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REVIEW ON THE PROPERTIES OF APIGENIN FLAVONOID

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ABSTRACT

Flavonoids are phenolic compounds found in fruits, vegetables, cereals, bark, roots, stems, flowers, tea, and wine. These natural products are well-known for their health-promoting properties, and researchers are working to extract the active compounds known as flavonoids. Flavonoids are currently widely used in nutraceutical, pharmacological, medical, and cosmetic products. Apigenin is a flavonoid with low toxicity and a variety of bioactivities. The pharmacokinetics, cancer chemoprevention, and apigenin drug interactions have been published using eukaryotic cells, animal models, or epidemiological research. The present review mainly focuses on the overview of various properties of apigenin flavonoids.

KEYWORDS

Flavonoids, Apigenin, Nutraceuticals and Cosmetics.

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INTRODUCTON

Flavonoids are a natural product that belongs to a group of plant secondary metabolites with a polyphenolic structure that can be found in various fruits, vegetables, and drinks[1]. They have a variety of beneficial biochemical and antioxidant properties that have been linked to diseases like cancer, Alzheimer's disease (AD), atherosclerosis, and others. Flavonoids are essential in several nutraceuticals, pharmacological, medical, and cosmetic uses because they have a wide range of health-promoting benefits. Flavonoids possess various antioxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic capabilities in combination with their anti-inflammatory, anti-mutagenic and anti-carcinogenic qualities.

Flavonoid chemicals are plant-derived molecules that can be found in various areas of the plant in nature. Vegetables need flavonoids to help them thrive and protect themselves against plaque. They are phenolic chemicals with a low molecular weight that are found throughout the plant kingdom. They are one of the most distinctive types of chemicals found in higher plants. In most angiosperm families, several flavonoids are easily recognized as floral pigments. Their presence, however, is not limited to flowers; they can be found in other parts of plants. Flavonoids are prevalent in plant-based meals and beverages such as fruits, vegetables, tea, and cocoa.

Plants, animals, and microorganisms all use flavonoids for a range of biological functions. Flavonoids have long been known to be synthesized in specific locations in plants. They are responsible for the color and aroma of flowers, as well as the color and aroma of fruits, which attract pollinators and, as a result, fruit dispersion, which aids in seed and spore germination, as well as the growth and development of seedlings[2]. Flavonoids are signal molecules, allopathic compounds, phytoalexins, detoxifying agents, and antimicrobial defensive compounds that protect plants from various biotic and abiotic stresses and act as unique UV filters. They also function as signal molecules, allopathic compounds, phytoalexins, detoxifying agents, and antimicrobial defensive compounds. Flavonoids may play a functional role in frost hardiness and drought resistance.

Classification

The carbon of the C ring on which the B ring is bonded and the degree of unsaturation and oxidation of the C ring can separate flavonoids into various subgroups. Isoflavones are flavonoids in which the B ring is connected in position 3 of the C ring[3]. Neoflavonoids are those in which the B ring is joined in position 4; those in which the B ring is linked in position two can be further split into numerous subgroups based on the structural properties of the C ring[4]. The subgroups are flavones, flavonols, flavanones, flavanols or catechins, anthocyanins and chalcones.

Flavones

Flavones are one of the most important flavonoid subclasses. Flavones are found as glycosides in leaves, flowers, and fruits. Flavones can be found in celery, parsley, red peppers, chamomile, mint, and ginkgo Biloba. This group of flavonoids includes luteolin, apigenin, and tangeritin. The polymethoxylated flavones tageretin, nobiletin, and sinensetin are abundant in citrus fruit peels. They have a double bond between positions 2 and 3 of the C ring and a ketone in position 4. At position 5 of the A ring, the hydroxyl group is found in most flavones from vegetables and fruits. In contrast, hydroxylation in other positions, primarily in position 7 of the A ring, is found in the minority.

Flavanols

Flavonoids with a ketone group are known as flavonols. Proanthocyanins are made up of these basic units. Flavonols can be found in abundance in a wide range of fruits and vegetables. Kaempferol, quercetin, myricetin, and fisetin are the most studied flavonols[5]. Flavonol consumption has been linked to various health advantages, including antioxidant potential and a lower risk of vascular disease.

Flavanones

Flavanones are another important class of compounds found in citrus fruits, including oranges, lemons, and grapes. This group of flavonoids includes hesperetin, naringenin, and eriodictyol. Because of their free radical-scavenging characteristics, flavanones are linked to various health advantages[6]. Citrus fruit juice and peel contain these chemicals, which give them a bitter taste. Citrus flavonoids have pharmacological actions that include antioxidant, anti-inflammatory, blood lipid-lowering, and cholesterol-lowering[7]. Because the C ring of flavanones, also known as dihydroflavones, is saturated, unlike flavones, the double bond between positions two a and 2 b is broken.

Isoflavonols

Flavonoids are divided into isoflavonoids, which constitute a big and separate subgroup. Isoflavonoids are found mostly in soybeans and other leguminous plants and have a limited distribution in the plant kingdom. Microbes have also been shown to contain certain isoflavonoids[8]. During plant-microbe interactions, they are also discovered to play a significant function as precursors for the formation of phytoalexins. Isoflavonoids have much potential in terms of

fighting illnesses. Because of their oestrogenic action in animal models, isoflavones like genistein and daidzein are widely classified as Phyto-oestrogens. Szkudelska and Nogowski examined the impact.

Neoflavonoids

Polyphenolic substances known as neoflavonoids are a type of polyphenol. Neoflavonoids contain a 4-phenylchromen backbone with no hydroxyl group substitution at position 2, whereas flavonoids have a 2-phenylchromen-4-one backbone[9]. Calophyllolide, derived from Calophyllum inophyllum seeds, was the first neoflavone discovered from natural sources in 1951. It can also be found in the bark and wood of the endemic Sri Lankan plant Mesua thwaites.

Anthocyanins

Anthocyanins are pigments that give plants, flowers, and fruits their colors. The most studied anthocyanins are cyanidin, delphinidin, malvidin, pelargonidin and peonidin. They are mostly found in the outer cell layers of cranberries, black currants, red grapes, merlot grapes, raspberries, strawberries, blueberries, bilberries, and blackberries, among other fruits[10]. These compounds' stability, combined with their health benefits, allows them to be used in a range of applications in the food business. The anthocyanin's color is affected by pH and methylation or acylation of the hydroxyl groups on the A and B rings.

Chalcones

The flavonoids known as chalcones are a kind of flavonoid. The absence of 'ring C' of the basic flavonoid skeleton structure distinguishes them. As a result, open-chain flavonoids are another name for them[11]. Phloridzin, arbutin, phloretin, and chalconaringenin are only a few examples of chalcones[12]. Because of their multiple nutritional and biological benefits, chalcones and their derivatives have received much attention. Food sources for all of the dietary flavonoids covered in this paper in terms of bioactivity and research trends.

Apigenin

Apigenin (4′, 5, 7-trihydroxyflavone), a natural substance in many plants and the aglycone of various naturally occurring glycosides, belongs to the flavone class. It is a yellow crystalline solid that's been used to dye wool for centuries`. This review is mainly focusing on the various properties and applications of apigenin.

Apigenin is a unique ingredient in chamomile (Matricaria chamomilla), an annual herb native to western Asia and Europe. It is derived from the Apium genus in the Apiaceae family, often known as Umbelliferae[13]. Apigenin levels in chamomile drinks range from 0.8 percent to 1.2 percent. Apigenin can also be found in a variety of different foods, such as celery seeds (78.65mg/100g), spinach (62.0mg/100g), parsley (45.04mg/100g), marjoram (4.40mg/100g), Italian oregano (3.5mg/100g), sage (2.40 mg/100g), chamomile (3 to 5mg/100g), and pistachio (0.03mg/100).

Apigenin can be found in a wide range of foods, including fruits and vegetables. Parsley, chamomile, celery, vine-spinach, artichokes, and oregano are the finest sources of apigenin, with dried forms being the richest[14]. Apigenin is a flavone found naturally in several plants. Apigenin, naringenin, luteolin, tangeritin and baicalein are examples of natural flavones with various biological roles. Apigenin can be found in abundance in a variety of fruits and vegetables.

Apigenin can be found in various fruits and vegetables, but the most common sources are parsley, celery, celeriac, and chamomile tea. Apigenin, which accounts for 68 percent of total flavonoids in chamomile flowers, is particularly plentiful. Apigenin can be found in dried parsley at 45mg/grams and dried chamomile flower at 3-5mg/gram. Fresh parsley has an apigenin level of 215.5mg/100 grams, which is substantially greater than the next highest food source, green celery hearts, which has 19.1mg/100 grams. This key ingredient in chamomile tea has been used to relieve anxiety and stress[14]. We look into whether scientific research backs up this ancient practice and how it relates to aging.

Apigenin chemistry

Flavonoids are a type of phytochemical found in practically all plant tissues, where they serve a variety of activities. They protect plants from harmful sunlight, defend against infections and herbivory, regulate plant metabolism, and serve as aesthetic attractants for pollinators, among other things. Flavonoids are made up of over 6000 distinct chemicals that have been identified so far.

Because they frequently feature one or more hydroxyl substituents in their structure, they can also be classed as polyphenols chemically. They are diphenyl-propanoids and have a flavone nucleus of 15 carbon atoms (C6-C3-C6). They are diphenyl-propanoids and have a flavone nucleus of 15 carbon atoms (C6-C3-C6). The C6 and C3 moieties are fused to produce two fused rings, the first is an oxygen-containing heterocycle, and the second is a benzene ring that forms the nucleus of a phenylchromane (2, 3-dihydro-2-phenylchroman-4-one).

A second phenyl substituent is attached to the phenylchromane base skeleton, resulting in flavones, isoflavones, and isoflavones, depending on the bond location (C2, C3, C4). The three rings' patterns (i.e., oxygenation) (flavones, flavonols, flavanones, flavanonols flavans, flavan-3-ols, anthocyanidins, etc.). Flavonoids can be found as aglycones, prenylated and methyl ethers, and glycosylated forms with sugar residues connected at many places along the three rings to produce O- and C-glycosides. Apigenin (4′, 5, 7-trihydroxyflavone) is a flavone that belongs to the flavone subclass and is one of the most widely distributed flavonoids in plants. The principal sources of this chemical are plants belonging to the Asteraceae family, such as those belonging to the Artemisia, Achillea, Matricaria, and Tanacetum genera. However, apigenin was found in the aglycone form and its C- and O-glucosides, glucuronides, O-methyl ethers, and acetylated derivatives in species from other families; the Lamiaceae, such as Sideritis and Teucrium, and the Fabaceae, such as Genista. Chemotaxonomic relevance has also been proven in several circumstances. Apigenin derivatives are typically found in gymnosperms in dimeric forms, with apigenin residues linked in various ways, such as CC linkage as in cupressuflavone and amentoflavone (I-8, II-8″, and I-3′, II-8″, respectively), or CO linkage as in hinokiflavone (I-4′, II-6″). Apigenin is a phenylpropanoid pathway product that can be made from two shikimate-derived precursors: phenylalanine and tyrosine. Cinnamic acid is generated from phenylalanine via non-oxidative deamination and then oxidation at C-4, then converted to p-coumaric acid. In contrast, p-coumaric acid is formed immediately from tyrosine via deamination. After being activated with CoA, p-coumarate is condensed with three malonyl-CoA residues and then aromatized by chalcone synthase to generate chalcone, which is then isomerized chalcone isomerase to form naringenin, which is then oxidized to apigenin by a flavanone synthase.

Antioxidant capabilities of flavonoids, in general, are well recognized, and apigenin's antioxidant properties have been reported in a large number of studies. Antihyperglycemic, anti-inflammatory, and anti-apoptotic actions have also been described (in myocardial ischemia). Several of its pharmacological actions, including cytostatic and cytotoxic activity against various cancer cells, anti-atherogenic and protective effects in hypertension, cardiac hypertrophy, and autoimmune myocarditis, have been reviewed in a recent study. The growing interest in apigenin's various biological activities has led to efficient extraction methods from natural sources, including modern extractive approaches such as dynamic maceration and ionic liquid analogs (deep eutectic solvents) as unconventional extractive solvents.

SOURCES IN NATURE

Apigenin is present in various fruits and vegetables, but the most common sources include parsley, celery, celeriac, and chamomile tea. Apigenin is plentiful in chamomile flowers, accounting for 68 percent of total flavonoids. Apigenin concentrations in dried parsley and dried chamomile flower range from 45 to 3-5mg/gram. Fresh parsley has an apigenin level of 215.5mg/100 grams, which is substantially greater than the next highest food source, green celery hearts, which has 19.1mg/100grams.

WHAT IS APIGENIN?

Apigenin is a flavonoid found in plants that are quite widespread and extensively dispersed. Flavonoids are a group of phytochemicals found in plant tissues that occur spontaneously. Plants use flavonoids to protect themselves from diseases and solar radiation. Some even help to pollinating insects like bees, butterflies, and moths find their way to your garden. Plants also use flavonoids to regulate their metabolism. It is the aglycone of several naturally occurring glycosides, which are

sugar-binding molecules. For millennia, it has been used in folk medicine to relieve anxiety and inflammation. It has a golden tint and is a solid crystalline structure.

HOW MUCH IS APIGENIN IN CHAMOMILE TEA?

Apigenin is found in chamomile, which is traditionally consumed as tea. The dried flowers of Matricariachamomilla, an annual herb native to Western Asia and Europe, are used to make it. In Australia and the United States, the plant has also become naturalized and now thrives wild. Apigenin levels in chamomile teas vary, with some teas having much more chamomile than others. Apigenin content in chamomile teas ranges from 0.8 percent to 1.2 percent.

WHAT FOOD CONTAINS APIGENIN?

Apigenin is present in parsley, celery, celeriac, red and white sorghum, tarragon, yarrow, basil, rutabagas, oranges, kumquats, onions, wheat sprouts, thyme, spearmint, and cilantro, among other fruits, vegetables, and herbs. While apigenin can be found in various foods, parsley is a particularly good source of it. Apigenin is found in dried parsley at a 45 mg/gram concentration and dried chamomile flowers at a concentration of 3-5mg/gram. Fresh parsley has been shown to have as much as 215.5mg of apigenin per 100grams. Green celery hearts have a maximum concentration of 19.1mg per 100grams. While research is limited, the large range of foods that contain apigenin makes it difficult to calculate an exact diet.

APIGENIN SUPPLEMENT

Apigenin Flavonoids are easily available as a nutritional supplement**.** The most common dose is 50mg. However, larger quantities are also available.

APIGENIN AND NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD+)

Apigenin and quercetin have both been demonstrated to suppress CD38 activity in the context of aging and metabolism. CD38 is an enzyme that consumes increasing amounts of nicotinamide adenine dinucleotide (NAD+) as we age. NAD+ is a coenzyme that can be present in all living things.

According to animal research, mice bred to be CD38 deficient show enhanced protection from mitochondrial dysfunction and are resistant to diabetes as they age. The mitochondrial sirtuin SIRT3 is responsible for this protective effect. Apigenin-treated mice have higher levels of NAD+ and are less susceptible to the effects of high-fat diets.

Given that CD38 aggressively destroys both NAD+ and NMN, using CD38 inhibitors like apigenin to enhance NAD+ levels rather than relying on precursors may be a better option. In other words, treating the cause of NAD+ loss is preferable to attempting to compensate for it. You may read more about how NAD+, CD38, and senescence are linked here.

APIGENIN SIDE EFFECTS

Apigenin is deemed safe when ingested in typical proportions through a diet rich in fruits, vegetables, and herbs. On the other hand, supplemented doses tend to offer substantially more apigenin than would normally be taken through diet. If you experience stomach discomfort after taking higher dosages of apigenin, you should stop taking it immediately and visit your doctor.

Some people are allergic to chamomile tea or apigenin, so you should discontinue use if you have any negative side effects.

THE FUTURE OF APIGENIN

Even though apigenin has been the subject of several interesting animal investigations, there is no human data available beyond cell studies. There is undoubtedly more to learn about apigenin, including its potential as a senolytic or xenomorphic, but further research is required before any judgments concerning its neuroprotective properties can be drawn.

APIGENIN DIETARY SOURCE AND DAILY INTAKE LEVELS

It is crucial to look at the dietary intake level of apigenin before discussing the effects of dietary apigenin on gut bacteria. Apigenin has a wide distribution in the plant kingdom, as it has been

detected in various vegetables, herbs, and fruits[15]. Apigenin-rich foods include fresh parsley, vine spinach, celery seed, green celery heart, Chinese celery, and dried oregano. Red and white sorghum, rutabagas, oranges, kumquats, onions, wheat sprouts, tea, and cilantro are among the plants that contain apigenin. Apigenin levels in dried parsley are significantly higher than in any other vegetables or plants.

Given that apigenin is widely dispersed in foods and that a diet rich in flavonoids has been linked to various health benefits, estimating apigenin consumption daily should aid in the proper interpretation of the association between health outcomes and apigenin. Although several individual flavonoids have been given strict dietary consumption values, relevant research on flavone apigenin is scarce[16]. One study estimated a daily food intake of flavonoids of 1g as glycosides or 650mg as aglycones in adults in the Netherlands. In contrast, another study estimated just 23mg/day in people in the Netherlands. The average flavanol and flavone intake among US health professionals was around 20-22mg per day in research conducted around 1990[17]. The majority of the average daily consumption, about 16mg/day, was attributed to quercetin in the study mentioned above in the Netherlands in 1988, while the real daily intake of apigenin was only about 0.69mg/day. However, according to another research of the Dutch diet, the average daily consumption of apigenin is around 1mg. A group of female Flemish dietitians reported a similar number, 1.5 4.9mg/day (range 0-30.3).

A more recent study looked at the average intake of flavonoid compounds in adults across the European Union, broken down by country, region, and overall. Using food consumption statistics from the European Food Safety Authority (EFSA) and the FLAVIOLA Food Composition Database, the European average apigenin intake is 3 1mg/day. In China, apigenin intake is 4.23mg/day and 0.13-1.35mg/d in the United States among middle-aged and older women. This consumption number among US women is similar to the 0.2-1.3mg/day found in a US nurses' health study from 1984 to 2002, including 66,940 married women[16]. The mean daily intake value of apigenin from the main dietary sources of favones was determined to be 0.45mg/day in adult Australians. The aforementioned information suggests that, as a phytochemical found in a variety of foods, determining dietary intake for apigenin is difficult and variable. Diet is affected by geography, culture, and specific demography, and it changes through time. Dietary assessment, which involves a diet history interview or meal frequency questionnaires, is one of the most common methods for estimating dietary intake levels, and it is compared to a food composition database. The accuracy of consumption levels acquired can be influenced by the dependability of the information collected from respondents, as well as the database's inclusiveness, extensiveness, and demographic specificity[18]. Aside from the data inaccuracy, there is more information on the daily amount of total or combined groups of favonoids than there is on a single favonoid of relevance. Apigenin's pharmacological characteristics. Apigenin has acquired popularity as a health-promoting drug in recent years due to its low intrinsic toxicity and dramatic effects on normal versus cancer cells when compared to other structurally related flavonoids.

Apigenin's great therapeutic potential against a variety of ailments has been demonstrated in various studies. To far, there is very little evidence that apigenin, when ingested as part of a normal diet, causes harmful metabolic effects in humans. However, other findings imply that oxidative stress causes liver damage in swiss mice, which could be attributed to the activation of several genes by apigenin at greater dosages. Apigenin's powerful antioxidant and anti-inflammatory properties may have a role in cancer prevention. Apigenin's powerful antioxidant and anti-inflammatory properties may have a role in cancer prevention. In cell culture and in vivo tumour models, apigenin has also been shown to increase metal chelation, scavenge free radicals, and induce phase II detoxification enzymes[19]. Apigenin inhibits cancer growth by triggering apoptosis in a variety of cell lines and animal models. Indirect support for this hypothesis can be found in a study that found that healthy human volunteers who ate flavonoid-free diets had lower levels of oxidative stress markers in their blood, such as plasma antioxidant vitamins, erythrocyte superoxide dismutase (SOD) activity,

and lymphocyte DNA damage, all of which are linked to increased disease risk, implying flavonoids' beneficial effects.

Apigenin's antioxidant and antigenotoxic effects, as well as its involvement in scavenging free radicals, have been linked to a range of biological consequences in a variety of mammalian systems in vitro and in vivo. Apigenin inhibits atherosclerosis by triggering apoptosis in oxidised low density lipoprotein (OxLDL)-loaded mouse peritoneal macrophages. Apigenin's pro-apoptotic activity was linked in part to the downregulation of plasminogen activator inhibitor-2 (PAI-2) through reducing AKT phosphorylation at Ser 473. It is also known to lower COX-2, IL-8, and TNF-expression in IPEC-J2 non-transformed intestinal epithelial cells, which reduces LPS-induced inflammation[20]. Apigenin inhibits osteoblastogenesis and osteoclastogenesis, as well as preventing bone loss in ovariectomized mice, according to Goto et al. Apigenin and its derivatives have been linked to a number of health benefits, including antioxidant, anti-inflammatory, and anti-carcinogenic qualities. Apigenin-7-glycoside, an apigenin derivative, protects against LPS-induced acute lung damage by inhibiting MAPK phosphorylation and down regulating oxidative enzyme expression. Apigenin had previously been found to cause autophagia (a type of cellular dormancy) which may explain its chemopreventive characteristics, but it also induces resistance to chemotherapy. Apigenin is a powerful competitive inhibitor of the enzyme CYP2C9, which is involved in the metabolism of numerous pharmacological medications in the body[21]. Apigenin has been demonstrated to reverse cyclosporine's side effects. The effects of apigenin on the reversal of cyclosporine-induced damage were studied using immunohistochemistry to measure bcl-2 and histological sections to measure apoptosis.

HEALING PROPERTIES OF APIGENIN

Apigenin has gained popularity as a helpful and health-promoting substance in recent years. Kashyap *et al*. have summarised apigenin's many therapeutic activities using in vitro and in vivo systems. Cell cycle arrest, apoptosis, anti-inflammatory, and antioxidant functions were all investigated as mechanisms underpinning apigenin's potential therapeutic activity. Apigenin causes cell cycle arrest at various stages of proliferation, such as G1/S or G2/M, by altering the expression of certain CDKs and other genes[22]. Apigenin is known to influence intrinsic apoptotic pathways by altering mitochondrial membrane potential and triggering the release of cytochrome C into the cytoplasm, which generates APFA, activates caspase 3 and triggers apoptosis. Apigenin, on the other hand, regulated extrinsic apoptotic pathways by activating caspase-8. Apigenin promotes apoptosis in cancer cells via altering the expression of the proteins Bcl-2, Bax, STAT-3, and Akt. Apigenin inhibits COX-2 activity through promoting anti-inflammatory pathways such as p38/MAPK and PI3K/Akt, as well as preventing IKB degradation and nuclear translocation of the NF-B. Apigenin has been shown in human cell cultures to inhibit nuclear factor kappa-light-chain-enhancer or stimulate B cells (NF-B) via reduction of LPS-induced phosphorylation of the p65 subunit[23]. Apigenin is thought to reduce the expression of adhesion molecules as a protective mechanism against oxidative stress, such as free-radical scavenging. To combat cellular oxidative and electrophilic stress, apigenin increases the expression of antioxidant enzymes such GSH-synthase, catalase and SOD. By suppressing the NADPH oxidase complex and their downstream target inflammatory genes, and raising the expression of nuclear translocation of Nrf-2, it also increases the expression of phase II enzyme producing genes[24]. In human cell culture models, apigenin has been shown to suppress metastasis and angiogenesis by interacting with signalling molecules in the three primary mitogen-activated protein kinase (MAPK) pathways: extracellular-signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK), and p38. In lipopolysaccharide (LPS)-activated mouse macrophages, apigenin significantly reduced levels of interleukin 6 (IL-6), which works as both a pro-inflammatory cytokine and an anti-inflammatory myokine[25].

Inhibition of interferon gamma (IFN-)-induced phosphorylation of signal transducers and activators of transcription 1 (STAT1) in murine microglia suppresses the production of cluster of differentiation 40 (CD40), tumour necrosis factor

(TNF-), and interleukin-6 (IL-6)[53]. Apigenin can also reach the brain via the circulatory system, where it can cross the blood-brain barrier before expressing its affinity with the GABAA-receptor and acting on the CNS, despite the fact that its effect at the level of increasing the clinical usage of benzodiazepines is unclear. Apigenin, a family of flavin-containing amine oxidoreductases found in human neurons and astroglia, inhibited rat-brain monoamine oxidases (MAOs) in vitro, according to Sloley *et al*. Uncontrolled MAO activity has been linked to a variety of mental and neurological illnesses, and inhibitors of MAO, such as apigenin, have been used to treat depression, anxiety, and Alzheimer's disease. The amount of *in vivo* studies employing the mouse, rat, or hamster as a model is quite minimal, despite the enormous number of *in vitro* studies on apigenin qualities. Clinical experiments that include individuals are in an even worse predicament[55]. The number of such research is quite limited, particularly in the case of this compound's effect on cancer, which could be owing to, among other things, ethical concerns. The key findings from the animal (Figure No.4A-C) and human research were reported in separate.

Properties of apigenin

Apigenin poses various types of proeprties. All the properties are depicted in the Figure No.6:

ANTI INFLAMATORY PROPERTIES

Apigenin promotes multiple anti-inflammatory pathways, including p38/MAPK and PI3K/Akt, and prevents IKB kinase degradation, which leads to proinflammatory NF-B activation and reduces COX-2 activity[11]. It's no surprise that apigenin promotes multiple anti-inflammatory pathways, including p38/MAPK and PI3K/Akt, and that apigenin prevents IKB kinase degradation, which leads to proceed.

To battle cellular oxidative and electrophilic stress, apigenin has been found to boost the expression of antioxidant enzymes such as GSH-synthase, catalase, and superoxide dismutase (SOD)[6]. To fight germs, our white blood cells create SOD and other reactive oxygen species. Apigenin inhibits NADPH oxidase, which promotes the production of phase II enzyme-encoding genes. Apigenin is a phytopolyphenol found in a wide range of foods. Apigenin, like many other flavonoids, has been shown to have anti-inflammatory properties, including reducing oxidative stress and inhibiting the production of various inflammatory factors[28].

APIGENIN FOR ANXIETY AND DEPRESION

Chamomile has also been used to treat anxiety and sadness in the past. In 2016, a long-term randomised clinicaltrial for the treatment of generalised anxiety disorder (GAD) was started.Participants in the study were given 1500mg of chamomile extract (three 500mg capsules) three times a day[3]. 179 people took part in the research's open-label phase, in which no information is concealed from trial participants, allowing them to know exactly what they're taking. In the second phase, 93 people were randomly assigned to receive either continuing chamomile medication or a placebo for 26 weeks in a double-blind research.

Participants who took chamomile extract had much lower levels of anxiety than those who took a placebo. Body weight and mean arterial blood pressure were also lower in the chamomile group[28]. Chamomile showed to be both safe and effective in treating GAD symptoms. In a randomised, double-blind, placebo-controlled experiment published in 2012, chamomile extract was utilised to treat GAD. Anxiety, co-morbid depression, or anxiety with a history of depression, and anxiety with no current or past depression were all given chamomile extract with a 1.2 percent apigenin concentration. The 57 volunteers were randomly assigned to receive either chamomile extract or a placebo. The results showed that chamomile medication reduced total Hamilton Depression Rating Scale scores significantly. This implies that chamomile extract may have antidepressant properties[29].

This is good news, because research has shown that despair can slow down our ageing process. In reality, a person's Grim Age is accelerated in major depression, according to the popular biological ageing clock Grim Age, which can reliably forecast life expectancy.

This review is mainly describes about the anti-inflammatory and antioxidant property of apigenin.

ANTI INFLAMMATORY AND ANTI OXIDANT PROPERTY

Many flavonoids are now recognised to be COX, LOX, PLA, and NOS inhibitors, both selective and non-selective. These chemicals have a crucial role in causing inflammation. Some flavonoids target just one inflammatory enzyme, while others target multiple enzymes. Flavones like luteolin and apigenin, for example, have been shown to reduce iNOS and COX 2 production, but flavanols like quercetin and myricetin are preferential LOX and PLA 2 inhibitors, with quercetin also inhibiting NOS. Furthermore, whereas flavonoids (quercetin, myrecetin, kaempferol, scutellarin) and biflavonoids (ochreflavone, amentoflavone, ginkgogetum, and isognetum) are PLA inhibitors, 2 amitoflavone, and apigenin showed no inhibition to PLA 2. Flavones' superior action in suppressing NO generation, iNOS, and COX is due to their C-2, 3 double bond and hydroxyl group substitution on the A and B rings, respectively. Apigenin, quercetin, and morin were reported to reduce NO generation in LPS-induced and INF-activated C6 astrocytes and LPS-induced RAW 264.7 cells, not by decreasing iNOS function, but by suppressing iNOS expression. IL-1, IL-6, INF-, IL-4, IL-5, TNF-, MCP-1 (Monocytechemotoactic protein), MIP-1 (Monocyte inflammatory protein), and ICAMS are also associated with inflammatory reactions in addition to iNOS/COX 2. Apigenin's potential role in inhibiting the production of many cytokine genes has been linked to a number of signal transduction protein kinases, including PKC, ERK, and MAPK. The DNA binding ability of transcription factors including NF-B, Fos-Jun, and AP-1 is regulated by inhibiting these molecules. Although some of the signalling molecules blocked by apigenin have been identified, many more are yet unknown. Apigenin-induced inflammatory modulation has been found to have a plausible route. In one of the investigations, Reuter discovered that ROS activates a variety of transcription factors, including NF-B, AP-1, p53, HIF-1, PPAR-, -catenin/Wnt, STAT-3, Sp-1, and Nrf2, all of which are known to play a role in cancer and inflammatory illnesses. More than 500 genes, including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory chemicals, can be expressed when these transcription factors are activated.

Apigenin has been demonstrated to interact with these transcription factors and modulate inflammatory pathways. Apigenin has been shown to inhibit TNF-induced NF-B, CCL2/MCP-1, and CXCL 1/KC expression. The activation of transcription factors involved in COX 2 and iNOS production is controlled by NF-B. The suppression of NF-B is accomplished in mouse macrophages by inhibiting LPS-induced IB kinase activity. Apigenin, on the other hand, had no influence on IB protein degradation, nuclear translocation, or DNA binding activity of NF-B p65. Apigenin's potential role in eliciting anti-inflammatory effects has been demonstrated. Apigenin has anti-inflammatory and antioxidant activities, which are mediated through antioxidant enzymes such as SOD, GSH-Px, catalase (CAT), NOS, glutathione reductase (GR), and reduced glutathione (GSH). In comparison to a group supplemented with a low flavones rich diet, human subjects treated with parsley providing apigenin for two weeks had higher levels of GR and SOD. Apigenin, at low concentrations (10, 20, and 40 mg/kg b.w.), protects rat livers from reactive oxygen species (ROS)-induced oxidative damage by reducing lipid peroxidation (LPO) and membrane protein damage, as well as the secretion of blood serum enzyme markers such as LDH, ALP, alanine amino transferase (ALT), and aspartate transaminase (AST) (AST). Apigenin's effect on the control of inflammatory and antioxidant molecules.

Apigenin injection (intragastric) at concentrations as high as 468 and 936mg/kg b;w, on the other hand, had the opposite effect on rat livers, indicating that apigenin can cause oxidative stress at extremely high levels. Reduced levels of SOD, CAT, GSH-Px, and total antioxidant capacity may contribute to this (T-AOC).Flavones apigenin and its other equivalents decrease expression of intracellular adhesion molecules (ICAM), giving protection against inflammation in various organs, including atherosclerosis in human aortic endothelial cells, according to Lotito and Frei and Panes *et al*. The authors also suggested that the primary structural prerequisites for inhibiting adhesion molecule expression were 5, 7-dihydroxyl substitution of a flavonoid A ring; 2, 3 double bond;

and 4-keto group of the C ring. Only hydroxyl substitutions on the B and C rings were required for antioxidant activity, but not on ring A[29]. Chemosensitivity experiments using control and MRP1-transfected HeLa cell lines revealed that the IC50 values for apigenin, naringenin, genistein, and quercetin were identical, suggesting that MRP1 over expression does not provide resistance to these bio-flavonoids.

The study's findings show that flavonoids increase MRP1-mediated GSH transport by boosting the transporter's apparent affinity for GSH, giving them antioxidant properties. Gout is caused by the enzyme xanthineoxidase, which is also responsible for oxidative damage to living tissues. Lin *et al*. Investigated the effects of apigenin and other flavonoids on xanthine oxidase (XO)-induced oxidative stress in human promyelocytic leukemic (HL-60) cells. Few studies have demonstrated that various flavonoids, including apigenin, have no anti-inflammatory effect when used as a medicinal drug.

ANTIGENOTOXIC

Genotoxicity is a feature of chemical compounds that causes mutations in a cell's genetic code, which can lead to cancer. Every cell has the ability to protect itself from chemically induced genotoxicity, either through DNA repair processes or by diverting the cell to apoptosis. However, it is possible that the damage will not always be repaired, resulting in mutations. Various approaches exist to assess the genotoxic effects of chemical compounds *in vitro* and *in vivo*, with differences in sensitivity, practicability, and genetic end-points evaluated. Micronucleus assay, sister chromatid exchange, and comet assay are the most often used genotoxic assays. All of these assays work well when DNA or chromosomes are fragmented as a result of a chemical compound's toxicity, but for other nuclear abnormalities like nucleoplasmic bridges and nuclear bud formation, which are also biomarkers of genotoxic events and chromosomal instability, a newly developed method called the cytokinesis block micronucleus cytome assay is used[6]. The Ames test, which involves the determination of the number of mutant revertants in the concerned cell culture after the application of test drug, is another extensively used and one of the oldest procedures used for *in vitro* testing. The Drosophila wing spot test is another straightforward way to evaluate genotoxicity without using celiac disease.

Fluorescent in situ hybridization is a procedure that produces more precise findings (FISH). This method can be used to assess if the genotoxic test substance is aneugenic or clastogenic. Apigenin's ability to defend against numerous genotoxic chemicals has been extensively researched. Different research groups employ different measures to detect the protective effect of apigenin as a parent compound or as plant extracts in vivo and *in vitro* against a variety of genotoxic substances. Apigenin can serve as a pro-oxidant, a genotoxicant, or an inhibitor of critical enzymes, causing a clastogenic impact in cancer cell lines, depending on the dose. Drug delivery systems based on apigenin several studies are being conducted to develop and assess a novel apigenin delivery method. Shen *et al* and Vanic proved in a recent study that the efficiency of apigenin encapsulation rises as the number of phospholipids in ethosome formulations increases. Ethosomes are small hydrophobic molecules made up of short chain alcohols and phospholipids (lipoid S 75). (Propylene glycol and ethanol). In both *in vivo* and *in vitro* models, apigenin-loaded ethosomes showed effective targeting of UV-B-induced skin tumorigenesis in mice. Apigenin's solubility in water was raised by 148 times, boosting its protective efficacy when utilised in polymeric micelles against HepG2 and MCF-7 cancer cell lines. Furthermore, the in vitro drug release investigation revealed that roughly 84 percent of apigenin was released from the micelles within 36 hours, indicating that it was a long-term release. The micelles were either 60 percent Cremophor EL + 30 percent Transcutol HP and 10 percent capryol 90 with a diameter of 17.1nm or 60 percent Cremophor EL + 30 percent Transcutol HP and 10 percent capryol 90 with a diameter of 16.9nm. Another study looked at pre-cutaneous apigenin absorption in three different vehicles: DMSO (D) alone, acetone+DMSO(A/D; 4:1), and polypropylene glycol+DMSO(PG/D; 4:1).

In vitro, apigenin absorption in mouse skin was in the order A/D > D > PG/D. Sub-tissue distribution

studies revealed that DMSO delivered more apigenin to the epidermis than A/D, whereas A/D deposited more apigenin in the stratum corneum. Both DMSO and A/D demonstrated saturation kinetics in an in vivo investigation, whereas apigenin in PG/D showed very poor absorption in the early stages of the trial, which was later enhanced but remained considerably below saturable limits. The same group of researchers found that apigenin (5mol) in A/D administered through the abdomina could not suppress 12-O-tetradecanoylphorbol-13 acetate (TPA) induced ornithine decarboxylase (ODC) activity in the dorsal skin of mice. As a result, they proposed that apigenin be delivered topically to the afflicted tissue for greater activity. Sen et al. reported that simultaneous administration of apigenin and 5-fluorouracil (clinically approved drug) loaded in a single liposome can successfully impart strong anti-neoplastic and anti-tumorigenic effect in nude mice xenograft model, overcoming drug resistance and 5-fluorouracil associated toxicity. Ding *et al*. created a considerably superior carbon nanopowder (CNP) solid dispersion drug delivery method. The pharmacokinetic characteristics and bioavailability of tetracycline were greatly improved by combining CNP with apigenin in a 6:1 ratio. When compared to treatment with apigenin alone, the drug's efficacy was enhanced by 275 percent. Organogels made from lecithin (phopholipid) could also be utilised to deliver pharmaceuticals (bioactive agents) to target areas in the future, according to future aspects of better drug delivery systems. Such gels can thus be utilised to treat conditions such as skin ageing, skin malignancies, and so forth.

ANTIDIABETIC PROPERTIES

Apigenin's anti-diabetic characteristics are due to its ability to suppress -glucosidase activity, boost insulin production, and interact with and neutralise reactive oxygen species (ROS) in the cell, all of which help to prevent diabetic complications[30]. Apigenin has also been found to provide endothelial cells with modest amounts of nitric oxide (NO), reducing the risk of endothelial cell injury and dysfunction caused by hyperglycemia[27]. In a diabetic rat model, Panda and Kar validated apigenin's ability to regulate hyperglycemia, thyroid dysfunction, and lipid peroxidation. Apigenin's ability to boost the activity of cellular antioxidants such as catalase (CAT) and superoxide dismutase (SOD), as well as glutathione, revealed a hepatoprotective role for this nutraceutical component when given to alloxan-treated mice (GSH).

Ren *et al*. found that when compared to a diabetic control group, there were lower levels of blood glucose, serum lipid, malonaldehyde, intercellular adhesion molecule-1, and insulin resistance index, increased SOD activity, and improved impaired glucose tolerance of apigenin[31]. Panda and Kar also found that apigenin reversed alloxan-induced elevations in blood cholesterol, whereas Ren *et al*. found that the apigenin group's pathological damage in the thoracic aorta was more remissive than the diabetic control group. The pathologic changes seen in diabetic cardiomyopathy-induced mice (e.g., increased cardiac dysfunction, fibrosis, over accumulation of 4 hydroxynonenal followed by down regulation of Bcl2, GPx, and SOD, upregulation of MDA, cleaved caspase3, and pro-apoptotic protein Bax, and contribution to the translocation of NF-kappa B) could be reversed *in vivo* by apigenin treatment.

Apigenin (20mg/kg) reduced renal failure, oxidative stress, and fibrosis in male albino Wistar rats (decreased transforming growth factor-beta1, fibronectin, and type IV collagen). Apigenin therapy *in vivo* reduced hemodynamic fluctuations, restored left ventricular function, and restored a balanced redox status, according to another study[32]. Myonecrosis, edoema, cell death, and oxidative stress were all reduced in rats, protecting them against cardiac injury. Cazarolli et al. investigated the effect of Averrhoa carambola L. leaves-derived apigenin-6-C-(2″-O—L-rhamnopyranosyl)-L-fucopyranoside on 14C-glucose absorption. After oral therapy in hyperglycemic rats, the authors found that this chemical had an initial effect on reducing blood glucose and stimulating glucose-induced insulin secretion in diabetic rats.

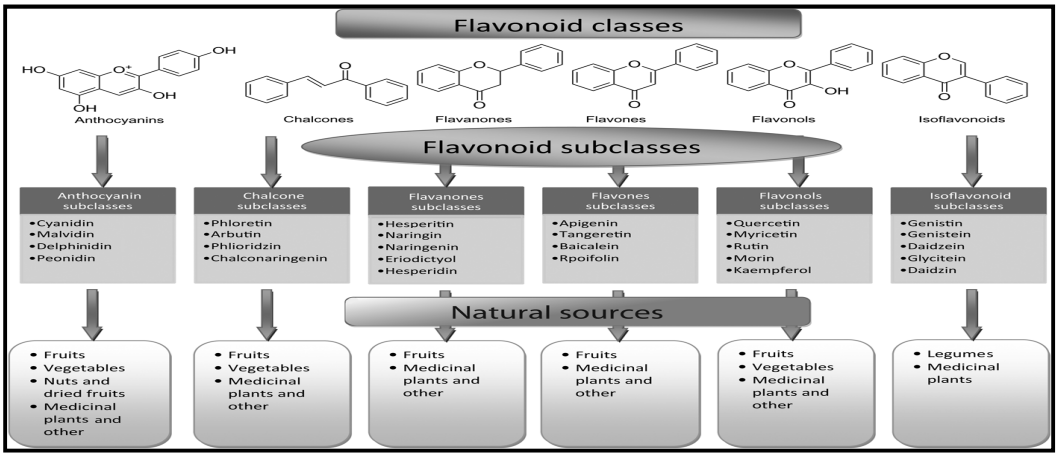

Figure No.1: Classification of Flavonoids

Figure No.2: Apigenin plant

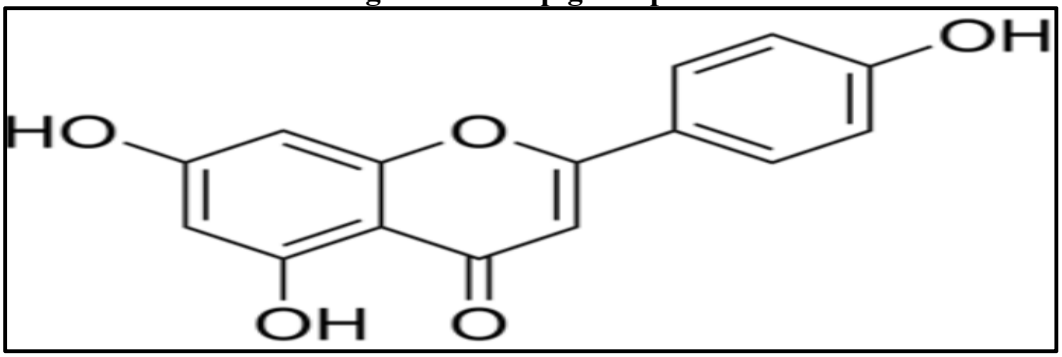

Figure No.3: Structure of Apigenin

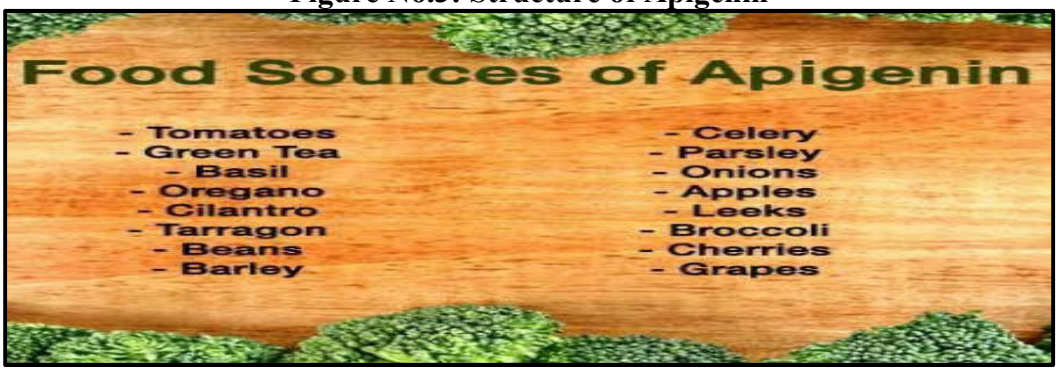

Figure No.4: Apigenin food sources

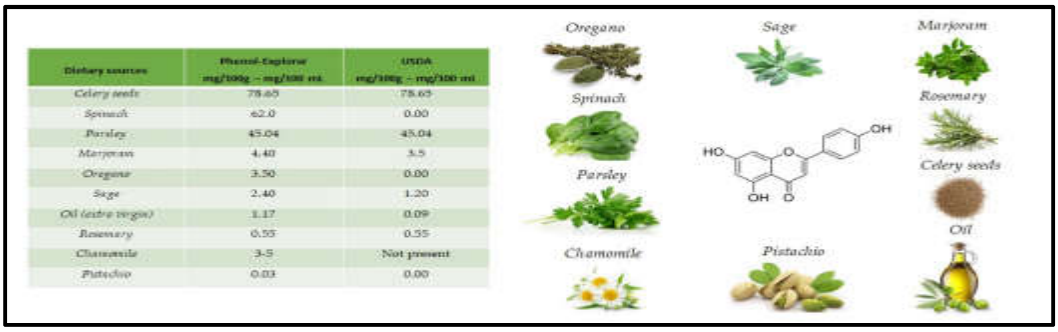

Figure No.5: Dietary sources of Apigenin

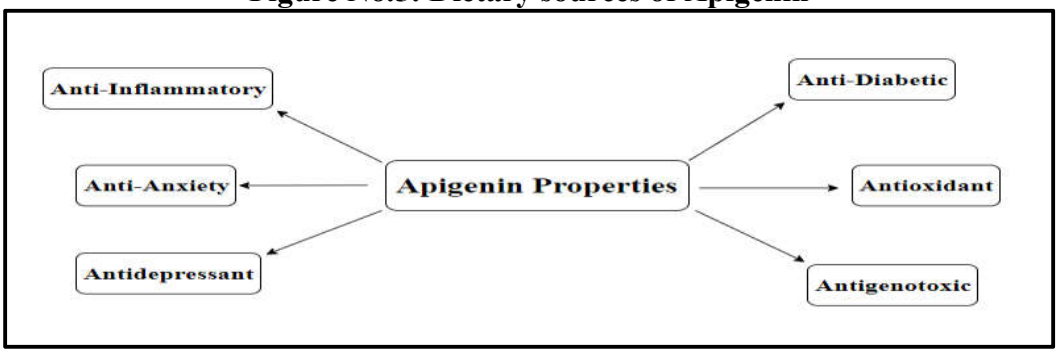

Figure No.6: Pharmacological properties of Apigenin

CONCLUSION

Apigenin is a flavonoid found in plants that are quite widespread and extensively dispersed. Flavonoids are a group of phytochemicals found in plant tissues that occur spontaneously. Plants use flavonoids to protect themselves from diseases and solar radiation.

Apigenin possesses antibacterial, antiviral, antifungal, and antiparasitic properties. Bacterial inhibitory effects are strain-specific. Although apigenin did not stop the growth of dangerous bacteria in some situations, it did reduce the production of toxin. Apigenin can be used to supplement or improve the efficiency of antibiotics. Apigenin's bioavailability is increased by its rapid absorbtion in the intestine and slow excretion. Its therapeutic effects are mediated by its antioxidant and anti-inflamatory properties as well as molecular targets.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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