CHAPTER 16

Unveiling the Defensive Role of Flavonoids: A Toxicant Countermeasure

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SUMMARY

Flavonoids are phytochemical substances found in many plants, fruits, vegetables, and leaves, and have potential uses in medicinal chemistry. They are plant-derived secondary metabolites with notable antioxidant capabilities. They are categorized based on their chemical composition, level of unsaturation, and carbon ring oxidation. Flavonoids are classified into many subgroups including anthoxanthins (flavanone and flavanol), flavanones, flavanonols, flavans, chalchones, anthocyanidins, and iso-flavonoids. Each of these flavonoids is ubiquitously found in nature. Consuming more foods rich in flavonoids offers several health advantages. Due to their beneficial impact on human health, there is a growing endeavor to extract these natural substances from different plants. Since these natural compounds have positive effects on human health, an increasing effort has been made to isolate these compounds from various plants. Flavonoids have several medical advantages such as anticancer, antioxidant, anti-inflammatory, and antiviral activities. They possess neuroprotective and cardio-protective properties. The biological effects are influenced by the specific flavonoid type, its potential mechanism of action, and its bioavailability. These affordable pharmaceutical ingredients exhibit notable biological activity and have been shown beneficial in treating many ailments. Recent research has focused on isolating them, creating analogs, and studying their impact on human health using diverse methods and animal models. An increasing number of flavonoids have been identified, with their discovery continuing to grow steadily. Thus, this chapter has endeavored to describe the protective function of flavonoids and their beneficial actions to enhance our comprehension of their impact on human health.

INTRODUCTION

Polyphenols are a large class of biologically active compounds that are present as secondary metabolites in different parts of plants. These compounds provide flavor and color to various parts of plants as well as protect them from environmental toxins owing to their potential biological abilities (Quideau et al., 2011; Daglia, 2012). Flavonoids are common polyphenolic compounds that exhibit a diverse range of biological as well as pharmacological potentials such as anti-cancer, anti-viral, antioxidant, anti-inflammatory, immune modulatory and anti-bacterial properties (Harborne & Williams, 2000). Various investigations revealed the palliative action of flavonoids to counteract various sorts of environmental toxicants. For many decades, pesticide contamination has become a global health concern. The residues of pesticides remain in air, soil, water and sediments through which humans are inevitably exposed to these pollutants (Chrisman et al., 2009). The epidemiological data elucidated that pesticide intoxication exerts deleterious effects on different body organs via endocrine disruption, epigenetic variations, oxidative stress, mitochondrial impairments and autophagy (Mostafalou & Abdollahi, 2013).

Flavonoids are well known for their broad-spectrum ameliorative abilities therefore considered as indispensable components of the pharmaceutical, nutraceutical as well as cosmetic industries. These compounds protect the tissues against oxidative stress owing to their reactive oxygen species (ROS) scavenging potentials (Metodiewa et al., 1997). Free radicals are always present in our bodies in response to normal physiological activity or exogenous damage. It is documented that free radicals directly attack the lipids of plasma membrane which disrupt its normal architecture and trigger a cascade or reaction called lipid peroxidation. The change in permeability alters the osmotic pressure which leads to bursting of cells (Walker et al., 2000). Therefore, flavonoids are considered as major break-through to mitigate the damaging effects of oxidative stress and its associated mechanisms. Various sources of flavonoids and their potential curative roles have been depicted in Fig 1.

The following flavonoids demonstrated marvelous anti-toxicant properties owing to their different attributes.

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QUERCETIN

Quercetin is a naturally occurring flavonoid that is widely present in pod vegetables, leaves and fruits of various plants. It is considered as indispensable part of our diet owing to its anti-oxidative, hepato-protective, cardio-protective, reno-protective as well as anti-atherosclerosis potentials (Liu et al., 2010; Cai et al., 2013; Lin et al., 2014). Various organs such as kidneys, liver, small and large intestine are responsible for the metabolism of quercetin. Quercetin is now extensively used as a food supplement as well as a remedial agent against cirrhosis, steatosis and hepatic inflammation. It is revealed that quercetin demonstrates its antioxidant abilities owing to its chemical structural configuration which enable it to donate free electrons and scavenge free radicals (Ramyaa & Padma, 2013).

Numerous investigations reported that quercetin potentially counteracts mycotoxins induced toxicities which are attributed to its antioxidant and anti-inflammatory abilities. Quercetin escalates the activities of antioxidant enzymes, reduces oxidative stress as well as prevents the onset of lipid peroxidation (Saleem et al., 2015). Quercetin ameliorates aflatoxin prompted oxidative stress and cytotoxicity via regulating Nrf2/keap1 pathways. Furthermore, quercetin supplementation prevents DNA damage as well as micronucleus owing to its antigenic abilities. Similarly, Quercetin administration inhibits ochratoxin instigated cytotoxicity and significantly reduces the levels of pro-inflammatory cytokines (Schoneberg et al., 2018). Moreover, quercetin reduces oxidative stress and prevents the onset of ischemia and reperfusion in cardiomyocytes via regulating xanthine oxidase system (Sanhueza et al., 1992).

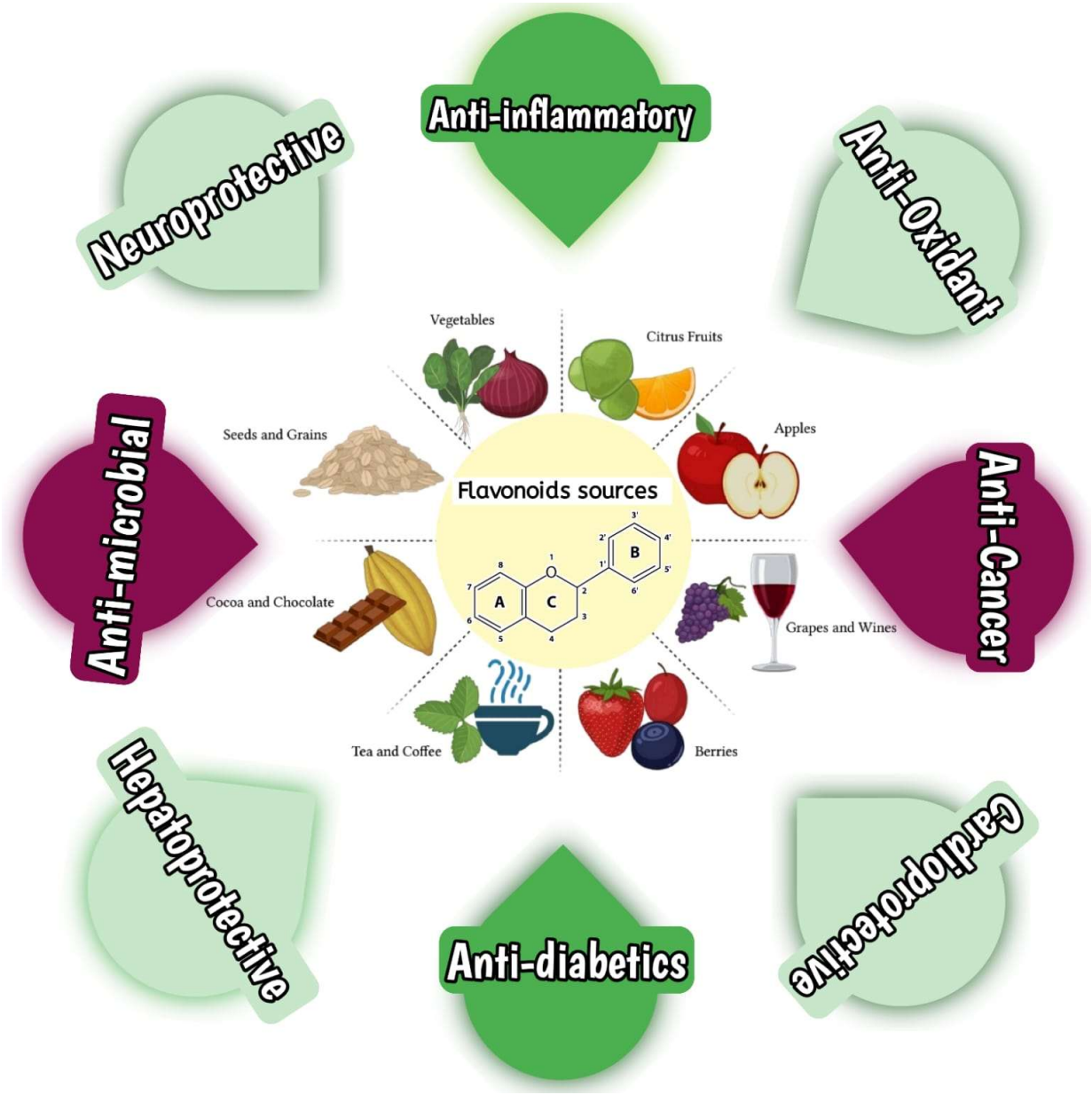

Fig 1. Some sources of flavonoids and their potential role

Aforementioned findings indicate that Quercetin is a potential therapeutic compound to avert various toxicities.

KAEMPFEROL

Kaempferol is an essential flavonoid that is found in various plants such as beans, kale, leek, grapes and broccoli. Numerous investigations have reported anti-microbial, antioxidative, anti-obesity, neuroprotective, cardioprotective and anti-cancerous properties. Rats treated with kaempferol showed a prominent reduction in the levels of inflammatory cytokines (Yeh et al., 2022). Recent investigation has documented the hepatoprotective abilities of kaempferol. It is revealed that kaempferol treatment remarkably reduced the liver function markers in CCl4 induced hepatotoxicity in rats (Zang et al., 2017). Furthermore, kaempferol prevents the alcohol prompted liver damage via reducing the expression of CYP2E1 while escalating the expression of cytoprotective antioxidant genes (Wang et al., 2015). Moreover, kaempferol binds to ALK5 which triggers the downregulation of TGF-β/Smads pathway thereby preventing the liver against fibrosis (Xu et al., 2019). Lipopolysaccharides (LPS) are potential compounds that trigger the development of hepatic fibrosis. LPS activates TLR4 receptors in hepatic and Kupffer cells (Singh et al., 2017). Furthermore, it triggers the activation of pro-inflammatory cytokines in hepatic tissues (Cheng et al., 2017). Additionally, LPS induces nitrosative as well as oxidative stress which ultimately reduces antioxidant activities and damages the liver (Latha et al., 2017). However, kaempferol administration reduces the expression of TLR4 receptor which ultimately inhibits the activation of pro-inflammatory cytokines particularly NF-κB in hepatic tissues (Islam et al., 2019). These findings elucidate that kaempferol can be used as a therapeutic agent against various toxicities. However, clinical trials should be conducted to evaluate the efficacy of kaempferol on human beings.

RUTIN

Rutin is classified as a flavonoid glycoside and is a part of the broader class of plant compounds known as flavonoids. This compound is found in various fruits, vegetables, and plant-based diets, contributing not only to their potential health benefits. Rutin is abundant in citrus fruits, buckwheat, asparagus, onions, and tea Ita consumption has been associated with several health-promoting effects, making it a subject of interest in both traditional medicine and modern scientific research (Chua, 2013). Rutin has been used widely in the field of medicine due to its numerous pharmacological properties including anti-allergic, vasoactive, anti-inflammatory, anti-bacterial, anti-tumor, anti-viral, and anti-protozoal properties (Calabrò et al., 2005). In addition, hypolipidemic and cytoprotective activities have also been reported (Casa et al., 2000). Due to its potent antioxidant properties and high radical scavenging activity, rutin has antiplatelet, antiviral and amp, anti-hypertensive qualities along with strength in blood vessel capillaries. The stability of the genome and the prevention of disease are two possible benefits of these characteristics. Based on certain research, rutin antioxidant properties in the Fenton reaction (Caillet et al., 2007) and its ability to inhibit low-density lipoprotein (LDL) peroxidation are dose-dependent (Jiang et al., 2007).

LUTEOLIN

Luteolin is a natural flavonoid that is found in many edible plants such as broccoli, celery, chrysanthemum flower, parsley and onion leaves, and (Lim et al., 2013). Luteolin acts as both a pro-oxidant and an antioxidant biochemically and it demonstrates a variety of biological benefits including anti-inflammatory, anti-allergy, and anti-cancer properties. In traditional Chinese medicine, plants that are high in luteolin have been used to treat conditions like cancer inflammatory disorders, and hypertension. The biological effects of luteolin may be connected functionally; for instance, the anti-inflammatory action may be connected to the cancer-preventing properties of luteolin. (Lin et al., 2008). In addition, anti-diabetic, cytoprotective (Kempuraj et al., 2021) and anti-angiogenic (Raffa et al. 2017), properties have also been reported. Furthermore, luteolin exhibits the ability to penetrate the blood-brain barrier and function as a neuroprotective agent (Theoharides et al., 2016). Researchers reported that LUT inhibits neuroinflammatory and systemic responses in coronavirus disease (Kempuraj et al., 2021). Luteolin demonstrates potent cardiovascular protection via intricate pathways that transmit signals and targeting effectors, which aligns with recent developments in our understanding of oxidative stress and inflammatory mechanisms of the cardiovascular system. A high luteolin diet probably lowers the risk of sudden cardiac arrest (Si et al., 2014). According to recent research, mast cell-induced neuroinflammation was inhibited by the phytosomal formulation of LUT, which reduced long-term COVID syndrome related to brain fog (Theoharides et al., 2021). In isolated peripheral blood mononuclear cells from human MS (multiple sclerosis) patients, luteolin may also have therapeutic immunomodulatory effects when used in separation. Moreover, pro-inflammatory cytokines like interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and the ratio of the cell migration mediator MMP-9 to its inhibitor TIMP-1 showed additive effects when luteolin treatment was administered (Sternberg et al., 2009).

MYRICETIN

Myricetin is a flavonoid that is abundant in natural plants belonging to various families, such as the Fagaceae, Vitaceae, Rosaceae, Leguminosae, Primulaceae, Myricaceae, Ericaceae and Compositae. It is frequently found as an essential active component and additive in many foods including vegetables, fruits, berries, merlot, tea and honey (Nardini & Garaguso, 2020). Further, it demonstrated a wide range of pharmacological properties, including antidiabetic, analgesic, antitumor, hepatoprotective, and anti-inflammatory effects When related to other flavonoids, myricetin's three hydroxyl groups on ring B are thought to contribute to its strong antioxidant action. Research conducted in vitro has demonstrated that the two hydroxyl groups and the double-bonded oxygen group are responsible for the mineral chelation effect (Wu et al., 2013).

Myricetin's prooxidative impact is caused by the catechol groups in its structure, which result in the formation of semi-quinone radicals. When the 4-hydroxyl group on the C ring and the 4-hydroxyl group on the B ring combine to produce a quinine, this radical gets oxidized. Myricetin has been linked to numerous health advantages, including lowered hepatic triglyceride levels, prevention of liver damage, less oxidative stress, and lower cholesterol levels The hepatoprotective properties of myricetin have been extensively studied by numerous experts worldwide (Semwal et al., 2016). Myricetin possesses various pharmacological properties against organ damage as shown in Fig 2.

CHRYSIN

Chrysin (CH) is a vital flavonoid that is prevalently present in numerous plant compositions, propolis and honey (Eldutar et al. 2017). According to recent investigations, CH possesses the potential to exhibit various medicinal and commercial properties such as anti-inflammatory (Kandemir et al. 2017a), antioxidant (Eldutar et al. 2017), anti-apoptotic, anti-diabetic, anti-cancerous, anxiolytic, anti-allergic (Du et al. 2012) and anti-estrogenic activities. Chrysin also acts as an anti-aging agent against D-galactose induced aging (Anand et al., 2012). Chrysin plays significant protective role against agent induced colitis(Dextran sodium sulfate, Dimethylhydrazine, cisplatin), neurotoxicity (Lipopolysaccharide, Streptozotocin, formalin) nephrotoxicity (Tetrachlorodibenzo-p-dioxin, Doxorubicin, Fluorouracil, ethanol, cisplatin, adenine, Carbon tetrachloride), respiratory toxicity(Ovalbumin, Bleomycin, Cigarette smoke), hepatotoxicity (Tert-butyl hydroperoxide, ethanol, Methotrexate), cardiovascular toxicity [Triton WR-1339, Streptozotocin, Doxorubicin, Mitoxantrone (Pingili et al., 2019)].

MTX is an efficient chemotherapeutic agent, its clinical use is limited due to its toxic effects on the liver (Hagag et al., 2015). Chrysin was discovered to have a protective role against the hepatotoxic effects of MTX by lowering the markers of liver injury (Ali et al., 2014). Cyclophosphamide (CYP) is widely used in Chemotherapy and also an alkylating drug of the oxazaphosphorin family (Ahlmann & Hempel, 2016). Due to its side effects including vomiting, alopecia, bone marrow suppression, nephrotoxicity, neurotoxicity, nausea, urotoxicity, hepatotoxicity, immunotoxicity and cardiotoxicity the clinical usage of this medication is restricted (Taslimi et al. 2019). According to some reports, chrysin is a very potent flavonoid that has a wide range of pharmacological actions, including inhibiting the activity of topoisomerases that deoxyribonucleic acid (Russo et al., 2012), anti-inflammatory activity by preventing the release of histamine and pro-inflammatory cytokine expression (Bae et al., 2011), and anticancer activity by supporting the degradation of caspase-8 and caspase 3 by TRAIL (Samarghandian et al., 2011).

The inhibitory impact on vascular endothelial growth factor (VEGF) instigated angiogenesis (Tsuji & Walle, 2007; Li et al., 2011), cardioprotective activity by enhancing post-ischemic functional recovery (Tian et al., 2014), inhibition of (HDACs) (Szkudelski, 2001), anti-asthmatic activity by suppressing NF-κB and stimulate nitric oxide synthase (Wadibhasme et al., 2011), inhibition of TNF-α and interleukin (IL)-1β (Bai et al., 2013), prevention of programmed cell death by initiation of estrogen receptor (Zeng et al., 2013), Reno-protective activity by glucose-induced renal tubular cell migration with diminishing matrix metalloproteinase-2 activity (Kang et al., 2015), antihypertensive (Farkhondeh et al., 2015), antidiabetogenic (Samarghandian et al., 2016), anti-hypercholesterolemic action (Anandhi et al., 2014), and stopping breast cancer cells from spreading metastatically (Lirdprapamongkol et al., 2013).

TANGERETIN

Bisphenol A, Benzo[a]pyrene (BaP) and Potassium dichromate (PD) are different toxicants that induce toxicity. TNG is a natural bioactive Polymethoxy flavones (in which all hydroxyl groups are capped by methyl residues) extracted from peel tissues of citrus species including citrus depressa and citrus tangerine. TNG processes neuroprotective, antioxidant, anti-inflammatory, anti-cancerous and anti-diabetogenic actions. Additionally, TNG play a substantial role in various pharmacological activities. The anti-cancer properties of TNG are attributed to their metabolic resistance, high membrane permeability and variety of biological activities, including cell growth inhibitory actions. It is anticipated that they will serve as biotherapeutic medications to preserve human health by aiding in the inhibition and cure of severe ailments like neurodegenerative diseases, lipid metabolism disorders, cancer and neurological diseases (Nahar et al., 2012).

BPA is an industrialized toxin that may harm the liver. The United States Environmental Protection Agency (EPA) has designated the BPA a third most harmful environmental toxicant TNG's antioxidant and anti-inflammatory potential significantly prevent liver damage caused by BPA. TGN's pharmacological abilities enable it to decrease ROS generation and increase antioxidant enzyme activity BPA can slow down organismal aging. Dietary TAN supplementation restored the transcript levels of heat shock proteins and mitigated the BaP-induced loss in motility, pumping, and poly-Q accretion (Roth et al., 2014).

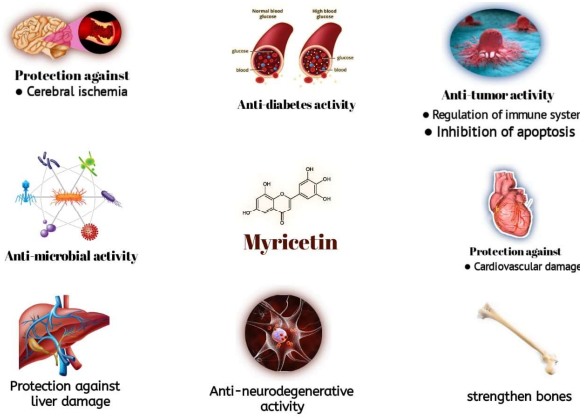

Fig 2. Demonstration of various pharmacological properties of Myricetin against organ damages

Environmental xenobiotic potassium dichromate (PD) is well known to be carcinogenic, mutagenic and teratogenic to both animals and humans. According to reports, TNG act as neuro-protective drug which protects the brain from damage caused by PD. TNG also reduced the expression of caspase-3 in the brain. TNG also plays a major neuroprotective role by regulating the (Nrf2) nuclear factor erythroid 2-related factor 2 signaling pathway, preventing the production of inflammatory mediators (interleukins, tumor necrosis factor and interferons), and inhibiting programmed cell death in response to PD-induced acute brain injury (Sharma et al., 2020).

Nrf2 has a cytoprotective and neuroprotective response through the regulation of several antioxidant genes. Recent research has shown that Nrf2 is upregulated in brain injury as an endogenous defensive response Apoptosis is a program of heritably regulated cell death which leads to internucleosomal DNA fragmentation and has a major influence on the pathophysiology of brain injury. In many illnesses of the central nervous system (CNS), initiation of caspase-3 is an eminent feature of neurodegeneration, and this pathway is thought to be a prospective target for therapy (Macks et al. 2022). Moreover, oxidative stress is a major component that triggers caspase-3-mediated apoptotic pathways Numerous studies claim that by lowering neuroinflammation in experimental animals, TNG mitigates cognitive and memory impairments (Yu et al., 2020). Research showed that the brain could be shielded from chromium-induced brain damage by activating the antioxidant pathways and inhibiting pro-apoptotic and inflammatory mediators (Xu et al. 2022).

MORIN

Morin, a natural flavonoid derived from the Moraceae family has antioxidant, anti-inflammatory, anti-carcinogenic, neuroprotective, antidiabetic and antiproliferative properties It has been found to alter the Nrf2 pathway in research. It has a systemic protective effect, lowering the harmful aftereffects of various medications deprived of interrupting with their functioning. It is thus regarded as a strong beneficial medication for all illnesses caused mostly by free radical damage (Kuzu M. et al. 2018).

Another research looked at whether morin protects against testicular toxicity induced by ifosfamide (IFOS), a drug used to treat a diversity of malignancies. The findings acquired demonstrated that IFOS accomplished oxidative stress in testicular tissues (Ozturk et al. 2014). Oxidative stress has been reported to induce ERS, irritation, apoptosis, DNA damage and autophagy. Morin therapy reduces oxidative stress. It reduced TNF-α and IL-1β protein levels, indicating anti-inflammatory activity (Miltonprabu et al., 2017). It also elevated mRNA transcript levels for the ERS markers ATF-6, PERK, IRE1, GRP-78, and CHOP, as well as the apoptotic markers Bax, Casp-3, and apaf-1. It increased expression of the anti-apoptotic protein Bcl-2 and the cell survival signal AKT-2 genes. Morin demonstrated an anti-autophagic action and decreased the levels of the protein beclin-1. Morin also reduced the quantity of 8-OHdG immune-positive cells and mitigated oxidative DNA damage (Cakmak et al., 2023).

The toxicity of cyclophosphamide (CPX) severely restricts its usage as an immunosuppressive or anti-cancer medication. Significant alterations are seen, such as in the hematological system, particularly in the numbers of leukocytes and platelets (Azevedo et al. 2007). Citrus extract, for instance, has been demonstrated to lessen CPX-induced genotoxicity in mouse bone marrow cells, especially in relation to its flavonoid contents with antioxidative activity (Hosseinimehr & Karami, 2005). The above-mentioned study found that adding morin to the treatment decreased the amount of body weight lost.

PELARGONIDIN

The pelargonidin is important flavonoid based on anthocyanins and is utilized in medications to treat skeletal myopathy, retinopathy, hypoglycemia, and other conditions. Studies demonstrate the effectiveness of anthocyanins in avoiding a range of chronic illnesses, including obesity, diabetes, and cardiovascular disease (Li et al., 2015). Based on their anti-inflammatory, antioxidant, anti-mutagenic, and antiangiogenic properties, besides their ability to induce cell differentiation, inhibit proliferation through signal transduction pathway modification, tempt cell cycle arrest, and promote autophagy in cancerous cells, anthocyanins may have antitumor effects Strawberries and food items with red coloring are the primary sources of pelargonidin (Praveena, R. et al. 2022).

Glycosyl flavonoids, including pelargonidin, chromenylium-3, glycosides, oxane-3,4,5-triol, are absorbed by the body and metabolized throughout the digestive process. Acetylated forms of pelargonidin glycosides were discovered in urine samples from experimental animals and people, according to studies on anthocyanins' absorption and metabolism (Karlsen, A. et al. 2007). Both pelargonidin (2-(4-hydroxyphenyl) chromenylium3,5,7-triol)—(C15H11O5+) and pelargonidin 3-O-β-glucopyranoside, also referred to as pelargonidin-3-Oglucoside— (C21H21O10 +)—have been utilized as food additive substitutes as a result of their antioxidant characteristics. Due to their proven ability to cause hyperglycemia, chromosomal abnormality, and DNA damage, these chemicals are recognized to constitute a major risk to human health (Habtemariam, 1997; Karlsen, A. et al. 2010).

Measurements of permeability, stimulation of pro-inflammatory proteins, adherence of neutrophil and migration in LPS-activated human umbilical vein endothelial cells (HUVECs) and mice were used to assess the anti-inflammatory properties of PEL (Mantawyet al., 2014). It was discovered that PEL prevented the rupture of the barrier caused by LPS, the production of CAMs, and the adherence and trans-endothelial relocation of neutrophils to endothelial cells of human (Li et al., 2011). Additionally, LPS-tempted hyper permeability and leukocyte exodus were inhibited in vivo by the impact of PEL on the barrier reliability of HUVECs was assessed using a permeability test (Miltonprabu et al., 2017). The barrier integrity remained unchanged after treatment with PEL (30 μM). The HUVECs were subjected to different PEL concentrations for six hours following the injection of LPS (100 ng/mL) for four hours. The outcomes indicate PEL the findings show that PEL prevents endothelial cells from experiencing LPS-mediated hyperpermeability; the best

effects are obtained at concentrations greater than 10 μM (Berman R.S., et al. 1993; (Ginis Z et. al. 2016).

It has been noted that the rings of pelargonidin are covered with electron accepting л* type ring road, sometimes referred to as lowest unoccupied molecular orbitals (LUMO) (Lee et al., 2017). The highest occupied molecular orbital (HOMO), or electron-donating л type orbitals, are discovered to be distributed throughout the entire molecular expanse, mostly above the B-ring, in case of flavonoids serves as the primary reactive or donor position Goldblum et al., 1993; Alvarez-Suarez et al., 2014). This finding unequivocally demonstrates that the carbonyl carbon and hydroxyl entities of the B-ring in pelargonidin play an electron-donating role which facilitate it to play its ROS scavenging properties (Ashrafizadeh et al., 2020).

CONCLUSION

Flavonoids are a diverse group of molecules that occur naturally in several plants, including fruits and vegetables, as well as in plant-derived products like coffee, chocolate, and tea. Flavonoids have been consistently documented to provide a variety of health advantages. These phytochemicals are abundant in antioxidants, offering our body innate immunological defenses against everyday external and internal poisons. It is strongly suggested to include various kinds of flavonoids into our daily diet to promote health and minimize the risk of serious illnesses including diabetes mellitus, cancer, stroke, and heart attack. Flavonoids have shown therapeutic benefits in most preclinical trials conducted on mouse models. Various groups of flavonoids have been identified with important biological properties including anticancer, antibacterial, antifungal, anti-diabetic, antimalarial, neuroprotective, cardio-protective, and anti-inflammatory effects. Thus, it is deduced that above-mentioned flavonoids compounds could be used as therapeutic candidates to cure several ailments.

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