GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Luteolin: A versatile flavonoid for anti-inflammatory, anti-cancer, and neuroprotective therapies

Summayya Maryam [1], Saliha Khalid [2, *], Ayesha Arshad [3], Sana Abid [1], Laraib Zafar Iqbal [1], Yumna Amjad [1] and Shah Faisal [4]

[1] *Department of Biochemistry, Faculty of Science and Technology, University of Central Punjab, Lahore, Pakistan.*
[2] *Department of Material Science and Nanotechnology, School of Engineering and Natural Sciences, Kadir Has University, Istanbul Turkey.*
[3] *Institute of Biochemistry and Biotechnology, University of Veterinary and Animal Sciences, Lahore, Pakistan.*
[4] *Biotechnology Program, Department of Mathematics and Natural Sciences, BRAC University, Dhaka, Bangladesh.*

GSC Biological and Pharmaceutical Sciences, 2024, 29(03), 119–137

Publication history: Received on 10 November 2024; revised on 09 December 2024; accepted on 12 December 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.29.3.0457

Abstract

Medicinal plants are the alternate source of medicine that performs dynamic biological functions due to the presence of certain bioactive compounds. This current review has also emphasized progress in the therapeutic effects of luteolin. Epidemiological pieces of evidence recommend that flavonoids may play a significant part in the reduction of chances of persistent illnesses related to a diet regimen that may be plentiful in plant-determined food sources. Luteolin shows particular anti-inflammatory reactions *via* its effects on fibroblast cell multiplication and immigration as well as anti-carcinogen activities, which may somewhat have been clarified through its antioxidants by free radical scavenging capacity. It is exposed for infiltration into human skins, enabling it an aspirant for avoidance as well as management of skin malignancy. It is also reported for anti-diabetic, and neurodegenerative effects in human beings. Diabetic wounds are prevalent health problems that affected about 16% of individuals with diabetes. Flavonoids are consistent constituents of plants utilized in traditional medication for the treatment of the extensive scope of infections. Luteolin has the capacity to repress angiogenesis, for promotion of apoptotic cell death, to anticipate carcinogenesis in creature models, to decrease tumor development *in vivo*, and to sensitized cancerous cells to cytotoxic impacts of several anti-cancerous medications endorses that this flavonoid has chemo-preventive and chemo-therapeutic potentials. Inhibition of ros, restraint of topoisomerases i and ii, a decrease of nf-kappa b and ap-1 movement, adjustment of p53, and hindrance of pi3k, stat3, igf1r, and her2 are conceivable processes engaged with the organic exercises of luteolin.

Keywords: Reactive oxygen species; Nuclear factor-kappa B; Active protein; Insulin-like growth factor 1; Phosphoinositide 3-kinases; Signal transducer and activator of transcription 3

1. Introduction

The herbal medications are provided medicine from major traditional systems. Around 90% of plant medicine and herbs are collected from the Indian forest. About 100 plants are newly introduced that produced new drugs in the market of the USA from 1950-1970. In the 1980s, Americans are promoted to a healthy lifestyle by using medicinal plants for illness treatment. In 1994 USA is greatly changed in the health dietary supplement and adjustment the medicinal plants in food [1]. In 2000 reported that herbal medicinal uses are improved and beneficial for health. Many countries like China, India, and Pakistan have used herbal medicine [2]. In Pakistan, more than 6000 species of plants are present, which is mostly in northern areas. But 600 to 1000 plants show medicinal properties. About 350 to 400 plants are used for the herbal medication [3,4].

* Corresponding author: Saliha Khalid

Some drugs are produced from higher plants such as reseinnamine, vincristine, and deserpidine. Medicinal plants are providing a large number of drugs to eliminate infection and disease despite advancements in synthetic drugs [5]. Many plants are also derived for the importance of drugs. The use of plants as medicine is increasing day by day all over the world. In recent research, plants and herbs have greater development in pharmacological and traditional medicines [6,7].

Medicinal plants contain secondary metabolites and compounds like alkaloids, flavonoids, and terpenoids. Flavonoids have therapeutic potency against anti-microbial activates. The plants derive from drugs are introduced from modern medicines that are linked to the plant material as an original cure in the traditional medicine system [8,9]. Some plants showed many properties like anticancer, antifungal, antidiabetic, antioxidant, and anti-inflammatory activities. The drugs derived from plants are used for skin disease, jaundice, hypertension, mental illness, and cancer. Medicinal plants and traditional medicines are used in many developing countries to maintain good health and oral disease that are the major health problem and infectious diseases. Oral health directly affects health that is linked to the chronic and causes many diseases [10]. All over the world, a lot of people died due to disease and lack of health care. In many countries, diseases are often due to malnutrition. In many countries, health care units are not established yet as they suffered from many diseases and lack of medicines [11,12].

Medicinal plants have traditional importance and industries of a pharmaceutical cannot be overemphasized. The herbs are used as a treatment for many diseases in industrialized societies, universal. In pharmaceuticals, physicians currently used herbal remedies include aspirin, quinine, and opium. Usage of medicinal plants is increased day by day all over the world [13]. Medicinal plants are used to maintain physical and mental health to treat specific conditions. The industrialized country is used plant medicines considered as “complementary and alternative” medicine. Traditional medicine maintains the popularity of all developed countries and industrialized country [14,15,16].

The chemical drugs act quickly but it has many negative side effects on the human body as compared to the medicinal plants that showed little probiotic and no side effect on our human body. In human culture, development uses of the medicinal plant are religious significance and regard to the health disease [17,18]. About 3000 years ago a large quantity of plants is used to treat health care like traditional medicine in India, Africa, China, and Western standards. WHO (World Health Organization) are reported that 80% of the earth's population on traditional medicine for primary health needs, most are involved in therapy by use of plant extract and active components [19,20,21].

1.1. Bioactive Compounds

Bioactive compounds encourage good health in our bodies. Bioactives are molecules that may have the therapeutic effect of mitigating pro-inflammatory, oxidative, and metabolic conditions [22]. Epidemiologic research shows higher consumption of food riches in bio-active are anti-oxidative components like vitamins, phytochemicals, and mainly phenolic compounds that may have optimistic effects on human’s fitness, which can decrease the chances of several disorders, such as tumors, cardiovascular disorder, stroke, Alzheimer's disorder, diabetes, cataracts, and age-related fatty disease [23]. Such as indoles, lignin, lycopene, resveratrol, and tannins are bioactive compounds. In foods, especially fruits, vegetables, and whole grains, bioactive compounds are present in small amounts that are good for health.

Bioactive compounds can modify metabolically procedures like antioxidant effects, receptive activity suppression, enzyme inhibition or induction, as well as induction/ inhibition of gene expression [24]. Several bioactive compounds are present in fruits, vegetables, or by-products, compounds such as phenol compounds, flavonoids, and carotenoids. This study focuses on “luteolin” as a bioactive compound found in fruits, vegetables, and by-products for daily use [25].

1.2. Classification of bioactive compounds

The major groups of bioactive compounds are phenolic compounds, alkaloids, terpenes, and terpenoids. In-plant materials, phenolic compounds are a key element in the human diet.

The biological properties of such bioactive compounds include antioxidants, anti-allergenic, anti-inflammatory, anti-microbial, and cardioprotective substances [26]. The most commonly found phytochemical classes of these compounds are important in the physiological and morphological activity of plants. In their growth and reproduction, they play an important part. In addition to the color and sensory characteristics of fruits and vegetables, they protect against predators and pathologists [27].

The phenolic content varies greatly between various fruits and vegetables, also varies between the same fruit and vegetables, depending on their complexity, geographical distribution, and the methods of extraction. Based on their processing and storage conditions, the amount of these compounds is recoverable [28].

Flavonoids class of polyphenol compound that's structure contains benzo- γ-pyrone. This is synthesized through the phenylpropanoid pathway [29,30]. Flavonoids are low molecular weight molecules in the structure of C6-C3-C6. They have 2 aromatic rings connected with a bridge of carbon rings, structurally furthermore, enlisted as flavones, flavonones, isoflavones, flavonols, and anthocyanin [31]. It is present in the human diet in the foam of flavonols, flavones, and Isoflavones. Flavonoids are responsible for taste, color, and also provide vitamins. Flavonoids show many pharmacological activities. Flavonoids are produced as a phenolic compound in response to plant microbial infection. Flavonoid nature depends on its class, structure, polymerization, and hydroxylation [32]. The flavonoids act as secondary defense like antioxidant activity to release biotic and abiotic stress in the tissues of plants. Its presents on the mesophyll cells where ROS generation occurs. Flavonoids also work as a growth factor of plant-like auxin.

In vitro and *in vivo* flavonoids act as dietary components which show promote the health effects [33]. Many studies reported that flavonoids are helpful against infection and diseases like cancer, neuroprotective disease, cardiovascular disease, and other biological disease in humans [34]. Due to their strong redox ability, flavonoids are an essential source of antioxidants, which enable them to be reduction agents. Flavonoid intake in high concentration helps reduce cardiovascular-related disorders [35]. Their vitamins, minerals, phytochemicals, and faster material make vegetables valuable for human health. The importance of human health is performed by antioxidant vitamins such as vitamin A, vitamin C, and vitamin E as well as food-borne fiber [36].

One of our most important dietary elements is vegetables. Vegetables provide our everyday activity with nutrients. As a source of nutrients, vegetables contain many bioactive substances that can be resistant to human diseases [37]. They are also an energy source. Vegetable folate is required for the production of new red blood cells in our bodies [38]. Vegetables have a lot of essential and life and body-saving nutrients. They include polyphenols and other bioactive substances for chronic disease prevention. Around 2.7 million deaths will be avoided by enough intakes of vegetables and fruits [39].

Vegetables also provide a major source of dietary fiber, although these vegetable ingredients are not clearly defined, vegetable fibers help transport the bioactive compounds from the intestine to the colon. Dietary vegetable fiber lowers blood cholesterol and decreases cardiovascular diseases [40]. Some commonly occurring medicinal plants containing luteolin as bioactive compound enlisted in Table No. 1 with their biological activities.

Table 1 Some commonly occurring medicinal plants with their biological activities

Medicinal plant	**Properties**
Neem (*Azadirachta indica*)	*A. Indica* (Neem) showed anti-inflammatory activity *via* NF-kβ (nuclear factor- kβ) in the signaling pathway of cancer. It also acts as a transcription factor. When neem is used as a treatment of cancer cells it shows the inhibition of carcinogenesis to the signal transducer expression, AP-1 (activator protein 1) and STAT1 by an over [41].
Tulsi (*Ocimum tenuiflorum*)	*O. tenuiflorum* (Tulsi) is used in the treatment of pyrexia and bronchitis and it is also used in the treatment of asthma, dyspnea, and epilepsy [42]. Tulsi is used in many skin disorders, like itching of the skin, rashes, and insect bites [43].
Mint (*Mentha piperita*)	*M.piperta* (Mint) is used for many centuries as herbal tea, flavoring agent. Mint has many properties act as anti-inflammatory, anti-allergic, insecticidal agents, and stomach tonic, also use as a mouth freshener for breath. Mint benefits for cooling in skin due to menthol and rosmarninic acid in mint leaves are beneficial to improving circulation of blood and skin hydrates [44].
Parsley (*Petroselinum crispum)*	*P.crispum* (Parsley) is one of the herbs which has low calorific herb. Its leaves are beneficial to control fats and cholesterol. It is rich in antioxidants, minerals, nutrients, and dietary fiber [45].
Aloe (*Aloe vera*)	*A.vera* (Aloe) also exhibits anti-diabetic, anti-microbial, and anti-inflammatory activity. The moisturizing effect of skin is occupational exposure by use *Aloe vera* gel on

	the skin. It decreases the wrinkle of acne. The *Aloe vera* gel is given a cooling effect on the skin [46].
Fenugreek (*Trigonella foenum-graecum*)	*T.foenum-graecum* (Fenugreek) is used in the treatment of leg edema, weakness and also to cure fever, blindness, and indigestion. The benefit of this herb is dyslipidemia like diabetes, chronic and obesity [47].
Lemon Grass (*Cymbopogon citratus)*	*C.citratus* (Lemongrass) many bioactive compounds are present that are important for the medicinal value. Due to its properties, it has many pharmacological applications [48]. Lemongrass is commonly used in tea due to its properties like anti-oxidant, anti-bacterial, and anti-inflammation. Its tea is non-toxic [49].
Khus *(Chrysopogon zizanioides)*	*C.zizanioides* (Khus) roots are famous for their cooling properties and their perfume. It has antipyretic, antiseptic, and anti-inflammatory characteristics. It helps reduce blood pressure, blood sugar, and insomnia [50].
Ajwain *(Trachyspermum ammi)*	*T. ammi* (Ajwain) seeds contain nutrients such as para-cymene, limonene, and b-pinene, and fiber are present [51]. Ajwain possesses many properties like antiseptic, antiviral, hepatoprotective, antiulcer, anesthetic, antimicrobial, antihypertensive [52]. Its oil is also used in perfume and toothpaste [53].
Garlic (*Allium sativum)*	*A.sativum* (Garlic) is used in many treatments like a metabolic disease, diabetes, hyperlipidemia, atherosclerosis, and cardiovascular disease [54]. It also showed anti-viral, anti-bacterial, and anti-fungal activities. The supplementation of garlic reduces the risk of cardiovascular diseases, hypertension [55].

1.3. Discovery of luteolin

Chevreul isolated luteolin for the first time as a bioactive compound in 1833 from *Reseda luteola* commonly known as yellow weed. It is isolated in the form of yellowish crystalline substances [56]. Luteolin is a bioflavonoid present with a prolonged history of pharmaco-therapeutic usage in various food products and herbs like Artichoke, one of the world's finest 'medicinal plants' [57]. Luteolin is present in a glycosylated form in green peppers, Perilla leaves, celery, and glycones form in another vegetable, for instance, Perilla seeds [58].

Normally, luteolin found in plants in the form of luteolin-7-O-glucuronides, luteolin-5-O-glucuronide or luteolin-3'-Glucuronide. Luteolin can be utilized in pharmaceutical formulations because of its biological activity in plants [59]. For example, plants such as Mentha, salvia, Origanum and Perilla are those species that contain flavonoids together with luteolin. These species can be utilized as herbal teas because of their medicinal properties. Chamomilla containing luteolin is effective to cure skin burns induced by its oil [60].

1.4. Nomenclature

The nomenclature of luteolin is 7-dihydroxy-4H-chrome-4-one, 2-(3, 4-dihydroxy phenyl)-5 [61]. Synonyms for the name of luteolin include: salifazide, luteola, digitoflavone, luteolin, 3', 4', 5, 7-tetrahydroxyflavone, flatiron, and 5, 7, 3, 4-tetrahydroxyflavone.

1.5. Sources of luteolin

Luteolin is phytochemical that is mostly present in fruits and vegetables. For example, orange, olive oil, broccoli, peppers, rosemary, cabbages, carrots, artichoke, and apple are rich sources of luteolin. Some natural sources of luteolin presented in table 2 including vegetables and fruits [62].

Table 2 Natural sources of luteolin

Sources	**Concentration (mg/kg)**
Onion	391.0
Broccoli	74.5
Carrot	37.5

Green chili	33.0
Celery	80.5
Red pepper	13-31
White radish	9.0
Orange	1028.00
Fresh sage	16.70
Lemon	1.50
Oregano	1028.75

1.6. Physical properties

Luteolin exhibits physical properties such as is yellow, moderately water-soluble, monohydrate (alkaline solution soluble), having flash point 239.5 °C, boiling point 616.1 °C, melting point 330 °C, 25 °C vapor pressure (9.03E-16 mmHg), and density1.654 g/cm3. They are weak acids. Luteolin is not utilized as a drug. Medicinal plants have luteolin as an active component [63].

1.7. Derivatives of Luteolin

Luteolin as flavonoid present in plants. In herbs, luteolin is mostly present for example *Chrysanthemum morifolium, Nepeta cateria, and Lonicera japonica.* [64]. In recent research, the authors reported that plants have shown medicinal benefits like anti-oxidant, anti-cancer, anti-inflammation, and also protect our skin. Luteolin also shows these properties. In past evident, luteolin and its derivatives like 7-sumbubioside, 7-galacturonide-4-glucoside, 7 glucuronide-3-glucoside and 7-O-rutinoside are derived [65].

1.8. Biochemistry of luteolin

Luteolin is considered to be the most ubiquitous flavone. The molecular formulae of luteolin are $C_{15}H_{10}O_6$ and the structure is shown in Figure 1. It naturally occurs in a variety of fruits and vegetables. Luteolin is absorbed through the small intestine. The daily median intake of luteolin is 0.01-2.00 mg/day. When the net oral intake of luteolin is 14.3mg/kg from diverse sources, the maximum concentration of plasma is 1.97-0.15g/ml. So, as it reaches its maximum concentration (C_{max}) that is 1.02-0.22 h, and the half-life of luteolin ($t_{1/2}$) was 4.94-1.2 h. During metabolism, it is converted to free luteolin, sulfate conjugates of luteolin, Diosmetin, and Glucuronide [66]. Free luteolin is also present in human plasma [67].

Luteolin showed biochemical targets like induce the topoisomerase I and II that causes apoptosis [68]. In the structure of the flavone (luteolin) backbone, a hydroxyl group (-OH) attached at the 5-, 7-, 3-, and 4-. This flavone distinguishes it from apigenin because of the 3- position of the hydroxyl group. *In vitro* and *in vivo*, as a medicinal plant show potent anti-inflammatory activity. Like, Luteolin-7-0-glucoside, the derivative of luteolin shows anti-inflammatory activity [69]. In Brazilian, Iran, and Chinese, plants having a high content of luteolin have been utilized as the management of disorders associated with inflammation. Due to the natural response towards harmful stimuli, inflammation occurs, such as injury, microbial invasion, and tissue stress [70].

Through the C-C bond, luteolin binds with sugars and produces C-glycoside. Isoorientin (Luteolin-6-C-glucoside) or orientin (Luteolin 8-C-glucosides) is the famous luteolin glycoside [71]. In luteolin glycosides, Glucose is the frequent sugar. Glucuronic acid, arabinose, xylose, apiose, galactose, rhamnose, or rutinose are added to sugars that are present in the glycosides of luteolin. *In vivo* and *in vitro* studies suggested that luteolin its glycosides have anti-inflammatory effects [72]. Many mechanisms have been included in the luteolin anti-inflammatory activity. It was found that activation of NF-kappa B enhanced expressions of chemokine, enzymes, and cytokine. Luteolin has the capability for inhibiting the actions of NF-kappa B at the low range molar concentration [73].

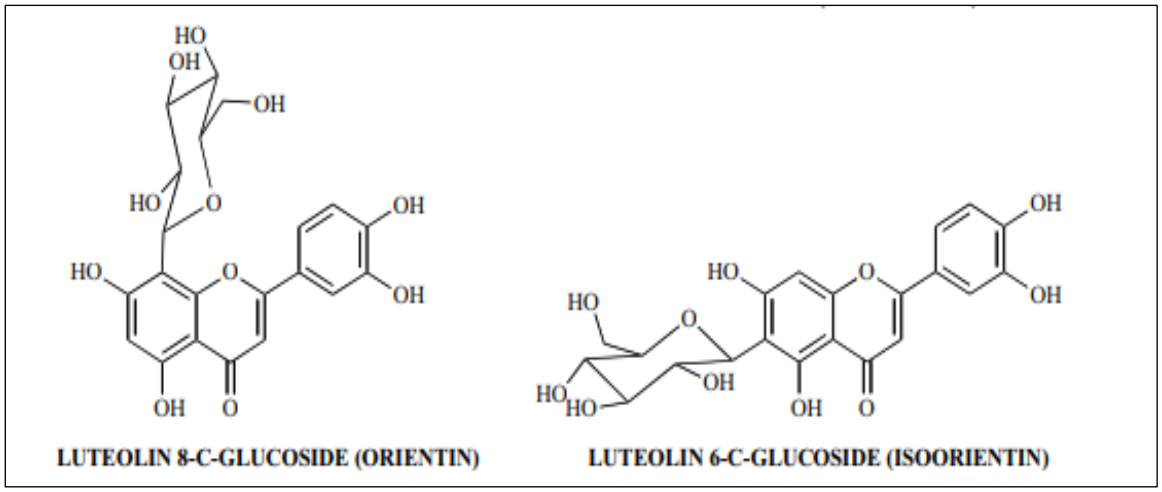

Figure 1 Classification of Luteolin

2. Biological Properties of Luteolin

Flavonoids are the largest group of secondary metabolites, in flavonoids luteolin is present that shows many pharmacological and therapeutical effects on the human body. Flavonoids are found in natural sources like vegetables, medicinal plants, and fruits. The use of flavonoids increases day by day due to their unique properties. In experiments, luteolin showed many biological activities (Figure No. 2) involve in the treatment and prevention of various ailments and diseases as well as maintenances of health [66].

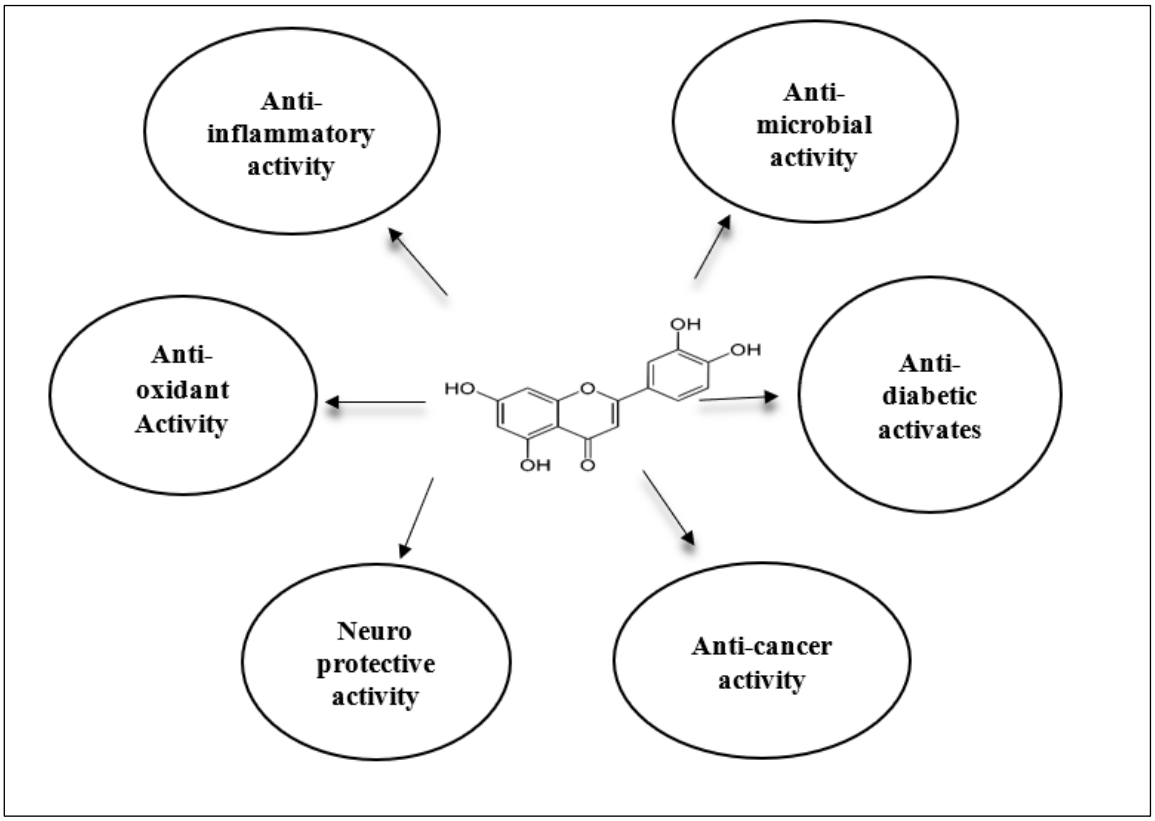

Figure 2 Biological activities of luteolin

2.1. Antioxidant activity

Free radicals like superoxide, hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2) are present in the body that are harmful. They attack the biomolecules like carbohydrates, lipids, nucleic acid, and protein and damage the tissues which ultimately induces oxidative stress and causes diseases like cancer, cardiovascular, aging, diabetics, and asthma. Flavonoids are a class of polyphenolic compounds including benzene rings and pyrene rings. It is naturally present in fruit and vegetables [74]. Luteolin, a bioactive flavonoid possesses antioxidant activity. It scavenges the ROS (reactive oxygen species). ROS is the second messenger of cellular signaling. Luteolin inhibits ROS to induced damage in the DNA, protein, and lipid. Luteolin exerts its antioxidants effect by protecting and enhancing endogenous antioxidants like GST (glutathione-S-transferase), GR (glutathione reductase), SOD (superoxide dismutase), and CAT (catalase) **[66].**

The antioxidant potential of luteolin was studied in female Wister rats. TBARS (Thiobarbituric acid was a reactive substance which increase the level of gallic acid without antioxidant control. An increase in the concentration of antioxidants causes a higher level of TBARS. Sulfhydryl protein level was sustained and restored until the end of the experiment and storage that received high and low concentrations of antioxidants. The result of this experiment shows that luteolin was beneficial for antioxidants and maintain the protein sulfhydryl in the whole blood of rats [75]. Luteolin is also involved to ameliorate MI/R (myocardial ischemia/reperfusion). Cell line H9c2 is used for changing antioxidant enzymes, cardiac function, release LDH. *In vivo* and *in vitro* studies revealed that luteolin shows a cardio protective effect by increase the expression of Bcl-2 and anti-apoptotic protein, decrease the activity of caspases and pro-apoptotic protein Bax with MI/R. Luteolin down-regulates of peroxiredoxin II by antisense of peroxiredoxin. The result indicated that luteolin protects MI/R injury by signaling in endogenous antioxidant enzyme and beneficial role as an antioxidant in the heart [76].

Mosses and liverworts are small plants of Phylum Bryophyte. They are the unique source of pharmaceutical products and they are used in important medicine against hepatitis [77]. *Marchantia* species are important for the Chinese herbs and play an important role in drug development. These herbs possess anti-inflammatory and antibiotic properties. It is reported that *Marchantia* has flavonoid and steroids by which it helps to reduce inflammation. It has activity against wounds, cuts, snake bites, and scalds [78]. HPLC technique was used to isolate chemicals and enzymes from *Marchantia*. After the results of HPLC, it was concluded that Luteolin in liverworts plays an important role in anti-oxidization. DPPH assay for scavenging has been reported as one of the best methods to measure the potential activity of methyl. This was reported in this research that *Marchantia* has antioxidant properties [77].

2.2. Anti-inflammatory activity

Anti-inflammatory activity is an activity that helps to reduce pain and decrease inflammation. Inflammation is the first response towards any infection or injury and is important for both innate and adaptive immunity. It is referred to as the complex biological molecule that generates a response towards the vascular tissues and some harmful irritants [40]. Some recent studies showed the activity of luteolin as an anti-inflammatory, luteolin has been referred to as the inhibition of iNOS (nitric oxygen synthase), scavenging of ROS (reactive oxygen species), and iNOS expression, and NO production. [58]. Inflammation molecules are TNF- α (tumor necrosis factor α), ILs (interleukins), and ROS. Luteolin causes an anti-inflammation effect by suppressing the production of cytokines and signals transduction pathways. Luteolin shows anti-inflammatory by regulating inflammatory mediators or cytokinesis by different *in vivo* and *in vitro* studies. When the inflammatory response occurs, the immune cells release many inflammatory mediators such as cytokines along with interleukins, interferons, and chemokines. These mediators help in eliminating pathogens and inhibit the repair process [80].

In vivo study, luteolin with Methoxy poly (ethylene glycol) reduces the inflammation of lung infection in the mice. Furthermore, reported that luteolin reduces the messenger RNA expression and induced inflammatory cytokines and chemokine in the macrophage process. Luteolin with MPEG-PLA enhanced the anti-inflammatory activity on lung epithelial cells and macrophages. Results revealed that luteolin/MPEG-PLA treatment could decrease the bond of *Klebsiella pneumonia* to lung epithelial cells of mice and improve the germicidal capacity of macrophages against *K. pneumonia*. [80].

Lipid polysaccharides induced the activation of NF-kB on lung homogenates from the male ICR mice. In pretreatment found that luteolin results show the reduced AKT activation on the concentration-dependent manner, with an IC_{50}. Further studies, luteolin down-regulated the LPS-induced the influx of the leukocytes into the alveolar space. In pulmonary inflammation, luteolin's effect on inflammatory signaling cascades and induced LPS (n-acetyl allosamine) though MAPK pathways inhibition was found. The effect mediate through significant the suppression on degradation on IkB, which is linked the activation of NF-kB. Rostoka was treated male Wistar rats with LPS and luteolin and found the luteolin inhibiting of induced LPS and expression of NF-kB in the lung but not in the brain cortex and myocardium.

Even in lung effect were limited by airway sub epithelium and not observed in the airway walls of alveolar and epithelium [81].

Another study reported that a male rat model of permanent focal cerebral ischemia through middle cerebral artery occlusion, luteolin treatment reduced the brain edema, infarct volume, and neurological deficit scores. The durable protection and efficiency conferred through the luteolin during stroke was also confirmed through molecular findings, included reducing the expression of NF-kB, TLR4, and TLR5. When the luteolin Implying that NF-kB, TLR4 and TLR5, could target this compound in its effectiveness against cerebral ischemia. Following luteolin, assessed by measuring the level of p65 level in the nucleus, inhibited the NF-kB activity in brain injury of a mouse. It reduces the inflammation in the injury of the brain [82].

Anti-inflammatory responses are identified by the coordination of different signaling pathways and anti-inflammatory mediators. Luteolin showed its effect when signaling pathways, are altered including AP-1/MAPK and NF-kB pathways. NF-kB signaling pathways are the most important factors for the transcription of pro-inflammatory mediators. NF-kB dimmers remain in the cytosol in the cell which is non-stimulated, its interaction with IkB (inhibitor of kappa B) proteins in the inactive form [83]. Upon the selective stimulation, IkB proteins were degraded through the IkB kinase (IKK) complex by the phosphorylation process. Luteolin has been reported to inhibit LPS induced TNF-α expression in fresh isolated neonatal mice. The study revealed that the significant degradation of cytosolic IkBβ increased the nuclear level in the NF-kB p65 subunit of LPS stimulated neonatal mice. After that, western blotting resulted from the localization of p65 and NF-kB. Luteolin reduced LPS induced which will result from the increase in NF-kB binding activity [84].

2.3. Anti-diabetic Activity

Diabetes mellitus is a disease characterized by hyperglycemia and caused by abnormal production of insulin in the blood. In 2010, globally 230 million people were affected due to diabetes (almost 6.2% of the total population), whereas, in 2019 this number increased to 8.8% and it has predicted in 2040 this rate will be increased more than 642 million the total world's population [85]. Effective treatment of type 2 diabetes and metabolic syndrome as a cause of diabetes will be of great benefit to the individual and the community. Flavonoids, as a rich natural resource, have received more attention because of their biological benefits. Most studies focused on the health effects of flavonoid-producing glycones, although flavonoids in natural foods are almost all available as their glycosides, indicating the need to study glycosides from flavonoids [86].

Luteolin is also one of the naturally occurring flavonoids; present in rich amount is many vegetables and fruits such as pepper and carrot. It possesses strong anti-inflammatory, antioxidant and [58] to improve insulin resistance in obese mice. In an *in vivo* study has been conducted in KK-*Ay* male mice to investigate the effect of luteolin and luteolin-7-*O*-glucoside (LUG) to check the anti-diabetic effect. The results of the study declared that blood glucose level, HbA_{1c}, insulin, and HOMR-IR levels have improved with the help of both luteolin (LU) and luteolin-7-*O*-glucoside (LUG) effect but luteolin has strong anti-diabetic potential as compared to luteolin-7-*O*-glucoside [86]. Another *in vivo* experiment was done on 3T3-L1 adipocytes, in terms of the anti-diabetic potential of luteolin has improved the diabetes-related key enzymes and improving insulin sensitivity in insulin-resistant adipocytes as a result of the enzymes [87]. Luteolin is a potentially beneficial flavonoid and has been reported to mediate many joint functions that promote luteolin as a significant anti-diabetic agent. Luteolin is considered a safe antioxidant. The production of free radicals followed by oxidative damage to pancreatic islet cells causes' diabetes. Luteolin can inhibit the production of reactive oxygen species (ROS) by inhibiting ROS-producing enzymes, can absorb ROS, and may protect against components of other antioxidant systems. Coupling of the anti-oxidant activity of the luteolin with hypoglycemic potential protects the pancreas and improves insulin secretion [88].

Luteolin is reported to improve insulin sensitivity by influencing Akt2 kinase.31 Akt2 inhibits the activation of the insulin receptor dephosphorylation and thus inhibits the slowing down of the insulin signaling process [89]. Akt2 is also responsible for regulating glucose uptake and this effect is regulated by the transfer of the GLUT4 glucose transporter to the cell surface. Luteolin can keep blood glucose levels at normal levels and thus prevent lipolysis [90]. This helps to keep triglyceride levels and total cholesterol within normal limits and prevents the onset of diabetes. Pan *et al*. suggest that Luteolin prevents the onset of diabetes with diabetes in the form of AKT / GSK 3β. In addition, luteolin has been shown to protect diabetic heart cells by performing the NOS method and improving ischemia/reperfusion injury [18].

Luteolin has great potential to treat diabetes. Several researchers have demonstrated the effect of luteolin in streptozotocin (STZ)-induced diabetic rats. The results show that luteolin significantly reduces blood glucose concentration, promotes non-invasive healing, and accelerates skin regeneration to streptozotocin (STZ) - diabetic rats [91].

2.4. Anti-carcinogenic activity

Cancer cells development can be blocked and delayed through luteolin, *in vitro* and *Vivo* studies show the inhibition of the tumor cell proliferation and apoptosis induction *via* the extrinsic and intrinsic signaling pathway. When it compared with the other flavonoids it is most effective than other, due to inhibiting the cell proliferation with lC_{50} value 50 μM [88].

It is reported some flavonoids are powerful inhibitors for multiple cancer cell lines, human normal fibroblasts, and keratinocytes in the low micromolar range. Luteolin was effective on all cell lines and among the most potent inhibitor with dihydroxyflavon, hydroxyflavoned, apigenin, and fisetin. These flavonoids also effectively inhibit bFGF (basic fibroblast growth factor) stimulated the growth of endothelial cells BBCE and VEGF (vascular endothelial growth factor) was induced *in vitro* angiogenesis of cells BME (bovine microvascular endothelial cells) [58].

Different flavonoids from the Citrus species are shown anti-proliferative activity on normal human cell lines and cancer cells, by using an assay with Alamar Blue, as an oxidation-reduction indicator. All types of flavonoids showed anti-proliferative affected on the normal human cell lines but only a few were affected at the lower concentrations on cancer cell lines. Luteolin was a stronger inhibitor in the IC_{50} 549 on carcinoma cells in human lung, 2.3 μM on the mouse 4A5 cells B16 melanoma, 2.0 μM in the human T-cell leukemia cells CCRF-HSB-2, and 1.3 μM on TGBC11TKB cells in human gastric cancer. Just natsudaidai was comparably compelling, trailed though tangerine quercetin. 4, 4'- Dihydrochalcone and luteolin were the most grounded inhibitors of human leukemic CEM-1 and CEM-C7 cell multiplication around 7 dietary substances. The results were affirmed though investigates P388 from the mouse in leukemic lymphocytes where luteolin has the most reduced IC_{50} esteem (1μM) of all flavonoids [92].

2.5. Anti-microbial activities

Flavonoids are also a very common source to provide essential substances against diseases and their treatments. There are the various types of flavonoids and one of them is luteolin. Luteolin is a compound that belongs to flavonoids is of the plant's secondary metabolites class. Epidemiological evidence suggests the important role of Luteolin against the therapies of various diseases [93]. Luteolin is widely present in plant sources and it is highly concentrated against microbes and their inhibition. There are many biological families in which the antimicrobial properties of luteolin have been identified. Those families are Bryophyte, Magnoliophyta, Pteridophyta, and Pinophyta. [66].

Some dietary sources of Luteolin encompass strong effects on microbes and their disease-related mechanisms. They are of poly-phenol class and have low molecular weight. The antibacterial activity depends on the structure. They have three mechanisms to show antibacterial activity against microbes. The first one is attenuated bacterial pathogenicity. In the second one, they synergistic-ally activate the antibodies. Thirdly, they kill the bacteria directly. The third one is further divided into three ways [85].

- Inhibition of nucleic acid synthesis.
- Inhibition of cytoplasmic membrane function.
- Inhibition of energy metabolism.
- Inhibition of nucleic acid synthesis: For example, in *Vibrio Harvey* cell, luteolin inhibit the synthesis of DNA and RNA with in 15 minutes in the bacteria cell.
- Inhibition of cytoplasmic membrane function: In galangin (7, hydroxylflavonol) potassium ions increased and damage the cytoplasmic membrane.

Inhibition of energy metabolism: Naringenin and apigenin and altered the outer membrane of cytoplasm in *E. coli*. It provides an exchange of nutrients and metabolites. It also supplies energy [94].

Luteolin derivatives have been isolated from the *Achillea tenuifolia's* ariel parts. After isolation, its purification is done by TLC, column chromatography, and some preparative techniques of column chromatography that helps in yielding compounds. Luteolin possesses some antibacterial activities against *Staphylococcus aureus (S.aureus)* which is methicilin resistant. The mechanism of anti-MRSA was analyzed by the viable assay in membrane permeability agents. By this mechanism over the dense suspensions that facilitate the activity of LUT and PGN completely blocks bacterial growth. So the LUT and PGN binding provides successful results and can be used for the antibacterial activity for low resistance [66].

In further study showed luteolin with manganese (II) by using the spectroscopy UV-visible thermogravimetric analysis. Luteolin-manganese (II) show antimicrobial activity, luteolin-manganese (II) complex are inhibition effect on xanthine oxidase was investigated. In spectroscopic results indicated, luteolin is reacted to manganese (II) by chelation of 4-

hydroxy and 5-hydroxyl molecules. When luteolin reacts with manganese (II) shows an antibacterial effect. Luteolin-manganese (II) complex are remarkable effect on hypoglycemic by increase glucose in liver tissues [95].

2.6. Antiviral activity of luteolin

Flavonoids enhance the production of interferon's β (IFN-β). It increases the activity of transcriptional nuclear factor; erythroid-related factor 2 (Nrf2). Luteolin shows low antiviral activity. It inhibits against influenza virus, targeting the COPI subunit (coat protein complex 1). It prevents the replication of the virus, blocks the virion absorption to the cell surface, and blocks the receptor-binding site of the viral hemagglutinin [97].

Luteolin act as the therapeutic agent against the Japanese encephalitis virus (JEV). It's a neurotropic flavivirus that causes (JE) disease. In humans, this disease leads to high fatality rates. As the studies suggested that luteolin has effective antiviral therapy against JEV. In A549 cells, luteolin showed extracellular virucidal activity against JEV. Luteolin directly inhibit the growth of the Japanese encephalitis virus at its post-entry stage. As the drug addiction time after replication gave successful results, so the luteolin can be used as an antiviral drug against JEV [97].

2.7. Antifungal activity of flavonoids

Flavonoids show spore germination of plant pathogenesis and propolis against dermatophytes. Candida spp. show highly content of flavonoids and galanin has found commonly in propolis samples [98].

2.8. Anticancer activity

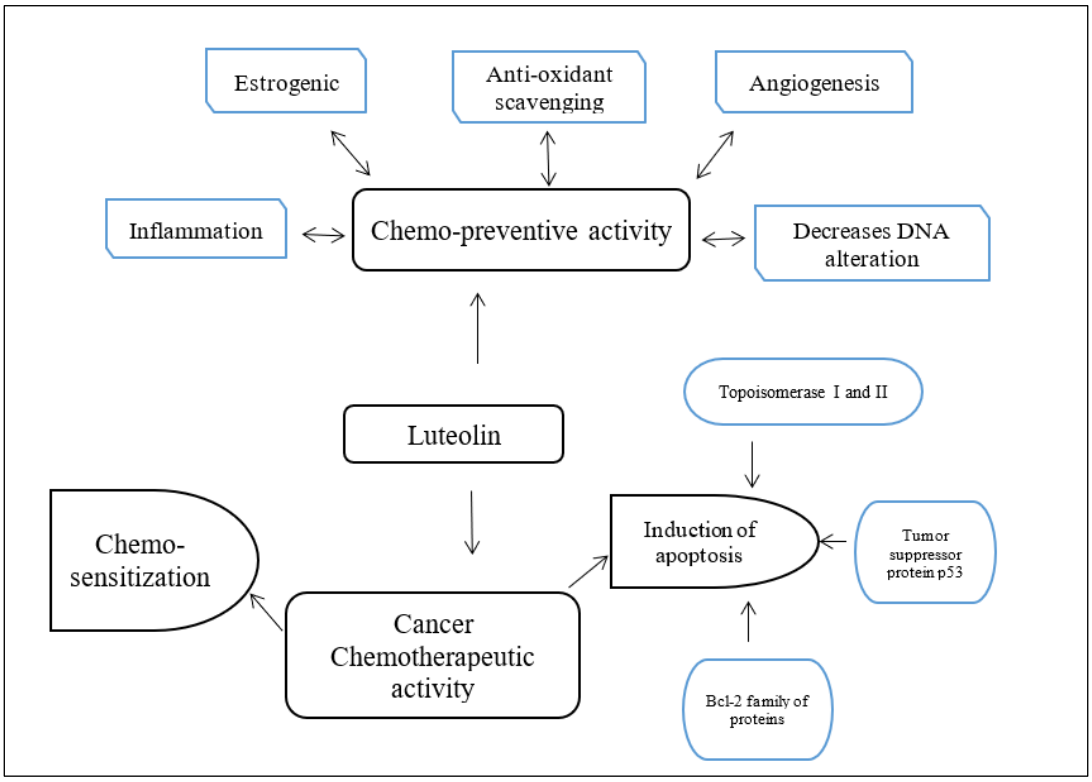

Figure 3 Mechanism of action of luteolin act as an anti-cancer agent

Flavonoids show anticancer activity, this activity reported in the last five years. Luteolin is a flavonoid that shows an anticancer agent against different types of human cancer like breast, colon, pancreatic, lung, and prostate cancer. *In vivo* and *in vitro* of luteolin block the cancer cell by the inhibition of tumor cell, activate the arrest cell cycle, protection the carcinogenicity, and induce apoptosis by signaling pathway [99]. Flavonoids are a source involving in antineoplastic molecules due to their ability of cancer-driving signaling pathways. Luteolin strongly effect on molecular mechanism and impact on targets such as DNA methylation and HDACs (histone deacetylase) enzyme are induce the cytotoxicity in cancer [100].

Luteolin was studied for its effective response against gastrointestinal cancerous cells. To treat gastrointestinal cancer, it is important to develop novel therapies and agents against cancerous cells. So, the exploitation of natural phytochemicals is a more effective therapy against the treatment of gastrointestinal cancer. Luteolin shows the inhibition of growth and apoptosis of a human cell line named Eca109; an esophageal squamous carcinoma cell line. By activation of ERK/MEK pathways that are signaling pathways, Luteolin exercises initial anti-migration and apoptotic effect on the cell lines of lungs that are A549. In advance, Luteolin impacts adenocarcinoma cells directly to inhibit the growth. It inhibits the migration of U87 MG cells by down-regulating Cdc42 expression. Luteolin is also effective against human glioblastoma cells. Mitochondrial membranes are targeted while down regulation of the Cdc42. miRNA expression is also targeted and regulated by luteolin to affect the progression of cancer [101].

Luteolin is an anti-cancer agent it exhibits anticancer potential in two ways, such as chemo-preventive and chemotherapeutic. Due to the antioxidant properties of luteolin against ROS, reduce DNA damage that help in treatment of breast cancer [102].

In chemo preventive activity, luteolin inhibits angiogenesis, decreases DNA alteration, estrogenic effect, antioxidant scavenging, and inflammation. This factor is mainly causing cancer. In chemotherapeutic activity, luteolin shows chemo-sensitization and induces apoptosis. Topoisomerase I and II, tumor suppressor protein, and the Bcl-2 family of proteins are involved in apoptosis. Luteolin stops the activity of cancer-causing factors and works as therapeutic agent [103].

By the activation of the antioxidant enzymes, luteolin induces HT29 colon cancer because it has antioxidant properties. This decreases the cell capability in colon cancer and does not affect normal colon cells. By activating of mitochondria-mediated caspase pathway in HT-29 cells luteolin reduced apoptosis. Due to luteolin activity, it enhanced the calcium level, the mitochondrial membrane action potential is lost, BAX proteins are regulated [104]. Superoxide dismutase and catalase are the enzymes that are activated when the luteolin have reduced the apoptosis in colon cancer. Luteolin enhanced the degree of decreased glutathione (GSH) and the declaration of GSH synthase, which catalyzes the second step of GSH biosynthesis. By the activation of the mitogen-activated protein kinase pathway, the apoptotic impact of luteolin was mediated. The current outcomes demonstrate that luteolin prompts apoptosis by developing cell reinforcement action and activating MAPK signaling in human colon disease cells [105].

MMS (methyl methanesulfonate) is an alkaline agent. It has shown cytotoxic effect and mutagenic effect. In the study of luteolin against methyl methanesulfonate toxic effect present in transgenic Drosophila. When drosophila is allowed to feed diet contain 10 μM of MMS with the 10, 20, and 40 μM of luteolin for 24 hours. After 24 hours, larvae were tested in ONPG assay, staining, and blue exclusion. If the dose increased the activity of β-glucosidase is decreased, damage of tissues such as Caspase-9/3 activated, apoptotic index, and damage of DNA observed in 10, 20, and 40 μM of luteolin with 10μM of MMS [106].

2.9. Neuroprotective effect of luteolin

Neurological disorders are medically defined as disorders that affect the brain and nerves throughout the human body and spinal cord [107,108,109]. Systemic structural, chemical or electrical disturbances in the brain, spinal cord, or other nerves can lead to a variety of symptoms. Flavonoids have many biological functions within the brain [110], including the ability to protect neurons from neurotoxin damage, the ability to suppress neuroinflammation, and the ability to stimulate memory, learning, and brain function [106]. Possible mechanisms include interaction with neuronal signaling pathways that are critical to regulating neuronal survival and differentiation and modulating function/multiple expression oxidative-related enzymes (e.g., endothelial NOS and SOD) and mitochondrial activity or neuroinflammation [111]. In experimental studies, the administration of flavonoids or flavonoid-rich diets (berry fruit) protects dopamine neurons from oxidative damage and apoptosis and inhibits the formation of synuclein fibrils. Because of these properties, it has been suggested that flavonoids (or their metabolites) passing through the blood-brain barrier (BBB) can reduce the risk of Parkinson's disease [112].

Luteolin plays an important role in neuron diseases like Alzheimer's disease, Parkinson's disease, and multiple sclerosis. According to *in vivo* study, dopaminergic neurons in Parkinson's disease are affected by lipopolysaccharide (LPS). The results suggest that luteolin may protect dopaminergic neurons from damage caused by LPS and its effect on inhibiting microglia production is less (Chen *et al*., 2018). Another study aims to investigate the effect of luteolin on memory impairment in streptozotocin (STZ) induced Alzheimer's mouse model. Luteolin significantly improved spatial learning and memory impairment resulting from STZ treatment. STZ significantly reduced the size of the CA1 pyramidal layer and luteolin treatment eliminated the inhibitory effect of STZ. Hence, luteolin has a protective effect on learning injuries and hippocampal structures in Alzheimer's disease (AD) [113].

2.10. Cardio protective effect of luteolin

Luteolin is a naturally occurring bioactive compound derived from vegetables and fruits with various uses including anti-inflammatory, anti-tumorigenic, anti-oxidative, and anti-inflammatory properties [114]. Cardiovascular diseases have become the leading cause of morbidity and mortality globally. In balanced diet with a sufficient intake of fruits and vegetables has been confirmed as the primary prevention of cardiovascular diseases. Plant constituents such as flavonoids have been shown to converse to healthy benefits. Luteolin exhibits strong cardiovascular protective effects by complex signal transduction pathways and target effectors. Moreover, food intake of rich sources of luteolin reduces the risk of myocardial infarction [115]. The cardioprotective effect mainly comes from moderated myocardial infarct size by increased left ventricular ejection fraction [67].

Sepsis-induced cardiomyopathy is the complication of severe sepsis and septic shock-induced due to invertible myocardial depression. Luteolin reduces lipid polysaccharides (LPS) induced myocardial injury by enhancing autophagy through AMP-activated protein kinases. Luteolin administration not only improved cardiac function but also reduced inflammatory response along with oxidative stress, improved autophagy that ultimately repressed cardiac apoptosis. Meanwhile, luteolin significantly reduced the phosphorylation of AMPK in septic heart tissue. So, in such a way, it could be considered as a promising therapeutic, bioactive compound, against sepsis-induced cardiopathy [116].

The potential impact of luteolin on doxorubicin-induced cardio toxicity was studied and the mechanisms involved in focusing on mitochondrial autophagy were. The use of luteolin (10 μM) in adult mouse cardiomyocytes significantly improved contractor doxorubicin dysfunction caused by high blood pressure and high speed/recovery as well as the normal duration of remodeling and recovery [117]. Luteolin reduced doxorubicin causing cardio toxicity including accumulation of ROS (reactive oxygen species), apoptosis, and loss of mitochondrial membrane. In addition, luteolin reduced doxorubicin-induced cardio toxicity by promoting mitochondrial autophagy in conjunction with Drp1 phosphorylation in Ser616 and improved TFEB expression. In addition, luteolin treatment reduced the dose of doxorubicin which reduced the expansion of mitochondria [118]. Treatment with the Divi-1, a Drp1 GTPase inhibitor, challenges the protective effect of luteolin at TFEB, LAMP1, and LC3B levels, as well as loss of mitochondrial membrane and cardiomyocyte contractile dysfunction when challenged of doxorubicin. Taken together, these findings provide insight into the effect of luteolin treatment against the cardio toxicity induced by doxorubicin and possibly on the formation of mitochondrial autophagy [98].

Another *in vivo* study aims to test whether luteolin can improve long-term cardiovascular preservation; this was achieved by cardiac examination following long-term retention in the University of Wisconsin (control group) solution and solutions containing three luteolin concentrations [119]. The effects of various conservation measures were assessed about cardiac function while the hearts were in systems made with *ex vivo* Lutgendorf perfusion. Various conservation approaches were explored about histology, ultrastructure and cardiac apoptosis rate, and cardiomyocyte function. In the presence of luteolin, the output of the left ventricular pressure was increased within 60 minutes of reactivation after 12-h maintenance, the coronary flow was elevated within 30 minutes of recurrence, contractile cardiac function was higher in all recurrence following 12- and 18 -h conservation, the upper left systolic pressure was significantly higher compared to the control group (total $P < 0.05$). The expression levels of the apoptosis regulator Bax and the apoptosis regulator Bcl-2 in the luteolin groups are greatly reduced and increased respectively (Yan *et al*., 2019). Lactate dehydrogenase, creatine kinase, and malondialdehyde enzymatic activity increased following long-term maintenance, while superoxide dismutase activity decreased significantly [120]. In addition, luteolin inhibits L-type calcium in the ventricular myocytes under hypoxia conditions. Therefore, luteolin has shown protective effects during long-term cardiac preservation in what appears to be a dose-dependent approach, which can be achieved by blocking hypoxia-dependent L-type channels [121].

2.11. Toxicity of luteolin

Luteolin present in the form of flavone, subclass of flavonoids as 5, 7, 3, 4-tetrahydroxyflavone. Luteolin investigated for its toxicity, experiment conducted on human lymphoblastoid TK6 cells and newly developed TK6 derived cell line which expresses stable human cytochrome P450. The other derivatives of CYP450 are CYP1A2, CYP2A6, CYP2B6, and CYP1A1 evaluated for luteolin induced genotoxicity and cytotoxicity and the action of different CPYs in the bioactivation of luteolin. Treatment with luteolin for 4-24 h induced the cytotoxicity, chromosomal and DNA damage, apoptosis and DNA damage in dose dependent manner. In micronucleus assay, it is observed that luteolin highly induced genotoxicity and cytotoxicity, by significantly increasing the TK6 cell transducers with CYP1A1 and CYP1A2. Additionally, DNA damage biomarkers (cleaved caspase 3, cleaved PARP-1, phosphorylated histone 2AX) and apoptosis, were increased in CYP1A1 and CYP1A2 expressing cell as compared to the empty vector controls [85].

MTX (Methotrexate) is the drug that uses in the treatment of autoimmune disease and cancer disease. The effect of MTX is shown in hepato-renal toxicity. Luteolin is helped to protect the effect toxicity of hepato-renal. Due to the properties of luteolin like anti-inflammation and anti-oxidant, it is helpful in the toxicity of MTX [122].

Further study showed that luteolin found to be protective against $A\beta_{25-35}$ (amyloid-beta) that induce toxicity in mice. In experimental mice, the $A\beta_{25-35}$ peptide injected. After oral administration of luteolin for 8 days and observed the changes in the ultrastructure of the cerebral cortex, neuronal changes, dysfunction of cerebrovascular of mice. Results indicated that after 8 doses of luteolin induces neurovascular protection against the $A\beta_{25-35}$ toxicity in mice. These effect modulation in microvascular function, clear the ROS and improve the neuronal system [123].

3. Conclusion

This review summarized the mechanism and effect of luteolin as a flavonoid. Its role in heart failure and protection against neurodegenerative disease, anti-microbial, anti-cancer, anti-inflammatory, cancer chemo preventive activity, cancer chemotherapeutic activity, and other biological activities like cardio protective, anti-diabetic, anti-allergic, etc. The diet and consumption of bioactive compounds from natural resources including fruits and vegetables have been studied for their preventive role against the variety of human diseases. This food-based product is considered to be safer and more effective against various ailments. In summary of luteolin can be considered as complementary medicine for the prevention and treatment of disease owing to its natural origin safety and low cost as compared to the synthetic drug. Flavonoids are also play important role in signal transduction and cell transformation. Luteolin is the capacity to repress angiogenesis for the promotion of apoptotic cell death. Flavonoids are regular constituents of plants utilize in traditional medication for the treatment of infection. Though most of the findings in the current work are based on in vitro and in vivo, studies do not significantly present its effect in humans. So, more work on multiple pharmacokinetics parameters and enrollment of human subjects. Furthermore, the development of dosage standing could also persuade in the clinical trial. Future achievements focused on the enhancement of bioavailability and provide a new era of flavonoid-based potential anticancer drugs and insights into their mechanism of cancer inhibition.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Craker LE, Gardner ZE. Medicinal plants and tomorrow's pharmacy: an American perspective. Frontis. 2006 Nov 1:29-41.

[2] Khan MS, Ahmad I. Herbal medicine: current trends and future prospects. InNew look to phytomedicine 2019 Jan 1 (pp. 3-13). Academic Press.

[3] Husain SZ, Malik RN, Javaid M, Bibi SA. Ethonobotanical properties and uses of medicinal plants of Morgah biodiversity park, Rawalpindi. Pak J Bot. 2008 Oct 1;40(5):1897-911.

[4] Rashid R, Mukhtar F, Niaz MM. Biological screening of Salvia cabulica. Pak. J. Bot. 2009 Jun 1;41(3):1453-62.

[5] Madikizela B. *Pharmacological evaluation of South African medicinal plants used for treating tuberculosis and related symptoms* (Doctoral dissertation).

[6] Hosseinzadeh S, Jafarikukhdan A, Hosseini A, Armand R. The application of medicinal plants in traditional and modern medicine: a review of Thymus vulgaris. International Journal of Clinical Medicine. 2015 Sep 2;6(9):635-42.

[7] Kalyani Pathak KP, Das RJ. Herbal medicine-a rational approach in health care system.

[8] Igoli JO, Ogaji OG, Tor-Ayiin TA, Igoli NP. Traditional medicine practice amongst the Igede people of Nigeria. Part II. African Journal of Traditional, Complementary and Alternative Medicines. 2005;2(2):134-52.

[9] Jain S, Mehata MS. Medicinal plant leaf extract and pure flavonoid mediated green synthesis of silver nanoparticles and their enhanced antibacterial property. Scientific reports. 2017 Nov 20;7(1):15867.

[10] Khan MS, Qais FA, Ahmad I. Indian berries and their active compounds: Therapeutic potential in cancer prevention. InNew Look to Phytomedicine 2019 Jan 1 (pp. 179-201). Academic Press.

[11] Mamedov N. Medicinal plants studies: history, challenges and prospective. Med Aromat Plants. 2012 Oct;1(8):e133.

[12] Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC. Heart failure: preventing disease and death worldwide. ESC heart failure. 2014 Sep;1(1):4-25.

[13] Kangas B. Hope from abroad in the international medical travel of Yemeni patients. Anthropology & Medicine. 2007 Dec 1;14(3):293-305.

[14] Payyappallimana U. Role of traditional medicine in primary health care: an overview of perspectives and challenging. 横浜国際社会科学研究= Yokohama journal of social sciences. 2010 Feb 20;14(6):57-77.

[15] Debas HT, Laxminarayan R, Straus SE. Complementary and alternative medicine.

[16] Jamshidi N, Cohen MM. The clinical efficacy and safety of Tulsi in humans: a systematic review of the literature. Evidence-Based Complementary and Alternative Medicine. 2017;2017(1):9217567.

[17] Masarkar N, Mukherjee S, Goel SK, Nema R. Naturally derived formulations and prospects towards cancer. Health. 2019 Jul 3;11(7):971-97.

[18] Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ, Zhang SF, Tang MK, Sun JN, Ko KM. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. Evidence-Based Complementary and Alternative Medicine. 2014;2014(1):525340.

[19] Karunamoorthi K, Jegajeevanram K, Vijayalakshmi J, Mengistie E. Traditional medicinal plants: a source of phytotherapeutic modality in resource-constrained health care settings. Journal of Evidence-Based Complementary & Alternative Medicine. 2013 Jan;18(1):67-74.

[20] Baharvand-Ahmadi B, Bahmani M, Naghdi N, Saki K, Baharvand-Ahmadi S, Rafieian-Kopaei M. Review on phytochemistry, therapeutic and pharmacological effects of myrtus (Myrtus communis). Der Pharmacia Lettre. 2015;7(11):160-5.

[21] Gunjan M, Naing TW, Saini RS, Ahmad A, Naidu JR, Kumar I. Marketing trends & future prospects of herbal medicine in the treatment of various disease. World Journal of Pharmaceutical Research. 2015 Jun 28;4(9):132-55.

[22] Azmir J, Zaidul IS, Rahman MM, Sharif KM, Mohamed A, Sahena F, Jahurul MH, Ghafoor K, Norulaini NA, Omar AK. Techniques for extraction of bioactive compounds from plant materials: A review. Journal of food engineering. 2013 Aug 1;117(4):426-36.

[23] Karasawa MM, Mohan C. Fruits as prospective reserves of bioactive compounds: a review. Natural products and bioprospecting. 2018 Oct;8:335-46.

[24] Kumari A, Bhawal S, Kapila S, Yadav H, Kapila R. Health-promoting role of dietary bioactive compounds through epigenetic modulations: a novel prophylactic and therapeutic approach. Critical Reviews in Food Science and Nutrition. 2022 Jan 25;62(3):619-39.

[25] Al-Juhaimi F, Ghafoor K, Özcan MM, Jahurul MH, Babiker EE, Jinap S, Sahena F, Sharifudin MS, Zaidul IS. Effect of various food processing and handling methods on preservation of natural antioxidants in fruits and vegetables. Journal of food science and technology. 2018 Oct;55:3872-80.

[26] Castellano G, González-Santander JL, Lara A, Torrens F. Classification of flavonoid compounds by using entropy of information theory. Phytochemistry. 2013 Sep 1;93:182-91.

[27] Sasidharan S, Chen Y, Saravanan D, Sundram KM, Latha LY. Extraction, isolation and characterization of bioactive compounds from plants' extracts. African journal of traditional, complementary and alternative medicines. 2011;8(1).

[28] Garcia-Salas P, Morales-Soto A, Segura-Carretero A, Fernández-Gutiérrez A. Phenolic-compound-extraction systems for fruit and vegetable samples. Molecules. 2010 Dec 3;15(12):8813-26.

[29] Mahomoodally MF, Gurib-Fakim A, Subratty AH. Antimicrobial activities and phytochemical profiles of endemic medicinal plants of Mauritius. Pharmaceutical biology. 2005 Jan 1;43(3):237-42.

[30] Pandey AK. Anti-staphylococcal activity of a pan-tropical aggressive and obnoxious weed Parthenium histerophorus: an in vitro study.

[31] Harborne JB, Marby H, Marby TJ. The flavonoids. Springer; 2013 Nov 11.

[32] Kumar S, Mishra A, Pandey AK. Antioxidant mediated protective effect of Parthenium hysterophorus against oxidative damage using in vitro models. BMC complementary and alternative medicine. 2013 Dec;13:1-9.

[33] Agati G, Azzarello E, Pollastri S, Tattini M. Flavonoids as antioxidants in plants: location and functional significance. Plant science. 2012 Nov 1;196:67-76.

[34] Du F, Zhang F, Chen F, Wang A, Wang Q, Yin X, Wang S. Advances in microbial heterologous production of flavonoids. African Journal of Microbiology Research. 2011 Sep 16;5(18):2566-74.

[35] Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. Journal of nutritional science. 2016 Jan;5:e47.

[36] Khan UM, Sevindik M, Zarrabi A, Nami M, Ozdemir B, Kaplan DN, Selamoglu Z, Hasan M, Kumar M, Alshehri MM, Sharifi-Rad J. Lycopene: Food sources, biological activities, and human health benefits. Oxidative medicine and cellular longevity. 2021;2021(1):2713511.

[37] Kim MJ, Moon Y, Tou JC, Mou B, Waterland NL. Nutritional value, bioactive compounds and health benefits of lettuce (Lactuca sativa L.). Journal of Food Composition and Analysis. 2016 Jun 1;49:19-34.

[38] Liu RH. Dietary bioactive compounds and their health implications. Journal of food science. 2013 Jun;78(s1):A18-25.

[39] Razavi-Azarkhiavi K, Iranshahy M, Sahebkar A, Shirani K, Karimi G. The protective role of phenolic compounds against doxorubicin-induced cardiotoxicity: a comprehensive review. Nutrition and cancer. 2016 Aug 17;68(6):892-917.

[40] Aziz N, Kim MY, Cho JY. Anti-inflammatory effects of luteolin: A review of in vitro, in vivo, and in silico studies. Journal of ethnopharmacology. 2018 Oct 28;225:342-58.

[41] Gupta SC, Prasad S, Tyagi AK, Kunnumakkara AB, Aggarwal BB. Neem (Azadirachta indica): An indian traditional panacea with modern molecular basis. Phytomedicine. 2017 Oct 15;34:14-20.

[42] Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H. Medicinal plants: Past history and future perspective. Journal of herbmed pharmacology. 2017 Dec 29;7(1):1-7.

[43] Kulkarni KV, Adavirao BV. A review on: Indian traditional shrub Tulsi (Ocimum sanctum): the unique medicinal plant. Journal of Medicinal Plants Studies. 2018;6(2):106-10.

[44] Bahadori MB, Zengin G, Bahadori S, Dinparast L, Movahhedin N. Phenolic composition and functional properties of wild mint (Mentha longifolia var. calliantha (Stapf) Briq.). International journal of food properties. 2018 Jan 1;21(1):183-93.

[45] Ajmera P, Kalani S, Sharma L. Parsley-benefits & side effects on health. International Journal of Physiology, Nutrition and Physical Education. 2019;4(1):1236-42.

[46] Sahu PK, Giri DD, Singh R, Pandey P, Gupta S, Shrivastava AK, Kumar A, Pandey KD. Therapeutic and medicinal uses of Aloe vera: a review. Pharmacology & Pharmacy. 2013 Nov 8;4(08):599.

[47] Singletary KW. Fenugreek: overview of potential health benefits. Nutrition Today. 2017 Mar 1;52(2):93-111.

[48] Bajaj M, Naaz A. A Review on Lemongrass Essential Oil-a Blessing to Human Being. Manya Bajaj, Aaliya Naaz, Dr. Vijay Singh," A review on lemongrass essential oil-A blessing to human being", International Journal of Creative Research Thoughts (IJCRT), ISSN. 2023 Dec 12:2320-882.

[49] Mumu SK, Hossain MM. Antimicrobial activity of tea tree oil against pathogenic bacteria and comparison of its effectiveness with eucalyptus oil, lemongrass oil and conventional antibiotics. American Journal of Microbiological Research. 2018 Jun;6(3):73-8.

[50] Kumar D, Nikhil K. Vetiver grass for manifold uses: a critical review. Int J Eng Tech Res. 2016 Feb;4(2):146-52.

[51] Rajeshwari CU, Kumar AV, Andallu B. Therapeutic Potential of Ajwain (Tracyspermum ammi L.) Seeds. InNuts and seeds in health and disease prevention 2011 Jan 1 (pp. 153-159). Academic Press.

[52] Singh A, editor. Herbalism, phytochemistry and ethnopharmacology. CRC Press; 2011 Apr 11.

[53] Mishra S. A review of super food ajwain and its pharmacological actions. International Journal of Research in Pharma & Pharmaceutical Science. 2020;1(1):30-3.

[54] Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutrition journal. 2002 Dec;1:1-4.

[55] Verma T, Aggarwal A, Dey P, Chauhan AK, Rashid S, Chen KT, Sharma R. Medicinal and therapeutic properties of garlic, garlic essential oil, and garlic-based snack food: An updated review. Frontiers in nutrition. 2023 Feb 16;10:1120377.

[56] Cerrato A, De Santis D, Moresi M. Production of luteolin extracts from Reseda luteola and assessment of their dyeing properties. Journal of the Science of Food and Agriculture. 2002 Aug;82(10):1189-99.

[57] Maher HM, Al-Zoman NZ, Al-Shehri MM, Al-Showiman H, Al-Taweel AM, Fawzy GA, Perveen S. Determination of luteolin and apigenin in herbs by capillary electrophoresis with diode array detection. Instrumentation Science & Technology. 2015 Nov 2;43(6):611-25.

[58] Seelinger G, Merfort I, Schempp CM. Anti-oxidant, anti-inflammatory and anti-allergic activities of luteolin. Planta medica. 2008 Nov;74(14):1667-77.

[59] Lin LC, Pai YF, Tsai TH. Isolation of luteolin and luteolin-7-O-glucoside from Dendranthema morifolium Ramat Tzvel and their pharmacokinetics in rats. Journal of agricultural and food chemistry. 2015 Sep 9;63(35):7700-6.

[60] Ramešová Š, Sokolová R, Tarábek J, Degano I. The oxidation of luteolin, the natural flavonoid dye. Electrochimica Acta. 2013 Nov 1;110:646-54.

[61] Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence and intake. The Journal of nutrition. 2003 Oct 1;133(10):3248S-54S.

[62] Mencherini T, Picerno P, Scesa C, Aquino R. Triterpene, antioxidant, and antimicrobial compounds from Melissa officinalis. Journal of natural products. 2007 Dec 28;70(12):1889-94.

[63] Du GH. Natural small molecule drugs from plants. Berlin/Heidelberg, Germany: Springer; 2018 Nov 19.

[64] Lin Y, Shi R, Wang X, Shen HM. Luteolin, a flavonoid with potential for cancer prevention and therapy. Current cancer drug targets. 2008 Nov 1;8(7):634-46.

[65] Manzoor MF, Ahmad N, Manzoor A, Kalsoom A. Food based phytochemical luteolin their derivatives, sources and medicinal benefits. Int. J. Agric. Life Sci. IJAL. 2017;3(11):1.

[66] López-Lázaro M. Distribution and biological activities of the flavonoid luteolin. Mini reviews in medicinal chemistry. 2009 Jan 1;9(1):31-59.

[67] Luo Y, Shang P, Li D. Luteolin: a flavonoid that has multiple cardio-protective effects and its molecular mechanisms. Frontiers in Pharmacology. 2017 Oct 6;8:692.

[68] Chowdhury AR, Sharma S, Mandal S, Goswami A, Mukhopadhyay S, Majumder HK. Luteolin, an emerging anti-cancer flavonoid, poisons eukaryotic DNA topoisomerase I. Biochemical Journal. 2002 Sep 1;366(2):653-61.

[69] Mukinda JT, Syce JA, Fisher D, Meyer M. Effect of the plant matrix on the uptake of luteolin derivatives-containing Artemisia afra aqueous-extract in Caco-2 cells. Journal of ethnopharmacology. 2010 Aug 9;130(3):439-49.

[70] Leopoldini M, Pitarch IP, Russo N, Toscano M. Structure, conformation, and electronic properties of apigenin, luteolin, and taxifolin antioxidants. A first principle theoretical study. The Journal of Physical Chemistry A. 2004 Jan 8;108(1):92-6.

[71] Fink BN, Gaudet MM, Britton JA, Abrahamson PE, Teitelbaum SL, Jacobson J, Bell P, Thomas JA, Kabat GC, Neugut AI, Gammon MD. Fruits, vegetables, and micronutrient intake in relation to breast cancer survival. Breast cancer research and treatment. 2006 Jul;98:199-208.

[72] Özgen U, Mavi A, Terzi Z, Kazaz C, Asçi A, Kaya Y, Seçen H. Relationship between chemical structure and antioxidant activity of luteolin and its glycosides isolated from T. sipyleus subsp. sipyleus var. sipyleus. Records of Natural Products. 2011;5(1):12.

[73] Francisco V, Figueirinha A, Costa G, Liberal J, Lopes MC, García-Rodríguez C, Geraldes CF, Cruz MT, Batista MT. Chemical characterization and anti-inflammatory activity of luteolin glycosides isolated from lemongrass. Journal of functional foods. 2014 Sep 1;10:436-43.

[74] Huy NT, Van Trang N, Xuyen NT, Hong CT, Anh VT, Thai VQ, Van Cuong B, Van TT, Dai Lam T, Hoan NT, Thuy PT. Studies on the antioxidant activity of apigenin, luteolin and nevadensin using DFT. Vietnam Journal of Science and Technology. 2021 Jan 15;59(1):19-29.

[75] Adeyanju AA, Oyedeji TA, Adebagbo WB, Oluyitan OP, Adeyanju SA. Protective Effects of Luteolin and Gallic Acid Against Storage-Induced Oxidative Damage in Whole Blood of Female Wistar Rats. Applied In Vitro Toxicology. 2021 Jun 1;7(2):61-70.

[76] Wei B, Lin Q, Ji YG, Zhao YC, Ding LN, Zhou WJ, Zhang LH, Gao CY, Zhao W. Luteolin ameliorates rat myocardial ischaemia–reperfusion injury through activation of peroxiredoxin II. British journal of pharmacology. 2018 Aug;175(16):3315-32.

[77] Gökbulut A, SatilmiŞ B, Batçioğlu K, Cetin B, Şarer E. Antioxidant activity and luteolin content of Marchantia polymorpha L. Turkish Journal of Biology. 2012;36(4):381-5.

[78] Asthana AK, Srivastava A, Sahu V. An Observation on Morphogenetic Response of Marchantia polymorpha subsp. ruderalis Bischl. and Boissel.-Dub. in Different Culture Media. INTERNATIONAL JOURNAL OF PLANT AND ENVIRONMENT. 2018 Jan 31;4(01):64-9.

[79] Azab A, Nassar A, Azab AN. Anti-inflammatory activity of natural products. Molecules. 2016 Oct 1;21(10):1321.

[80] Miao J, Lin F, Huang N, Teng Y. Improving anti-inflammatory effect of luteolin with nano-micelles in the bacteria-induced lung infection. Journal of Biomedical Nanotechnology. 2021 Jun 1;17(6):1229-41.

[81] Kuo MY, Liao MF, Chen FL, Li YC, Yang ML, Lin RH, Kuan YH. Luteolin attenuates the pulmonary inflammatory response involves abilities of antioxidation and inhibition of MAPK and NFκB pathways in mice with endotoxin-induced acute lung injury. Food and Chemical Toxicology. 2011 Oct 1;49(10):2660-6.

[82] Nunes C, Almeida L, Barbosa RM, Laranjinha J. Luteolin suppresses the JAK/STAT pathway in a cellular model of intestinal inflammation. Food & function. 2017;8(1):387-96.

[83] Oeckinghaus A, Ghosh S. The NF-κB family of transcription factors and its regulation. Cold Spring Harbor perspectives in biology. 2009 Oct 1;1(4):a000034.

[84] Kim HJ, Lee W, Yun JM. Luteolin inhibits hyperglycemia-induced proinflammatory cytokine production and its epigenetic mechanism in human monocytes. Phytotherapy research. 2014 Sep;28(9):1383-91.

[85] Li X, He X, Chen S, Le Y, Bryant MS, Guo L, Witt KL, Mei N. The genotoxicity potential of luteolin is enhanced by CYP1A1 and CYP1A2 in human lymphoblastoid TK6 cells. Toxicology letters. 2021 Jun 15;344:58-68.

[86] Tobey N. A Multiphasic Phylogenetic and Genomic Characterization of the Fungal Endophyte Stemphylium Strain PNW2016-02 and a Semi-Automated Bioinformatic Approach to Investigating the Strain Secretome (Master's thesis, Purdue University).

[87] Swain A. Luteolin and its derivatives as potential antidiabetic drug ingredients. Chemistry & Biology Interface. 2021 May 1;11(3).

[88] Ashrafizadeh M, Ahmadi Z, Farkhondeh T, Samarghandian S. Autophagy regulation using luteolin: new insight into its anti-tumor activity. Cancer Cell International. 2020 Nov 4;20(1):537.

[89] Mackenzie RW, Elliott BT. Akt/PKB activation and insulin signaling: a novel insulin signaling pathway in the treatment of type 2 diabetes. Diabetes, metabolic syndrome and obesity: targets and therapy. 2014 Feb 13:55-64.

[90] Babu PV, Liu D, Gilbert ER. Recent advances in understanding the anti-diabetic actions of dietary flavonoids. The Journal of nutritional biochemistry. 2013 Nov 1;24(11):1777-89.

[91] Chen HQ, Jin ZY, Wang XJ, Xu XM, Deng L, Zhao JW. Luteolin protects dopaminergic neurons from inflammation-induced injury through inhibition of microglial activation. Neuroscience letters. 2008 Dec 26;448(2):175-9.

[92] Stefan SM, Wiese M. Small-molecule inhibitors of multidrug resistance-associated protein 1 and related processes: A historic approach and recent advances. Medicinal Research Reviews. 2019 Jan;39(1):176-264.

[93] Adamczak A, Ożarowski M, Karpiński TM. Antibacterial activity of some flavonoids and organic acids widely distributed in plants. Journal of clinical medicine. 2019 Dec 31;9(1):109.

[94] Gallegos MT, Vargas Gallego PA, Rodríguez-García I. Antibacterial actions of flavonoids.

[95] Dong H, Yang X, He J, Cai S, Xiao K, Zhu L. Enhanced antioxidant activity, antibacterial activity and hypoglycemic effect of luteolin by complexation with manganese (II) and its inhibition kinetics on xanthine oxidase. Rsc Advances. 2017;7(84):53385-95.

[96] Cushnie TT, Lamb AJ. Antimicrobial activity of flavonoids. International journal of antimicrobial agents. 2005 Nov 1;26(5):343-56.

[97] Fan W, Qian S, Qian P, Li X. Antiviral activity of luteolin against Japanese encephalitis virus. Virus research. 2016 Jul 15;220:112-6.

[98] Xu X, Pu R, Li Y, Wu Z, Li C, Miao X, Yang W. Chemical compositions of propolis from China and the United States and their antimicrobial activities against Penicillium notatum. Molecules. 2019 Oct 4;24(19):3576.

[99] Imran M, Rauf A, Abu-Izneid T, Nadeem M, Shariati MA, Khan IA, Imran A, Orhan IE, Rizwan M, Atif M, Gondal TA. Luteolin, a flavonoid, as an anticancer agent: A review. Biomedicine & Pharmacotherapy. 2019 Apr 1;112:108612.

[100] Ganai SA, Sheikh FA, Baba ZA, Mir MA, Mantoo MA, Yatoo MA. Anticancer activity of the plant flavonoid luteolin against preclinical models of various cancers and insights on different signalling mechanisms modulated. Phytotherapy Research. 2021 Jul;35(7):3509-32.

[101] Pu Y, Zhang T, Wang J, Mao Z, Duan B, Long Y, Xue F, Liu D, Liu S, Gao Z. Luteolin exerts an anticancer effect on gastric cancer cells through multiple signaling pathways and regulating miRNAs. Journal of Cancer. 2018;9(20):3669.

[102] Ahmed S, Khan H, Fratantonio D, Hasan MM, Sharifi S, Fathi N, Ullah H, Rastrelli L. Apoptosis induced by luteolin in breast cancer: Mechanistic and therapeutic perspectives. Phytomedicine. 2019 Jun 1;59:152883.

[103] Kato H, Naiki-Ito A, Suzuki S, Inaguma S, Komura M, Nakao K, Naiki T, Kachi K, Kato A, Matsuo Y, Takahashi S. DPYD, down-regulated by the potentially chemopreventive agent luteolin, interacts with STAT3 in pancreatic cancer. Carcinogenesis. 2021 Jul 1;42(7):940-50.

[104] Mehta RS, Nishihara R, Cao Y, Song M, Mima K, Qian ZR, Nowak JA, Kosumi K, Hamada T, Masugi Y, Bullman S. Association of dietary patterns with risk of colorectal cancer subtypes classified by Fusobacterium nucleatum in tumor tissue. JAMA oncology. 2017 Jul 1;3(7):921-7.

[105] Kang KA, Piao MJ, Ryu YS, Hyun YJ, Park JE, Shilnikova K, Zhen AX, Kang HK, Koh YS, Jeong YJ, Hyun JW. Luteolin induces apoptotic cell death via antioxidant activity in human colon cancer cells. International journal of oncology. 2017 Oct 1;51(4):1169-78.

[106] Siddique YH, Akhtar S, Rahul, Ansari MS, Shakya B, Jyoti S, Naz F. Protective effect of Luteolin against methyl methanesulfonate-induced toxicity. Toxin reviews. 2021 Jan 2;40(1):65-76.

[107] Feigin VL, Vos T, Alahdab F, Amit AM, Bärnighausen TW, Beghi E, Beheshti M, Chavan PP, Criqui MH, Desai R, Dharmaratne SD. Burden of neurological disorders across the US from 1990-2017: a global burden of disease study. JAMA neurology. 2021 Feb 1;78(2):165-76.

[108] Graus F, Saiz A, Dalmau J. GAD antibodies in neurological disorders—insights and challenges. Nature Reviews Neurology. 2020 Jul;16(7):353-65.

[109] Chaudhuri A, Behan PO. Fatigue in neurological disorders. The lancet. 2004 Mar 20;363(9413):978-88.

[110] Khan A, Ikram M, Hahm JR, Kim MO. Antioxidant and anti-inflammatory effects of citrus flavonoid hesperetin: Special focus on neurological disorders. Antioxidants. 2020 Jul 10;9(7):609.

[111] Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology. 2012 Apr 10;78(15):1138-45.

[112] Kroon PA, Clifford MN, Crozier A, Day AJ, Donovan JL, Manach C, Williamson G. How should we assess the effects of exposure to dietary polyphenols in vitro?. The American journal of clinical nutrition. 2004 Jul 1;80(1):15-21.

[113] Wang H, Wang H, Cheng H, Che Z. Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. Molecular medicine reports. 2016 May 1;13(5):4215-20.

[114] Garg P, Awasthi S, Horne D, Salgia R, Singhal SS. The innate effects of plant secondary metabolites in preclusion of gynecologic cancers: Inflammatory response and therapeutic action. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2023 Jul 1;1878(4):188929.

[115] Qi L, Pan H, Li D, Fang F, Chen D, Sun H. Luteolin improves contractile function and attenuates apoptosis following ischemia–reperfusion in adult rat cardiomyocytes. European journal of pharmacology. 2011 Oct 1;668(1-2):201-7.

[116] Zhu M, Sun Y, Su Y, Guan W, Wang Y, Han J, Wang S, Yang B, Wang Q, Kuang H. Luteolin: A promising multifunctional natural flavonoid for human diseases. Phytotherapy Research. 2024 Apr 26.

[117] Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacological reviews. 2004 Jun 1;56(2):185-229.

[118] Settembre C, Ballabio A. TFEB regulates autophagy: an integrated coordination of cellular degradation and recycling processes. Autophagy. 2011 Nov 1;7(11):1379-81.

[119] Benhabbouche S, Crola da Silva C, Abrial M, Ferrera R. The basis of ischemia-reperfusion and myocardial protection. InAnnales Francaises D'anesthesie et de Reanimation 2011 May 1 (Vol. 30, pp. S2-16).

[120] Zohier AS, Baraka TA, Abdelgalil AI, Aboelmaaty AM, Yehia SG. Oxidative stress biomarkers status in selected equine sports. Comparative Clinical Pathology. 2023 Jun;32(3):461-6.

[121] Yan Q, Li Y, Yan J, Zhao Y, Liu Y, Liu S. Luteolin improves heart preservation through inhibiting hypoxia-dependent L-type calcium channels in cardiomyocytes. Experimental and therapeutic medicine. 2019 Mar 1;17(3):2161-71.

[122] Dar AA, Fehaid A, Alkhatani S, Alarifi S, Alqahtani WS, Albasher G, Almeer R, Alfarraj S, Moneim AA. The protective role of luteolin against the methotrexate-induced hepato-renal toxicity via its antioxidative, anti-inflammatory, and anti-apoptotic effects in rats. Human & Experimental Toxicology. 2021 Jul;40(7):1194-207.

[123] Liu R, Gao M, Qiang GF, Zhang TT, Lan X, Ying J, Du GH. The anti-amnesic effects of luteolin against amyloid β25–35 peptide-induced toxicity in mice involve the protection of neurovascular unit. Neuroscience. 2009 Sep 15;162(4):1232-43.