Review: Flavonoids, their types, chemistry and therapeutic efficacy

Fatima Saiwan Sabah

Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq.

Email :fsaiwan73@gmail.com

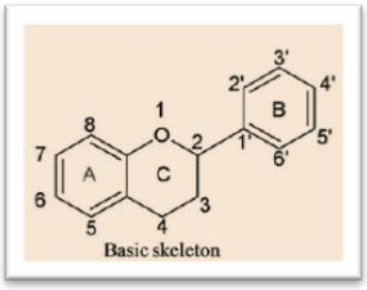
Abstract

In recent years, interest in plants and their contents of various compounds has increased, which are secondary metabolites of plants, and among these compounds are flavonoids. Flavonoids are known to contain aromatic rings that carry a number of hydroxyl groups and are found in all parts of plants such as leaves, fruits and roots. They appear in the form of aglycones, glycosides and methylated derivatives. They are used as antioxidants, anticancers, antibacterials, heart protective factors, anti-inflammatories, and the immune system Strengthening and protecting the skin from UV rays and an interesting candidate for pharmaceutical and medical application. A few decades ago, research studies focused on flavonoids of medicinal plant species have increased significantly due to Its various benefits for human health.

Keywords: Flavonoids. Antioxidant , Antibacterial ,Anthocyanins, Flavones

Flavonoids describe a variety of natural products that include the C6-C3-C6 carbon structure, and have a special structure that is phenylbenzopyrene. Depending on where the aromatic ring is attached to the benzopyrano moiety (chromano) moiety fig(1).

Natural flavonoids all possess three hydroxyl groups, two of which are on the A ring in the fifth and seventh positions, and one on the B ring, and these groups affect the metabolism of each compound. It can exist as free or bound forms aglycones or -glycosides (1-14).

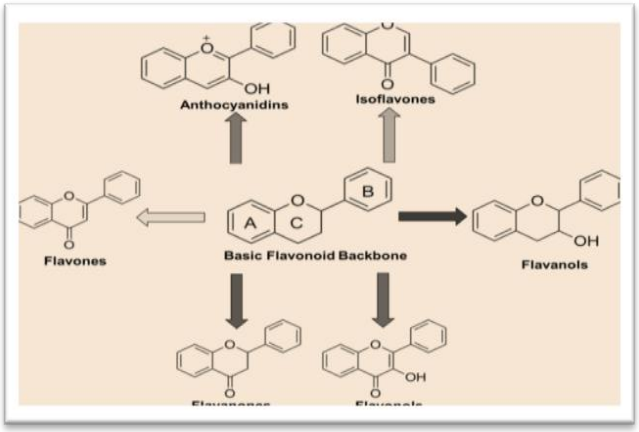


Fig(1) Basic flavonoid structure

Types of flavonoids

Flavonoids are present in plants with different subgroups depending on the carbon in the C ring to which the B ring is attached, the degree of unsaturation and oxidation of the C ring (Fig. 1). The flavonoids in which the B ring is attached at position 3 of the C ring are called isoflavones. Those in which the B ring is attached at position 4 are called neoflavonoids. Those in which the B ring is attached at position 2 can be divided into several subgroups based on the structural structure of the C ring. These subtypes are: flavones, flavonols, flavanones,

flavanonols, flavanols or catechins. , anthocyanins and chalcone Figure (2) (15, .(16).

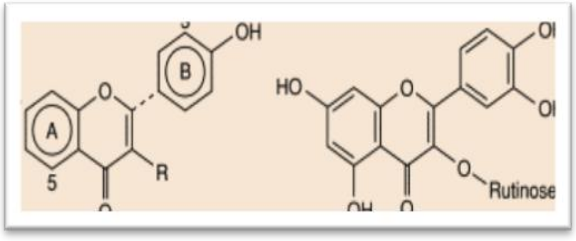


Fig(2)Flavonoid classes

1- Flavones

Flavones are one of the subtypes of flavonoids and are found abundantly in fruits, flowers, roots and leaves such as mint, red pepper, chamomile, celery, (parsley and ginkgo 17-20).

Flavones are characterized by an unsaturated 3-C chain and have a double bond between C-2 and C-3, like flavonols, but differ from them by the absence of a hydroxyl in position 3 (21-23). And this simple difference in structure between flavonoids and flavonols has a very important influence on the biogenesis, physiological, pharmacological, phylogenetic and chemical roles of these compounds. Flavones are widely distributed among higher plants in the form of aglycones or glycosides (24-30).



Fig(3) Type of flavones

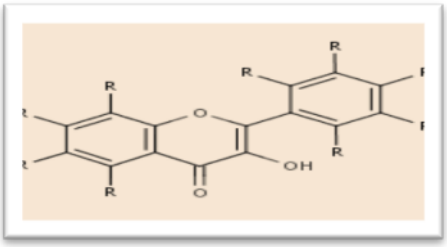
A number of studies have been conducted on flavonoids and foods that contain these compounds. These studies led to the fact that flavonoids have a range of treatments, including increasing the activities of the antioxidant enzyme in the blood, as well as superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase (31). The effect of artichoke leaf extract was also studied as a source of apigenin, and the proportion of the treatment group had lower cholesterol than those who took the drug. placebo, but no significant differences were found in HDL cholesterol, LDL cholesterol, or TGs (32). It also studied the extract of hawthorn rich in vitexin and found that it reduced total cholesterol and LDL cholesterol after 6 months of treatment, and it had no effect on HDL cholesterol or TGs (33). Diosmetin and rutinozide supplements were used successfully in a European study to reduce bleeding and improve wound healing (34). The proposed experimental mechanisms include increased venous tension and anti-inflammatory. Identical mediators of anti-inflammatories have shown activity of flavones in animal studies (35).

2-Flavonols

Flavonols include their flavonoids with a ketone group. They are the building blocks of proanthocyanins. These compounds are

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

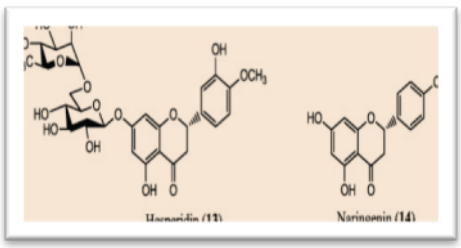
abundant in a variety of vegetables and fruits such as onions, turnips, lettuce, tomatoes, apples, grapes and berries, in addition to their presence in herbs. Examples of these compounds are kaempferol, quercetin, myricetin and fisetin. It has broad health benefits, acts as an antioxidant and reduces the risk of vascular disease. Its structure contains a hydroxyl group at position 3 of the C ring, and is glycosylated (36).



Fig(4) structure of Flavonol

3-Flavanone

These compounds are widely present in all citrus fruits such as oranges, lemons, and grapes. The most famous types are hesperitin, naringenin, and eriodactol. These compounds are due to the bitter taste of citrus peels and have health benefits and therapeutic uses in a broad way. They are called a dihydroflavone because they contain the C ring. saturated (37).



Fig(5) Type of Flavanone

4-Isoflavonoids

They are 4-benzopyrone derivatives formed by the shikimic acid pathway. These compounds are characterized by having a limited distribution, Figure (6). It is found abundantly in the plant kingdom in leguminous plants such as soybeans. Isoflavonoids have effective roles in treating a number of diseases.

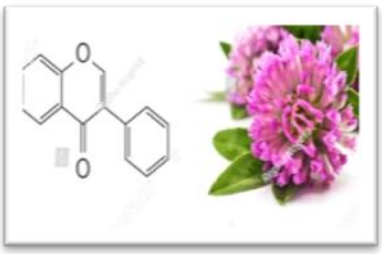


Fig (6)structure of Isoflavonoids

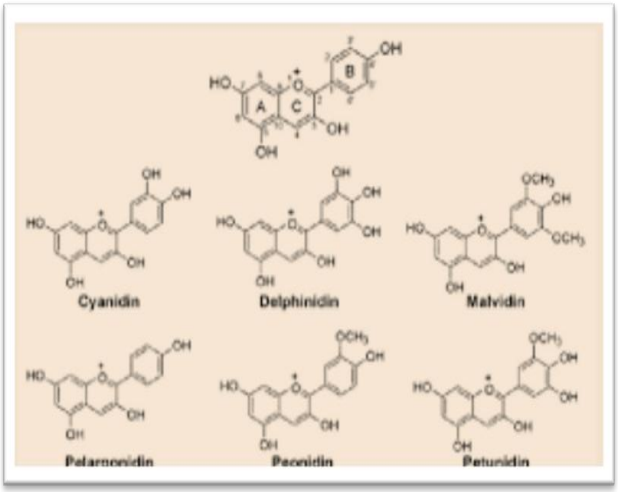
Including it is used to treat diabetes, some types of allergies, infections, including bacterial and viral infections, and to reduce high levels of cholesterol and triglycerides (38). It has also been used to regulate hormone levels, as it binds to estrogen receptors and acts as a selective and agonist of estrogen receptors (39). It regulates the concentration and receptor of endogenous estrogen and the identification of target tissues. And the biological effect of isoflavonoids on intestinal bacteria was studied, because bacterial enzymes in the intestine convert isoflavonoids into different metabolites. Known as Phytoestrogens (40-44)

5-Anthocyanins

They are water-soluble pigments found in the sap of the neonate cells and excreted by the secondary metabolism of plants. They give fruits, vegetables, flowers and leaves a multi-graded color from orange to blue. These compounds are found in types:

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

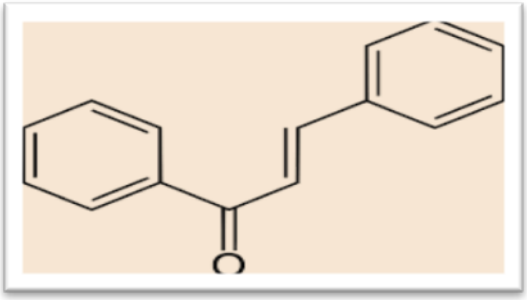
Cyanidin, delphinidin, malvidin, pelargonidine and pionidin and are concentrated in the outer layers of cells Such as cranberries, black currants, red grapes, merlot grapes, cranberries, strawberries, cranberries, blackberries and figs (7). And benefit from these compounds because of their health benefits and were used in the food industries and food coloring instead of industrial dyes (45). The color of anthocyanins depends on the pH and the methyl or acyl group, as well as on the hydroxyl groups in the A and B rings. Anthocyanins are derived from flavonols, and have the structural formula of the flavylium ion, which is anoxic ketone in fourth place. Used as an appetite suppressant, stimulant, and choleretic agent (46, 47).



Fig(7) type of anthocyanins

6-Chalcone

It is a sub-compound of flavonoids called open-chain flavonoids. Chalcone is an aromatic ketone characterized by the absence of a "C-ring" from the basic skeletal structure of flavonoids and which is the central core of many important biological compounds, called chalcones. They are the genetic precursors of flavonoids and isoflavonoids, and are abundant in plants (48-51). It is considered one of the compounds in the field of medicinal chemistry and has been widely used to treat many diseases. It is considered as anti-inflammatory, anti-gout, anti-histamine, anti-obesity and anti-spasmodic (52-59).

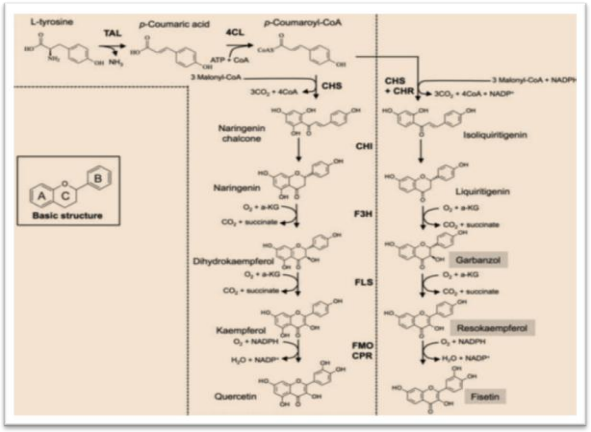


Fig(8) Structure of Chalcone

Biosynthesis of flavonoids:-

These compounds are made through the phenylpropanoid metabolism pathway that uses the amino acid phenylalanine to produce coumaroyl-CoA. Which in turn reacts with manlonyl-CoA to produce the backbone of flavonoids called chalcones, which in turn contain two phenyl rings. and triflavonoid structure. Thus the metabolic pathway continues through a series of enzymatic reactions to produce flavonoids → dihydroflavonol → anthocyanins. (60,61).

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X



Fig(9) Biosynthesis of flavonoids

Metabolism of Flavonoids in Humans

After the food is exposed to the process of digestion automatically in the mouth and then to the stomach, flavonoids are released, which are absorbed in the small intestine, whether in the form of glycoside or aglycone (62).

Aglycans are easily absorbed from the small intestine, and flavonoid glycosides into glycan water. Flavonoid glucosides such as quercetin are then transported through the small intestine by the sodium-dependent glucose transporter (SGLT1). An alternative mechanism has been proposed that flavonoid glucosides are hydrolyzed by lactase fluoride (LPH), a beta-glucosidase located on the outside of the brush border membrane of the small intestine. The released aglycone is then absorbed via the small intestine [63]. The substrate specificity of this LPH enzyme varies greatly depending on the wide range of glycosides (glucosides, galactosides, xylosides, and rhamnooids) which are flavonoids.

As for the glycosides that do not have digestive enzymes, they move to the colon, where there are types of bacteria that have the ability to break down these flavonoid glycosides, and at the same time they work to break down the liberated flavonoid aglycones, because the absorption capacity of the colon is much less than the small intestine, where little absorption of the glycosides is transported Flavonoids are transported to the liver via glucuronide, sulfur or methylation. They are converted into smaller phenolic compounds via conjugation reactions, and no free flavonoids were found in plasma or urine, except for catechins. The bioavailability of some flavonoids varies markedly, the absorption of quercetin contained in onions is four times greater than that of apples or tea. Flavonoids are excreted with the bile in the intestine and those in the colon are broken down by intestinal bacteria, thus breaking down the structure of the flavonoid ring. Some flavonoids can be affected by stomach acid (63-66). Observed in a study on green tea extract after ingestion of green tea, the content of flavonoids is rapidly absorbed as indicated by their elevated levels in plasma and urine. It enters the blood circulation shortly after ingestion and causes a significant increase in the antioxidant status in plasma (66-70).

Biological Activities of Flavonoids:-

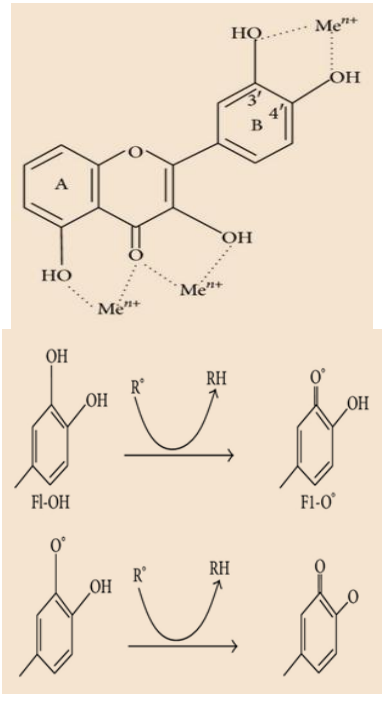
1-Antioxidant Activity

Flavonoids have chemical properties depending on the structure of the hydroxyl groups around the nuclear structure and from this property their ability to act as antioxidants. The mechanisms of antioxidant activity are radical scavenging and the ability to chelate a heavy metal ion (71, 72). B-ring hydroxyl formation is the most important determinant of ROS and RNS scavenging as it gives hydrogen and electron to hydroxyl, peroxyl, and peroxynitrite radicals, stabilizing them and causing composition-stable flavonoid radicals (73). Flavonoids act as a combined

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

result of radical scavenging activity and interaction with enzyme functions. Whereas, flavonoids inhibit the enzymes involved in the generation of reactive oxygen species, ie, microsomal nitrogen monoxide, glutathione S-transferase, mitochondrial succinoxidase, NADH oxidase (71.69).

Flavonoids protect lipids from peroxide radicals caused by oxidative stress. [72,73]. Free metal ions enhance ROS formation by reducing hydrogen peroxide formation while generating highly reactive hydroxyl radical. Due to their low redox susceptibility, their flavonoids (Fl-OH) are dynamically able to reduce highly oxidative free radicals such as superoxide, peroxyl, alkoxyl, and hydroxyl radicals by donating a hydrogen atom. Due to their ability to chelate metal ions (iron and copper), flavonoids also inhibit the generation of free radicals (74-77). Quercetin is well known for its iron ion chelating properties and the trace minerals iron is stabilized by binding at specific positions of different rings of flavonoid structures (78),fig(10).



Fig(10) (a) Scavenging of ROS () by flavonoids (Fl-OH) and (b) binding sites for trace metals where indicates metal ions.

2- Protective activity of the liver

Flavonoids such as catechins, apigenin, quercetin, naringin and rutin are characterized by their hepatoprotective activities [81]. Diabetes mellitus is a chronic disease that leads to clinical manifestations. Such as a decrease in the expression of the stimulatory subunit (Gclc) and glutathione and ROS levels in the livers of diabetic mice when dosed with anthocyanin extracts [82]. Anthocyanin cyanidin-3-O-β-glucoside (C3G) has been observed to increase hepatic expression of Gclc by increasing cAMP levels to activate protein kinase A (PKA), which in turn regulates CMP-binding protein phosphorylation (CREB) to enhance protein binding. (CREB) CREB-DNA and increased Gclc transcription. Thus increased Gclc expression results in a decrease in hepatic ROS levels. In addition, C3G treatment reduces hepatic lipid peroxidation, inhibits the release of proinflammatory cytokines, and reduces the progression of hepatic steatosis. Silymarin is a flavonoid containing three structural components, silibinin, silidianin, and silicristin extracted from the seeds and fruits of milk thistle Silybum marianum (Compositae). Ban was found to have a role in DNA synthesis and cell proliferation, which leads to the regeneration of hepatocytes in the damaged liver [83]. Silymarin increases hepatocyte proliferation in response to FB1 (Fumonisin B1, a fungal toxin produced by Fusarium verticillioides) causing cell death without modulating cell proliferation in normal liver. The pharmacological properties of Silymarin are regulation of cell membrane permeability and integrity,

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

leukotriene inhibition, scavenging ROS, suppressing NF-κB activity, inhibiting protein enzymes and collagen production [84].Silymarin has other clinical applications including reducing ischemic injury and treating toxic hepatitis caused by various toxins such as acetaminophen and poisonous mushrooms (85).

The effect of flavonoids isolated from Laggera alata against infection caused by carbon tetrachloride and its effect on cultured neonatal primary hepatocytes and in rats with hepatic damage was studied. Flavonoids in a concentration range of 1 to 100 µg/mL improve cell viability and inhibit CCl-induced extracellular aspartate aminotransferase (ALT) enzyme. Flavonoids at oral doses of 50, 100, and 200 mg/kg also significantly reduced the levels of AST, ALT, total protein and albumin in the blood serum, and levels of hydroxyproline and sialic acid in the liver, Histopathology was also examined where improvement in liver damage was observed with flavonoids (86).

A number of clinical studies have confirmed the efficacy and safety of flavonoids in the treatment of hepatic dysfunction and digestive problems such as fullness, loss of appetite, nausea and abdominal pain. These flavonoids, Equisetum arvense, isolated hirustrin and avicularin have the potential to confer protection against chemically induced hepatotoxicity in HepG2 cells (87)..

3-Antibacterial activity

Flavonoids isolated from plants play an important role in microbial infection, the effect of these compounds was tested in vitro against microorganisms and the activity of plant extracts rich in flavonoids on different types of bacteria (88 9). The flavonoids include apigenin, galangin, flavones, glycosides, flavonols, isoflavones, flavonoids and chalcone, which have strong antibacterial activity (90).

And the reasons for the effectiveness of flavonoids were revealed. The tendency of bacteria to various cellular factors, including its molecular actions, is the complex formation of proteins through non-specific forces such as the formation of hydrogen bonds and hydrophobic effects or through the formation of covalent bonds. This helps explain its antimicrobial mode of action related to its ability to disrupt microbial adhesions, enzymes and cell envelope transport proteins. Lipophilic flavonoids also disrupt microbial membranes 91, 92).(

Extensive research was conducted on catechins, which were found to have antibacterial activity in vitro against Vibrio cholerae, Streptococcus mutans, Shigella, and other bacteria (93, 94). , 96]. Robinetin myricetin and epigallocatechin are known to inhibit DNA synthesis [97] as it has been suggested that the B ring of flavonoids may interfere or form hydrogen bonds with the stacking of DNA bases in addition to inhibiting DNA and RNA synthesis in bacteria. Another study demonstrated the inhibitory activity of quercetin, apigenin and 3,6,7,3,4'-pentahydroxyflavone against Escherichia coli DNA gyras(98).

A role for compounds such as Naringenin and sophoraflavanone G has been revealed to have antibacterial activity of methicillin-resistant Staphylococcus aureus (MRSA) and Streptococcus tog. This is attributed to changing the membrane fluidity in the hydrophilic and hydrophobic regions, and this effect indicates that flavonoids may reduce the fluidity of the outer and inner layers of the

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

membranes (99). The relationship between antibacterial activity and membrane interference supports the argument that flavonoids may exhibit antibacterial activity by reducing membrane fluidity in bacterial cells. By containing the A-ring on the 5,7,2,4 or 2,6'-dihydroxylation of the B-ring in the flavanone structure is important for anti-MRSA activity (100). The hydroxyl group at position 5 in flavanones and flavones is important for its activity against MRSA(101).

There is a suggestion that the site of inhibition of these flavonoids was between CoQ and cytochrome in the bacterial respiratory electron transport chain (102). A number of studies support the diversity of edible ingredients and derivatives of medicinal plants as potent antibacterial agents(103,104).

4-Anti-Inflammatory Activity

Inflammation results from a normal biological process in response to tissue injury, pathogenic bacterial infection, or chemical irritation. Inflammation is initiated by the migration of immune cells from the blood vessels and the release of mediators at the site of the affected. The inflammatory cells are then recruited, releasing ROS, RNS, and proinflammatory cytokines to eliminate foreign pathogens, and the injured tissue is then repaired. Normal inflammation is rapid and self-limiting. (105).

To strengthen the immune system is done through diet, pharmaceutical agents, environmental pollutants and naturally occurring food chemicals. Some elements of flavonoids significantly affect the function of the immune system and inflammatory cells [106]. A number of flavonoids such as hesperidin, apigenin, luteolin and quercetin have been studied and their anti-inflammatory and analgesic effects have been noted. Flavonoids affect the generating function of inflammatory processes especially protein kinases tyrosine and serine-threonine enzyme that are involved [107, 108]. The explanation for the inhibitor of kinases is due to the competitive binding of flavonoids with ATP at the catalytic sites on enzymes. Thus these enzymes are involved in the processes of signal transduction and cell activation that includes cells of the immune system. And it was reached to a number of flavonoids able to inhibit the effect of inducible nitric oxide, cyclooxygenase, lipooxygenase, which are enzymes responsible for the production of a large amount of nitric oxide, prostanoids, leukotrienes in addition to the generation of a number of mediators of the inflammatory process such as cytokines, chemokines or adhesion molecules (109). And flavonoids inhibit phosphodiesterases involved in cell activation. As well as its role in the anti-inflammatory effect via biosynthesis of protein cytokines that mediate leukocyte diffusive adhesion at injury sites. A number of flavonoids have been found to act as potent inhibitors of the production of prostaglandins, molecules that make up powerful pro-inflammatory signals (110 -113).

5-Anticancer activity

Dietary factors such as fruits and vegetables play a clear role in the prevention of cancers. A number of studies have been conducted on flavonoids about their inhibition of initiating and enhancing the stages of cancer, as well as their effect on growth and hormonal activities (114,115). Its role in regulating mutant p53, cell cycle arrest, tyrosine kinase inhibition, heat shock protein inhibition, susceptibility to estrogen

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

receptor binding, inhibition of protein secretion where p53 mutations are the most common genetic abnormalities in human cancers. Inhibition of p53 expression stops cancer cells in the G2-M phase of the cell cycle. Flavonoids that downregulate the mutant p53 protein have been detected to marked levels in human breast cancer cell lines (116).

Tyrosine kinases are proteins in the cell membrane responsible for transmitting growth factor signals to the nucleus. It has a role in tumorigenesis by controlling the natural control of regulatory growth. Drugs that inhibit tyrosine kinase activity are potential antitumor agents without the cytotoxic side effects seen with conventional chemotherapy. The first compound, Quercetin, a tyrosine kinase inhibitor, was tested in phase I human trials (117). It was found that flavonoids inhibit the production of heat shock proteins in many malignant cell lines, including breast cancer, leukemia and colon cancer (118).

Recently studied the effect of the flavanol compound epigallocatechin-3-gallate on inhibiting the activity of fatty acid synthesis (FAS) in prostate cancer cells, an effect closely related to growth arrest and cell death (119, 121). compared to normal tissue

The effect of genistein, daidzein and biochanin A isoflavones on breast cancer was investigated by Barnes with a comprehensive review of the anticancer effects of genistein in in vitro and in vivo models(122-124). The study demonstrated that genistein inhibits the development of chemically induced breast cancer without reproductive toxicity or endocrine impact, and the subsequent non-development of induced breast cancer was observed in rats (125).

Hesperidin, a flavanone glycoside, has a role in the treatment of ozoxymethanol-induced colon and breast cancer in mice (126). The anti-cancer properties of flavonoids found in citrus fruits were studied by Carroll et al. (127). Several flavonols, flavones, flavanones and biochanin A isoflavones were found to have strong anti-mutagenic activity (128). Flavonoid-8-acetic acid has antitumor effects (129). In previous studies, ellagic acid, robinin, quercetin, and myricetin were shown to inhibit the formation of BP-7, 8-diol-9 and 10-epoxide-2 tumors on study mouse skin (130).

6-Antiviral activity

Natural products are an important resource for the development and discovery of new antiviral drugs and the reason for their availability and low side effects. The effect of isolated flavonoids on viruses was observed. The need to search for an effective drug against HIV has led to a structural-functional relationship between flavonoids and enzyme inhibition activity. Girdyn and Srensu (131) showed that flavan-3-o1 was more effective than flavones and flavones in selectively inhibiting HIV-1, HIV-2, and similar HIV infections. Baicalin, a flavonoid isolated from Scutellaria baicalensis (Lamieaceae) has a role in preventing HIV-1 infection and recurrence. A study revealed the role of robostaflavone and hinoclavon in inhibiting HIV-1 reverse transcriptase (132) and HIV-1 entry into cells expressing CD4 receptors, cardiac chemokines and an HIV-1 reverse transcriptase antagonist (133). The role of catechins in inhibiting HIV-1 DNA polymerase has been implicated, and demethylated gardenine A

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

and robinitin inhibit HIV-1 proteinase (134). The role of flavonoids such as chrysin, oxetine and apigenin have been studied in inhibiting HIV-1 activity through a novel mechanism. Involve inhibition of viral transcription (135**)..(**

Compounds such as Kaempferol and luteolin have been shown to have a synergistic effect against herpes simplex virus (HSV) and Pseudomonas infection (136). A study by Zande and others. The antiviral properties of quercetin, hesperetin, naringin and daidzein have been demonstrated in different stages of DENV-2 (Dengue virus type 2) infection. Quercetin was found to be most effective against DENV-2 in Vero cells. The flavonoids dihydroquercetin, dihydrovisitin, leucocyanidin, pelargonidin chloride and catechin, show activity against several types of viruses including herpes simplex virus, poliovirus, respiratory syncytial virus and sandpix virus. (134)

Conclusion

In recent years, interest in plants and herbs and their use for prevention and treatment of diseases because they contain chemicals, especially flavonoids, are known.Fruits and vegetables are natural sources of flavonoids. A variety of flavonoids found in nature possess their own physical, chemical, and physiological properties. The structure-function relationship of flavonoids is an example of key biological activities. The medicinal efficacy of several flavonoids has been demonstrated as antibacterial, hepatoprotective, anti-inflammatory, anticancer, and antiviral. This material is more commonly used in developing countries. The therapeutic use of new compounds must be validated using specific biochemical tests. By using genetic modifications, it is now possible to produce flavonoids on a large scale. More achievements will provide newer insights and will surely lead to a new era of flavonoid-based pharmaceutical agents for the treatment of many infectious and degenerative diseases .

References

[1] Shimokoriyama M. (1988) Classification of plant pigments and its properties. In Plant Pigments – An Introduction to Research and ExprimentsHayashi K. (Ed). Yokendo, Tokyo. 12-22.
[2] Macheix JJ, Fleuriet A, Billot J. (1990) Main phenolics of fruits, In Fruit phenolics, Macheix JJ, Fleuriet A, Billot J. (Eds). CRC Press, Boca Raton.1-103.
[3] Harborne JB. (Ed) (1994) The Flavonoids - Advances in Research Since 1986. Chapman and Hall, London.
[4] Iwashina T. (1992) Distribution and characteristic of flavonoid compounds in plants. Shokuhin to Kaihatsu, 27, 39-44.
[5] USDA Database for the Flavonoid Content of Selected Foods, Release 2.1 (2007) Prepared by the Nutrient Data Laboratory, Food Composition Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, and U.S. Department of Agriculture.
[6] Kyle JAM, Duthie GG. (2006) Flavonoids in foods. In Flavonoids. Chemistry, Biochemistry and Application, Andersen ØM, Markham KR. (Eds). CRC Press, Boca Raton. 219-262.
[7] Grotewold E. (Ed) (2008) The Science of Flavonoids, Springer, New York.

www.misan-jas.com (Arabic Impact Factor) - 1.1 ISSN (Paper)-1994-697X (Online)-2706-722X

[8] Iwashina T. (1994) Flavonoids in foods, and their functions, Shokuhin Kogyo, 37 (12): 52-70, 37(14): 67-79, 37(16): 67-81, 37(18): 55-69.
[9] Rice-Evans CA, Packer L. (2003) Flavonoids in Health and Disease. Marcel Dekker, New York.
[10] Nakabayashi T. (1995) Polyphenols and the discoloration. In Shokuhin no Henshoku no Kagaku, Kimura S, Nakabayashi T, Kato H. (Eds). Korin, Tokyo. 1-157.
[11] Ina K, Sakata K, Tomita I, Isemura Y. (2002) Chemical Constituents of Tea and Functions. Kougaku Syuppan, Tokyo.
[12] Tadokoro T. (1995) Various food ingredients - pigments. In Handbook of Data for Nutrition and Food Science, Japan Society of Nutrition and Food Science (Ed). Doubun Shoin, Tokyo. 165-168
[13] Majewska M., Czeczot H.: Flavonoids in prevention and therapy diseases. Ter Leki 2009; 65(5):369-377.
[14]. Małolepsza U., Urbanek H.: Plant flavonoids as biochemical active compounds. Wiad Bot 2000;44(3/4):27-37.
[15]Burak M & Imen Y (1999) Flavonoids and their antioxidant properties.Turkiye Klin Tip Bil Derg 19, 296–304.
[16]Ovando C, Hernandez D, Hernandez E, et al. (2009) Chemical studies of anthocyanins: a review. Food Chem 113, 859–871.
[17] Hollman PCH.(2004) Absorption, bioavailability, and metabolism of flavonoids. Pharm Biol;42:74–83.

[18] Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. (2004)Polyphenols: food sources and bioavailability. Am J Clin Nutr;79:727–47.

[19]. Manach C, Williamson G, Morand C, Scalbert A, Remesy C.(2005) Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr;81:230S–242S.

[20]. Williamson G, Manach C.(2005) Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr;81:243S–255S.

[21]Martens S, Mithöfer A.(2005) Flavones and flavone synthases. hytochemistry;66:2399–407.

[22] Harborne JB, Grayer RJ. Flavonoids and insects. In: Harborne JB, editor. (1994). The flavonoids: advances in research since 1986. 1st ed. London: Chapman & Hall; p. 589–618.

[23] Harborne JB, Williams CA. (2000)Advances in flavonoid research since 1992. Phytochemistry;55:481–504.

[24]Bruns B, Hahlbrock K, Schäfer E.(1986) Fluence dependence of the ultraviolet-light-induced accumulation of chalcone synthase mRNA and effects of blue and far-red light in cultured parsley cells. Planta;169:393–8.

[25]Justesen U, Knuthsen P, Leth T. (1998)Quantitative analysis of flavonols, flavones, and flavanones in fruits, vegetables and beverages by highperformance liquid chromatography with photo-diode array and mass

spectrometric detection. J Chromatogr A;799:101–10. [26]Pedneault K, Léonhart S, Gosselin A, Papadopoulos AP, Angers P, Dorais M. (2002)Variations in concentration of active compounds in four hydroponically-and field-grown medicinal plant species. Acta Hortic;580:255–62. [27] Wildanger W, Herrmann K.(1973) Flavonols and flavones of vegetables. 1. Flavonols of Brassicae. Z Lebensm Unters Forsch;152:134–7.

[28] McNally DJ, Wurms KV, Labbé C, Quideau S, Bélanger RR.(2003) Complex C-glycosyl flavonoid phytoalexins from Cucumis sativus. J Nat Prod;66:1280–3. [29]Lattanzio V, De Cicco V, Di Venere D, Lima G, Salerno M. (1994) Antifungal activity of phenolics against fungi commonly encountered during storage. Ital J Food Sci;6:23–30.

[30] Heimler D, Isolani L, Vignolini P, Romani A.(2009) Polyphenol content and antiradical activity of Cichorium intybus L. from biodynamic and conventional farming. Food Chem;114:765–70.

[31]Nielsen SE, Young JF, Daneshvar B, Lauridsen ST, Knuthsen P, Sandström B, Dragsted LO.(1999) Effect of parsley (Petroselinum crispum) intake on urinary apigenin excretion, blood antioxidant enzymes and biomarkers for oxidative stress in human subjects. Br J Nutr;81: 447–55. 107. Janssen K, Mensink RP, Cox FJ, Harryvan JL, Hovenier R

[32]Bundy R, Walker AF, Middleton RW, Wallis C, Simpson HCR. (2008); Artichoke leaf extract (Cynara scolymus) reduces plasma cholesterol in otherwise healthy hypercholesterolemic adults: a randomized, double blind placebo controlled trial. Phytomedicine 15:668–75.

[33]Dalli E, Colomer E, Tormos MC, Cosín-Sales J, Milara J, Esteban E, Sáez G. (2011)Crataegus laevigata decreases neutrophil elastase and has hypolipidemic effect: a randomized, double-blind, placebo-controlled trial. Phytomedicine;18:769–75.

[34]. Guilhou JJ, Dereure O, Marzin L, Ouvry P, Zuccarelli F, Debure C, Van Landuyt H, Gillet-Terver MN, Guillot B, Levesque H, et al. (1997) Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomized, controlled versus placebo trial in 107 patients. Angiology; 48:77–85.

[35] Misra MC, Parshad R. (2000)Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids. Br J Surg;87:868–72.

[36] Crozier A, Lean MEJ, McDonald MS, Black C (1997b) Quantitative analysis of the flavonol content of commercial tomatoes, onions, lettuce and celery. J Agric Food Chem 43:590-595.

[37]Yoshida H, Takamura N, Shuto T, Ogata K, Tokunaga J, Kawai K, Kai H.Biochem Biophys Res Commun.(2010)The citrus flavonoids hesperetin and naringenin block the lipolytic actions of TNF-alpha in mouse adipocytes;394(3):728-32.

[38] Kocjan R., Strzemski M., Sowa I., Polski a., Szwerc W., Świeboda R., Blicharski T., (2011) Phytoestrogens - classification, occurrence and significance in the prevention and treatment of osteoporosis, Ann. UMCS Sect. DDD, , 24, 195-203.

[39] Aisyah S., Gruppen H., Andini S., Bettonvil M., Severing E., Vincken J.-P., (2016)Variation in accumulation of isoflavonoids in Phaseoleae seedlings elicited by *Rhizopus*, Food Chem., , 196, 694–701.

[40] Dixon R.A., Achnine L., Kota P., Liu C.-J., Reddy M.S.S., Wang L., (2002)The phenylpropanoid pathway and plant defence: A genomics perspective, Mol. Plant Pathol., , 3, 371–390.

[41] Ralston L., Subramanian S., Matsuno M., Yu O., (2005)Partial reconstruction of flavonoid and isoflavonoid biosynthesis in yeast using soybean type I and type II chalcone isomerases, Plant Physiol., , 137, 1375–1388.

[42] Baber R., (2010)Phytoestrogens and post reproductive health, Maturitas, , 66, 344–349.

[43] Lagari V.S, (2014)Levis S., Phytoestrogens for menopausal bone loss and climacteric symptoms, J. Steroid. Biochem. Mol. Biol., , 139, 294–301.

[44] Simons R., Vincken J.-P., Roidos N., Bovee T.F.H., Van lersel M., Verbruggen M. A., Gruppen H., (2011)Increasing soy isoflavonoid content and diversity by simultaneous malting and challenging by a fungus to modulate estrogenicity, J. Agric. Food Chem., , 59, 6748–6758.

[45] Khoo HE, Chew LY, Ismail A, et al. (2012) Anthocyanins in purple colored fruits. In: Sun J, Prasad KN, Ismail A, et al., editors. Polyphenols: chemistry, dietary sources and health benefits. New York: Nova Science Publisher;. 133–152.

[46]Ahmadiani N(2012) Anthocyanin based blue colorants [dissertation]. Ohio: Ohio State University; .

[47] Mori K, Goto-Yamamoto N, Kitayama M, et al. . (2007) Loss of anthocyanins in red-wine grape under high temperature. J Exp Bot;58(8):1935–1945.

[48]Ni, L.; Meng, C.Q.; Sikorski, J.A. (2004)Recent advances in therapeutic chalcones. Expert Opin. Ther. Pat., 14, 1669–1691.

[49] Sahu, N.K.; Balbhadra, S.S.; Choudhary, J.; Kohli, D.V. (2012) Exploring pharmacological significance of chalcone scaffold: A review. Curr. Med. Chem., 19, 209–225.

[50]Wong, E. The role of chalcones and flavanones in flavonoid biosynthesis. Phytochemistry 1968, 7, 1751–1758.

[51]Evranos Aksöz, B.; Ertan, R. (2011)Chemical and structural properties of chalcones I. FABAD J. Pharm. Sci., 36, 223–242.

[52] Israf, D.; Khaizurin, T.; Syahida, A.; Lajis, N.; Khozirah, S.(2007) Cardamonin inhibits COX and iNOS expression via inhibition of p65NF-κB nuclear translocation and Iκ-B phosphorylation in

RAW 264.7 macrophage cells. Mol. Immunol., 44, 673–679.

[53]Kim, D.W.; Curtis-Long, M.J.; Yuk, H.J.; Wang, Y.; Song, Y.H.; Jeong, S.H.; Park, K.H.(2014) Quantitative analysis of phenolic metabolites from different parts of Angelica keiskei by HPLC–ESI MS/MS and their xanthine oxidase inhibition. Food Chem., 153, 20–27.

[54] Yamamoto, T.; Yoshimura, M.; Yamaguchi, F.; Kouchi, T.; Tsuji, R.; Saito, M.; Obata, A.; Kikuchi, M.(2004) Anti-allergic activity of naringenin chalcone from a tomato skin extract. Biosci. Biotechnol. Biochem., 68, 1706–1711.

[55]Aoki, N.; Muko, M.; Ohta, E.; Ohta, S. (2008)C-geranylated chalcones from the stems of Angelica keiskei with superoxide-scavenging activity. J. Nat. Prod., 71, 1308–1310.

[56]Birari, R.B.; Gupta, S.; Mohan, C.G.; Bhutani, K.K.(2011)Antiobesity and lipid lowering effects of Glycyrrhiza chalcones: Experimental and computational studies. Phytomedicine, 18, 795–801.

[57]Chen, M.; Christensen, S.B.; Blom, J.; Lemmich, E.; Nadelmann, L.; Fich, K.; Theander, T.G.; Kharazmi, A. Licochalcone A, (1993) a novel antiparasitic agent with potent activity against human pathogenic protozoan species of Leishmania. Antimicrob. Agents Chemother., 37, 2550–2556.

[58]Cho, S.; Kim, S.; Jin, Z.; Yang, H.; Han, D.; Baek, N.I.; Jo, J.; Cho, C.W.; Park, J.H.; Shimizu, M.; et al.(2011) Isoliquiritigenin, a chalcone compound, is a positive allosteric modulator of GABA A receptors and shows hypnotic effects. Biochem. Biophys. Res. Commun., 413, 637–642.

[59]Sato, Y.; He, J.-X.; Nagai, H.; Tani, T.; Akao, T. .(2007) Isoliquiritigenin, one of the antispasmodic principles of Glycyrrhiza ularensis roots, acts in the lower part of intestine. Biol. Pharm. Bull, 30, 145–149.

[60] Kogawa K. , Kazuma K, N., Kato, N. Noda, and Suzuki, M. 2007 “Biosynthesis of malonylated flavonoid glycosides on basis of malonyl transferase activity in the petals of Clitoria ternatea,” Journal of Plant Physiology, vol. 164, no. 7, pp. 886–894,.

[61] Ghoulami S., A. I. Idrissi, and S. Fkih-Tetouani, (2001) “Phytochemical study of Mentha longifolia of Morocco,” Fitoterapia, vol. 72, no. 5, pp. 596–598.

[62] Hollman P. C. H., Buijsman M. N. , van Y., Gameren, P. J.Cnossen, J. H. M. de Vries, andM. B. Katan, (1999) “The sugar moiety is a major determinant of the absorption of dietary flavonoid glycosides inman,” *Free Radical Research*, vol. 31,no. 6, pp. 569–573,.

[63] Day A. J., F. J. Canada, J. C. Diaz et al., (2000) “Dietary flavonoid andisoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase,” *FEBS Letters*, vol. 468, no. 2-3,pp. 166–170,

[64] Walle T.,(2004) "Serial review: flavonoids and isoflavones (phytoestrogens:absorption, metabolism, and bioactivity): absorption and metabolism of flavonoids," *Free Radical Biology and Medicine*, vol. 36, no. 7, pp. 829–837.

[65] Scheline R. R., (1973) "Metabolism of foreign compounds by gastrointestinal microorganisms," *Pharmacological Reviews*, vol. 25, no. 4, pp. 451–532.

[66] Bravo L.,(1998)Polyphenols: chemistry, dietary sources,metabolism, and nutritional significance," *Nutrition Reviews*, vol. 56, no. 11, pp. 317–333.

[67] Hollman P. C. H., (2004)"Absorption, bioavailability and metabolism of flavonoids," *Pharmaceutical Biology*, vol. 42, pp. 74–83.

[68] Hollman P. C.H., van Trijp J.M. P., Buysman M. N.et al.(1997), "Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man," *FEBS Letters*, vol. 418, no. 1-2, pp. 152–156.

[69] Spencer J. E., Chaudry F., Pannala A. S., Srai S. K., Debnam E., and E. C. Rice, (2000) "Decomposition of cocoa procyanidins in the gastric milieu," *Biochemical and Biophysical Research Communications*, vol. 272, no. 1, pp. 236–241.

[70] Benzie I. F. F., Szeto Y. T., Strain J. J., and Tomlinson B., (1999)"Consumption of green tea causes rapid increase in plasma antioxidant power in humans," *Nutrition and Cancer*, vol. 34, no. 1, pp. 83–87.

[71]. Kelly E. H, Anthony R. T., and Dennis J. B., (2002) "Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships," *Journal of Nutritional Biochemistry*, vol. 13, no. 10, pp. 572–584.

[72] Pandey A. K., Mishra A. K., and Mishra A.(2012). "Antifungal and antioxidative potential of oil and extracts derived from leaves of Indian spice plant *Cinnamomum tamala*," *Cellular and Molecular Biology*, vol. 58, pp. 142–147,

[73]. Cao G, E. Sofic, and R. L. Prior,(1997) "Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships," *Free Radical Biology and Medicine*, vol. 22, no. 5, pp. 749–760.

[74] Kumar S.and. Pandey A. K,(2012) "Antioxidant, lipo-protective and antibacterial activities of phytoconstituents present in *Solanum xanthocarpum* root," *International Review of Biophysical Chemistry*, vol. 3, no. 3, pp. 42–47.

[75]. Brown J. E, Khodr, R. C. Hider, and C. Rice-Evans, (1998) "Structural dependence of flavonoid interactions with Cu^{2+} ions: implications for their antioxidant properties," *Biochemical Journal*, vol. 330, no. 3, pp. 1173–1178.

[76] Mishra A., Sharma A. K., S. Kumar, A. K. Saxena, and A. K. Pandey,(2013) "*Bauhinia variegata* leaf extracts exhibit considerable antibacterial, antioxidant and anticancer activities," *BioMed Research International*, vol. 2013, Article ID 915436, 10 pages.

[77Van, S. A. van den Berg, D. J. ,Tromp J. L. et al., (1996)"Structural aspects of antioxidant activity of flavonoids," *Free*

Radical Biology and Medicine, vol. 20, no. 3, pp. 331–342,.

[78]. Kerry N. L and Abbey M., (1997) "Red wine and fractionated phenolic compounds prepared from red wine inhibit low density lipoprotein oxidation *in vitro*," *Atherosclerosis*, vol. 135, no. 1, pp. 93–102.

[79] Tapas A. R., Sakarkar D. M., and R. B. Kakde, (2008)"Flavonoids as nutraceuticals: a review," *Tropical Journal of Pharmaceutical Research*, vol. 7, pp. 1089–1099.

[80] Zhu W., Jia Q., Wang Y., Zhang Y., and M. Xia, (2012) "The anthocyanin cyanidin-3-O-*β*-glucoside, a flavonoid, increases hepatic glutathione synthesis and protects hepatocytes against reactive oxygen species during hyperglycemia: involvement of a cAMP-PKA-dependent signaling pathway," *Free Radical Biology and Medicine*, vol. 52, no. 2, pp. 314–327.

[82]Sonnenbichler J. and I. Zetl, (1986)"Biochemical effects of the flavonolignan silibinin on RNA, protein and DNA synthesis in rat livers," in *Progress in Clinical and Biological Research*, V. Cody, E. Middleton, and J. B. Karborne, Eds., vol. 213, pp. 319–331, Alan R. Liss, New York, NY, USA,.

[83] He Q., Kim J., and R. P. Sharma, (2004) "Silymarin protects against liver damage in balb/c mice exposed to fumonisin b1 despite increasing accumulation of free sphingoid bases," *Toxicological Sciences*, vol. 80, no. 2, pp. 335–342.

[84] Saller R., Meier R., and R. Brignoli, (2001) "The use of silymarin in the treatment of liver diseases," *Drugs*, vol. 61, no. 14, pp. 2035–2063.

[85] Wu, Y., Wang F., Q. Zheng et al., (2006) "Hepatoprotective effect of total flavonoids from *Laggera alata* against carbon tetrachloride-induced injury in primary cultured neonatal rat hepatocytes and in rats with hepatic damage," *Journal of Biomedical Science*, vol. 13, no. 4, pp. 569–578.

[86] Spencer J. P. E. , Vauzour D., and Rendeiro C., (2009) "Flavonoids and cognition: the molecular mechanisms underlying their behavioural effects," *Archives of Biochemistry and Biophysics*, vol. 492, no. 1-2, pp. 1–9.

[87] Kim S. M, Kang K.,. Jho E. H et al., (2011) "Hepatoprotective effect of flavonoid glycosides from *Lespedeza cuneata* against oxidative stress induced by tert-butyl hyperoxide," *Phytotherapy Research*, vol. 25, no. 7, pp. 1011–1017.

[88] Mishra A., Kumar S., Bhargava A., Sharma, B. and A. K. Pandey, (2011) "Studies on *in vitro* antioxidant and antistaphylococcal activities of some important medicinal plants," *Cellular and Molecular Biology*, vol. 57, no. 1, pp. 16–25.

[89] Pandey A. K., Mishra A. K., Mishra A., S. Kumar, and A. Chandra, (2010)"Therapeutic potential of *C. zeylanicum* extracts: an antifungal and antioxidant perspective," *International Journal of Biological and Medical Research*, vol. 1, pp. 228–233.

[90] Cushnie T. and Lamb, A.(2005) "Antimicrobial activity of flavonoids," *International Journal of Antimicrobial Agents*, vol. 26, no. 5, pp. 343–356.

[91] Cowan, M. M.(1999)"Plant products as antimicrobial agents," *Clinical Microbiology Reviews*, vol. 12, no. 4, pp. 564–582.

[92] Mishra, A. Mishra, H Kehri, Sharma B. and Pandey, A. K. (2009) "Inhibitory activity of Indian spice plant *Cinnamomum zeylanicum* extracts against *Alternaria solani* and *Curvularia lunata*, the pathogenic dematiaceous moulds," *Annals of Clinical Microbiology and Antimicrobials*, vol. 8, article 9

[93] Borris, R. P. (1996) "Natural products research: perspectives from a major pharmaceutical company," *Journal of Ethnopharmacology*, vol. 51, no. 1–3, pp. 29–38.

[94] Moerman, D. E. (1996). "An analysis of the food plants and drug plants of native North America," *Journal of Ethnopharmacology*, vol. 52, no. 1, pp. 1–22.

[95] Nakahara, K., Kawabata, H. Ono et al., 1993 "Inhibitory effect of oolong tea polyphenols on glucosyltransferases of mutans streptococci," *Applied and Environmental Microbiology*, vol. 59, no. 4, pp. 968–973.

[96] Mori A., Nishino C., Enoki N., and Tawata, S.(1987)"Antibacterial activity and mode of action of plant flavonoids against *Proteus vulgaris* and *Staphylococcus aureus*," *Phytochemistry*, vol. 26, no. 8, pp. 2231–2234.

[98] Tsuchiya H.and. Iinuma, M (2000)"Reduction of membrane fluidity by antibacterial sophoraflavanone G isolated from *Sophora exigua*," *Phytomedicine*, vol. 7, no. 2, pp. 161–165.

[99] Haraguchi H., Tanimoto K., Y. Tamura, K. Mizutani, and Kinoshita, T. (1998) "Mode of antibacterial action of retrochalcones from *Glycyrrhiza inflata*," *Phytochemistry*, vol. 48, no. 1, pp. 125–129.

[100] Alcaraz L. E., Blanco S. E., Puig, O. N. Tomas F., and F. H. Ferretti, (2000) "Antibacterial activity of flavonoids against methicillin-resistant *Staphylococcus aureus* strains," *Journal of Theoretical Biology*, vol. 205, no. 2, pp. 231–240.

[101] Osawa, H. Yasuda, T. Maruyama, H. Morita, K. Takeya, and H. Itokawa, ,(1992) "Isoflavanones from the heartwood of *Swartzia polyphylla* and their antibacterial activity against cariogenic bacteria," *Chemical and Pharmaceutical Bulletin*, vol. 40, no. 11, pp. 2970–2974.

[102] Maurya A., Chauhan P., Mishra A., and Pandey A. K.,(2012.) "Surface functionalization of TiO2 with plant extracts and their combined antimicrobial activities against *E. faecalis* and *E. Coli*," *Journal of Research Updates in Polymer Science*, vol. 1, pp. 43–51.

[103] Mishra, A. K. Singh A., and Pandey A. K.,(2010) "*In vitro*-antibacterial activity and phytochemical profiles of *Cinnamomum tamala* (Tejpat) leaf extracts and oil," *Reviews in Infection*, vol. 1, pp. 134–139.

[104] Mishra A. K, Mishra A., Bhargava A., and Pandey, A. K. (2008) "Antimicrobial activity of essential oils from the leaves of *Cinnamomum* spp.," *National Academy*

Science Letters, vol. 31, no. 11-12, pp. 341–345.

[105] Pan, M. H. Lai, C. S. and Ho C. T. (2010), "Anti-inflammatory activity of natural dietary flavonoids," *Food and Function*, vol. 1, no. 1, pp. 15–31.

[106] Middleton E. and Kandaswami, C. (1992) "Effects of flavonoids on immune and inflammatory cell functions," *Biochemical Pharmacology*, vol. 43, no. 6, pp. 1167–1179,

[107] Nishizuka, Y. (1988)"The molecular heterogeneity of protein kinase C and its implications for cellular regulation," *Nature*, vol. 334, no. 6184, pp. 661–665,.

[108] Hunter, T. (1995) "Protein kinases and phosphatases: the yin and yang of protein phosphorylation and signaling," *Cell*, vol. 80, no. 2, pp. 225–236,.

[109] Tunon M. J., Garcia-Mediavilla M. V., Sanchez-Campos, S. and Gonzalez-Gallego, J. (2009) "Potential of flavonoids as anti-inflammatory agents: modulation of pro-inflammatory gene expression and signal transduction pathways," *Current Drug Metabolism*, vol. 10, no. 3, pp. 256–271.

[110] Manthey J. A. (2000) "Biological properties of flavonoids pertaining to inflammation," *Microcirculation*, vol. 7, no. 1, pp. S29–S34.

[111] Cumella J. C., Faden H., and Middleton F., (1987) "Selective activity of plant flavonoids on neutrophil chemiluminescence (CL)," *Journal of Allergy and Clinical Immunology*, vol. 77, article 131.

[112] Beretz A.and Cazenave J. P., (1988) "The effect of flavonoids on blood-vessel wall interactions," in *Plant Flavonoids in Biology and Medicine II: Biochemical, Cellular and Medicinal Properties*, V. Cody, E. Middleton, J. B. Harborne, and A. Beretz, Eds., pp. 187–200, Alan R. Liss, New York, NY, USA,.

[113] Corvazier E.and Maclouf J. (1985) "Interference of some flavonoids and non-steroidal anti-inflammatory drugs with oxidative metabolism of arachidonic acid by human platelets and neutrophils," *Biochimica et Biophysica Acta*, vol. 835, no. 2, pp. 315–321.

[114] Block, G. Patterson, B. and Subar, A. (1992) "Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence," *Nutrition and Cancer*, vol. 18, no. 1, pp. 1–29.

[115] Duthie G. G., Duthie S. J., and. Kyle, J. A. M (2000) "Plant polyphenols in cancer and heart disease: implications as nutritional antioxidants," *Nutrition Research Reviews*, vol. 13, no. 1, pp. 79–106.

[116] Davis W. L. and Matthew, S. B,(2000) "Antioxidants and cancer III: quercetin," *Alternative Medicine Review*, vol. 5, no. 3, pp. 196–208.

[117] Ferry D. R., Smith A., and Malkhandi, J. (1996**)** "Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition," *Clinical Cancer Research*, vol. 2, no. 4, pp. 659–668.

[118] Brusselmans K., de Schrijver E., Heyns, W. Verhoeven G., and Swinnen J.V., (2003) "Epigallocatechin-3-gallate is a potent natural inhibitor of fatty acid synthase in intact cells and selectively induces apoptosis in prostate cancer cells," *International Journal of Cancer*, vol. 106, no. 6, pp. 856–862.

[119] Swinnen J. V., Roskams T., Joniau S. et al. ,(2002) "Overexpression of fatty

acid synthase is an early and common event in the development of prostate cancer," *International Journal of Cancer*, vol. 98, no. 1, pp. 19–22.

[120] Markaverich B. M., Roberts R. R., Alejandro M. A., Johnson, B. S. Middleditch G. A., and Clark J. H.,(1988) "Bioflavonoid interaction with rat uterine type II binding sites and cell growth inhibition," *Journal of Steroid Biochemistry*, vol. 30, no. 1–6, pp. 71–78.

[121] Singhal R. L., Yeh Y. A., Prajda N., Olah, E. Sledge G. W., and Weber, G. (1995) "Quercetin down-regulates signal transduction in human breast carcinoma cells," *Biochemical and Biophysical Research Communications*, vol. 208, no. 1, pp. 425–431.

[122] Barnes, S. (1995). "Effect of genistein on *in vitro* and *in vivo* models of cancer," *Journal of Nutrition*, vol. 125, no. 3, pp. 777S–783S.

[123]. Lamartiniere C. A, Moore J., Holland M., and Barnes S., (1995) "Neonatal genistein chemoprevents mammary cancer," *Proceedings of the Society for Experimental Biology and Medicine*, vol. 208, no. 1, pp. 120–123

[124] Ren W., Qiao, Z. , Wang, H. , Zhu L. and Zhang L.,(2003) "Flavonoids: promising anticancer agents," *Medicinal Research Reviews*, vol. 23, no. 4, pp. 519–534.

[125]. Carroll K. K, Guthrie N., So, F. V. and. Chambers, A. F (1998) "Anticancer properties of flavonoids with emphasis on citrus flavonoids," in *Flavonoids in Health and Disease*, C. A. Rice-Evans and L. Packer, Eds., pp. 437–446, Marcel Dekker, New York, NY, USA.

[126] Edenharder R., Von I. P., and Rauscher, R.(1993) "Antimutagenic effects of flavonoids, chalcones and structurally related compounds on the activity of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and other heterocyclic amine mutagens from cooked food," *Mutation Research*, vol. 287, no. 2, pp. 261–274.

[127] Thomsen L. L., Ching, L. M., Zhuang L., Gavin J. B., and Baguley B. C., (1991) "Tumordependent increased plasma nitrate concentrations as an indication of the antitumor effect of flavone-8-acetic acid and analogues in mice," *Cancer Research*, vol. 51, no. 1, pp. 77–81.

[128]. Chang R. L, Huang, M. T. Wood A. W. et al., (1985) "Effect of ellagic acid and hydroxylated flavonoids on the tumorigenicity of benzo[a]pyrene and (+/-)-7 beta, 8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene on mouse skin and in the newborn mouse," *Carcinogenesis*, vol. 6, no. 8, pp. 1127–1133.

[129] Siess M. H., Le Bon A. M., Canivenc-Lavier M. C. et al., (1996) "Flavonoids of honey and propolis: characterization and effects on hepatic drug-metabolizing enzymes and benzo[a]pyrene-DNA binding in rats," *Journal of Agricultural and Food Chemistry*, vol. 44, no. 8, pp. 2297–2301.

[130] Gerdin B.and Srensso, E. (1983) "Inhibitory effect of the flavonoid on increased microvascular permeability induced by various agents in rat skin," *International Journal of Microcirculation, Clinical and Experimental*, vol. 2, no. 1, pp. 39–46.

[131] Cushnie T. P. T. and Lamb, A. J. (2005) "Antimicrobial activity of

و glycosides ومشتقات methylated. فهي تستخدم كمضادات للأكسدة ، ومضادات للسرطان ، ومضادات للبكتيريا ، وعوامل وقاية للقلب ، ومضادات للالتهابات ، وجهاز المناعة. قبل بضعة عقود ، زادت الدراسات البحثية التي تركز على مركبات الفلافونويد من أنواع النباتات الطبية بشكل كبير بسبب فوائدها المختلفة لصحة الإنسان.

.

flavonoids," *International Journal of Antimicrobial Agents*, vol. 26, no. 5, pp. 343–356.

[132] Li B. Q., Fu T., Dongyan Y,Mikovits., J. A., Ruscetti F. W., and Wang, J. M. ,(2000) "Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry," *Biochemical and Biophysical Research Communications*, vol. 276, no. 2, pp. 534–538.

[133]. Critchfield J. W, Butera S. T., and Folks, T. M. (1996)"Inhibition of HIV activation in latently infected cells by flavonoid compounds," *AIDS Research and Human Retroviruses*, vol. 12, no. 1, pp. 39–46.

[134] Zandi, K. Teoh B. T., Sam S. S., Wong P. F., Mustafa M. R. and Abubakar S., (2011) "Antiviral activity of four types of bioflavonoid against dengue virus type-2," *Virology Journal*, vol. 8, article 560.

مركبات الفلافونيدات وأنواعها وكيميائها وفعاليتها العلاجية

فاطمة صيوان صباح

قسم الكيمياء –كلية العلوم –جامعة البصرة -العراق

Email :fsaiwan73@gmail.com

المستخلص

في السنوات الأخيرة ، ازداد الاهتمام بالنباتات ومحتوياتها من المركبات المختلفة ، والتي تعد مستقلبات ثانوية للنباتات ، ومن بين هذه المركبات مركبات الفلافونويد. من المعروف أن مركبات الفلافونويد تحتوي على حلقات عطرية تحمل عددًا من مجموعات الهيدروكسيل وتوجد في جميع أجزاء النباتات مثل الأوراق والفواكه والجذور. تظهر في شكل aglycones