturally occurring compounds with varying phenolic structures that may be discovered in tea, wine, cereals, roots, flowers, fruits, and vegetables. The health benefits of these natural compounds are widely known, and attempts are being undertaken to separate the components known as flavonoids. Nowadays, flavonoids are seen as an essential component of many pharmacological, cosmetic, dietary supplement, and medical uses. A variety of fruits, vegetables, and leaves contain phytochemicals called flavonoids, which may have uses in medical chemistry. Many health advantages are associated with flavonoids, such as their antiviral, anticancer, and antioxidant qualities. They also have cardio- and neuroprotective properties. The kind of flavonoid, its (potential) method of action, and its bioavailability all affect these biological functions. These reasonably priced pharmaceutical ingredients contain substantial biological activity and have been shown to be beneficial for a range of illnesses. Using a range of methods and animal models, the latest research focuses on their separation, the synthesis of their analogues, and their impact on human health. The number of flavonoids that have been effectively isolated continues to rise, reaching thousands. To better comprehend the impacts of isolated flavonoids on human health, we have thus attempted to summarise them using practical actions.

KEYWORDS: Flavonoids, Anti-inflammatory, Nanoparticles, Nanotechnology, Nanomedicine.

INTRODUCTION

Flavonoids are a significant group of natural products. Specifically, they are a type of secondary metabolites from plants that have a polyphenolic structure and are commonly present in fruits, vegetables, and certain drinks. They are known to possess a variety of advantageous biochemical and antioxidant properties linked to a number of disorders, including cancer, Alzheimer's disease (AD), atherosclerosis, etc. Flavonoids are an essential component in many nutraceutical, pharmacological, medical, and cosmetic uses and are linked to a wide range of health-promoting benefits. This is a result of their ability to alter important cellular enzyme activities in addition to their antioxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic qualities. Additionally, they have a reputation for being strong inhibitors of a number of enzymes, including phosphoinositide 3-kinase, lipoxygenase, cyclo-oxygenase (COX), and xanthine oxidase (XO).[1,2]

Flavonoid chemicals are by-products of plant extraction that are present in many plant components in nature. Vegetables utilise flavonoids to support their development and protect themselves against plaque. They are a member of a group of low-molecular-weight phenolic substances which are found across the kingdom of plants. In higher-growing plants, they make up among the many distinctive types of chemicals. In the majority of angiosperm groups, several flavonoids are easily identifiable as floral pigments. But they are not limited to flowers; they may be found in every part of the plant. Dietary flavonoids are so named because they are plentiful in plant-based meals and beverages, including fruits, vegetables, tea, chocolate, and wine.[3]

There are multiple subclasses of flavonoids, such as isoflavones, chalcones, flavones, and flavonols. Each of these subgroups possesses distinct primary sources. For instance, two important nutritional sources of flavonols and flavones are onions and tea. Numerous biological functions are carried out by flavonoids in microbes, plants, and animals. Flavonoids have been shown to be synthesised at specific locations in plants and are in charge of giving flowers their colour and scent. They also assist fruits disperse by drawing pollinators, which aids in seed and spore germination as well as promoting the development of seedlings. In addition to acting as special UV filters and shielding plants from various biotic and abiotic challenges, flavonoids also serve as

signal molecules, allopathic substances, phytoalexins, detoxifying agents, and antimicrobial defence compounds.[4]

Plant heat adaptation and cold tolerance may be facilitated by flavonoids, which also have functions in drought resistance and frost hardiness. According to Jorgensen, functional gene silencing in plants was linked to flavonoid biosynthesis, and the early developments in floral genetics were mostly caused by mutation approaches impacting flavonoid-derived flower hues. Positive benefits on the health of humans as well as animals have been scientifically attributed to flavonoids, and at the moment, chemoprevention and disease treatment are of particular interest. Presently, fruits, herbs, vegetables, and medicinal plants have vivid pigments due to the presence of around 6000 flavonoids.[5] Dixon and Pasinetti conducted a thorough analysis of plant flavonoids and isoflavonoids and spoke about how they may be used in agricultural and human neurology. The preventive properties of flavonoids against human illnesses and their actions in plants were reviewed by Kumar & Pandey. In recent years, Panche et al. thoroughly examined the applications of flavonoids as plant secondary metabolites for the treatment of AD and the underlying processes while examining AD and existing therapy approaches. Efforts are being attempted to address the wide taxonomy, uses of flavonoids as dietary supplements and health advantages, and future research prospects in the present overview.[6,7]

CLASSIFICATION

A number of factors, including the carbon of the C ring, to which the B ring is linked, as well as the degree of unsaturation and oxidation of the C ring, flavonoids can be classified into several subgroups (Fig. 1). Isoflavones are flavonoids that have a linkage between the B and C rings at position 3. Neoflavonoids are those that occur when the B ring is linked in position 4, whereas those in which the B ring is linked in position 2 can be further separated into many subgroups based on the structural characteristics of the C ring. These subgroups include catechins, anthocyanins, chalcones, flavones, flavonols, flavanones, and flavanonols.[8]

1. Flavones

One of the significant subgroups of flavonoids is flavones.As glucosides, flavones are found in leaves, flowers, and fruits in large quantities. Main sources of flavones include celery, parsley, red peppers, chamomile, mint, and *Ginkgo biloba*. Tangeritin, luteolin, and apigenin are flavonoid subclass members. Citrus fruit peels are rich in tageretin, nobiletin, and sinensetin, four poly-methoxylated flavones. In the C ring, they have a ketone at position 4 and a double bond between positions 2 and 3. While hydroxylation at other places, primarily in position 7 of the A ring or 3′ and 4′ of the B ring, might vary depending on the taxonomic classification of the specific vegetable or fruit, most flavones found in vegetables and fruits contain a hydroxyl group in position 5 of the A ring.[9]

2. Flavonols

Ketone groups on flavonoids are called flavonols. These are the proanthocyanin components. Numerous fruits and vegetables are rich in flavonols. The flavonols quercetin, myricetin, fisetin, and kaempferol have been investigated most extensively. Significant sources of flavonols include onions, kale, lettuce, tomatoes, apples, grapes, and berries. In addition to fruits and vegetables, flavonols can also be found in tea and red wine. Consuming flavonols has been linked to several health benefits, such as decreased risk of vascular disease and antioxidant capacity.[10]

Position 3 of the C ring in flavonols has a hydroxyl group, which is also potentially glycosylated, in contrast to flavones. Similar to flavones, flavonols exhibit a wide range of methylation and hydroxylation patterns. Taking into account the variations in glycosylation patterns, in vegetable and fruit products, they are presumably the most prevalent and sizable subclass of flavonoids. As an instance, many plant-based diets include quercetin.[11,12]

3. Flavanones

Another significant class that is frequently discovered in all citrus fruits, including oranges, lemons, and grapes, is flavanones.The aforementioned category of flavonoids includes hesperitin, naringenin, and eriodictyol as examples. Flavonones' ability to scavenge free radicals is linked to a multitude of health advantages. The bitter flavour of citrus fruit peel and juice is caused by these chemicals. As anti-inflammatory, blood lipid-lowering, cholesterol-lowering, and anti-oxidant agents, citrus flavonoids have intriguing pharmacological effects. The sole structural difference among the two families of flavonoids is that, unlike flavones, dihydroflavones, or flavanones, contain a saturated double bond across positions 2 and 3. There have been substantially more flavanones within the previous fifteen years.[13]

4. Isoflavonoids

Among the many different subgroups of flavonoids are isoflavonoids. Isoflavonoids are mostly found in soyabeans along with other leguminous plants, and they are only widely distributed throughout the plant kingdom. Microbes were additionally discovered to contain certain isoflavonoids. Additionally, it has been discovered that they are crucial as precursors for the synthesis of phytoalexins during interactions between plants and microbes. Isoflavonoids show great promise in the treatment of several illnesses. Isoflavones with oestrogenic action in some animal models, such genistein and daidzein, are often considered phyto-oestrogens. The impact of genistein on hormonal and metabolic alterations, which can impact several disease pathways, was examined by Szkudelska & Nogowski.[14,15]

5. Neoflavonoids

One group of polyphenolic substances is called neoflavonoids. Neoflavonoids feature a 4-phenylchromen spine without a hydroxylgroup substitution at position 2, in contrast to flavonoids' 2-phenylchromen-4-one backbone. Calophyllolide, a neoflavone derived from Calophyllum inophyllum seeds, was originally isolated from natural sources in 1951. Additionally, Mesua thwaitesii, an indigenous shrub of Sri Lanka, has it in its bark and lumber.[16]

6. Flavanols, flavan-3-ols or catechins

Flavanonols are the 3-hydroxy derivatives of flavanones, commonly referred to as dihydroflavonols or catechins. They constitute an extremely varied and multisubstituted class. Because the hydroxyl group is always attached to position 3 of the C ring, flavanols are also known as flavan-3-ols. There isn't a double bond between positions 2 and 3, in contrast with numerous flavonoids. Bananas, apples, pears, peaches, blueberries, and apples are rich sources of flavanols.[17]

7. Anthocyanins

Vegetation, flowers, and fruits get their colour from pigments called anthocyanins. The anthocyanins that are most often researched are peonidin, pelargonidin, cyanidin, delphinidin, and malvidin. The outermost cell layers of a variety of fruits, including raspberries, strawberries, blueberries, bilberries, blackberries, red grapes, black currants, and raspberries, are where they are mostly found. These chemicals' stability and health advantages make it possible for the food sector to employ them in a range of applications. The pH and methylation or acylation at the hydroxyl groups on the A and B rings affect the anthocyanin's hue.[18,19]

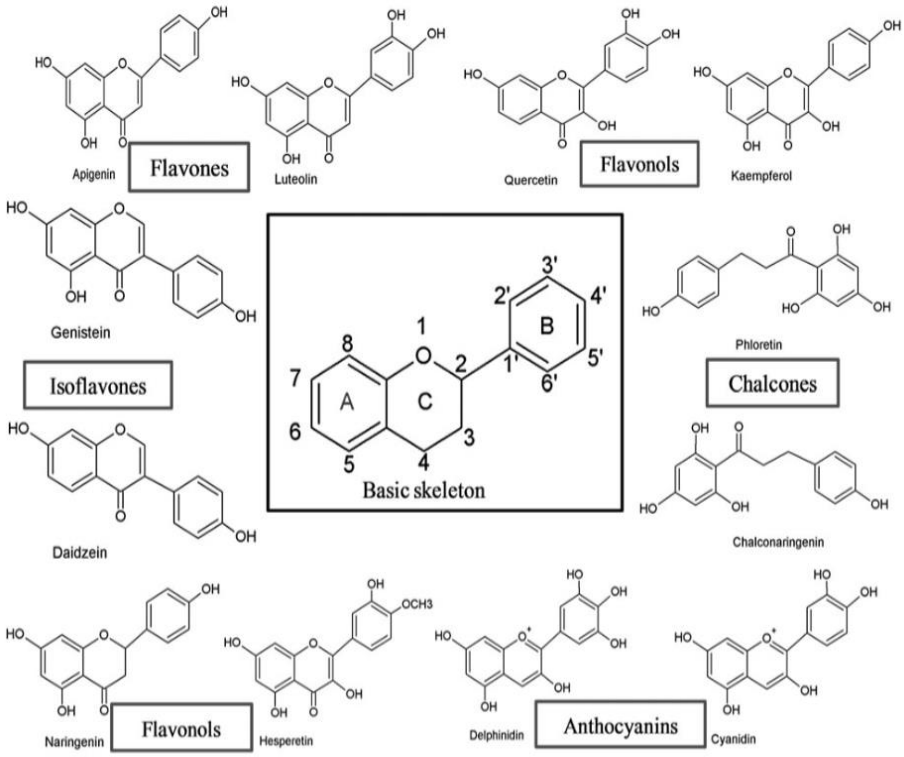

Fig 1: Basic Skeleton of Flavonoids and its classification.

PHARMACOLOGICAL POTENTIAL

Many health advantages are associated with flavonoids, such as their antiviral, anticancer, and antioxidant qualities. They also have cardio- and neuroprotective properties. The kind of flavonoid, its (potential) method of action, and its bioavailability all affect these biological functions.[20]

1. Anticancer Action

A serious health issue brought on by aberrant cell proliferation is cancer. Of the many anticancer medications on the market, only a small number exhibit inhibition against oncogenesis, and the majority are toxic and have unfavourable side effects. The foundation for cancer prevention and therapy is laid by naturally occurring biomolecules with secondary metabolites that contain phytomediated content and exhibit biological actions throughout a broad spectrum. It is well known that flavonoids have anticancer properties and stop cell development. The use of artificial or natural materials to stop the development of cancer is known as chemoprevention. Here are several instances of flavonoids being used as anticancer drugs.[21,22]

Hesperedin (Hsp) is a significant flavonoid with potent anticancer properties. Hesperidin nanoparticles (HspNPs)

were created by synthesising polylactic-co-glycolic acid (PLGA) nanoparticles and loading them with Hsp. This was done to explore the potential of HspNPs as an anticancer drug against C6 glioma cells. When Hsp was encapsulated and released under regulated conditions, the cytotoxicity of PLGA was reduced and the encapsulated Hsp showed lower in vitro cell viability against the C6 glioma cell line. A different approach flavonoid which is currently widely employed as an anticancer drug is aurone, a benzo-furanone. With so many potential targets, different aurone analogues exhibit distinct actions against cancer cells. Among these targets are microtubules, telomerase, adenosine receptor, histone deacetylase, cyclin-dependent kinase, and sirtuins.[23]

One naturally occurring flavonoid found in plants and widely consumed foods including grains, berries, and green tea is quercetin. The greatest successful use of it has been for colorectal cancer. The chemopreventive benefits of quercetin in colorectal cancer are attributed to a number of mechanisms, including cell cycle arrest, a boost in apoptosis, antioxidant replication, manipulation of oestrogen receptors, control of signalling pathways, suppression of metastasis, and angiogenesis.[24] The G2/M stage of the cancer cell cycle is stopped by luteolin, a naturally occurring flavonoid that has pro-apoptotic action in hepatocellular carcinoma (HCC) cells. Due to its direct targeting of flotillin-1, luteolin was discovered to upregulate the overexpressed miR-6809-5p in HCC. One naturally occurring flavanol that can lower the risk of cancer is kaempferol. It increases the body's antioxidant defences against cancer-causing free radicals.[25]

Myricetin is a significant flavonoid with anti-inflammatory and anticancer properties. It also has antimitotic actions in liver cancer and targets many mitochondrial metabolic processes that cause cancer cells to die. The flavonoid concentration of chamomile flower, Matricaria recutita L., is 157.9 ± 2.22 mg/g QE of dry extract. It showed dose-dependently increased HepG2 cell death in HCC. Angiogenesis is a crucial mechanism that cancer progresses by manipulating. Through VEGF receptors, vascular endothelial growth factor (VEGF) promotes angiogenesis, the process that forms new blood vessels. The synthesised extract effectively inhibited VEGF expression in a dose-dependent manner, indicating its potential as an anticancer treatment.[26]

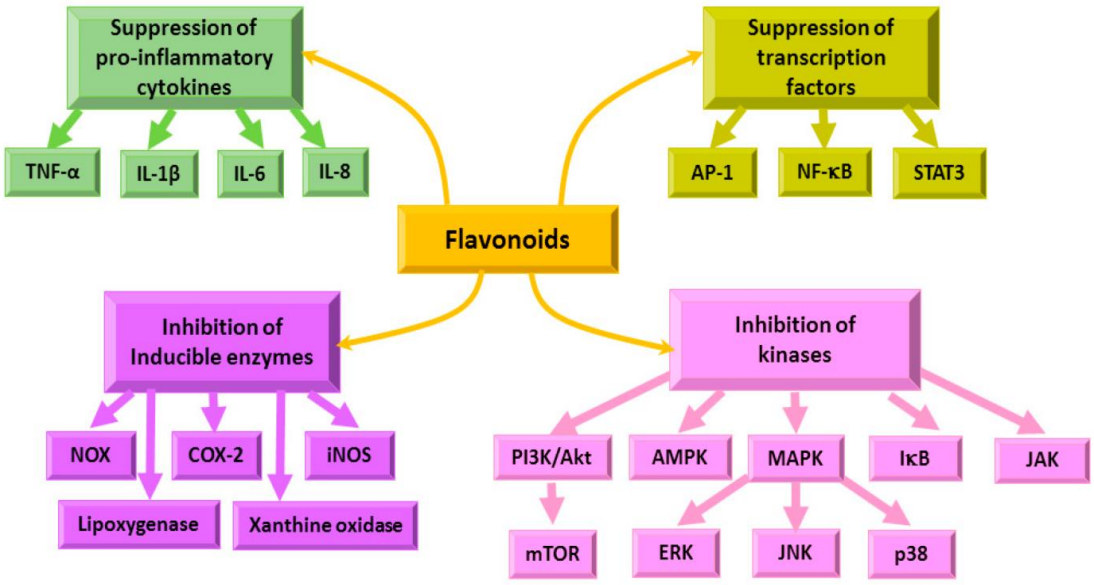

Fig 2: Anticancer mechanism of Action.

Gastrocotyle hispida aerial portions were air dried and utilised for extraction in one study. A flavonoid concentration of 178 mg/g QE was found in the extract. The extract's anticancer efficacy against cell lines representing kidney, liver, and breast cancer was assessed using an in vitro test. According to several research, the reason flavonoids have anticancer properties is because they inhibit protein kinases, which are involved in the regulation of cellular processes. Because of their structural similarities, prenylated chalcone and flavonoids are frequently regarded as analogues of one another. In vitro studies were conducted to examine the possible anticancer properties of prenylflavonoids. The cytotoxicity of four prenylated flavonoids extracted from *Sinopodophyllum hexandrum* fruits against the human breast cancer cell line T47D was recently examined.[27]

Emblica officinalis contains flavonoids that exhibit a variety of pharmacological properties, including antioxidant, anti-inflammatory, anticancer, and immunomodulatory effects. Flavonoids found in berries can help prevent esophageal cancer. The methoxy-flavone exhibited chemopreventive qualities against cancer as well. Cocoa polyphenols have antioxidant, anti-inflammatory, and anticancer properties.

Proanthocyanidin B2, proanthocyanidin B4, and epicatechin—flavonoids that were isolated from litchi—have demonstrated anti-breast cancer properties. Prostate cancer is effectively prevented by soy isoflavons. Lung cancer risk is decreased by flavonoids, which are present in tea along with other foods high in flavonoids like onions, apples, and so on.[28]

In addition to being naturally separated, flavonoids may also be produced in a lab setting utilising various methods. Macgown et al. synthesised new bisflavonoids with the use of a microwave technique, and these compounds shown anticancer efficacy against cell lines of colorectal, breast, and liver cancer. Many flavonoids are being considered for cancer treatment and are in various stages of clinical trials, despite the fact that the bulk of these research on the anticancer properties of multiple flavonoids and related compounds are in the pre-clinical study phase. Icaricin (ICT), for instance, is now in the final phase of a clinical trial intended to treat hepatocellular cancer. Prenylated flavonoids inhibit many receptors, including ERα36, the splice version of the oestrogen receptor, STAT3, NFκB, and CXCR4.[29]

2. Anti-oxidant Potential

The position and quantity of -OH groups in a compound's molecular makeup, conjugation and resonance implications, environmental factors that alter the thermodynamically favoured antioxidant site and a compound's specific antioxidant mechanism are all linked to flavonoids' antioxidant potential. The two antioxidant supplements that are most often utilised are C and E. Compared to vitamins C and E, flavonoids have a stronger antioxidant capacity. Thus, it's critical to consistently eat fruits and vegetables high in flavonoids in your daily diet. For instance, flavonoids promote bone health because of their increased and well-known anti-inflammatory and antioxidant capabilities. There is a lot of promise for bone tissue engineering when using flavonoids in biomaterials.[30]

Citrus fruits and mushrooms contain two flavonoids called hesperetin and hesperidin, which have been shown to have anticancer, anti-inflammatory, antibacterial, and antioxidant properties. Propolis is being utilised in the pharmaceutical business after many years of usage as a folk remedy. Its many constituents, particularly flavonoids, are what give it its pharmacological qualities, which include antibacterial, anti-inflammatory, antioxidant, and anti-proliferative effects. The flavonoid rutin shown several biological properties, such as antioxidant, cytoprotective, and anticancer properties.[31] In vitro, sorghum has strong antioxidant activity. The greatest antioxidants are found in sorghum flavonoids and tannins. These findings indicated that sorghum grains and their byproducts have to be pushed for use in meals.

The small intestine absorbs a considerable amount of sorghum flavonoids. While the grains are unfit for human eating due to their abundance of tannins, alkaline boiling decreases the tannin content by 73%. Consequently, it's crucial to genetically alter sorghum's tannin-producing pathways in order to eliminate tannins from its grains. This crop can thrive in severe environments and is also good for desert situations. The human population worldwide will have access to sorghum grains high in flavonoids in this way.[32] One family of polyphenols with antioxidant properties are called carotenoids. Fisetin is a flavonoid that has both anti-inflammatory and antioxidant properties (3, 3′, 4′, 7-tetrahydroxy flavone). *Eleutherine bulbosa* (Mill.) Urb.'s aerial parts, such as its bulbs, leaves, and flowers, have a high flavonoid quantity and demonstrated antioxidant activity. Onions, Allium cepa L., shown antioxidant properties.The therapeutic aromatic herbs parsley (*Petroselinum crispum* Mill.) and dill (*Anethum graveolens* L.) have phenolic and flavonoid compounds that makes them good antioxidant agents that help prevent ROS-mediated disorders including cancer and cardiovascular problems by reducing ROS species. These molecules have the capacity to act as antioxidants through a variety of methods, such as breaking down peroxides and chelating metal ions that catalyse oxidation. The phenolic (PC) and flavonoid (FC) content are linked to this antioxidant activity; generally speaking, the higher the PC and FC, the higher the antioxidant activity displayed by the herbal plant.[33]

Using sesame (Sesamum indicum) as the initial substance, a Friedel-Crafts reaction produced a unique flavonolignans series by reacting dihydrochalcone, chalcone, flavanone, flavonol, and flavone. Twenty distinct compounds with antioxidant and antidiabetic potential were produced in a single step. DPPH was used to measure the antioxidant activity, and an animal model was used to study the α-glucosidase inhibition. The (−)-flavonol (2R,3R)Cinnamon extract's 5- 7,7-dimethoxy-3′,4′-methylenedioxy-flavan-3-ol stimulates nuclear factor erythroid 2-related factor 2 (Nrf2), an effective oxidative stress-reduction agent.[34]

3. Impacts on the Heart and Circulatory System

Tea consumption lowers the risk of cardiovascular illnesses since it is a high source of flavonoids. Flavonoids such as anthocyanidin and proanthocyanidin have been shown to be beneficial in the treatment of heart conditions. Vascular health is enhanced by isoflavone, anthocyanins, and cocoa flavan-3-ols. Increased intake of these flavonoids lowers arterial stiffness, lowering the risk of cardiovascular illnesses. The sea buckthorn plant, Hippophae rhamnoides, contains a variety of oils from its leaves and fruits, including flavonoids that have been shown to have beneficial benefits on the cardiovascular system. High levels of biological activity, including anti-inflammatory, anti-cancer, and cardiovascular disease prevention, were demonstrated by morin hydrate. Brazil nuts are a great source of flavonoids, which can help prevent cancer and heart disease.A flavone called hrysin has protective

properties for the nervous system, reduces neuro-inflammation, and helps treat depression and epilepsy.[35]

Adult Wister rats were used for the purpose of the study, and the rats were split into three groups: the control group, the intact group, and the group that underwent the experiment. *Primula veris* L. herbal extract was provided to them, whereas a comparable medication was given to the second experimental group.[36] While cardiac contraction rate was calculated digitally, cardiodynamic alterations were ascertained surgically. The enzyme-linked immune-sorption assay (ELISA) was employed to identify the markers associated with CHF. *Primera* L. biological indicators were polymethoxylated flavonoids. Polymethoxylated flavonoids, flavonoid aglycons, and their glycosides were extracted from the extract along with their components. Its cardio-protective action is most likely due to the presence of flavonoids, which also inhibit the formation of peroxide and reduce the creation of ROS. Using animal models, the bioflavonoid morin has demonstrated cardio-protective properties. The rats were split up into categories, and the experimental group received dose-dependent oral administration of morin. After inducing myocardial necrosis, the outcome revealed enhanced antioxidant effects as well as apoptosis. The MAPK/NF-kappa B/TNF-alpha pathway modification was revealed as an explanation responsible for this cardioprotection.[37]

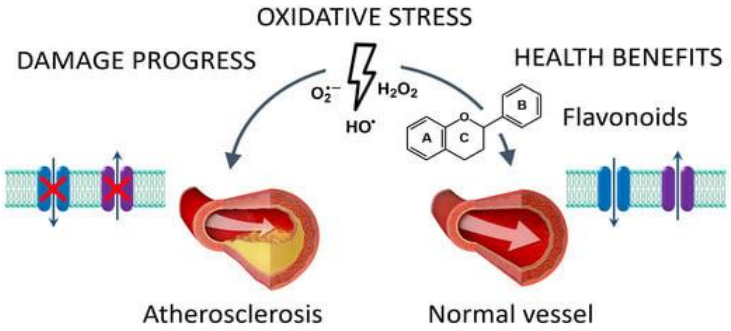

Fig 3: Impacts on the Heart and Circulatory System.

4. Impacts on the Nervous System

Two flavonoids with neuro-pharmacological properties that include neuroprotective, depressive, and memory-enhancing properties are hesperetin (Hst) and esperidin (Hsd). Many naturally occurring flavonoids, including polyphenolic substances like stilbene and anthocyanins, are found in berries. It has been shown that these flavonoids have antibacterial, anti-mutagenic, and anti-neurodegenerative properties. The antioxidant flavonoid epicatechin, which is widely present in wood plants, produces an analogue called 3-O-methyl epicatechin that reduces neurotoxicity in vitro. The polyphenolic flavonoid luteolin contains anti-aging-related neurodegenerative properties as well as neuroprotective properties. Dried fruit and Chinese medicinal herb *Forsythia suspensa* has been shown to have antiviral and neuroprotective properties, in addition to antioxidant activity, when used to treat infectious disorders.[38]

Drinking too much alcohol damages the brain and leads to a number of health problems. When exposed to low concentrations of ethanol, the flavonoid acetylpectolinarin (ACP) derived from *Linaria vulgaris* Mill. has been shown to improve the spontaneous network activity of cultured hippocampus neurons, hence alleviating hangover symptoms. It accomplishes this by acting agonistically on GABAergic synapses through the SK potassium channel.[39]

5. Alzheimer's disease (AD) treatment

Since anthocyanins are effectively incorporated into the amyloid beta fibril groove, their pseudo aromatic ring C contributes to the fibril's structural planarity and facilitates the rupture of amyloid fibrils. In addition, they have the ability to pass the barrier that divides the cerebrospinal fluid from the blood and stop neuron degeneration. Consequently, the anthocyanin subcategory's chemicals may be used as therapeutic agents to treat disorders where oxidative stress plays a role. Thus, anthocyanin cyanidin-3-O-glucoside may have neuroprotective properties. Similarly, Alzheimer's disease and age-associated dementia may benefit from the usage of gangobilobia, another plant high in flavonoids. Human blood plasma contains an enzyme called butyrylcholinesterase.[40]

The *Stachys cretica* extracts reduced melisma, hyperglycemia, Alzheimer's disease, and oxidative stress. The Stachys cretica extract has been shown to contain a variety of phenolic chemicals. The fruits of *Actinidia arguta* contain one anthocyanin, seven flavanols, seven phenolic acids, and six flavonols that can inhibit BChE and AChE. Preclinical research using mouse models have demonstrated the anti-addiction properties of the majority of the aforementioned extracts and pure flavonoids, with extremely positive outcomes. Therefore, it's critical to investigate these flavonoids in clinical studies so that AD sufferers can benefit from them.[41]

6. Preventing Neuropathy

The extract of the root of Cichorium intybus has been prepared using a solution of alcoholic solvent and water. A coenzyme in biological functions, pyridoxine, often known as vitamin B6, damages peripheral neurons when taken in excessive doses. We refer to this phenomenon as neuropathy produced by pyridoxine. Cichorium intybus is a herbal remedy that has flavonoids, saponins, and tannins among other advantageous biochemical components. These chemicals' ability to decrease oxidative stress allows them to potentially interact with the GABAergic and glutamatergic amino acid systems, which are involved in nerve damage and neuropathy.[42]

Hesperidin and flavanoglycone have been investigated tested for their effects on DN pain brought on by streptozotocin in adult Sprague-Dawley rats. The animals were primarily split into two groups: those with diabetes and those without it. Following the experiment, the blood serum of the employed animals was tested for several parameters such as cholesterol and insulin levels, and the animals who were slain had their sciatic nerves removed shortly before they were subjected to biochemical and molecular investigations. At the conclusion of week 8, there was a dose-dependent decrease in the treated rats' body weight ($p < 0.05$). Compared to the control group, there was an observed elevation in the plasma glucose level. Hesperidin and insulin together significantly reduced neuropathic pain, resulting in a neuroprotective effect.[43]

Two groups of thirty rats each—one for diabetic neuropathy and the other for control—were created. The diabetic neuropathy group was fed a high-fat meal during the three-week experiment, whereas the control group received a diet consisting of pellets. Insulin resistance was verified by the glucose intolerance test once the trial was completed. A dose-dependent injection of streptozotocin was then administered. The diabetic rats were once more divided into control and FRFHI fed rats ten days later. After taking the extract orally for a further three weeks, the diabetic neuropathy was evaluated using body weight, biochemical markers, and behavioural markers such the walking test, temperature, motion, and cold tolerance.[44]

7. **Antimalarial Properties**

Plants of the genus Prosopis have long been utilised for therapeutic reasons. Among its constituents include alkaloids, flavonoids, and tannins. These bioactive substances have antibacterial, antimalarial, and antiulcer properties. Psiadia species extract contains terpenoids, phenylpropanoids, coumarins, and flavonoids. It has pharmacological properties include antiviral, antibacterial, antimalarial, and anti-inflammatory properties. Certain plant extracts, such those from *Psiadia dentata* and *Psiadia arguta*, stop Plasmodium falciparum from growing. Extract from Waltheria indica (syn. *Waltheria americana*) contains flavonoids, epicatechin (−) kaempferol, quercetin, sterols, and other compounds. It is used to cure inflammation, reduce oxidative stress, and treat infections such as diarrhoea caused by Escherichia coli and lung infections caused by *Klebsiella pneumoniae*. It is also employed for treating malaria. Digofera oblongifolia leaf extract has noteworthy anti-malarial properties and provides antioxidant and anti-inflammatory benefits to shield the liver from P. chabaudi-induced liver damage.[45,46]

8. Antiviral Actions

Houttuynia cordata Eastern Asian plants called thunb have demonstrated antiviral properties in vitro against enveloped viruses including the influenza virus, herpes simplex virus-1, and human immunodeficiency virus-1. Flavonoids, both synthetic and natural, have the potential to treat a wide range of illnesses, including HIV. Two flavonoids, glabranine and 7-O-methyl-glabranine, were isolated from the Tephrosia madrensis plant in Mexico. The results of the plaque assay verified that these isolates had antiviral properties and prevent the dengue virus from replicating. After spectroscopically determining the isolates' structures, the [3H]-thymidine test was used to assess the stoichiometry and cytotoxicity of the samples.[47]

Daidzein and murine norovirus are reduced by epicatechin 3-gallate, fisetin, quercetin, and kaempferol, whereas feline calicivirus is reduced by kaempferol. Four flavonoids that were isolated from Mosla scabra—5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-6,7-dimethoxyflavone, acacetin, and apigenin—show antiviral action against influenza viruses. The bioactive phytoconstituents found in Castanea crenata burs (involucre)—which include flavonoids, tannins, phenolic acids, coumarins, phenylpropanoids, and steroids—are responsible for a variety of biological activity. Using HeLa or Vero cells and the cytopathic effect (CPE) reduction test, the SRB technique was used to assess the extract's antiviral efficacy. Kaempferol, the isolated flavonoid, exhibited improved antiviral capabilities against PR8, CVB3, and HRV1B.[48]

9. Antimicrobial Activity

A plant genus in the Phyllanthaceae family called Bridelia is used as a painkiller in South Africa and Asia. Flavonoids such as isoflavone, myricetin-3-glycosides, gallocatechin-(4′-O-7)-epigallocatechin, and quercetin are present in its extract. Its antibacterial, anti-inflammatory, and antimalarial properties are attributed to these flavonoids. Anthocyanidin is effective against drug-resistant strains of Mycobacterium TB and tuberculosis. Research has indicated that two flavonoids with excellent antibacterial action are hesperetin and hesperidin. Numerous biological activity of Cuscuta flavonoids, such as antiproliferative, hepatoprotective, anxiolytic, and antibacterial properties, have been documented. Tyrosinase inhibitors and antimicrobials can be found naturally in Turbina corymbose. There is a wealth of research on plants high in flavonoids that have antibacterial properties, including the flowers of Acacia

saligna (Labill.), the roots, and the aerial extract of *Lamium album*.[49]

10. Antifungal Characteristics

Two flavonoids, sacriflavone A and sacriflavone B, are present in the extract of Artemisia sacrorum, and they both possess antifungal properties. Furthermore, a naturally occurring prenyl flavonoid isolated from Dalea elegans, 2′,4′-dihydroxy-5′-(1‴,1‴-dimethylallyl)-8-prenylpinocembrin (8PP), has antifungal properties against Candida albicans biofilms.[50]

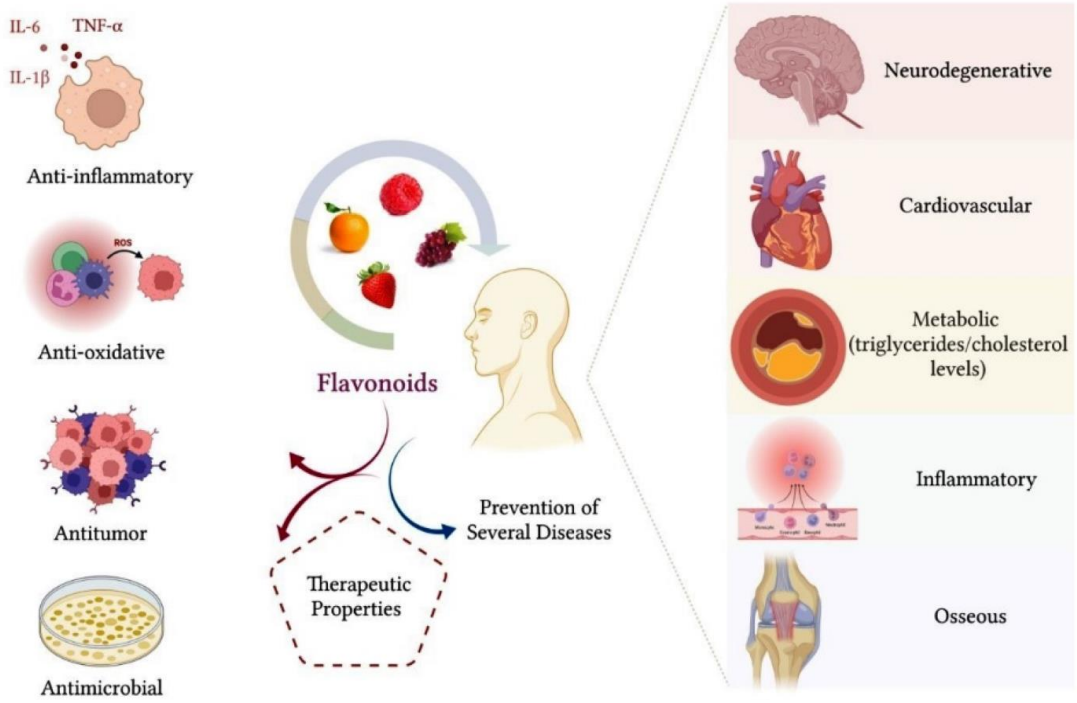

Fig 4: Flavonoids Pharmacological Potential.

AMANLGAMATION OF FLAVONOIDS AND NANOPARTICLES

Nanocarriers have the potential to increase flavonoid bioavailability. Flavonoid nanoparticles have demonstrated potential anticancer efficacy against A549 lung cancer cells, B16F10 melanoma cells, MCF-7 breast cancer cells, HepG2 liver cancer cells, or CT26 colorectal cancer cells in both in vitro and in vivo experiments.

1. EGCG, or epigallocatechin-3-gallate

In this work, polylactic acid-polyethylene glycol (PLA-PEG) containing EGCG nanoparticles enclosed was utilised. When compared to free EGCG, these nanoparticles were found to be more than ten times more efficient against 22Rr1 prostate cancer cells. Utilising PLA-PEG nanoparticles may help to reduce EGCG's toxicity and increase its bioavailability. Injection EGCG PLA-PEG nanoparticles enhance the pharmacokinetics and pharmacological characteristics of this flavonoid while reducing carrier-induced undesired cytotoxicity. These encouraging outcomes have sparked research regarding additional flavonoids and nanoparticles that may be useful in the treatment of cancer. Gold nanoparticles coupled with EGCG are another example.[51]

Because of their tiny size, non-toxicity, and immunogenicity, which allow them to cross natural barriers in the body of humans and regulate the release of medications at different sites, gold nanoparticles have been shown to be effective in the treatment of cancer. Moreover, radiation sensitization and imaging are the two principal applications for gold nanoparticles. EGCG was physically affixed to the surface of nanogold particles in the Hsieh et al. investigation. Subcutaneous implantation of MBT-2 murine bladder tumour cells in mice resulted in death of the cancer cells, which inhibited their growth. Subsequent research on EGCG gold nanoparticles injected into tumours similarly verified a noteworthy decrease in tumour development in B16F10 melanoma cells and PC-3 prostate cells.[52]

In recent Siddiqui et al. research, Mel928 melanoma cells underwent apoptosis due to EGCG-encapsulated chitosan. Mucoadhesive characteristics define chitosan nanoparticles. Chitosan nanoparticle-encapsulated flavonoids stick to the gastrointestinal system longer after oral delivery, which results in a prolonged release of the medication. On prostate cancer cells, more study was done. When compared to free EGCG, oral treatment of chitosan-based EGCG dramatically reduced the development of prostate cancer cells in a xenograft model. The EGCG-loaded folic acid-poly(ethylene glycol)-FA-PEG nanoparticles and EGCG-encapsulated

chitosan-coated nanoliposomes (CALIPPO) suppressed MCF-7 breast cancer cells and caused apoptosis in the in vitro system.[53]

2. Quercetin

PEG, PLA, and poly(lactic co-glycolic acid) nanoparticles (PLGA) are the most often utilised nanoparticles containing quercetin. PEG nanoparticles have been shown to improve quercetin's solubility and stability while also extending the amount of time it spends in circulation in the blood. According to Tan et al.'s study, quercetin's anticancer efficacy was enhanced by PEG-derivatized phosphatidylethanolamine nanomicelles. It has been shown that these nanoparticles outperformed free quercetin in their ability to inhibit A549 lung cancer cells. In a different research, Xing et al. demonstrated that in A459, MCF-7, and HepG2 cancer cells, de-PEGylated nanoparticles based on triphenylphosphine-quercetin (TPP-PEG) were more potent therapeutic agents than pure quercetin.[54]

In a comparable manner it was possible to suppress the angiogenesis of ovarian cancer by using PEG-liposomal nanoparticles loaded with quercetin. The 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethylene glycol) (DSPE-MPEG) is an effective adjuvant nanocarrier for anticancer drug delivery, according to a research by Zhao et al. There have been several studies demonstrating the use of PLGA-loaded quercetin nanoparticles in the treatment of hepatocellular carcinoma. The PLGA nanoparticles coated with quercetin in the Ghosh et al. study fully shielded the liver's mitochondrial membrane against diethylnitrosamine-induced malignancy. PLGA nanoparticles loaded with quercetin and tamoxifen (TMX) inhibited tumour angiogenesis in MCF-7 breast cancer cells following oral treatment.[55]

PLA nanoparticles have been demonstrated to suppress the formation of hepatocellular carcinoma in a different investigation (Mandal et al.). In hepatocellular cells, the gold-quercetin in PLA nanoparticles inhibited the caspase/Cyto-c pathway. Poly-lactic acid nanoparticles have been proven to exhibit anticancer properties against A549 lung cancer cells, according to a research by da Luz et al.

3. Genistein

While genistein-loaded M-PLGA-TPGS (poly(d,l-lactide-co-glycolide)-d-α-tocopheryl polyethylene glycol 1000 succinate) demonstrated a linear apoptotic effect against HepG2 liver cancer cells, genistein-loaded TPGS-b-PCL (d-α-tocopheryl polyethylene glycol 1000 succinate-poly(ε-caprolactone)) inhibited the growth of HeLa cervical tumour cells and had a higher level of cytotoxicity compared to genistein-loaded PCL nanoparticles. Sadly, the increased genistein bioavailability brought about by the use of nanoparticles is linked to significant damage in normal cells. In vitro studies were conducted on colon cancer HT29 cells with genistein-loaded PEGylated silica hybrid nanomaterials, lung cancer A549 cells with genistein-miRNA-29b-loaded hybrid nanoparticles-GMLHN, and hematopoietic cancer cells with genistein-carboxymethylated chitosan nanoparticles-Fe3O4-CMC to investigate the anticancer activity (apoptosis and autophagy of cancer cells).[55]

4. Silibinin

Xu et al.'s work on silibinin nanoparticles explained how they affect cancer cells and prevent breast cancer from spreading. These TPGS and phosphatidylcholine-containing silibinin-loaded lipid nanoparticles (SLNs) were created and made using a thin-film hydration technique.[66] In a different research (Gohulkumar et al.), oral carcinoma cells treated with silibinin encapsulated in PVA-Eudragit nanoparticles shown antitumor effectiveness. A different research demonstrated the cytotoxic effects of silibinin encapsulated in PEG nanoparticles on breast cancer (MCF 10A) in vitro. Limited solubility and insufficient dissolution of free silibinin result in limited oral bioavailability.[56]

According to the Sahibzada et al. investigation, there are two ways to produce silibinin nanoparticles that enhance its solubility and might be used as an oral cancer therapy drug: APSP, or anti-solvent precipitation with a syringe pump, and EPN, or evaporative precipitation of nanosuspension. According to Huo et al., silibinin and paclitaxel (PTX) loaded dextran-deoxycholic acid (Dex-DOCA) nanoparticles may be used in combination treatment to effectively aggregate in cancer areas by passive targeting and reduce tumour development in mice by improving intratumoral penetration. In a different research, 4T1 breast cancer cells were suppressed by silibinin and IPI-549 nanoparticles (AEAA-PEG-PCL, aminoethyl anisamide-polyethylene glycol-polycaprolactone), which resulted in alterations in the tumour microenvironment.[57]

5. Apigenin

Nowadays, PLGA nanoparticles are widely utilised to increase the bioavailability of flavonoids. Apigenin loaded in PLGA nanoparticles had an anti-proliferative impact on A475 skin cancer cells, according to a research by Das et al. The fact that these nanoparticles were successful in sustaining photodegradation under UV light should be emphasised. Additional research on apigenin encapsulated in PLGA nanoparticles shown that this molecule was successfully administered intravenously to HepG2 and Huh-7 cells in vitro, as well as the liver of animals prone to cancer, and it also prevented the formation of hepatocellular carcinoma in rats. Recently, new materials have been studied that improve apigenin's solubility and bioavailability by preparing solid dispersions of mesoporous silica nanoparticles.[58]

CONCLUSION

Flavonoids are compounds are naturally occurring groupings of different substances that are present in a

wide variety of plants, including fruits, vegetables, and plant-based foods like tea, coffee, and chocolate. Numerous reports have indicated that flavonoids provide an extensive array of health advantages. Flavonoids, for instance, are abundant in antioxidants that provide our bodies built-in defences against endogenous poisons and the everyday environment. Thus far, multiple groups of flavonoids have been identified that exhibit numerous noteworthy biological properties, including anti-inflammatory, anti-cancer, antibacterial, antifungal, anti-diabetic, antimalarial, and cardio-protective properties. Therefore, it is strongly advised to incorporate various forms of flavonoids into one's diet on a daily basis in order to maintain good health and lessen the chance of developing several serious illnesses, including diabetes mellitus, cancer, stroke, and heart attack.

Preclinical research conducted on mouse models have overwhelmingly demonstrated the therapeutic benefits of flavonoids. In order to avoid compromising the absorption and bioavailability of flavonoids, distinct methodologies have to be employed in clinical studies. Enzymes from their biosynthetic pathway should be expressed in other plants and species that grow quickly in order to boost their output. Because flavonoids have a wide range of applications in health and well-being, funding bodies ought to support research on them. Moreover, flavonoid conjugates with other significant medications may increase the efficacy of such substances. In order to unravel the structures of more flavonoids and explore their potential medicinal uses, more study is unquestionably required. Research on the structures of flavonoids continues to be inspiring for the creation and synthesis of novel, potent medications for a variety of illnesses.

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REFERENCES

1. Saleh HA, El-Nashar YI, Serag-El-Din MF, Dewir YH. Plant growth, yield and bioactive compounds of two culinary herbs as affected by substrate type. Scientia horticulturae, Jan. 3, 2019; 243: 464-71.
2. Lago JH, Toledo-Arruda AC, Mernak M, Barrosa KH, Martins MA, Tibério IF, Prado CM. Structure-activity association of flavonoids in lung diseases. Molecules, Mar. 24, 2014; 19(3): 3570-95.
3. Xie Y, Yang W, Tang F, Chen X, Ren L. Antibacterial activities of flavonoids: structure-activity relationship and mechanism. Current medicinal chemistry, Jan. 1, 2015; 22(1): 132-49.
4. Krishna S, Chandrasekaran S, Dhanasekar D, Perumal A. GCMS analysis, antioxidant and antibacterial activities of ethanol extract of Anisomeles malabarica (L.) R. Br. ex. Sims leaves. Asian J. Pharm. Pharmacol, 2019; 5: 180-7.
5. Fidelis QC, Ribeiro TA, Araújo MF, de Carvalho MG. Ouratea genus: chemical and pharmacological aspects. Revista Brasileira de Farmacognosia, Jan. 1, 2014; 24(1): 1-9.
6. Harborne JB. The flavonoids: advances in research since, 1980.
7. Grotewold E. The science of flavonoids, 2006.
8. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacology & therapeutics, Nov. 1, 2002; 96(2-3): 67-202.
9. Cushnie TT, Lamb AJ. Antimicrobial activity of flavonoids. International journal of antimicrobial agents, Nov. 1, 2005; 26(5): 343-56.
10. Birt DF, Jeffery E. Flavonoids. Advances in Nutrition, Sep., 2013; 4(5): 576-7.
11. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. The scientific world journal, Oct. 7, 2013; 2013.
12. Andersen OM, Markham KR, editors. Flavonoids: chemistry, biochemistry and applications. CRC press, 2005 Dec 9.
13. Yao LH, Jiang YM, Shi J, Tomas-Barberan FA, Datta N, Singanusong R, Chen SS. Flavonoids in food and their health benefits. Plant foods for human nutrition, Jul., 2004; 59: 113-22.
14. Marais JP, Deavours BE, Dixon RA, Ferreira D. The stereochemistry of flavonoids. The science of flavonoids, 2006; 1-46.
15. Barron D, Ibrahim RK. Isoprenylated flavonoids—a survey. Phytochemistry, Nov. 1, 1996; 43(5): 921-82.
16. McClure JW. Physiology and functions of flavonoids. InThe flavonoids, 1975; 970-1055. Boston, MA: Springer US.
17. Holiman PC, Hertog MG, Katan MB. Analysis and health effects of flavonoids. Food chemistry, Sep. 1, 1996; 57(1): 43-6.
18. Rice-Evans CA, Packer L, editors. Flavonoids in health and disease. CRC Press, 2003 May 20.
19. Samanta A, Das G, Das SK. Roles of flavonoids in plants. Carbon, 2011; 100(6): 12-35.
20. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. Food chemistry, Nov. 30, 2019; 299: 125124.
21. Ielpo MT, Basile A, Miranda R, Moscatiello V, Nappo C, Sorbo S, Laghi E, Ricciardi MM, Ricciardi L, Vuotto ML. Immunopharmacological properties of flavonoids. Fitoterapia, Aug. 1, 2000; 71: S101-9.

22. Treutter D. Significance of flavonoids in plant resistance: a review. Environmental Chemistry Letters, Aug., 2006; 4(3): 147-57.
23. Ciumărnean L, Milaciu MV, Runcan O, Vesa ȘC, Răchișan AL, Negrean V, Perné MG, Donca VI, Alexescu TG, Para I, Dogaru G. The effects of flavonoids in cardiovascular diseases. Molecules, Sep. 21, 2020; 25(18): 4320.
24. Miura YH, Tomita I, Watanabe T, HIRAYAMA T, Fukui S. Active oxygens generation by flavonoids. Biological and Pharmaceutical Bulletin, Feb. 15, 1998; 21(2): 93-6.
25. Buer CS, Imin N, Djordjevic MA. Flavonoids: new roles for old molecules. Journal of integrative plant biology, Jan., 2010; 52(1): 98-111.
26. Rufino AT, Costa VM, Carvalho F, Fernandes E. Flavonoids as antiobesity agents: A review. Medicinal Research Reviews, Jan., 2021; 41(1): 556-85.
27. Jäger AK, Saaby L. Flavonoids and the CNS. Molecules, Feb. 10, 2011; 16(2): 1471-85.
28. Erdman Jr JW, Balentine D, Arab L, Beecher G, Dwyer JT, Folts J, Harnly J, Hollman P, Keen CL, Mazza G, Messina M. Flavonoids and heart health: proceedings of the ILSI North America flavonoids workshop, May 31–June 1, 2005, Washington, DC. The Journal of nutrition, Mar. 1, 2007; 137(3): 718S-37S.
29. Cotelle N. Role of flavonoids in oxidative stress. Current topics in medicinal chemistry, Dec. 1, 2001; 1(6): 569-90.
30. Kanadaswami C, Lee LT, Lee PP, Hwang JJ, Ke FC, Huang YT, Lee MT. The antitumor activities of flavonoids. In vivo, Sep 1, 2005; 19(5): 895-909.
31. Nijveldt RJ, Van Nood EL, Van Hoorn DE, Boelens PG, Van Norren K, Van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. The American journal of clinical nutrition, Oct. 1, 2001; 74(4): 418-25.
32. Van Acker SA, Tromp MN, Griffioen DH, Van Bennekom WP, Van Der Vijgh WJ, Bast A. Structural aspects of antioxidant activity of flavonoids. Free radical biology and medicine, Jan 1, 1996; 20(3): 331-42.
33. Saija A, Scalese M, Lanza M, Marzullo D, Bonina F, Castelli F. Flavonoids as antioxidant agents: importance of their interaction with biomembranes. Free Radical Biology and Medicine, Oct. 1, 1995; 19(4): 481-6.
34. Javadi F, Ahmadzadeh A, Eghtesadi S, Aryaeian N, Zabihiyeganeh M, Rahimi Foroushani A, Jazayeri S. The effect of quercetin on inflammatory factors and clinical symptoms in women with rheumatoid arthritis: a double-blind, randomized controlled trial. Journal of the American college of nutrition, Jan. 2, 2017; 36(1): 9-15.
35. Arman Ahmadzadeh MD, Mozhdeh Zabihiyeganeh MD, Rahimi A, Shima Jazayeri MD. The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial.
36. Bonner MR, Rothman N, Mumford JL, He X, Shen M, Welch R, Yeager M, Chanock S, Caporaso N, Lan Q. Green tea consumption, genetic susceptibility, PAH-rich smoky coal, and the risk of lung cancer. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Apr. 4., 2005; 582(1-2): 53-60.
37. Ohno Y, Wakai K, Genka K, Ohmine K, Kawamura T, Tamakoshi A, Aoki R, Senda M, Hayashi Y, Nagao K, Fukutna S. Tea consumption and lung cancer risk: a case-control study in Okinawa, Japan. Japanese journal of cancer research, Nov., 1995; 86(11): 1027-34.
38. Ohno Y, Wakai K, Genka K, Ohmine K, Kawamura T, Tamakoshi A. Tea consumption and lung cancer risk: A case-control study in Okinawa, Japan. Lung Cancer, 1996; 2(14): 377.
39. Imam SS, Agarwal S. A Pragmatic Approach To Treat Lung Cancer Through Loading Theaflavin - 3,3'-Digallate And Epigallocatechin Gallate In Spanlastic. Asian J Pharm Clin Res., Nov. 7, 2021; 14(11): 1-8.
40. Imam SS. The future of non-invasive ways to treat cancer. Int J Pharm Sci & Res., 2021; 12(8): 4684-96.
41. Imam SS, Imam ST, Mdwasifathar, Kumar R, Ammar MY. Interaction Between Ace 2 And Sars-Cov2, And Use Of EGCG And Theaflavin To Treat Covid 19 In Initial Phases. International Journal of Current Pharmaceutical Research, Mar, 2022; 14(2): 5-10.
42. Imam SS, Sharma R. Natural compounds promising way to treat Lung Cancer. International Journal of Pharmaceutical Research and Applications, 2023; 8(2): 552-558.
43. Imam SS, Sharma S, Kumari D, Khan S, Pathak P, Katiyar D. An Expedient Approach to Treat Asthma through Non-Steroidal, Natural Transferosomes Aerosol System. Innovare journal of medical sciences, 2022; 10(6): 7-11.
44. Imam SS, Imam ST, Agarwal S, Kumar R, Ammar MY, Athar MW, Akthar A. Lung Cancer Therapy Using Naturally Occurring Products and Nanotechnology. Innovare journal of medical sciences, 2022; 10(4): 1-5.
45. Imam ST, Imam SS. The Cream which relieves the pain of Menstrual cramps without interfering with the Hormones or Period Cycle. Research Journal of Pharmacy and Technology, 2023; 16(3): 1239-6.
46. Imam SS. Topical Formulation Constituted with Transferosomes for the Treatment Of Non-Melanoma Skin Cancer. Asian J Pharm Clin Res., May. 7, 2023; 16(5): 27-32.
47. Awan FT, Jones JA, Maddocks K, Poi M, Grever MR, Johnson A, Byrd JC, Andritsos LA. A phase 1 clinical trial of flavopiridol consolidation in chronic lymphocytic leukemia patients following

chemoimmunotherapy. Annals of hematology, Jun., 2016; 95: 1137-43.
48. Cisár P, Jány R, Waczulíková I, Sumegová K, Muchová J, Vojtaššák J, Ďuračková Z, Lisý M, Rohdewald P. Effect of pine bark extract (Pycnogenol®) on symptoms of knee osteoarthritis. Phytotherapy Research, Aug., 2008; 22(8): 1087-92.
49. Bogdanski P, Suliburska J, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. Nutrition research, Jun. 1, 2012; 32(6): 421-7.
50. Cospite M. Double-blind, placebo-controlled evaluation of clinical activity and safety of Daflon 500 mg in the treatment of acute hemorrhoids. Angiology, Jun. 2, 1994; 45.
51. Rizza S, Muniyappa R, Iantorno M, Kim JA, Chen H, Pullikotil P, Senese N, Tesauro M, Lauro D, Cardillo C, Quon MJ. Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. The Journal of Clinical Endocrinology & Metabolism, May. 1, 2011; 96(5): E782-92.
52. Zern TL, Wood RJ, Greene C, West KL, Liu Y, Aggarwal D, Shachter NS, Fernandez ML. Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. The Journal of nutrition, Aug. 1, 2005; 135(8): 1911-7.
53. Ji X, Wei X, Qian J, Mo X, Kai G, An F, Lu Y. 2′, 4′-Dihydroxy-6′-methoxy-3′, 5′-dimethylchalcone induced apoptosis and G1 cell cycle arrest through PI3K/AKT pathway in BEL-7402/5-FU cells. Food and Chemical Toxicology, Sep. 1, 2019; 131: 110533.
54. Zhang Y, Chen S, Wei C, Rankin GO, Ye X, Chen YC. Flavonoids from Chinese bayberry leaves induced apoptosis and G1 cell cycle arrest via Erk pathway in ovarian cancer cells. European journal of medicinal chemistry, Mar. 10, 2018; 147: 218-26.
55. Kabala-Dzik A, Rzepecka-Stojko A, Kubina R, Iriti M, Wojtyczka RD, Buszman E, Stojko J. Flavonoids, bioactive components of propolis, exhibit cytotoxic activity and induce cell cycle arrest and apoptosis in human breast cancer cells MDA-MB-231 and MCF-7: A comparative study. Cellular and Molecular Biology, 2018; 64(8): 1-0.
56. Lin Z, Lin Y, Shen J, Jiang M, Hou Y. Flavonoids in Ageratum conyzoides L. Exert potent antitumor effects on human cervical adenocarcinoma HeLa cells in vitro and in vivo. BioMed Research International, May 4, 2020.
57. Kubatka P, Mazurakova A, Samec M, Koklesova L, Zhai K, Al-Ishaq R, Kajo K, Biringer K, Vybohova D, Brockmueller A, Pec M. Flavonoids against non-physiologic inflammation attributed to cancer initiation, development, and progression—3PM pathways. Epma Journal, Dec. 1, 2021: 1-29.
58. Kwon KH, Murakami A, Tanaka T, Ohigashi H. Dietary rutin, but not its aglycone quercetin, ameliorates dextran sulfate sodium-induced experimental colitis in mice: attenuation of pro-inflammatory gene expression. Biochemical pharmacology, Feb. 1, 2005; 69(3): 395-406.