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A COMPREHENSIVE REVIEW ON FLAVONOIDS

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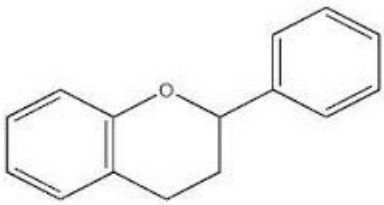
ABSTRACT

Flavonoids are naturally occuring polyphenolic compounds obtained from plants which are very useful as a dietary constituents having Antioxidant property followed by Anticancer,Hepatoprotective etc.Flavonoids are compounds that protects cells against damaging from free radicals such as oxygen species these are present in all type of plant in yellow or orange pigments from which they can be extracted through Ethanolic,Ethyl acetate extract.Flavonoids can also be synthesized in labs using lab chemicals such as benzaldehyde and acetophenone.In present review all possible synthesis and activities were explained.

KEYWORDS: Flavonoids,Antioxidants,Polyphenolic compounds.

INTRODUCTION

The term “Flavonoids” is generally used to describe a broad collection of natural products that include a C6-C3-C6 carbon framework, or more specifically phenylbenzopyran functionality.



Basic structure of flavonoids

Flavonoids are a group of common natural occurring polyphenolic compounds. That are widely found in the plant kingdom. They occur naturally as plant pigments in a broad range of fruits and vegetables as well as beverages such as tea, red wine, coffee and beer.[1]

Flavonoids generally occur in plants as glycosylated derivatives, and they contribute to the brilliant shades of blue, scarlet, and orange, in leaves, flowers, and fruits.[2]

Flavonoids play different roles in the ecology of plants. Due to their attractive colors, flavones, flavonols, and anthocyanidins may act as visual signals for pollinating insects.

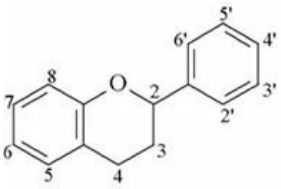
Because of their astringency, catechins and other flavanols can represent a defense system against insects harmful to the plants.[3]

Flavonoids act as catalysts in the light phase of photosynthesis and/or as regulators of iron channels involved in phosphorylation. They can also function as stress protectants in plant cells by scavenging ROS produced by the photosynthetic electron transport system.[4]

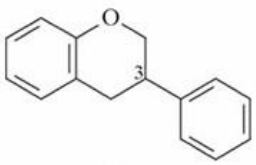
Furthermore, because of their favorable UV absorbing properties, flavonoids protect plants from UV radiation of sun and scavenge UV-generated ROS.[5]

The term “flavonoid” is generally used to describe a broad collection of natural products that include a C6-C3-C6 carbon framework, or more specifically phenylbenzopyran functionality.

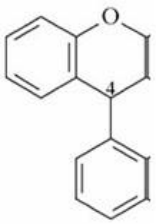
Depending on the position of the linkage of the aromatic ring to the benzopyrano (chromano) moiety, this group of natural products may be divided into three classes: the flavonoids (2-Phenylbenzopyrans), Isoflavonoids (3-Phenylbenzopyrans), and the Neoflavonoids (4-phenylbenzopyrans). These groups usually share a common chalcone precursor, and therefore are biogenetically and structurally related.



Basic structure



Isoflavonoids

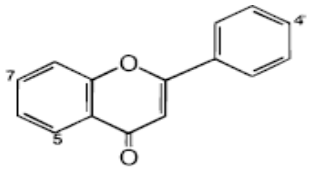


Neoflavonoids

Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactiveoxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, aging,

atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases (Parkinson's and Alzheimer's).Flavonoids may help provide protection against these diseases by contributing, along with antioxidant vitamins and enzymes, to the total antioxidant defense system of the human body. Epidemiological studies have shown that flavonoid intake is inversely related to mortality from coronary heart disease and to the incidence of heart attacks.

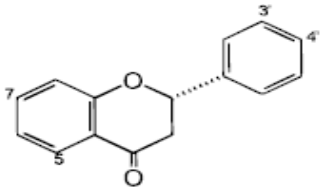
CLASSIFICATION



Flavones

	5	7	3′	4′
luteolin	OH	OH	OH	OH
apigenin	OH	OH		OH
chrysin	OH	OH		

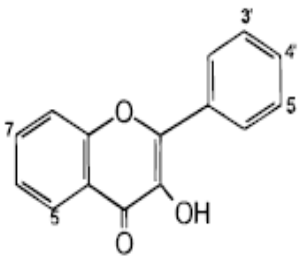
A) Flavones



Flavanones

	5	7	3′	4′
hesperetin	OH	OH	OH	OCH_3
naringenin	OH	OH		OH

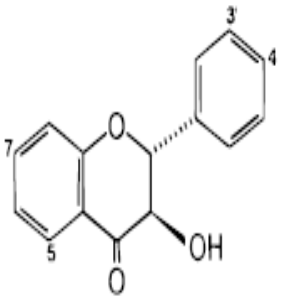
B) Flavonones



Flavonols

	5	7	3′	4′	5′
quercetin	OH	OH	OH	OH	
kaempferol	OH	OH		OH	
galangin	OH	OH			
fisetin		OH	OH	OH	
myricetin	OH	OH	OH	OH	OH

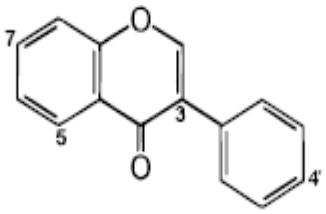
C) Flavonols



Flavanonol

	5	7	3′	4′
taxifolin	OH	OH	OH	OH

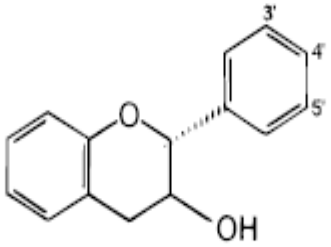
D) Flavononol



Isoflavones

	5	7	4′
genistein	OH	OH	OH
genistin	OH	Oglc	OH
daidzein		OH	OH
daidzin		Oglc	OH
biochanin A	OH	OH	OCH_3
formononetin		OH	OCH_3

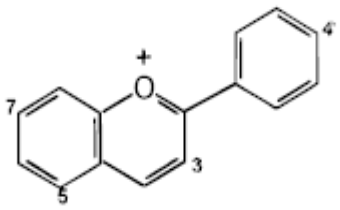
E) Isoflavones



Flavan-3-ols

	3	5	7	3′	4′	5′
(+)-catechin	βOH	OH	OH	OH	OH	
(−)-epicatechin	αOH	OH	OH	OH	OH	
(−)-epigallocatechin	αOH	OH	OH	OH	OH	OH

F) Flavon-3-ol



Flavylium Salts

	3	5	7	3′	4′
cyanidin	OH	OH	OH	OH	OH
cyanin	O-glc	OH	OH	OH	OH
pelargonidin	OH	OH	OH	–	OH

G) Anthocyanidis

BIOLOGICAL ACTIVITY

Flavonoids are a large family of natural polyphenolic compounds known for their wide range of biological and pharmacological activities including antioxidant, cytotoxic, anticancer, cardio protective, hepatoprotective, neuroprotective and antimicrobial activities. These compounds show varied biological activities including activity against HIV,1,2 dengue,3 influenza virus as well as antitumor and antioxidant effects.

1) Antioxidant activity: The antioxidant activity of flavonoids depends upon the arrangement of functional groups about the nuclear structure. The configuration, substitution, and total number of hydroxyl groups substantially influence several mechanisms of antioxidant activity such as radical scavenging and metal ion chelation ability.[7]

2) Hepatoprotective activity: Anthocyanins have drawn increasing attention because of their preventive effect against various diseases. Zhu et al. demonstrated that anthocyanin cyanidin-3-O-β-glucoside (C3G) increases hepatic Gclc expression by increasing cAMP levels to activate protein kinase A (PKA), which in turn upregulates cAMP response element binding protein (CREB) phosphorylation to promote CREBDNA binding and increase Gclc transcription. Increased Gclc expression results in a decrease in hepatic ROS levels and proapoptotic signaling. Furthermore, C3G treatment lowers hepatic lipid peroxidation, inhibits the release of proinflammatory cytokines, and protects against the development of hepatic steatosis.[8]

3) Antibacterial activity: Catechins, the most reduced form of the C3 unit in flavonoid compounds, have been extensively researched due to their antimicrobial activity. These

compounds are reported for their in vitro antibacterial activity against Vibrio cholerae, Streptococcus mutans, Shigella, and other bacteria.[9,10]

4) Anti-inflammatory activity: Flavonoids may affect specifically the function of enzyme systems critically involved in the generation of inflammatory processes, especially tyrosine and serine-threonine protein kinases. The inhibition of kinases is due to the competitive binding of flavonoids with ATP at catalytic sites on the enzymes. These enzymes are involved in signal transduction and cell activation processes involving cells of the immune system.[11]

5) Anticancer activity: Dietary factors play an important role in the prevention of cancers. Fruits and vegetables having flavonoids have been reported as cancer chemopreventive agents.[12,13] Consumption of onions and/or apples, two major sources of the flavonol quercetin, is inversely associated with the incidence of cancer of the prostate, lung, stomach, and breast. In addition, moderate wine drinkers also seem to have a lower risk to develop cancer of the lung, endometrium, esophagus, stomach, and colon.[14] The inhibitory effect of luteolin on the development of cancer cells was investigated in vitro and in vivo. Its antitumor mechanism was associated with the protection against carcinogenic stimuli,inhibition of tumor cell proliferation, induction of cell cycle arrest, and induction of apoptosis via intrinsic and extrinsic signaling pathways.Diosmetin also showed significant cytotoxicity on some human tumor cells, such as colon carcinoma cell (HT-29, Caco-2) and breast carcinoma cell (MCF-7).[15]

6) Antihypertensive activity: Anngiotensin II a potent vasoconstrictor, regulates the blood pressure and is important in pathogenesis of hypertension.[16] Mechanism of antihypertensive activity include, potentiation of hypotensive effect of bradykinin, decrease in endothelin levels, decrease in thromboxane B2[17] and increase in nitric oxide mediated vasodilation.Vasodilation effect of flavonoids can also mediated by their superoxide anion scavenging activity thereby preventing nitric oxide degradation by free radicals.[18]

FLAVONOIDS AS NEUTRACEUTICALS

"Nutraceutical" is a term coined in 1979 by Stephen DeFelice (DeFelice, 1992). It is defined "as a food or parts of food that provide medical or health benefits, including the prevention and treatment of disease." Subsequently, several other terms (medical food, functional food, and nutritional supplements) were used. A nutraceutical is any nontoxic food extract

supplement that has scientifically proven health benefits for both the treatment and prevention of disease (Dillard and German, 2000). Nutraceuticals may range from isolated nutrients, dietary supplements, and diets to genetically engineered "designer" food, herbal products, and processed products, such as cereals, soups, and beverages.[19]

The major active nutraceutical ingredients in plants are flavonoids. As is typical for phenolic compounds, they can act as potent antioxidants and metal chelators.[20]

IDENTIFICATION TESTS

- **Phytochemical Screening**

The dry extracts were subjected to various chemical tests in order to detect the presence of different phytoconstituents.

[1] Flavonoids

i) To detect the flavonoid in plant extract, the addition of KOH (1%) to alcoholic extract led to the formation of yellow colour and this was a result of the presence of flavonoid.

ii) The ethanol extract (5 ml) was added to a concentrated sulphuric acid (1 ml) and 0.5g of Mg. A pink or red coloration that disappear on standing (3 min) indicates the presence of Flavonoids.[21]

[2] Phenolic compound

Detected by a portion of the aqueous filtrate of each plant extract, 5ml was added to (1-2) drops of 1% of ferric chloride. A blue-green indicated the presence of phenolic compounds.

[3] Double bind test: using KMnO4 reagent, brown solution formed indicate the presence of double bond.

[4] Aldehyde & keton test: using 2, 4 dinitrophenyl hydrazine, in which the presence of yellow precipitate indicates that the extracted compound has aldehyde & keton groups.[22,23]

Chemical Identification

(1) Thin layer chromatography (TLC)

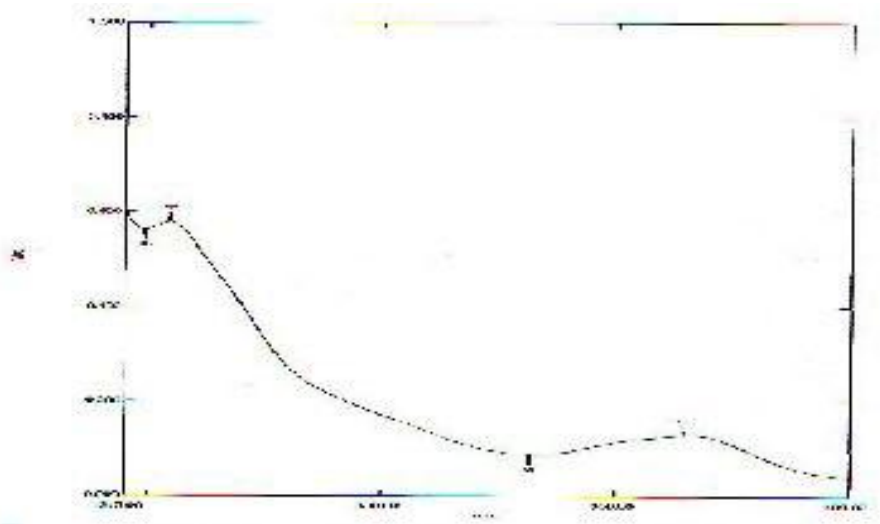
The crude extract was dissolved in ethanol and spotted on TLC plates (5x 20 cm) coated with silica gel .These plates were developed in chromatography chamber containing solvent mixture of (butanol, acetic acid and water (70:25:5, v/v/v) and let to stand for 1 hr. The developed plates were air dried and visualized under UV light. The plates were then placed in

a chamber saturated with ammonia vapours to observe the colour of spot and plates were also placed in a chamber saturated with I2 vapours to observe the colour of spot. Rf values were calculated for isolated sample.[24]

(2) Structural analysis of major components

(i) Ultraviolet-Visible spectroscopy

UV-Visible absorption in the range of (200-800) nm was recorded using ethanol as a solvent.



(ii) Infrared spectroscopy

FT-IR spectrum was analyzed to fined the most important Functional groups of flavonoid extract by KBr disk technique usingFT-IR.

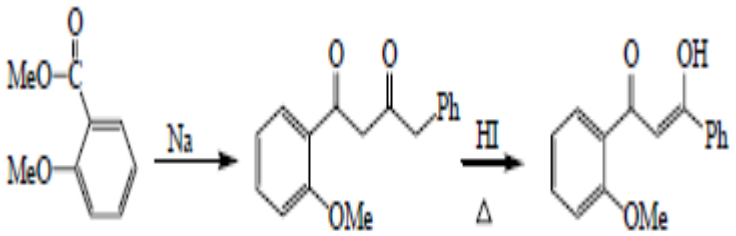
The functional groups of the purified flavonoid compound from IR-spectrum.

Wave number (cm-1)	Band shape	Band	Functional group
3500-3200	Broad	O-H	Stretching of phenolic-OH
1348	Broad	O-H	Bending of phenolic -OH
1612	Medium, broad	C=O	Stretching of ketone Carbonyl
1620	Strong, sharp	C=C	Stretching of olfenic C=C

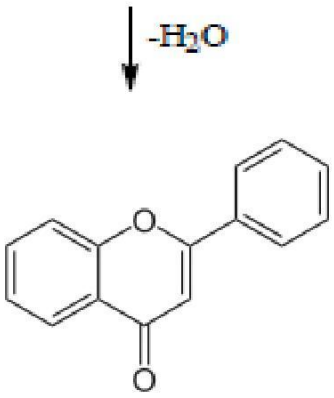
SYNTHESIS OF FLAVONOIDS

1) The Von-Konstanecki Method

This is a general method for synthesizing flavones which involves a reaction *o*methoxybenzoate (**I**) and acetophenone (**II**) in the presence of sodium , The reaction occurs is the Claisen condensation. This is followed by treatment with an acid to form compound (**III)** followed by elimination of water in order to form the flavone.



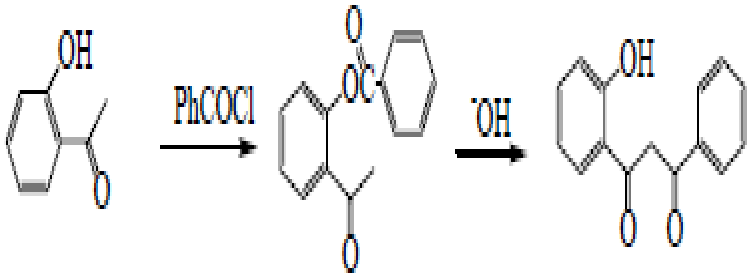
(I) **(II)** **(III)**



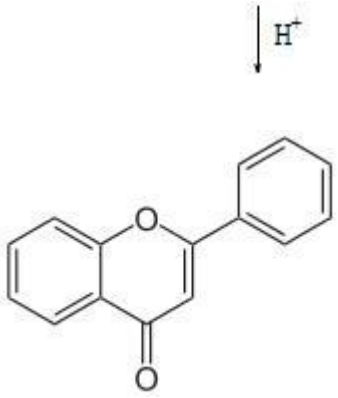
Flavone

2) The Baker-Venkataraman Method

The Baker-Venkataraman approach would be the most convenient route to the synthesis of flavone. In Baker-Venkataraman reaction,2- hydroxyacetophenone(I) was converted to ester (II), which then underwent rearrangement by intramolecular Claisen condensation in the presence of potassium hydroxide and pyridine to afford 1,3-diketone (III). Compound (III) was then cyclised to flavone under rather harsh conditions for either by treatment with concentrated sulphuric acid or heating with glacial acetic acid.



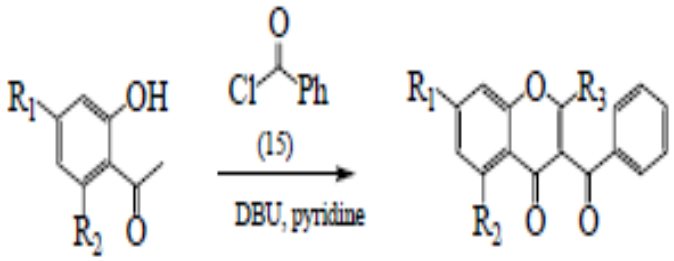
I **II** **III**



Flavone

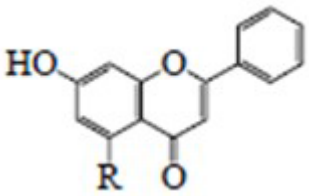
3) Ganguly's Synthesis of Flavone

Over a period of years several groups have investigated and improved upon the experimental conditions of Baker–Venkataraman reaction amongst which the work of Ganguly and colleagues. Using modified Baker–Venkataraman reaction, a novel class of 3- acylflavones which is the precursors to flavones have been synthesised. In their procedure, compounds such as 2', 4'-dihydroxyacetophenone **(Ia)** and 2',4',6'-trihydroxyacetophenone **(Ib)** were heated with acyl chloride in the presence of 1,8-diazabicycloundec-7-ene (DBU) and pyridine to obtain 3-acyl flavones **(IIa)** and **(IIB)**. On heating under reflux with an aqueous solution of 5% potassium carbonate, compound **(IIa)**and **(IIb)** yielded (**IIIa**) and (**IIIb**), respectively.



(Ia)R1 = OH, R2 = H **(IIa) R1= OH, R2= H, R3= Ph (Ib) R1 = R2 = OH**

(IIb) R1=R2= OH, R3=Ph



(IIIa) R = H

(IIIb) R = OH

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19. FLAVONOIDS AS NUTRACEUTICALS JEN-KUN LIN1 AND MENG-SHIH WENG *Institute of Biochemistry and Molecular Biology, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-ai Road, Taipei, Taiwan.*
20. Flavonoids as Nutraceuticals: A Review AR Tapas*1, DM Sakarkar1, and RB Kakde2 1 Department of Pharmaceutical Chemistry, Sudhakarrao Naik Institute of Pharmacy, Pusad- 445204, Dist.-Yavatmal (Maharashtra INDIA) 2University Department of Pharmaceutical Sciences, R.T.M. Nagpur University, Nagpur- 440033, Maharashtra, INDIA.
21. Phytochemical Screening and identification of some compounds fromMallow Sabri Fatima Zohra1 Belarbi Meriem1 Sabri Samira2 AlsayadiMuneer M.S1 1Laboratoire des produits naturels, activite biologique et syntheses (LAPRONA), Departement de biologie moleculaire et cellulaire, BP 119 Imama. Universite Abou Bekr Belkaid. Tlemcen, ALGERIA 2Laboratoire de Recherche ≪Ecologie et gestion des ecosystemes naturels≫,Departement d'ecologie et environnement, BP 119 Imama.Universite Abou Bekr Belkaid. Tlemcen, ALGERIA.

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