1. Introduction

1.1-General approach

Natural products are compounds produced by living organisms and include both small and macromolecules. All of these compounds are derived biosynthetically, from precursors called primary metabolites, which include amino acids, carbohydrate, and fatty acids.These metabolites are considered to be building blocks of life and are necessary for regular cellular functions.

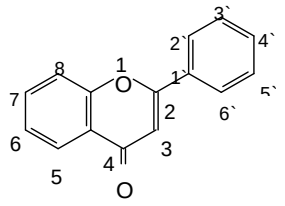
Some of the small molecular do not have a clearly defined function. They are considered secondary metabolites and make up the majority of work on natural products. Secondary metabolites are generally considered to be specific. [1]

Flavonoids are phenolic substances is isolated from a wide range of vascular plant.There are more than 8150 different flavonoids have been reported [2].Flavonoids are located inside the cell or in the surface of the various functions of plants [3].They act in the plants as antioxidants, antimicrobials, photoreceptors, visual attractors, feeding repellents and for light screening [4].Many studies have shown that flavonoids exhibit biological and pharmacological activities, including antioxidant ,cytotoxic, anticancer ,antiviral ,antibacterial, cardioprotetive, neuroprotective ,antimalarial, antileshmanial ,antitrypanosomal and antiambebial properties [5] .

These biological and pharmacological properties are usually attributed to their free radicals scavenging efficacies, metal complexion capabilities, and their ability to bind to proteins with a high degree of specificity [6].

The basic flavonoid structure contain the flavones nucleus which consist of 15 carbons atoms derived from a C_6-C3-C6 skeleton .Flavonoid skeleton is composed of two aromatic rings (commonly designated as A and B) which are linked by three carbon chain the connecting carbon chain which combines with an oxygen to form a heterocyclic central or C ring for most flavonoids with the exception of chalcones-2 in which the carbon chain between the A and B ring is linear [7].

The numbering scheme for chalcones differs from three ring flavonoids in that the A ring rather than the B ring carbons are labeled as prime.



Flavone

Depending on the position of the linkage of the aromatic B-ring to the benzopyrano (chromano) . Mostly, this group of natural products may be divided into three classes[7]:

- flavonoids (2-phenylbenzopyrans) 1,1 iso flavonoids

- 3 –phynylbenzopyrans
- Neoflavonoids .4-phynylbenzopyrans -4

These groups usually share common chalcone precursor and they are biological and structurally related.

Based on the degree of oxidation and saturation present in the heterocyclic C ring. Flavonoids may be divided into the following groups

- Flavones
- Flavonols
- Flavanones
- Dihydroflavonols
- Flavans
- Chalcones
- Aurones
- Isoflavones
- Anthocyanidins

The chemical nature of flavonoids depends on the structural class,degree of hydroxylation and other substitution pattern(methylations, prenylation and arylmigration) and degree of polymerization. Flavonoids are widespread in plants and are also found in some lower plants, including algae. They are found in fruits, vegetable, nuts, seeds, stem, leaves and flowers as well as tea[7].

Most flavonoids are yellow compounds, and contribute to the yellow colors of flowers and the fruits. Anthocyanidin are responsible for flowers colors in majority of angiosperms, but colorless of the flavonoids are also abundant.

The flavonoids may be modified by hydroxylation or O- glycosylation of hydroxyl groups as well as C –glycosylation directly to each carbon atom of the flavonoid skeleton in addition alkylation,methoxylation…etc. Sometimes additional rings are condensed to the basic skeleton of the flavonoid core .Flavonoid glycosides are frequently acylated with aliphatic or aromatic acid molecules[8].

1.2. Chemistry of flavonoids

Flavonoids are the largest group of natural compounds with variable phenolic structures and are found in plants .In 1930 a new substance was isolated from oranges. At that time it was believed to be a member of a new class of vitamins and was designated as vitamin P.Later on it became clear that this substance was a flavonoid (rutin) and still now more than 4000 varieties of flavonoids have been identified [9].

Chemically flavonoids are based upon a fifteen carbon skeleton consisting of two benzene rings (A and B) joined by a 3-carbon chain.

Flavonols differ from flavones by hydroxyl group at the 3-position. Flavonoids are often hydroxylated in position 3, 5, 7, 2, 3, 4, and 5.

Methyl ethers and acetyl esters of the alcohol group are known to occur in nature .When glycosides are formed, the glycosidic linkage is normally located in position 3 or 7and the carbohydrate can be L-rhamnose, D-glucose, glucorhamnose, galactose or arabinose [10].

1.3- Spectral characteristic of flavonoids

Studies on flavonoids by spectroscopy have revealed that most flavones and flavonols exhibit two major absorption bands. Band I (320-385nm) represents the B ring absorption, while Band II (250-285nm)corresponds to the A ring absorption. Functional groups attached to the flavonoid skeleton may cause a shift in absorption such as from 367nm in kaempferol (3,5,7,4,-hadroxyle groups) to 374 nm in myricetin (3,5,7,3,4,5, hydroxyl group)[11]. The absence of a 3-hydroxyl group in flavones distinguishes them from flavonols. Flavanones have a saturated heterocyclic C ring, with no conjugation between the A and B rings, as determined by their UV spectral characteristics [12].Flavanones exhibit a very strong Band II absorption maximum between 270and 295 nm, normally , normally with a shoulder at 300-340nm (taxifolin), and only one peak(270nm) in compounds with a mono substituted B ring.They exhibit two peaks - or one peak 258nm with a shoulder(272nm)-when a di, tri, or o-substituted B ring as present. As anthocyanins show distinctive Band l peak in the 450-560nm region due to hydroxyl cinnamoyl system of the B ring and Band ll peaks in the 240-280 nm region due to the

benzoyl system of the A ring.The color of the anthocyanins varies with the number and position of the hydroxyl groups[12].

1.4-Flavonoid -rich food and medicinal plant

Flavonoids are the most common and widely distributed group of plant phenolic compounds, occurring virtually in all plant parts, particularly the photosynthesis plant cells. They are a major coloring component of flowering plants .Flavonoids are an integral part of human and animal diet [13].Some food source containing different classes of flavonoids are displayed in Table (1)

Table (1):Classification, structure and food sources of some dietary flavonoids.

Class	Flavonoid	Dietary source
Flavanol	(+)Catechin(-)Epicatechin Epigallocatechin Chrysin,apigenin	Tea (14)
Flavone	Rutin ,Luteolin ,and Luteolin glucosides	Fruit skins , red wine ,buckwheat ,red pepper and tomato skin (15)
Flavonol	Kaempferol , quercetin , myricetin, myricetin ,and tamarixetin	Onion, red wine ,olive oil,berries,and grapefruit(16)
Flavanone	Naringin , naringenin , taxfolin ,and heseridin	Citrus fruits, grapefruit , lemons,and oranges(17)
Isoflavone	Genistin ,daidzin	Soyabean(18)
Anthocyanidin	Apigendin, cyanidin	Cherry,easberry,and strawberry (18)

Being photochemical, flavonoids cannot be synthesized by humans and animals [19]. Thus flavonoids found in animals are of plant origin than being biosynthesized *in situ*. Flavonoids are the most abundant in foods. Flavonoids in food are generally responsible for color, taste, prevention of fat oxidation, and protection of vitamins and enzymes .Flavonoids found in highest amounts in the human diet include: the isoflavones, flavonols, and the flavones. Although most fruits and some legumes contain catechins, the levels vary from 4.5 to 610mg/kg .Preparation and processing of food my decrease flavonoid levels depending on the methods used.Accurate estimation of the average dietary intake of flavonoids is difficult, because of a wide varieties of available flavonoids and the extensive distribution in various plants and also the diverse consumption in humans [20].

Recently there has been an upsurge of interest in the therapeutic potential of medicinal plants which might be due to their phenolic compounds, specifically to flavonoids. Flavonoids have been consumed by humans since the advent of human life on earth that is, for about 4 million years. They have extensive biological properties that promote human health and help reduce the risk of diseases. Oxidative modification of LDL cholesterol is thought to play a key role during atherosclerosis. The isoflavone glabridin, a major polyphenolic compound found in *Glycyrrhiza glabra* (Fabaceae) inhibits LDL oxidation via mechanism involving scavenging of free radicals.Several epidemiological studies have suggested that either green or black tea may lower blood cholesterol concentration and

blood pressure thereby providing some protection against cardiovascular disease .Flavonoids are also known to influence the quality and stability of food by acting as flavorants, colorant and antioxidants. Flavonoid contained in berries may have a positive effect against Parkinson's disease and may help to improve memory in elderly people. Antihypertensive effect has been observed in total flavonoid fraction of *Astragalus complanatus* in hypertensive rats. Table 2 shows some of the medicinal plant rich in flavonoid content. Solubility may play major role in the therapeutic efficacy of flavonoids. Low solubility of flavonoid aglycones in water coupled with its short residence time in the intestine as well as its lower absorption does not allow humans to suffer acute toxic effect from the consumption of flavonoids, with the exception of a rare occurrence of allergy. The low solubility of the flavonoids in water often presents a problem for its medicinal applications[21].

Table (2) Medicinal plants rich in flavonoids contents

Plant	Family	Flavonoid
Aloe Vera	Asphodelaceae	Luteolin (22)
Acalypha indica	Euphorbiaceae	Kaempferol glycoside (22)
Betula pendula	Betulceae	Quercetrin (22)
Citrus medica	Rutaceae	Hesperidin (22)
Azadirachta indica	Meliaceae	Quercetin (23)
Andrographis paniculata	Acanthaceae	5-hydroxy-7.8-dimethoxyflavone (23)

Clerodendum phlomidis	Verbenaceae	Pectolinarigenin ((23)
Bacopa moneirra	Scrophulariaceae	Luteolin (24)
Butea monospermea	Fabaceae	Genistein (24)
Calendula officinalis	Compositae	Isorhamnetin (24)
Cannbis sativa	Compositae	Quercetin (24)
Glyccheriza glabra	Leguminosae	Liquiritin (24)
Passiflora incarnate	Passifloraceae	Vitexin (24)
Tilia cordate	Tiliaceae	Hyperoside(24)
Bauhinia monandra	Fabaceae	Quercetin3-O-rutinoside(25)
Brysonima crassa	Malphigaceae	+-Catechin (26)
Clitoria ternatea	Fabaceae	Kaempferol-3-neohesperidoside (27)
Mimosa pudica	Mimosoideae	Isoquercetin (28)
Limnophila indica	Scrophulariaceae	3.4-methlenedioxyflavones (28)
Oroxylum indicum	Bignoniaceaea	Chrysin (28)
Tephrosia purpurea	Fabaceae	Purpurin (28)
Mentha longifolia	Lamiaceae	Luteolin-7-o-glycoside (29)
Momordica charantia	Curcurbitaceae	Luteolin (30)
Pongamia pinnata	Fabaceae	Pongaflavonol (31)

1.5 -Classification of flavonoids

Flavonoids can be classified according to their biosynthetic origins. Some flavonoids are both intermediates in biosynthesis and end-

products, e.g. chalcones, flavanones, flavanon-3-ols and flavan-3, 4-diols. Other classes are only known as the end-products of biosynthesis, e.g. anthocyanins, flavones and flavonols. Two further classes of flavonoids are those in which the 2- phenyl side-chain of flavonoid isomerizes to the 3-position (giving rise to isoflavones and related isoflavonoids) and then to the 4-position (giving rise to the neoflavonoids). Many flavonoids in foods occur as large molecules (tannins). These include condensed tannins (proanthocyanidins), derived and hydrolysable tannin [31]. For convenience, flavonoids rings are labeled A, B, and C. The individual carbon atoms are based on a numbering system which uses ordinary numerals for the A and C and "primed" numerals for B-ring. Primed modified numbering system is not used for chalcones , isoflavone derivatives, pterocarpans and the rotenoids [32]. The different ways to close this ring associated with the different oxidation degrees of A ring provide the various classes of flavonoids .The six-membered ring condensed with the benzene ring is either a pyrone (flavones, flavonols or its dihydroderivative (flavonones) or pyrane as flavan-3-ols) [33] . Flavonoids fall into two major categories according to whether the central heterocyclic ring is unsaturated or not .When unsaturation is present, as in anthocyanins, flavones and flavonols, the molecule is planar (occasionally distorted, e.g. by the substitution of the 2 ′-hydroxyl group in a 3-O-methyl flavonol). Saturated flavonoids (flavanones, flavans) have one or more chiral centres. Optical activity may also be present in flavonoids due to the presence of glycosidic substituents. Flavonoids may also be

classified according to molecular size. Most flavonoids occur naturally associated with sugars in conjugated form as glycosides. The glycosidic linkage is normally located at position 3 or 7 and the carbohydrate unit can be L-rhamnose, D-glucose, glucorhamnose, galactose or arabinose [18] and within any one class may be characterized as monoglycosidic, diglycosidic, triglycosidic etc. There are, for example, over 62,000 glycosides of the flavones and flavonols that have been isolated to date and glycosidic complexity is considerable. Flavonoids occur as aglycones (i.e., flavonoids without attached sugar) and methylated derivatives which occur in a variety of structural forms. All contain fifteen carbon atoms in their basic nucleus: two six-membered rings linked with a three carbon unit which may or may not be part of a third ring (34). A, fairly, considerable number of C-glycosylated flavonoids occur naturally. These are, readily, distinguished from O-glycosyl derivatives by their resistance to acid hydrolysis. They, commonly, have one or two sugar residues directly linked by a carbon-carbon bond at C-1 of the sugar moiety to the 6- or 8-position of the flavone nucleus. Thus, the flavone (apigenin) can occur with glucose at C-6 (isovitexin) or at C-8 (vitexin) or at both C-6 and C-8 (vicenin). Other apigenin C-glycosides are known where the carbon linked sugar is arabinose, galactose or xylose or two of these monosaccharides.C-Glycosides of flavones, commonly, occur with further sugars, O-glycosidically, linked. These glycosides, readily, lose their O-linked sugar(s) on acid hydrolysis. Such O-glycosidic residues may be attached either to a

hydroxyl of the C-sugar or directly to one of the free phenolic groups. By contrast, C-glycosides of other classes of flavonoid (flavanols, flavanones, and isoflavones) are of rare occurrence.

1.6- Nomenclature

Individual flavonoids names may be assigned in three different ways:

I. Trivial names are employed extensively and sometimes indicate flavonoid compound class depending on:

a)Names ending as in 'nidin' can denote an anthocyanidin (e.g. pelargonidin) and the ending 'etin' a flavonol (e.g. Quercetin).

b)Position of bonding as glycosides of quercetin has related names such as quercitrin (the 3-rhamnoside), isoquercitrin (the 3-glucoside) and quercimeritrin (the 7- glucoside).

c)Plant source - as many names have been derived from the generic or specific name of plant source (e.g. tricin from *Triticum Corniculatusin*) [34].

II- Semi – systematic chemical names are based on trivial names such as flavones or chalcone as the parent structure, giving precedence to substituents: e.g. 3, 5, 7, 3′, 4′-pentahydroxyflavone. In which the A- and B ring substituents precede C-ring substituents. In other cases the substituents are ordered numerically (e.g.3, 3′, 4′, 5, 7-pentahydroxyflavone).

III- Systematic chemical names: - e. g. 3, 4- dihydro -2 –phenyl - 2H-1- benzopyran for flavan, but this method is cumbersome and rarely used as it's easy to get wrong in cases of poly substitution **1**. There are two conventions for drawing flavonoid formulae:

a)With the heterocyclic oxygen at the top.

b)With the heterocyclic oxygen at the bottom.

1.7- Type of flavonoids

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:

a)The flavonoids (2-phenylbenzopyrans), where C2 is the position of the benzenoid substituent.

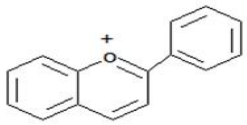
B)The neoflavonoids (4-phenylbenzopyrans)

1.8- Flavonoids subclasses

1.8.1-The anthocyanidins

Anthocyanidins are intensely colored plant pigments found throughout vascular plants.The sugar – free anthocyanidin aglycones are relatively few and vary according to the number and position of hydroxyl and methoxy substituent.Structural complexity is associated

with the sugar substituent that is present in the water – soluble anthocyanins. The anthocyanin range from simple structures such as cyaniding- 3-glucoside (chrysanthemin) to ternatin A1, delphinidin derivative which is substituted by seven glucose ,four p-coumaric acid and one malonic acid moiety. A third of all the known anthocyanins have malonic acid or other aliphatic dicarboxylic acid residues linked through sugar[34].



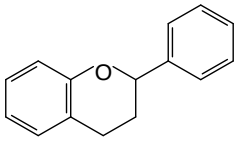
Anthocyanidin

1.8.2- Flavans and flavanols

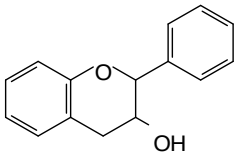
Flavans are formed by reduction of flavanones with flavan – 3 – ols as Intermediates. This is apparent from the facts that they may co-occur with the related flavanone and that they have the same 2S configuration.

There are a small number of natural flavans, most of which are lipid soluble and occur, notably, as leaf surface constituents as 4 ′, 7-dihydroxy-8 –ethylflavan (phytoalexins). The flavan – 3 – ols (or catechins) make up by far the largest class of monomeric flavans. Two substances with the 3, 3′, 4′, 5, 7-pentahydroxy substitution pattern, namely catechin` and epicatechin, are, extremely, widespread. Almost all flavan - 3- ols, such as catechin, are of the 2R, 3S

configuration. Those with the 2R, 3R configuration are prefixed with ‘epi’, e.g. epicatechin. Those with a 2S configuration are distinguished by the enantio (ent-) prefix[34].



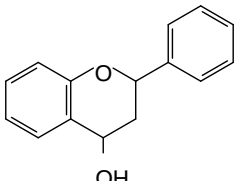
Flavan



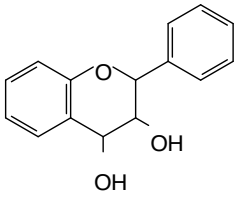
Flavan-3-ol

In addition to flavans and flavan -3 –ol, other occurs as flavan-3, 4-diols and also a fourth but small class of flavans, the flavan- 4 -ols.Flavan- 3, 4- diols are of biosynthetic importance, since they have recently been

recognized as the, immediate, precursors of the anthocyanins. Most naturally occurring 3, 4- diols have been obtained by extracting the heartwood of legume trees[34].



Flavan-4-ol



Flavan-3,4-diol

1.8.3- Flavolans ((proanthocyanidins)

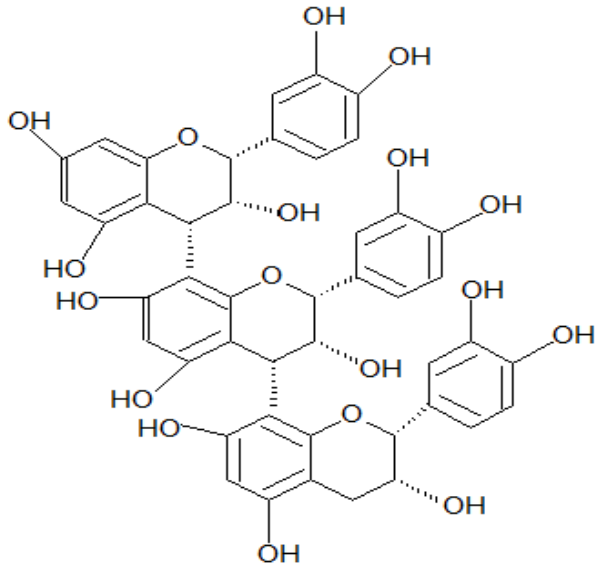
Flavonoids in foods occur as a series of flavan-3-ol oligomers or consist of monomeric units of flavans linked through carbon - carbon and other linkages. Fifteen subclasses of proanthocyanidins have been identified[27], which are usually based on a C - C link from the 8 –

position of one flavan unit (terminal unit) to the 4 – position of a second unit (extender unit) [28].

They produce colored anthocyanidins on heating with mineral acid, but they have the additional property of binding to protein. The best known flavolans are procyanidins, based on catechin and/or epicatechin units, and oligomers up to the hexamer have now been found in plants.

The interflavonoid linkage in flavolans is indicated in the same way as for polysaccharides, the bond and its direction being contained in parentheses (4′). The configuration of the interflavonoid bond at C-4 is indicated by the IUPAC nomenclature within the above parentheses.

Thus common procyanidin dimmers are described as epicatechin-(4′, 8) - catechin and ent-epicatechin- (4″-8)-picatechin respectively[28].

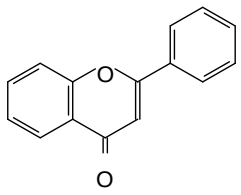


Epicatechin trimer（Condensed tannin)

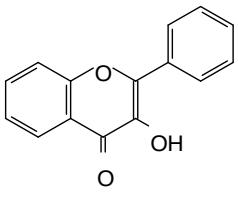
1.8.4-Flavones and flavonols

Flavones are a class of polyhydroxy flavonoid based on the structure of flavones (2-phenyl-4H-1-benzopyran-4-one or phenylchromone) which itself occurs, naturally, as a farina on Primula plants. Flavonols are flavones with a 3-hydroxy substituent and they share the same nomenclature. It is convenient to separate these two classes, mainly, because so many structures are known; some 1000 aglycones and over 2,000glycosides.They differ in their spectroscopic and chromatographic properties and can, readily, be distinguished by these means.They are, biosynthetically, distinct, flavones being formed by oxidation of flavanones, flavonols by oxidation of dihydroflavonols. There are also differences in the way they occur naturally; C-glycosides are common in the flavones series but rare among flavonols[28].

Free lipophilic flavones and flavonols occur at the upper surface of leaves in the wax or in bud exudates. There are also many O – glycosides, which are found within the leaf in the cell vacuole and in other parts of the plant.There are at least 200 different glycosides of quercetin and 250 of the related flavonol, kaempferol[28].



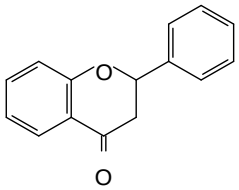
Flavone



Flavonol

1.8.5-Flavanones

Flavanones have a wide occurrence in plants. Flavanones are 2,3-dihydro -2-phenyl-4H-1-benzopyran-4-ones. The simplest known natural flavanone is the 7-hydroxy derivative, while the commonest is 4′, 5, 7-trihydroxyflavanone (naringenin). Flavanones are isomeric with chalcones and arise, biosynthetically, from chalcones by an isomer catalysed reaction.They have a centre of chirality at C-2 and, usually, occur in optically active form with the 2S-configuration.They commonly occur as glycosides. A variety of more complex derivatives with methyl and/or prenyl substituents has been described[28].

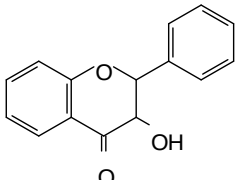


Flavanone

1.8.6- Dihydroflavonols

Dihydroflavonols can be described as 3- hydroxyflavanones (flavanon-3-ols).They are formed, biosynthetically, by oxidation at C-3 of flavanones, without inversion at C-2, and are the immediate precursors by a further oxidation of the flavonols. Dihydroflavonols have two chiral centres at C-2 and C-3; most naturally occurring compounds possess the (2R, 3R) stereochemistry.

Dihydroflavonols such as dihydroquerectin have a wide occurrence in nature being present in the freestate in woody plant tissues. They also occur in glycosidic combination in other plant parts.



Dihydroflavonol

1.8.7-Biflavonoids and polyflavonoids

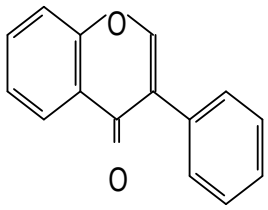
The structural variety present in biflavonoids is best illustrated with reference to dimmers of apigenin (4′, 5, 7-trihydroxyflavone).

Amentoflavone is the dimmer in which two apigenin units are linked by a carbon – carbon bond from the 8 - position of one unit to the 3‴of the other.Biapigenins with other C - C linkages have been discovered, where the linkage is 3′-3‴, 3-8″, 3-3‴, 6-8″, 8-8″, 6-6″, or 6-5‴.Linkage through a C-O-C bond may also occur, as in hinokiflavone, where the two apigenin units are linked at the 6 and 4‴′positions.

Mixed biflavonoids are also possible, e.g. flavone-flavanone dimers, as well as compounds based on two flavanone units (e.g. rhusflavanone).The first polyflavonoids as triflavonoid has been reported, based on three units of luteolin (3′, 4′, 5, 7-tetrahydroxyflavone[28].

1.8.8-Isoflavones

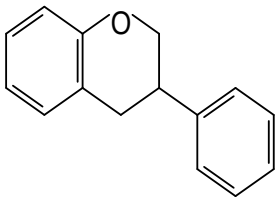
Isoflavans are another class of isoflavonoid which have been mainly isolated as phytoalexins after fungal inoculation of plant tissues. They are, also, metabolites of dietary isoflavones. Equol (4′,7-dihydroxyisoflavan) which has been isolated from the urine of mammals, has estrogenic activity.The numbering system of isoflavans is the same as that of the isoflavones[28].



Isovlavone

1.8.9- Isoflavanones

In isoflavanones the 2, 3-bond is reduced. Such compounds are much rarer than the isoflavones, isoflav-3-ene and isoflavanol.

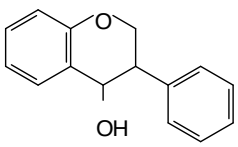


Isoflavanone

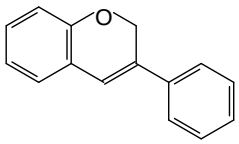
1.8.10-Rotenoids

Rotenoids are a class of isoflavonoids characterized by the presence of an extra carbon atom in an additional heterocyclic ring .This system is

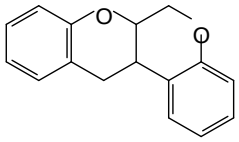
derived by oxidative cyclisation of a 2′-methoxyisoflavone. Besides rotenoids, there are a small number of hydroxyrotenoid and dehydrorotenoids, in which there is a double bond introduced at the 6a–12a position.



Isoflavanol



Isovlav-3-ene

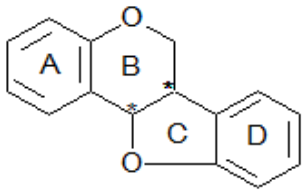


Rotenoids

1.8.11- Pterocarpans

Pterocarpans contain a tetracyclic ring system derived from the basic isoflavones skeleton by an ether linkage between the 4- and 2′-positions. The systematic numbering is distinctive for this particular carbon skeleton. The majority of natural pterocarpans possess antifungal activity. They are conveniently subdivided into simple pterocarpan flavonoids, 6a-hydroxypterocarpan and pterocarpene, in which unsaturation is introduced at the 6a, 11a - position. The best known structure is pisatin, a 6a-hydroxypterocarpan. Although pterocarpans have two chiral centres, only R,R and S,S configurations are sterically possible. Most pterocarpan phytoalexins that have been

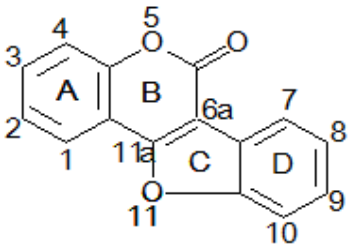
isolated are levorotatory and have the 6aR, 11aR absolute configuration; a few are dextrorotatory and can be assigned to the 6aS, 11aS series.



Pterocarpan

1.8.12-Coumestans

The simplest structure is coumestrol (7,9-dihydroxycoumestan) but a variety of prenylated derivatives have also been characterised. The numbering system used is the same as in the pterocarpan series and coincides with the CA systematic numbering.



Coumestane

1.8.13- Neoflavonoids (4- phenylbenzopyrans)

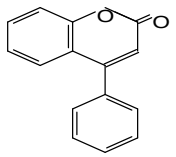
This term refers to a small group of C-15 naturally occurring substances, structurally and biogenetically, related to the flavonoids and isoflavonoids. They have limited distribution, occurring with

isoflavonoids in the subfamily Papilionoideae of the Leguminosae. Other families where they have been encountered are the Guttiferae, Rubiaceae, Passifloraceae, Compositae and Polypodiaceae.

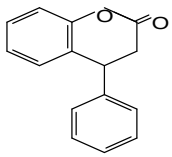
The neoflavonoids are, structurally and biogenetically, closely related to the flavonoids and the isoflavonoids and they have three main subdivisions of structures[25].

i. 4-arylcoumarins (4-aryl-2H-1-benzopyran-2-ones),
ii. 3,4-dihydro-4-arylcoumarins,
iii. Neoflavenes.

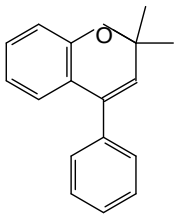
Representative structures are: dalbergin and the two related opened ring compounds, 4-methoxydalbergione and obtusaquinol



4-arylcoumarin



3,4-dihydro-4-arylcoumarin



Flavene

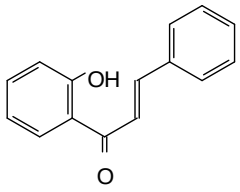
1.8.14- Minor Flavonoids

Natural products such as chalcones and aurones also contain open-chain C6-C3-C6 backbone and are considered to be minor

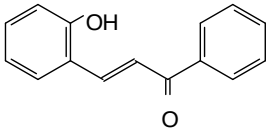
flavonoids.These groups of compounds include the 2′-hydroxychalcones, 2′-OH-dihydrochalcones, 2′-OH-retro-chalcones, aurones (2-benzylidenecoumaranone), and auronols [26].

1.8.15- Chalcones and dihydrochalcones

Chalcones such as butein are the first intermediates of flavonoid biosynthesis. They occur, sporadically, in plants as yellow pigments, some 200 structures being known. The numbering system of chalcone substituents differs from that in ring closed flavonoids[26,28].



2-Hydroxychalcone



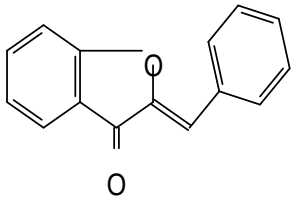
2-Hydroxy-retrochalcone

The majority of chalcones have hydroxy/methoxy substituents at the 2′, 4, 4′, 6′-positions. In dihydrochalcones such as phloridzin, the double bond in the -β- position is reduced and the compounds are colorless or retro chalcone[26,28].

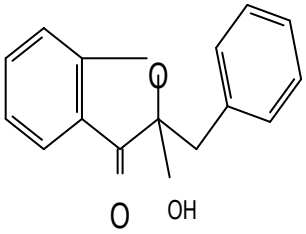
1.8.16- Aurones

Aurones are a small group of yellow pigments, based on the 2-benzylidenecoumaranone nucleus. These are formed by oxidation of chalcones and may co-occur with the related chalcone precursors. The numbering system differs from that in the chalcone series, so that the most common hydroxylation pattern, that of the pigment aureusidin, is 3′,4,4′,6-tetrahydroxyaurone. The auronols (2-hydroxy-2-

benzylcoumaranones) are a closely related series of colorless compounds.



Aurone



Auronol

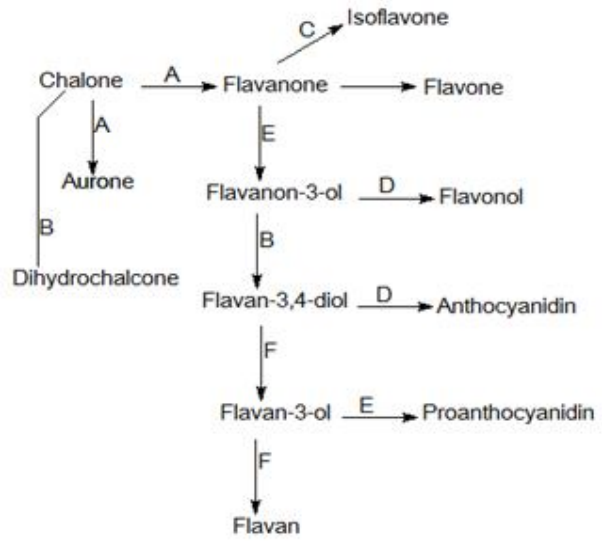
1.9- Synthesis of flavonoids

1.9.1--Flavonoid biosynthesis

The flavonoid pathway is part of the larger phenylpropanoid pathway, which produces a range of other secondary metabolites, such as phenolic acids, lignins, lignans, and stilbenes[26].The key flavonoid precursors are phenylalanine, obtained via the shikimate pathway, and malonyl-CoA derived from citrate produced by the TCA cycle.

Structurally, flavonoids are derivatives of 1, 3- diphenylpropane. One of the phenyl groups, ring B, originates from the shikimic acid pathway, while the other ring, ring A, is from the acetate pathway through ring closure of a polyketide. One hydroxyl group in ring A is always situated in the ortho position to the side chain, and involved in

the formation of the third sixmembered ring or a five-membered ring (only found in aurones), ring C. The 2-phenyl side-chain of the flavonoid skeleton isomerizes to the 3-position, giving rise to isoflavones, e.g. formononetin **9**.Biosynthetic relationship of flavonoids depends on the following chemical processes: cyclisation, bioreduction, aryl dehydrogenation, hydroxylation, migration, and dehydroxylation which are explained by the scheme (1)[26,28]:



A=Cyclisation,B=Bioreduction,C=Arylmigration,D=Dehydrogenation
E=Hydroxylation,F=Dehydroxylation

Schem:1: Biosynthetic relationship of flavonoids

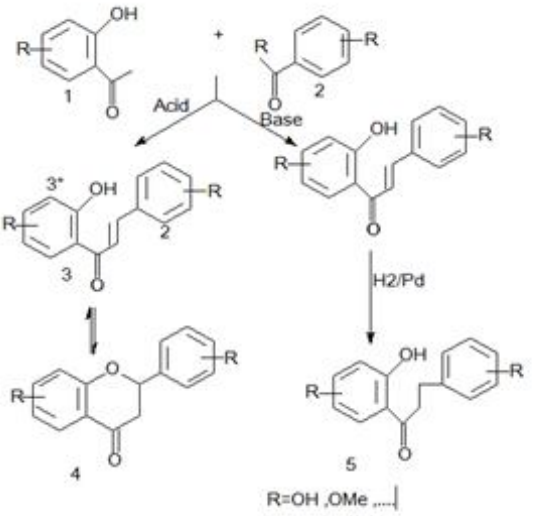
1.9.2- Biosynthesis of flavonoids precursors

The first flavonoids, the chalcones, are formed from HCA-CoA esters, usually 4-coumaroyl- CoA, in three sequential reactions involving, the ‘extender’’ molecule, malonyl-CoA which formed from Acetyl CoA by Acetyl-CoA carboxylase.4-Coumaroyl-CoA is produced from the amino acid phenylalanine by what has been termed

the general phenylpropanoid pathway, through three enzymatic conversions catalyzed by phenylalanine ammonialyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumarate[26].

1.9.3- Stereoselective synthesis of some flavonoids

Chalcones and dihydrochalcones are considered to be the primary C6-C3-C6 precursors . Chalcones are readily accessible via two well-established routes comprising a base-catalyzed aldol condensation or acid- mediated aldolization of 2-hydroxyacetophenones (1) and benzaldehydes (2) [29, 30]. The base-catalyzed aldol condensation is usually the preferred route towards chalcone (3) formation, since under acidic conditions cyclization of the ensuing chalcone leads to formation of corresponding racemic flavanones (4) [31]. Dihydrochalcones (5) are generally obtained via reduction (H_2/Pd) of the preceding chalcones



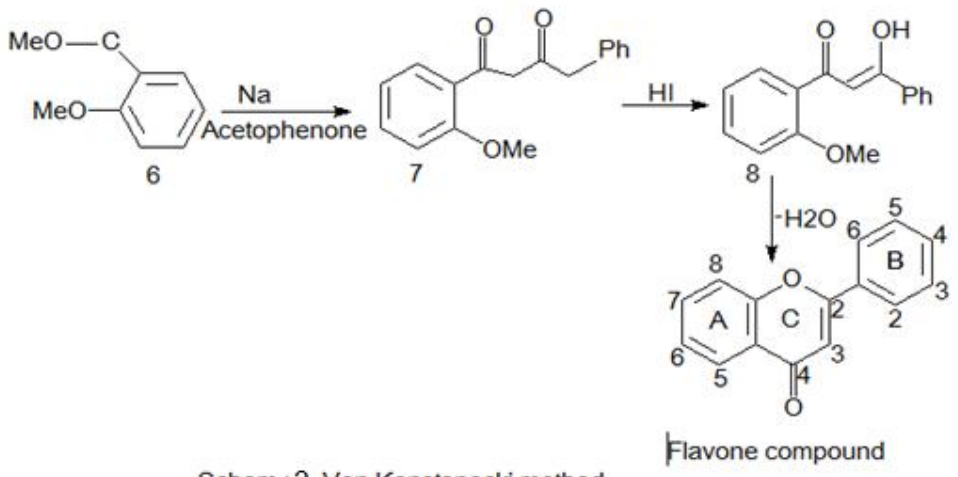
Schem : 2 Acid -and base -catalyzed synthesis of chalcones,racemic flavanones, and dihydrochalcones

1.9.4- Synthesis of flavones

There are a number of methods reported for the synthesis of flavones:

i)The Von-Konstanecki method

This is a general method for synthesizing flavones which involves a reaction of dimethoxybenzoate (6) and acetophenone in the presence of sodium to form (7) as shown in Scheme (1.3). The reaction is a Claisen condensation. This is followed by treatment of (7) with an acid to form compound (8) followed by elimination of water in order to form the flavone [32](Scheme 3).

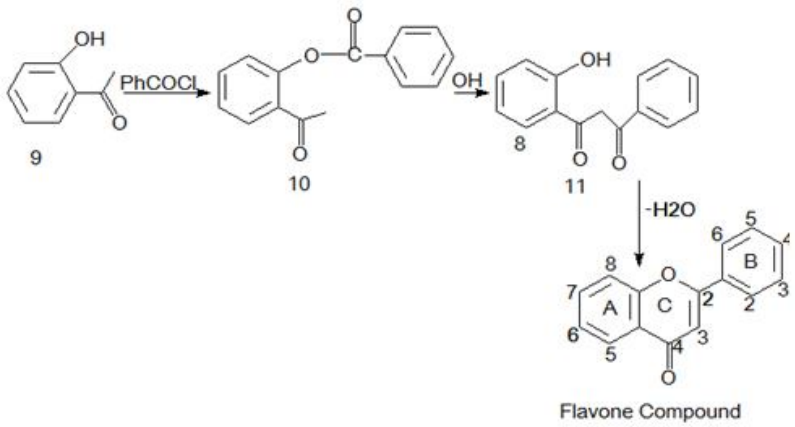


Schem :3 Von Konstsnecki method

ii-The Baker-Venkataraman method

The Baker-Venkataraman approach Scheme (1.4) would be the most convenient route to the synthesis of flavone, 2- hydroxyacetophenone (9) is converted to ester (10), which then undergoes rearrangement by intramolecular Claisen condensation in the presence of potassium hydroxide and pyridine to afford 1, 3-diketone (11). Compound (11) is

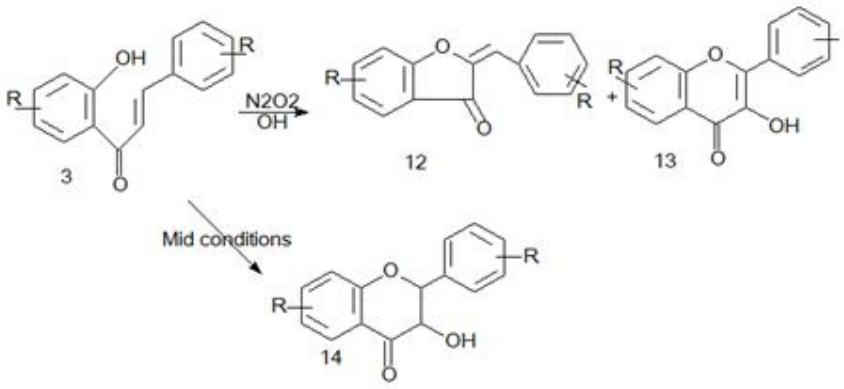
then cyclised toflavone under rather harsh conditions either by treatment with concentrated sulfuric acid or heating with glacial acetic acid to eliminate water [33](Scheme 4).



Scheme : 4:Baker-Venkataraman method

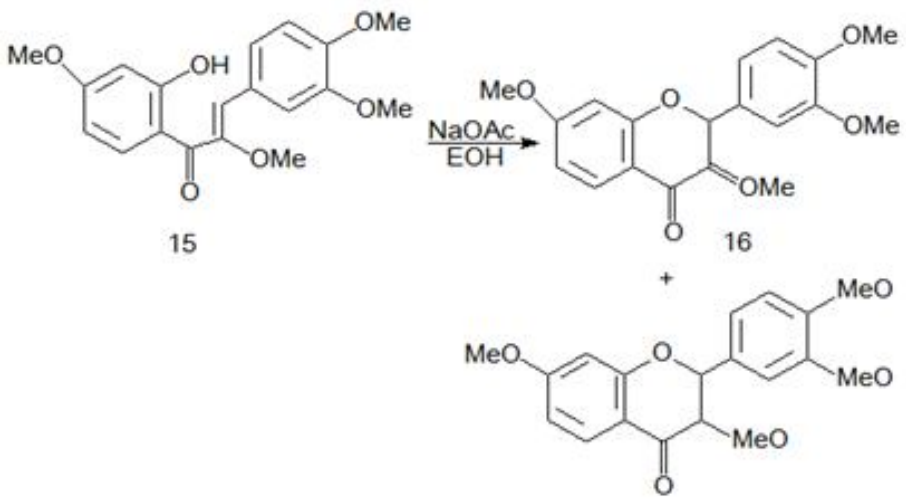
1.9.5- Synthesis of aurones and dihydroflavonols

The Algar-Flynn-Oyamada (AFO) protocol [34, 35] is, mainly, used for the synthesis of aurones (12) and flavonols (13) by oxidation of chalcones (3). It was demonstrated that these reactions can be adapted for the formation of racemic dihydroflavonols (14) [36, 37] in moderate to good yields (Scheme 5).



Schem: 5:AFO protocol for systhesis of aurone,flavonol and dihydroflavonol

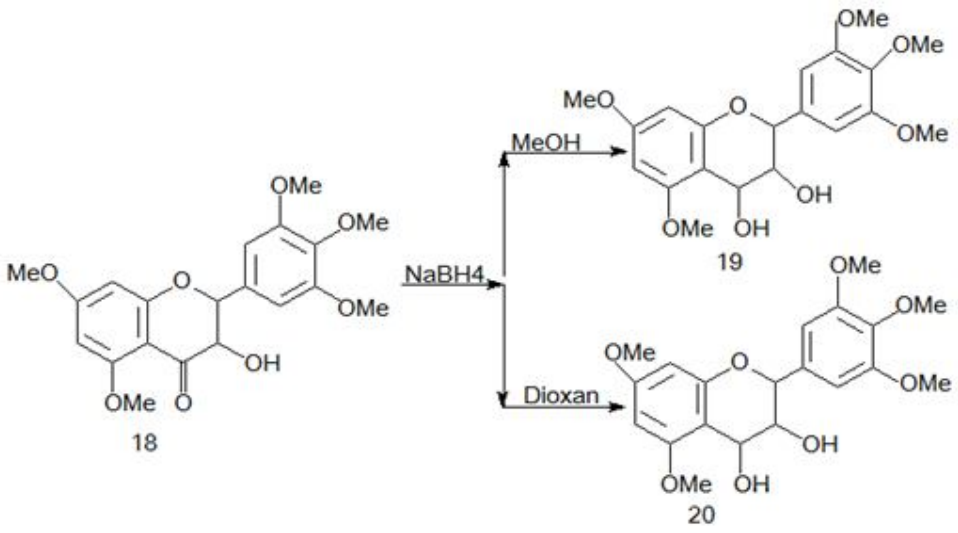
Cyclization of 2′-hydroxy-α,3,4,4,7-tetramethoxychalcone (15) with sodium acetate in ethanol furnished both 3,3,4,7-O-tetramethyl-2,3-transand3,3,4,7-O-tetramethyl-2,3-cis-dihydroflavonols (16) and (17) in 22% and 11% yields, respectively (Scheme 6) [38].



Scheme 6: Chalcone cyclization with NaOAC IN EtOH to yield Trans-and cis-dihydroflavonols

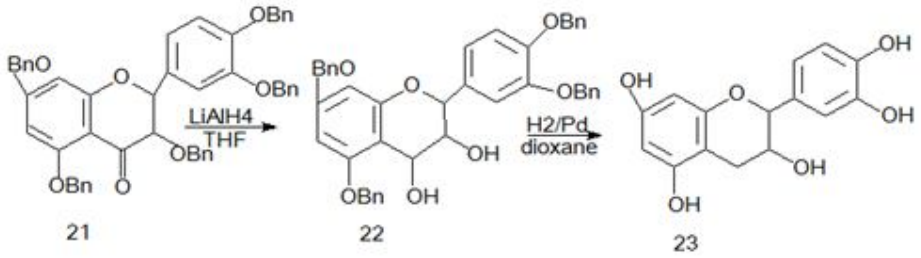
1.9.6- Flavan-3-ols and flavan- 3, 4-diols

One of the most common ways for the synthesis of flavan-3-ols and the closely related flavan-3,4-diol analogues involves the reductive transformation of dihydroflavonols. Reduction of the dihydroflavonols (18) with sodium borohydride in methanol affords the 2 , 3-trans-3,4-trans-flavan-3,4-diols (19), while reduction in an aprotic solvent like dioxane yields,Exclusively, the C4-epimers (20) (Scheme 7) [39, 40].



Schem:7: Reduction of dihydroflavonols with NaBH4 to afford **flavan**-3,4-diols

Catechin represents the only flavan-3-ol synthesized from the corresponding dihydroflavonol [41, 42]. Consecutive treatment of 2,3-trans-3-Oacetyldihydroquercetin tetra-O-benzyl ether (21) with LiAlH4 gave the free phenolic flavan-3-ol (22) which gave catechin (23) (with H2/Pd) in optically pure form (Scheme 8).

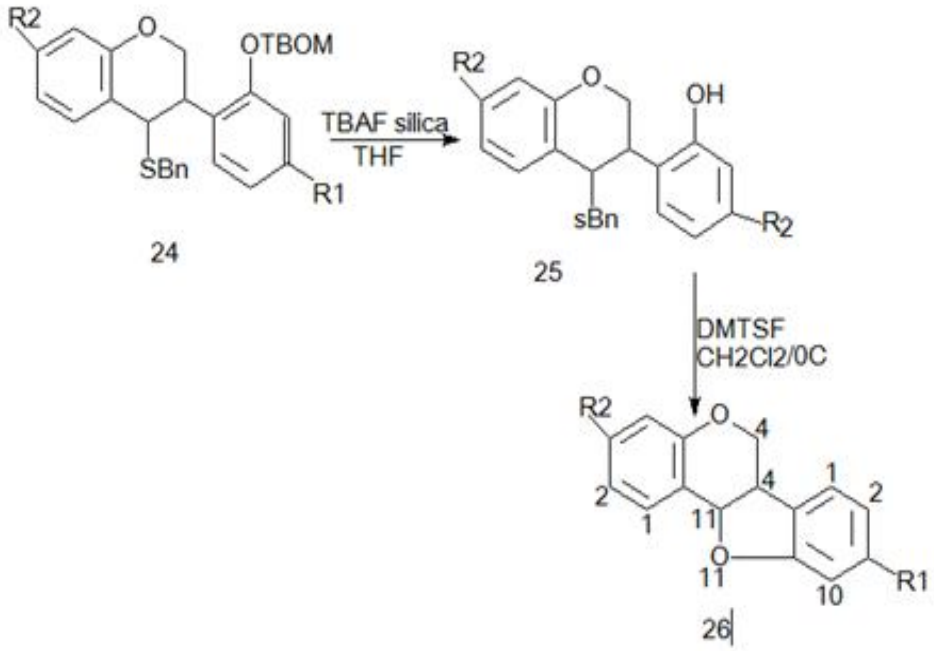


Schem :8: Reduction of 2,3-Trans-3-O-acetyldihydroquercetin tetra-O-Benzyl ether to yield catechin

1.9.7- Isoflavonoids

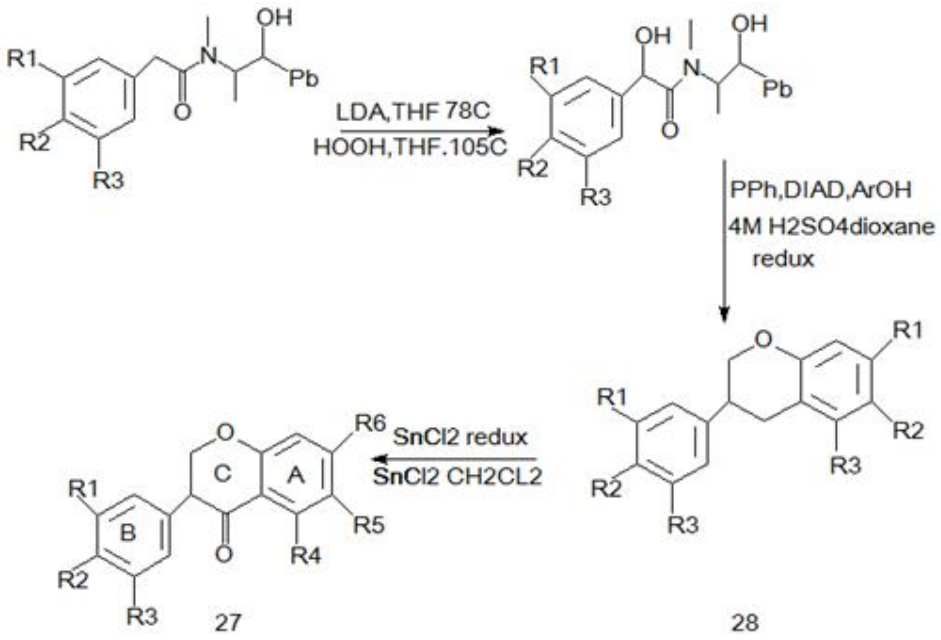
Cleavage of the silyl ethers (24) using tetrabutylammonium fluoride (TBAF) on silica[43] of 4-benzylsulfanylisoflavans, gives 4-benzylsulfanyl-20-hydroxyisoflavans (25) which is converted to the

6a,11a-cis-pterocarpans (26) using the thiophilic Lewis acids, dimethyl(methylthio) sulfonium tetrafluoroborate (DMTSF) or silver trifluoromethanesulfonate [44,45] (Scheme 9).



Schem 9: Synthesis of (6a,11a) -cis-pterocarpans

The synthesis of isoflavanones starts by an asymmetric aldol reaction between (S, S) - (+)-pseudoephedrine arylacetamide and formaldehyde to introduce chirality in the isoflavanone carbon framework at C-3.This is followed by the introduction of the B-ring as phenol ether under Mitsunobu conditions and subsequent removal of the chiral auxiliary. Acids (27) are then converted, by an intramolecular Friedel–Crafts acylation, to isoflavanones (28) in good yields and essentially enantio pure [26]-Scheme (10)



Schem 10 :Stereo selective synthesis of isoflavanones

1.10-Biological potential of flavonoids

Plants as alternative sources of antimicrobial substances represent a starting point for drug discovery due to their disease preventive properties [49].

Although some plants remain to be the source of many powerful antimicrobial products for the global population, many species remain unexplored [50]. More awareness is being drawn towards the discovery, promotion and use of naturally- occurring substances as antimicrobial agents because in most cases they continue to be the only form of medicine available in under developed countries.

The activity of natural extracts has been found to depend on the active components of the raw materials, the type and polarity of extracting

solvent [46]. Most naturally occurring compounds (e.g. flavonoids), possess some biological or pharmaceutical activity (47). Flavonoids are one of the largest groups of secondary metabolites, and they play an important role in plants as defense and signaling compounds in reproduction, pathogenesis and symbiosis. Plant flavonoids are involved in response mechanisms against stress, as caused by elevated UV radiation, infection by microorganisms or herbivore attack. Flavonoids are also involved in the production of root nodules as a nitrogen fixation system after infection by Rhizobium bacteria in a variety of leguminous plants. They also affect human and animal because of their role in the diet, which is ascribed to their antioxidant properties or their estrogenic action and to a wide range of antimicrobial and pharmacological activities [48].

Plants as alternative sources of antimicrobial substances represent a starting point for drug discovery due to their disease preventive properties [49]. Although some plants remain to be the source of many powerful antimicrobial products for the global population, many species remain unexplored [50]. More awareness is being drawn towards the discovery, promotion and use of naturally- occurring substances as antimicrobial agents because in most cases they continue to be the only form of medicine available in under developed countries.

A number of flavones, flavonols, flavanones, and isoflavones, as well as some of their methoxy, isoprenyl, and acylated derivatives, show antimicrobial activity[17].In ethnopharmacology research, the

antimicrobial susceptibility test (AST) is used to determine the efficacy of potential antimicrobials from biological extracts against a number of different microbial species. AST is methods are used to screen plant extracts for antimicrobial activity but are, largely, used to determine the usefulness of an antimicrobial in combating infections by determining its minimum inhibitory concentration (MIC). In clinical research *in vitro* susceptibility tests are particularly important if an organism is suspected to belong to a species that has shown resistance to, frequently, used antimicrobial agents. They are also important in epidemiological studies of susceptibility and in comparisons of new and existing microbial agents [51]. Owing to the widespread ability of flavonoid compounds to inhibit spore germination of plant pathogens, they have been proposed for use against fungal pathogens of man [17]**.** A prenylated flavanone isolated from the shrub *Eysenhardtia texana* has been identified as 5, 7, 4' - trihydroxy-8-methyl-6-(3-methyl-[2-butenyl])-(2*S*) –flavanone and shown to possess activity against the opportunistic pathogen *Candida albicans*[52]. The flavonoid 7- hydroxy-3', 4'-(methylenedioxy) flavan, isolated from *Terminalia bellerica* fruit rind, has also been shown to possess activity against *Candida albicans*[53]. Three flavones from *Artemisia giraldi*, were identified as 6, 7, 4'- trihydroxy-3',5'-dimethoxyflavone, 5, 5'- dihydroxy-8,2',4'-trimethoxyflavone and 5, 7, 4'-trihydroxy-3',5'-dimethoxyflavone have been reported to exhibit activity against *Aspergillus flavus* [54].

The activity of propolis against dermatophytes and *Candida* spp. has been attributed at least partially to its high flavonoid content [55]. Galangin, a flavonol commonly found in propolis samples [56], has been shown to have inhibitory activity against *Aspergillus tamarii*, *Aspergillus flavus*, *Cladosporium sphaerospermum*, *Penicillium digitatum* and *Penicillium italicum.* The antibacterial activity of flavonoid compounds is being increasingly documented. Crude extracts from plants with a history of use in folk medicine have been screened in vitro for antibacterial activity by many research groups. Flavonoid-rich plant extracts from species of *Hypericum*, *Capsella* and *Chromolaena* [57] have been reported to possess antibacterial activity. Many other phytochemical preparations with high flavonoid content have also been reported to exhibit antibacterial activity [58, 59, 60]. Many research groups have gone one step further and isolated and identified the structure of phenolic compounds that possess antibacterial activity. Examples of such flavonoids are apigenin[61-64], pinocembrin[65], ponciretin[66],genkwanin[67],sophoraflavanone G and its derivatives[68], naringin and naringenin [60], epigallocatechin gallate and its derivatives [69,70], luteolin and luteolin 7-glucoside [62,71], quercetin, 3-*O*-methylquercetin and various quercetin glycosides[72] and kaempferol and its derivatives [62,73].

Flavonoids are well known for their antioxidant activates[74]. Antioxidants are compounds that protect the cell against the oxidative effect of reactive oxygen species, such as singlet oxygen, peroxyl radical, hydroxyl radical, superoxide radical, nitric oxide and

peroxynitrite. Oxidative stress leads to cellular damage which is linked to various diseases such as diabetes, cancer, cardiovascular disorders, neurodegenerative disorders, and ageing. Antioxidants interfere with radical producing systems and increase the function of endogenous antioxidants, protecting the cells from damage by these free radicals. Intake of flavonoids via fruits, vegetable and whole grains helps to increase levels of anti-oxidants in the body[75].The strong antioxidant property of flavonoids is attested by a number of studies [76-81]. Flavonoids are known to exhibit an inhibitory effect on excessive generation of the free radicals.This prevents the damaging effect of reactive oxygen species that includes lipid proxidation, and oxidation of sulfhydril and other susceptible group in proteins[82-84] . Quercetin is well known for its ability to act as antioxidant, it protects the body against reactive oxygen species. Studies have suggested that it helps in suppressing lipid proxidation in model systems[85]. The flavonoids : myricetin, quercetrin and rutin are also known to inhibit the production of superoxide radicals[86,87].

Different studies demonstrated that tea polyphenols- which belong to a sub- class of flavonoids possess potential antioxidant capabilities. A study by Nakagauta *et. al*., suggested that drinking green tea helps in prevention of cardiovascular disorder by increasing the antioxidant capacity of plasma in humans[88].

Citrus flavonoids, similar to tea polyphenols, are antioxidants that may protect against oxidative stress linked to inflammation and help reduce the risk of macromolecule damage caused by free radicals.

Studies by Zielinska – Przyjemska *et al*., [89] indicated the antioxidant effect of citrus flavonoids such as naringin, naringenin and hesperidin by counteraction the effects of reactive oxygen species on apoptosis.

Naturally occurring flavonoids have been recognized for their antimicrobial activity. Many research groups have isolated and identified flavonoids possessing antifungal, antiviral and antibacterial activities. This property of flavonoids enables them to be used extensively in the nutrition, food safety and health. The antiviral effect of flavonoids was studied[90]. Naturally occurring flavonoids such as quercetin, naringin, hespertin possess a variable spectrum of antiviral activity. They affect the replication and infectivity of certain RNA and DNA viruses[91] . Quercetain and apigenin are known to exhibit antibacterial activies[92,93].

Certain flavonoids exhbit hormone- like activies. They show resemblance to estrogen and other steroid hormones. These compounds exist in fruits, vegetables adn tea. Esterogens possess a neuroprotective effect on the brain. Studies have been carried out by various research groups to investigate the estrogenic activity of genistein, daidzein and equalin[94]. The studies determined their treatment of chronic diseases such as hormone- dependent cancer, cardiovascular disorders and osteoporosis.

Genstein is the most promising compound to prevent post-menopausal bone loss in women[95]. Flavonoids are also known to exhibit anti-thyroids effects in animals and humans. Many studies have shown that ingestion of dietary genistein resulted in

concentration changes of hormones, such as insulin, thyroids hormones, adrenocorticotropic hormone, cortisone and corticosterone as well as lipid metabolic changes [96].

Flavonoids work as immune modulators. Effects of flavonoids including quercetin on a variety of inflammatory processes and immune functions have been extensively reviewed[97,98]. Studies by Park *et.al*.[99] domostrated significant anti-inflammatory activity of quercetin.

A large number of studies have highlighted the role of dietary flavonoids in reducing the risk of caner[100-102].Flavonoids have been intensely investigated in the treatment of ovarian, breast, cervical, pancreatic and prostate cancer. A citrus flavonoid- tanageritin - is known to inhibit cancer cell prolleration[103]. Flavonoids such as 3-hydroxy flavones, 3, 4-dihydroxyflavone, 2,3-dihydroxy flavone, fisestin, apgenin and luteolin are potential inhibitors of tumor cell proliferation[104].Daidzein and genistein have been shown to inhibit both hormonal and on-hormonal type of cancer cells.

Neuro-degenerative disease results from the combined effect of oxidative stress, inflammation and transition metal accumulation ; flavonoids have potential interest for their neuroprotective properties. This was attested by studies which suggested that higher consumption of dietary flavonoids is associated with lower population rates of dementia[105]. Similarly a study carried out by Hwang. et, al. suggested that citrus flavones such as hesperidin, hesperidin, and neo-hesperidins could traverse the blood brain

barrier and play effective role in the intervention for neurodegenerative diseases[106].

The hepatoprotective activity of flavonoids has been well studied . Flavonoids such as baicalin and quercetin attenuate ion overload - induced mouse liver injury[107]. There are reports which showed the hepatoprotective activity of flavonoids from German Chamomile.They are found to effect sphingolipid metabolism in the aged liver and regulate the levels of their key enzymes[108].Some flavonoids isolated from *Silybum marianum*, have strong antioxidant activity, in addition they exhibit hepartoprotective, and ion chelating properties [109].

Flavonoids have been studied for their anti-diabetic activity. Flavonoids may help to repair beta cell function by reducing free radical-induced tissue damage. They also reduce the hyperglycemic effects by controlling the blood sugar levels.

Studies have shown that intake of specific types of flavonoids, including querecetin and myricetin, is inversely associated with the risk of type 2 diabetes [110]. This is attested by another study which showed that querecetin may relief diabetic symptoms[111]. Quercetin was found to inhibit the enzyme : aldose reductase. It is the first enzyme of the sorbitol-aldose reductase pathway. It plays an active role in converting glucose to sorbitol (a sugar alcohol) in the body. This result in development of secondary problems, such as neuropathy, retinopathy, diabetic cataracts and nephropathy[112].

Hyperglycaemia leads to the production of free radicals from mitochondria. This free radicals are known to be associated with diabetic micro- and macro-vascular complications and mitochondrial membrane damage. Studies carried out by Waisundaraet et.al. suggested that baicalin, a flavonoid, reduces hyperglycaemia- induced mitochondrial membrane damage and also enhances the effects of metformin which is an ant-diabetic drug. This was observed in the metformin and baicalin treated groups [113].

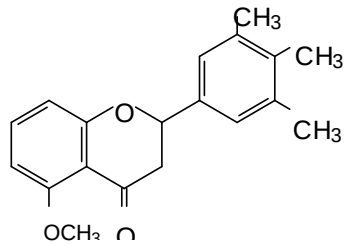
Oxidative stress resulting from the generation of oxygen free radicals is one of the causes responsible for various pathological conditions and ageing. Flavonoids are known as anti-oxidants to fight free radicals, thus reducing the signs of ageing. EGCG, a compound found in green tea, have gained the interest of various researchers due to its unique range of anti-aging [114,115].

Upcoming research studies have confirmed the effect of flavonoids on skin health. Flavonoids work as anti-oxidizing agents and free radical scavengers, they penetrate deeper into the skin and protect it from UV radiation damage. *Camellia sinensis* and *Ginkgo biloba* extracts and green tea are involved in cosmetic formulations and it was suggested that they protect the skin against UV-induced damage and skin aging[116].

Myricetin is considered to be the flavonoids which have the cabability to neutralize the effects of the free radicals which cause photo-aging within the skin. Huang *et, al.*[117] analyzed the protective effects of myricetin on ultraviolet B- induced damage to keratinocytes. In

another study, Fahlmanet *et. al*. investigated the ability of quercetin to guard the skin against U.V. radiation- induced damage[118-121]. They suggested that neutralization of UV damage by flavonoids may, in part, be attributed their capacity to scavenge free radicals generated by UV rays [122-124].

. A flavanone: 5-methoxy-3`, 4`, 5`- trimethylflavanone(1) was isolated from the leaves of Sudanese *Albizia amara* and its structure was deduced on the basis of its spectral data(IR,UV,^{1}HNMR and MS)[125].

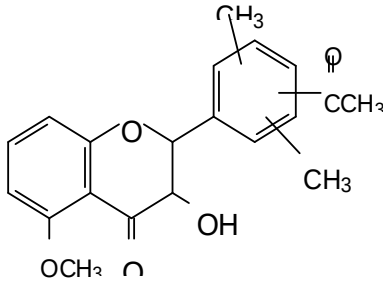


(1)

5-methoxy-3`, 4`, 5`- trimethylflavanone

The isolate was evaluated for its antimicrobial activity against six standard human pathogens : two Gram positive(*Staphylococus aureus* and *Bacillus subtilis*) , two Gram negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria and two fungal species **(***Aspergillus niger*, *Candida albicans*) and promising results suggested that the flavanone is a plausible candidate for further optimization[125].

Also dihydroflavonol(2) was isolated from the same species by different chromatographic techniques and identified via a combination of spectral tools (IR, UV, ^{1}HNMR and mass spectroscopy)[125].

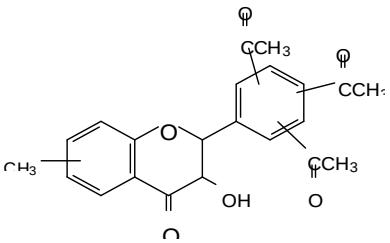


(2)

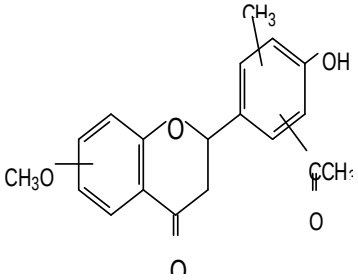
It was screened for its antimicrobial activity against six standard human pathogens (*Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillas niger*, *candida albicans),* and significant results were obtained[125].

A successive silica gel column chromatography followed by further purification via thin layer chromatography allowed for the isolation[126] of two flavonoids(compounds 3 and 4) from fruits of *Vangueria infausta* . Identification of these compounds was based on extensive UV shifting reagents,IR, ^{1}HNMR and mass spectroscopy data. In well diffusion method, the chloroform fraction of *Vangueria infausta* , compounds I and II were evaluated for their antimicrobial activity[126].

The chloroform fraction of *Vangueria infausta* did not show antibacterial activity , but it showed significant inhibitory activity against the fungi : *Candida albicans* and *Aspergantillus niger* . Compounds 3 and 4 also showed antifungal activity. However, they did not reveal antibacterial activity[126].

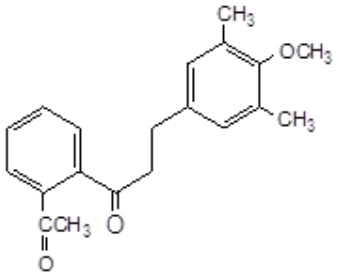


Compond 3

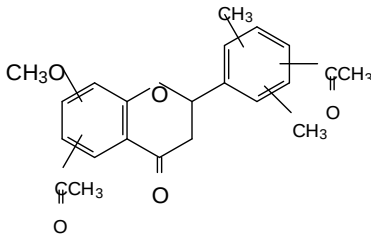


Compound 4

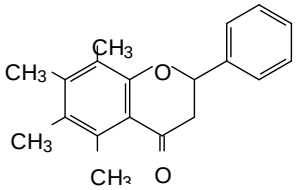
The following compounds were isolated[127] from the leaves of *Catharanthus roseus* and *Narissus brussonetii* . Compounds (5) and (6) were isolated from *Catharanthus roseus* ,while compound (7) was isolated as yellow powder from *Narissus brussonetii* leaves by silica gel TLC using BAW(4:1:4) as solvent.



(5)



(6)



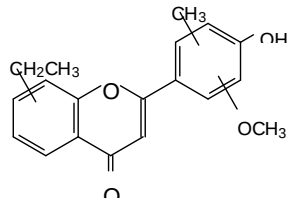
(7)

In cup plate agar diffusion assay ,the isolates were screened for antimicrobial activity against five standard human pathogens.

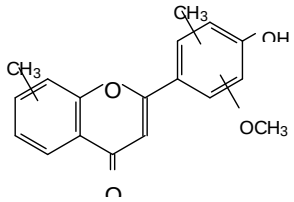
Compound 5 showed significant activity against the bacterial strain *Bacillus subtilis* and the fungal species *Candida albicans* , while compound 6 was active against *Escherichia coli , Bacillus subtilis* and the fungus *Candida albicans*. However, compound 7 gave significant antifungal activity and partial antibacterial activity.

Phytochemical screening of the alcoholic extract of the roots of *Leptadenia heterophella* revealed[128] the presence of tannins, saponins, terpenes, flavonoids and steroids. Alkaloid and glycosides were not detected. The crude alcoholic extract was fractionated by thin layer chromatography. After the usual workup, the following compounds(8 and 9) were isolated. The structures of these isolates

were elucidated by a combination of spectral tools(UV,IR, ^{1}HNMR and MS).



(8)



(9)

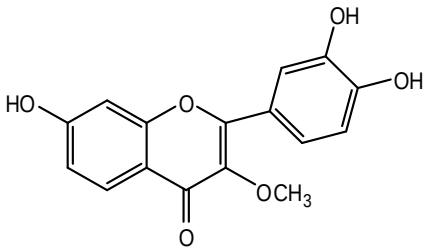
Different fractions of *Maytenas senegalensis* were evaluated for their antimicrobial activity using the cup plate agar diffusion method. The ethanolic and ethyl acetate fractions of *Maytenas senegalensis* showed activity against all test organisms. The n-butanol fraction was active against all test organisms except *Escherichia coli* and the fungus *Aspergillus niger*. However, the chloroform extract showed partial activity against the bacterial strains but it did not show any antifungal activity(Table 3).

Table (3) : Antibacterial activity of *Maytenas senegalensis* extracts :M.D.I.Z (mm)

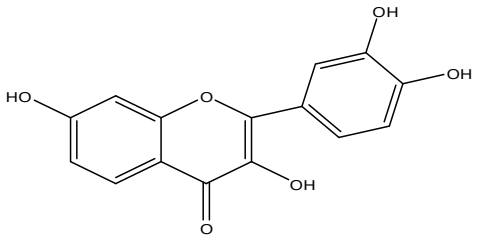
Extract	Conc.(mg/ml)	Ec	Pa	Sa	Bs	Ca	An
Ethanolic	100	13	15	16	14	15	14

Ethyl acetate	100	16	14	15	16	13	13
n-butanol	100	12	13	13	16	13	12
Chloroform	100	12	12	12	12	-	-

From the methanolic extract of the heartwood of, *acacia nilotica* var *nilotica,* two compounds (10 and 11) were isolated (7, 3`, 4`-trihydroxy-3-methoxyflavone and compound II was a 7, 3`, 4`-trihydroxyflavonol respectively). The compounds were purified by different chromatographic techniques and identified via spectroscopic tools: IR, UV, ^{1}HNMR and Mass spectroscopy. The isolated compounds were evaluated for their antimicrobial potential against Gram negative *(Escherichia coli* and *Pseud*om*onasa eruginos*) and Gram positive (*Bacillus subtilis, Bacillus cereus & Staphylococcus aureus)* bacteria. The two compounds showed varying biological activity. compounds (10) and (11) were active against both Gram positive and Gram negative bacteria.

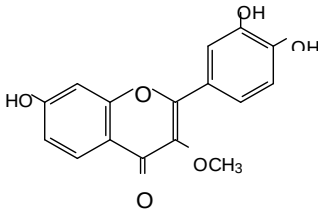


(10)



(11)

Phytochemical investigation[129] of *Acacia nilotica* var *adstringens* heartwood led to the isolation of a flavones(12) : 7,3`,4`-trihydroxy-3-methoxyflavone from the methanolic extract. The crude extract was purified by a combination of chromatographic techniques(polyamide and Sephadex columns and paper chromatography) . Structure of isolate was elucidated on the basis of extensive spectroscopic procedures including : IR, UV, ^{1}HNMR and MS. The isolated flavonoid was evaluated for its antibacterial potential against Gram negative *(Escherichia coli* and *Pseud*om*onasa eruginos*) , Gram positive (*Bacillus subtilis, Bacillus cereus* and *Staphylococcus aureus)* bacteria. Compound I showed varying antibacterial responses. It showed high potency against Gram positive human pathogens : *Staphylococcus aureus* and *Bacillus subtilis.*



(12)

In well diffusion method[130], all fractions from *Albizia.Amara* roots showed inhibitory activity against *Streptococcus mutans* (Sm) and *Lacto bacillus* (Lb).The activity is expressed as less active, if the zone of inhibition is 9-12 mm, moderate: 15-16 mm and high if greater than 17 mm. The ethyl acetate extract showed high activity on *Streptococcus mutans* (Sm) , while the n-butanol extract showed high activity on *Lacto bacillus* (Lb). The results of antimicrobial activity of the *A. amara* extracts against the microbial strains are depicted in Table 4.

DMSO was used as solvent since it has no effect on the growth of any of the test microorganisms. Standard discs inhibited the growth of all the test microorganisms. . There has been an increasing effect on microbial growth inhibition with increasing concentration of the extracts However, the effects observed were less than those produced by the standard chemotherapeutic.

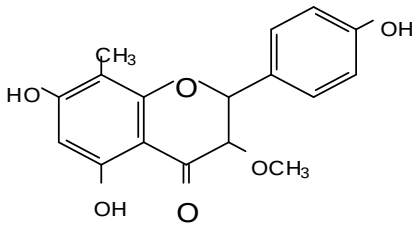
Table : Antibacterial activity of different fractions

Microrganism	Fractions	300µl	200 µl	100 µl
Lacto bacillus (LB)	PT	20	19	18
	CH	12	11	12
	EA	14	12	11
	BU	22	22	20
	ET	21	19	18
	AMP	25	25	25
	DMSO	-	-	-
	PT	9	10	11

Streptococcus mutans (SM)	CH	15	14	12
	EA	20	23	22
	BU	18	14	15
	ET	20	20	20
	AMP	25	25	25
	DMSO	-	-	-

(ET = 0.09 , CH = 0.08, EA = 0.1 , P =0.03 , BU = 0.03) mg/ml , 100 µl of sample + ml of DMSO.

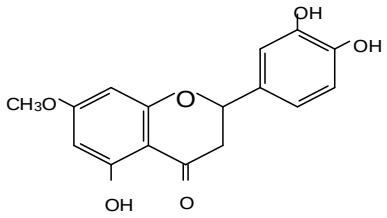
Phytochemical screening[131] of *Anogeissus leiocarpus* fruits indicated the presence of flavonoids, terpenes, tannins and saponins. Compound (13) was isolated from ethanolic extract by column and thin layer chromatography and its structure was established on the basis of its spectral data (IR, UV, NMR and MS) .In *in vitro* studies , the isolated flavonoid gave promising antibacterial activity against *Escherichia coli* and moderate activity against *S. aureus.*



(13)

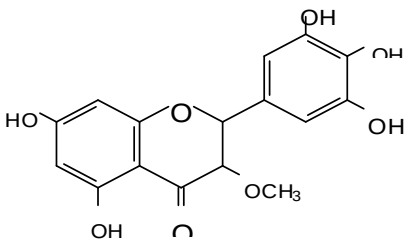
A flavanone(14) (5,3`,4`-trihydroxy-7-methoxyflavanone)was isolated from the Saudi material of *Cassia Italica*.[132] The flavonoid was isolated from the ethyl acetate fraction by column chromatography. The structure was elucidated by sensitive analytical tools (UV,IR,^{1}H NMR,^{13}C NMR,^{1}H-^{1}H-COSY NMR and MS). The flavanone was

evaluated ,*in vivo*,for anti-inflammatory and anti-ulcer potential and significant results were obtained.



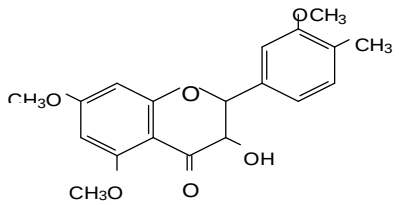
(14)

Phytochemical screening[133] of the leaves of *Geigeria alata* revealed the presence of flavonoids, tannins and alkaloids. Compound (15) was isolated from ethanolic extract by column and thin layer chromatography and its structure was established on the basis of its spectral data (IR, UV, NMR and MS). Compound I and different extracts (ethanolic, chloroform, n- butanol and ethyl acetate) of *Geigeria alata* were screened for their antimicrobial activity against six standard human pathogens. The ethyl acetate fraction showed significant antimicrobial activity followed by the n-butanol fraction. However, the chloroform fraction exhibited moderate activity. Though, compound I showed significant antibacterial activity it did not afford any antifungal properties.



(15)

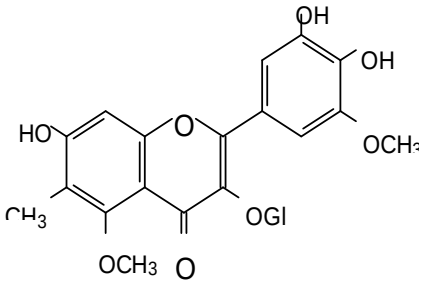
A dihydroflavonol(16) was isolated[134] from the leaves of Sudanese *Tamarix nilotica*. The isolate was purified by different chromatographic techniques and identified via a combination of spectral tools(IR, UV, ^{1}HNMR and Mass spectroscopy). The isolated flavonoid , ethyl acetate and n-butanol fractions were evaluated(*in vitro*) for their antimicrobial potential against Gram negative *(Escherichia coli, Salomonella typhi*) and Gram positive (*Bacillus subtilis , Staphylococcus aureus)* bacteria and the fungi :*Candida albicans* and *Aspergillus niger* and promising results were obtained.The isolated dihydroflavonol seems to be a suitable candidate for future optimization.



(16)

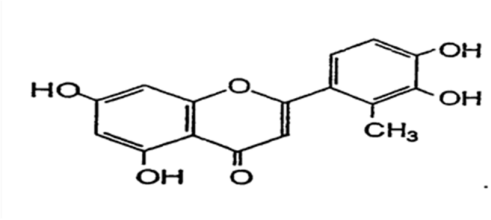
From the leaves[135] of *Vitex doniana* (Sweet) a flavone (17) was isolated and characterized. The isolate was purified by different chromatographic techniques and identified via a combination of spectral tools(IR, UV, ^{1}HNMR and Mass spectroscopy). The methanolic fraction of *Vitex doniana* was evaluated(*in vitro*) for its antimicrobial potential against Gram negative *(Escherichia coli, Salomonella typhimurium* and *Pseud*om*onasa eruginos*a) and Gram positive (*Bacillus subtilis, Bacillus aureus* and *Staphylococcus aureus)* bacteria and the fungus *Candida albicans* .Promising results

were obtained. *In vitro* antioxidant assay for the methanolic extract was conducted . Evaluation of the antioxidant activity was carried out by measuring the capacity of the extract against stable DPPH radical. The extract showed significant antioxidant activity.



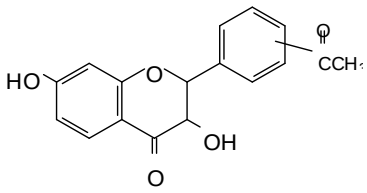
(17)

The crude ethanolic extract of *Croton Zambesicus* gave after paper chromatography a pure flavonoid (18) isolated as brown powder from ethanolic extract of the seeds of *Croton Zambesicus* .



(18)

Compound (19) was isolated as yellow powder from ethanolic extract of the seeds of *Coriandrum Stivum.* In cup plate agar diffusion assay,the crude extracts of *Croton Zambesicus* , *Coriandrum Stivum* and compounds (19 and 20) showed l different antimicrobial responses against test organisms(Tables 5 and 6).



(19)

Table 5: The antimicrobial activity crude extractives of *Croton Zambesicus* and compounds (18) ad (19)

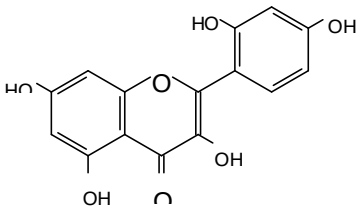
Organism	Inhibition growth zone diameter (MIZD) 100 mg \ 100 ml		
	Crude extract	Compound I	Compound II
Bacillus subtitles	22	20	19
Staphylococcus aureus	21	20	17
Escherichia coli	22	19	18
Pseudomonas aeruginosa	22	20	18
Aspergillus niger	19	16	15
Condida albacans	16	15	14

Table 6: The antimicrobial activity crude extractives of *Coriandrum Stivum*

Organism	Crude extract
Bacillus subtitles	20
Staphylococcus aureus	20

Escherichia coli	19
Pseudomonas aeruginosa	22
Aspergillus niger	18
Condida albacans	20

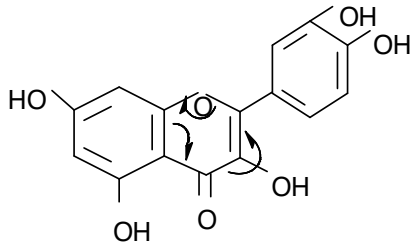
From the ethyl acetate[136] extract of the leaves *Cassia occidentalis* (Leguminosae) a flavonol: 5,7,2',4'-tetrahydroxyflavonol(20) was isolated . The structure was elucidated via a combination of spectral techniques(UV,IR,1H NMR and MS) and its biological potential was evaluated. The flavonol exhibited promising anti-inflammatory and anti-ulcer activity.



(20)

The antibacterial activity[137] of the crude extract and pure flovonoids of *Withania somnifera* against five human pathogens was carried out. The cup-plate agar diffusion method was adopted with some minor modifications. The test organisms were: *Bacillus subtilis, Escherichia coli, Neisseria gonorrhoeae, Pseudomonas aeruginosa* and *Staphylococcus aureus*. The methanolic extract of *W. somnifera* showed moderate inhibition against *Escherichia coli,*

Pseudomonas aeruginosa and *Staphylococcus aureus* and weak inhibition against *Neisseria gonorrhoeae* and *Bacillus subtilis.* A flavonoid of *Withania somnifera* (21) exhibited a moderately inhibition against all five test organisms. Another flavonoid (22) showed weak inhibition against test organisms.



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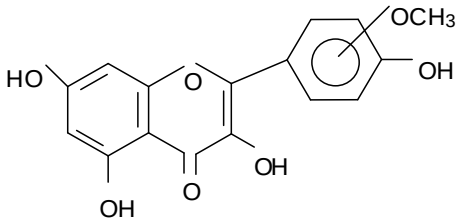

(22)

1.11-The target species

i) *Lipidium sativum* (Crusifereae)

Lipidium sativum (Crusifereae) is an annual plant about 50cm in height. The plant can grow easily tolerating difficult environmental conditions[138,139]. It has many branches on the upper parts and white-pinkish flowers[140,141] .The plant is genetically related to mustard and

Lipidium sativum

watercress and is known in some regions as garden cress, garden pepper cress,pepperwort, pepper grass[142,143].

Lipidium sativum L. contains significant amount of iron , calcium , folic acid beside vitamins A and C . It also contains protein(25%) ; leucine (8.21%); glutamic acid(19.3%) and methionin(0.97%) . Seeds mainly contain alkaloids, calcium, iron, carotene, riboflavan, uric acid, phosphorus, thiamine and niacin. Seed oil contains palmitic, linoleic, stearic, behenic, oleic , arachidic and lignceric acids[144].

Lipidium sativum is a key species in African system of medicine where it is mainly used against bronchitis. In some Asian communities the plant is used against a wide array of human disorders[145,146].It was reported that garden cress possesses anti-inflammatory, analgesic, anticoagulant[147] ,diuretic[148], antihypertensive[149] ,antirheumatic[150] ,antidiarrheal ,antispasmodic, laxative[151] and hypoglycemic[152] properties.

Aqueous extracts of seeds exhibited significant water excretion in spontaneously hypotensive models without any significant change in heart rate.. The petroleum ether extract of seeds showed antimicrobial activity against some standard human pathogens, while oral administration of seeds proved a hypoglycemic effect[144] . It was reported that *Lipidium sativum* juice possess chemoprotective effect[144].The aqueous methanolic extract of seeds showed important improvement in various parameters of pulmonary function in a clinical experiment[153] . In another clinical study , the seeds were evaluated for the management of osteoarthritis. Seeds showed considerable relief of joints pain , swelling, stiffness and other symptons associated with osteoarthritis[154] .

It seems that *Lipidium sativum* seeds are well tolerated . In clinical experiments of the effect of seed administration on bronchial asthma, none of the test subjects showed the presence of adverse effects or any other problems physically or at hematological profile(www.bioline.org.). Feeding model animals with *Lipidium sativum* seeds (2%w/w) for six weeks was non-toxic , while a dose of 50%(w/w) was lethal(www.worldscientific.com).

ii) *Negella sativa* (Ranunculaceae)

Negella sativa (Ranunculaceae) is a small herb about 45cm in height. The plant is cultivated in many countries for its economic value. This plant is widely used in ethnomedicine to treat a wide array of human disorders.The popularity of this herb in Islamic communities is

Negella sativa

probably due to ideological belief that the herb is a remedy for multidisease. It is used as astringent, stimulant, diuretic, emmenagogue and anthelmintic. It is also used for fever, dyspepsia, piles and skin diseases[157-159]. Seed oil is used as a local anesthetic.The alcoholic fraction constitutes about 20%(w/w) ; aqueous extract 15%(w/w); fixed oil 25-32% (w/w) ; volatile oil 0.42%(w/w)[160,161].Seeds contain , among others, nigellone[162] ; negellidine[163;] negellimine ; steroids; terpenoids; tannins; oleic acid; linoleic acid; saponins; protein; reducing sugar and bitter principle[157,164,165].

Studies on pancreatic cancer cells testifies that thymoquinone- a major constituent of seed oil- is synergic with gemcitabine and oxaliplatin [166.] . Thymoquinone was also found cytotoxic for several types of human cancer cells[167].Also it was reported that thymoquinone inhibited benzopyrene – induced carcinogenesis in model animals[168].

Some thymoquinone conjugates were found to be active against some resistant tumor cells[169]. A combined dose of selenium and *Negella sativa* thymoquinone resulted in decreased cell count, decreased alkaline phosphotase level and decreased glutathione level on the proliferation of osteoblast cells(MG 63) [170]. Thymoquinone was found to inhibit tumor incidence and tumor burden significantly in 20-methylcholanthrene-induced fibrosarcoma [171]. It was demonstrated that it protects rats against NAME-induced hypertension and renal damage probably by its antioxidant potential[172].

The essential oil of and ethyl acetate fraction were cytotoxic against P815 cell line[173]. A decoction comprising *Negella sativa* seeds, *Hemidesmus indicus* root bark and *Smilax glabra* rhizomes is said to inhibit DEN-mediated expression of GST-P. It also inhibited histopathological changes leading to tumor development in model animals[174,175]. *In vitro* studies testified that the ethanol extract of seeds inhibited cancer cells and endothelial cell progression [176,177], while *in vivo* studies demonstrated that topical application of seed extract inhibited skin carcinogensis[178].The aqueous and ethanol extracts inactivated MCF-7 breast cancer [179].

Aqueous exract of seeds inhibited electrogenic intestinal absorption of glucose *in vitro*. After chronic oral administration , seed extract improved glucose tolerance and body weight in model animals[180]. Such findings validate the traditional use of *Negella sativa* seeds against diabetes. The ethanol extract of seeds significantly reduced

elevated blood glucose, plasma insulin and improved antioxidant enzymes like superoxide dismutase. Furhemore , it reduces glutathione and glutathione peroxidase in liver and kidney[181,182].

It was reported that *Negella sativa* oil corrects STZ-diabetes- induced alterations in cardiac creatine kinase muscle and brain monoamines due to its antioxidant properties[183]. Seed ethanolic extract was found to induce a significant insulin- like stimulation of glucose uptake in C2C12 skeletal muscle cells following 18h administration[184].

Intrinsic cardiac contrile properties without evidence of increased cardiac work load was observed in models following oral supplement of *Negella sativa* seeds for two months[185-186]. The effect of *Negella sativa* aqueous extract on heart rate and contractility was studied. A Potent inhibitory effect on heart rate and contractility was reported[187].The fixed oil from *Negella sativa* reduced serum cholesterol, glucose level , triglycerides , count of leukocytes and platelets. Furthemore , the oil significantly increased hemoglobin and hematocrit levels. However, crushed seeds afford the same effects[188] . In another study, seed extract was found to protect against cisplatin-induced fall in hemoglobin level and leukocyte count. An aqueous suspension of seeds significantly prevented gastric ulcer formation induced by necrotizing agents in model animals[189-191]**.**

iii)*Peganum harmala*

Peganum harmala L. (Zygophyllaceae) is native to eastern Mediterranean region[190]. *Peganum harmala* is a perennial plant which

Peganum harmala

can grow to about 0.8 m tall. It blossoms between June and August in the northern hemisphere . The flowers are white and are about 2.5–3.8 cm in diameter[192,193]. *Pregnan harmala* is used traditionally in the treatment of a wide array of human disorders. β-Carboline alkaloids were identified in different parts(seeds,roots,barks) of *Pregnan harmala*. Pharmacological surveys testified that harmala alkaloids namely; harmaline, harmine, harmalol and harmol are biologically active compounds[194,195].

The plant is employed in ethno-medicine to treat hypertension and cardiac disease[196,197] . Extracts of seeds are said to exert vasorelaxant effects[8] and alkaloids of *Pregnan harmala* were shown to have anti-platelet aggregation effects[198]. Furthermore,these alkaloids were shown to be psychoactive in mammalian body[199].Various studies demonstrated a wide range of effects produced by *Pregnan harmala* extracts including ;analgesic[200,201] ,hallucination, excitation[202] and

antidepressant[203] effects. Harmal alkaloids were shown to be involved in pathogensis of Parkinson`s disease.

Various studies indicated antiparasidal[204],antifungal[205,206],anti-bacterial[207,208] and insecticidal[209,210] effects for Harmal alkaloids. Significant antileishmanial activity was exhibited by *Peganum harmala* seeds extract[211] .Also Harmal methanolic extracts produced a dose- dependent decrease in litter size of model animals[212]. Frequent abortion was observed in animals that feed the plant[213].

iv)*Phoenix Sylvestris*

Scientific name: *Phoenix Sylvestris*

Common name: Wild Date Palm, Toddy Palm, Sugar Date Palm

Silver Date Palm.Taxonomy is depicted in the following Table

Table 1.1:Taxonomy of Phoenix Sylvestris

Kingdom	**Planate- Plants**
Subkingdom	Viridiplantae
Superdivision	Embryophyta
Division	Tracheophyta
Class	Magnoliopsida
Order	Arecales
Family	Arecaceae

Genus	Phoneix
Species	Phoenix sylvestris

Palm is native to India and southern portions of Pakistan. In both countries, it occurs in areas where there is sparse vegetation mainly composed of scrub species and along flat lands where monsoons occur. Though slow growing, it can reach heights of up to 50 feet and grows well in areas of the United States where temperatures do not fall below 15°F. Leaves are pinnately compound and blue-green, and they can grow to 10 feet in length. Leaflets can reach approximately 18 inches long and grow opposite to one another on the rachis in such a way that the entire leaf looks flat. The petiole, or stem that attaches the leaf to the trunk, is 3 feet long and armed with spines. Young trunks bear triangular shaped leaf scars (the place where leaves once attached to the trunk) that become more diamond-shaped with age. On older trees, aerial roots tend to be present at the base of the trunk. Yellow inflorescences can reach lengths of 3 feet, are heavily branched, bear small white blossoms, and grow among the leaves. The oblong fruits are 1 inch long and occur in orange clusters, turning dark red to purple when mature.(123)

Phoenix Sylvestris

Phoenix Sylvestris

1.8- Aim of work

This work was aimed :

-to extract fixed oil and flavonoids from target species.

-to isolate flavonoids from palm pollen using different chromatographic techniques, including column chromatography and sephadex filtration .

-to Identify isolates using: UV, ^{1}H NMR,^{13}C NMR

-to analyze extracted oil by GC-MS.

- To evaluate antimicrobial potential of crude extract.

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1.6.2- Antiviral activity of Flavonoid compounds:-

The development of viral resistance towards antiviral agents enhances the need for new effective compounds against viral infections. Medicinal plants have a variety of chemical constituents, which have the ability to inhibit the replication cycle of various types of DNA or RNA in viruses. Compounds from natural sources are of interest as possible sources to 30 control viral infection. Naturally occurring polyphenols as flavonoids have been found to possess antiviral activity. An early study, suggested that flavonoidic extracts of the leaf of the (74) .Rubus idaeus probably act against most viruses by clumping the virus particles together into complexes, which are largely noninfective. It was deduced (75) that viral inactivation in vitro is, directly, attributable to preferential binding of polyphenols to the protein coat of the virus, whereas, in a systematic study of the antiviral activity of a very wide range of natural products it was concluded (76) that flavonoids act, principally, by binding to virus and/ or protein of host cell membrane and thus arrest absorption of the virus. Sakagami (77) has put forward a number of possible mechanisms whereby polyphenols may exert their antiviral mechanism. He suggested that the major part of the antiviral activity in polyphones.is probably derived from their direct inactivation of the virus and/ or from inhibition of the virus binding to the cells. It was noted that although flavonoids are known to inhibit viral replication enzymes (such as RT for HIV and RNA polymerase for influenza virus) and other enzymes (e.g. poly

(ADP-ribose-glycohydrolase), these effects seem to be rather nonspecific. The most pronounced *in vitro* selectivity of anti-influenza and anti-herpes type 1 and type 2 actions were confirmed against polyphenolic complexes isolated from the Bulgarian medicinal plant Geranium sanguineum (L.) (78 ,79).The chemical constituent (s) present in the plants belonging to the genus *Phyllanthus* which is (are) responsible for HIV action is (are) not well defined, although it is believed that hydrolyzed tannins, namely ellagic 31acid, might account for beneficial effect of Phyllanthus plant against HIV 80.

For the purpose of discovering anti-HIV-1 agents from natural sources, water and EtOH extracts of Coleus parvifolius Benth.(aerial parts) showed potent activity against HIV-1 IN with an IC50 value of 9.2 μg/ ml. From this extract, 11 compounds were isolated and identified. Among these compounds rosmarinic acid, rosmarinic methyl ester, luteolin and luteolin 7-methyl ester exhibited inhibitory activities against HIV-1 IN (81). Quercetin, morin, rutin, taxifolin, dihydrofisetin, catechin, hesperitin, leucocyanidin, pelargonidin chloride, apigenin and naringenin have been reported to possess antiviral activity against some types of viruses (82). The flavonols quercetin and fisetin have been found to inhibit HIV virus replication, whereas 5, 6, 7- trimethoxy flavone showed antiviral activity against herpes. Mitrocotsa and coworkers (83) have examined kaempferol and its glycosides for their

antiviral activity against human cytomegalovirus (HCMV) and they reported that flavonoids bearing acyl substituents were the most active.

1.6.3- Antioxidant activity:-

The best-described property of almost all groups of phenolic compounds is their capacity to acts as antioxidants. The flavones and catechins seem to be the most powerful phenolic compounds for protecting the body against reactive oxygen species (ROS). Body cells and tissues are continuously threatened by the damage caused by free radicals and ROS which are reduced during normal oxygen metabolism or are induced by exogenous damage (84).

Quercetin, kaempferol, morin, myricetin and rutin exhibited as several 32 beneficial antioxidant effects, such as anti-inflammatory, antiallergic, antiviral as well as an anticancer activity. They have also been suggested to play a protective role in liver diseases, cataracts, and cardiovascular diseases. Quercetin and silybin acting as free radical scavengers were shown to exert a protective effect in reperfusion ischemic tissue damage (85). The scavenging activity of flavonoids has been reported to be in the order:

Myricetin > quercetin> rhamnetin > morin > diosmetin > naringenin > apigenin > catechin > 5,7- dihydroxy-3',4',5'-trimethoxyflavone > robinin > kaempferol > flavone (86).

Examples for flavonoid compounds with anti-oxidant activity are diosmetin, kaempherol, quercetin, kaempherol 3-*O*-glucoside (astragalin),Quercetin 3-rhamnoside (quercitrin), quercetin 3-*O*-xyloside and quercetin 3- *O*-galactoside (hyperoside), those were isolated from Rosa agrestis leaves and were found to possess antioxidant activity (87). Also rutin and apigenin were found to be potent inhibitors of lipid peroxidation and oxidation of beta-carotene (88). Several flavonoids were isolated from the leaves of Licania licaniaeflora and reported quercetin derivatives were found to possess the strongest antioxidant activity where as 8-hydroxy naringen and kaempferol 3-*O*-α-rhamnoside show low antioxidant activity (89). Dietary flavonoids like epicatechin, epigallocatechin, galate, gallic acid, and quercetin-3-glucoside possess strong antioxidant activity (90).

1.6.4- Anti-inflammatory activity:-

Inflammation is the integrated response of many defense systems of the body to the invasion of a foreign body. Inflammation involves action of the complement system, blood coagulation, humeral and cellular immunity, cytokines, tissue hormones, angiogenesis, and repair processes. It is a free radical generating process (91).

The anti-inflammatory activity of flavonoid compounds in many animal models has been reported. For example hesperidin, a citrus flavonoid possesses significant anti-inflammatory and analgesic effects (92). Also

apigenin, luteolin, quercetin are known to possess anti-inflammatory activity (93). Various flavonoids (e.g. apigenin, tea catechins) have also been shown to have anti-inflammatory activity by inhibiting cycloxygenase-2 (COX2) and inducible nitric oxide synthesis (94). Quercetin and hesperidins given at a daily dose of 80 mg/kg inhibit both acute and chronic phase of inflammation while rutin was found to be effective only in chronic case (95). Kaempferol, quercetin, myricetin, fisetin are reported to possess cyclooxygenase (COX) and lipooxygenase (LOX) inhibitory activities. Nepetin, jaceosidin and hispidulin were found to possess a potent anti-inflammatory activity (96).

1.6.5- Anti-cancer activity:-

Cancer is a diseases caused by disturbance in growth metabolism. Flavonoid compounds are highly effective scavengers of most types of oxidizing molecules, including singlet oxygen and various free radicals, which are, possibly, involved in DNA damage and cancer promotion. Phenolic compounds may also have a beneficial effect through their impact on the bio-activators of carcinogens. They are potent bioactive molecules that possess anti-carcinogenic effects since they can interfere with the Initiation, development and progression of cancer by the modulation of cellular proliferation, differentiation, apoptosis, angiogenesis and metastasis (97). Flavonoids (like quercetin and kaempferol) exhibit some potential to inhibit, in vitro, the proliferation of certain cancer cell lines (i.e. colon and breast) (98). 34 Vertex, a

medicinal plant extract from the Vitex agnus-castus, found, mainly, in Southern Europe and the Middle East, suppresses growth and promote apoptosis in colon and gastric cancer cells. Vitex contains several kinds of flavonoids, one of them, luteolin which has anti-inflammatory effects. Luteolin is the primary compound responsible for the inhibition of colon cancer, and the induction of apoptosis. This compound induces DNA fragmentation which is one of several apoptotic events. Studies showed that the induction of apoptosis mediates the mechanism of action that differs from the conventional oxidative stress pathway of most cancer cells (99). Baicalin and baicalein are two flavonoids isolated from the root of scutellaria baic alensis which is a Chinese herbal medicine to treat diarrhea and hepatitis. Studies have shown that this compound inhibits prostate cancer growth by apoptosis (100). Baicalein also inhibits breast cancer cells by the inhibition of the matrix metalloproteinases (MMPs), which are a family of zinc-dependant proteinases involved with cancer cells. These proteins play an important role in the metastasis of cancer cells (101). The inhibitory activity of catechins, especially (-) – epigallocatechin gallate (EGCG), against carcinogenesis were discovered from tea, since EGCG is the most abundant catechin in tea. The anticancer activity in tea has been demonstrated in different animal models for organ sites such as skin, lung, esophagus, stomach, liver, small intestine, pancreas, colon, bladder, and mammary gland (102). The inhibition of EGCG against skin,

stomach, colon, and lung carcinogenesis (103-105), as well as the growth of human prostate and breast tumors in athymic mice have been reported (106). Quercetin and apigenin inhibited melanoma cell (B16-BL6) growth and metastatic potential in syngenetic mice (107), also anthocyanin and related 35 flavonoid phytochemicals not only possess antioxidant activity but also mediate other physiological functions related to cancer suppression (108).

1.6.6- Hepatoprotective activity:-

Flavonoids compounds have been found to possess hepatoprotective activity. In a study carried out to investigate silymarin, apigenin, quercetin and naringenin as putative therapeutic agents microcrystin LR-induced hepatotoxicity, silymarin was found to be the most effective one (109). The flavonoids, rutin and venoruton, showed regenerative and hepatoprotective effects in experimental cirrhosis(110). Hepatoprotective studies on Phyllanthus emblica have showed that if the extract is producing hepatoprotection at a dose of 100 mg/ 100 kg, then quercetin is producing hepatoprotection at a dose of 15 mg/ 100 kg; thus concluding that quercetin is a potent hepatoprotective agent (111). It was observed that hirustrin, avicularin and quercetin possess hepatoprotective action against t-BHP in HepG2 cells, whereas isovitexin and trifolin possess no protective effect (112). Among various flavonoids - apigenin, onitin, luteolin, kaempherol-3

-Oglucoside and quercetin-3-O-glucoside - isolated from Equisetum arvense, onitin and luteolin exhibited hepatoprotective activity against tacrineinduced cytotoxicity in human liver-derived Hep G2 cells (113). The hepatoprotective activity of 41 phenolic compounds (some as flavonoids) on human liver-derived Hep G2 cells was investigated and their structure- activity relationships were evaluated, and it has been found that many of them are potent hepatoprotective agents. The hepatoprotective activity of catechin (cyanidanol), which has been used to treat chronic hepatitis, was almost equal to that of glycyrrhizin at 200 μM (114).

1.6.7- Antidiabetic activity:-

Diabetes mellitus is a serious chronic disease. Effective control of the blood glucose level is a key step in preventing or reversing diabetic complications and improving the quality of life in both types 1 and 2 diabetic patients (115). It has been reported by several researchers that quercetin possess antidiabetic activity and it has been found that it brings about regeneration of pancreatic islets and increases insulin release in streptozotocin-induced diabetes. Also, it has been reported to stimulate Ca^{2+} uptake from isolated islet cells, thus suggesting it to be effective even in non-insulin dependent diabetes.The phenolic compounds isolated from *ipmoea batalas* leaf possess antidiabetic activity against alloxan-induced diabetes at a dose of 100 mg/kg (116). Also fisetin was found to be a therapeutic agent for treatment of diabetes mellitus at a dose of 10

mg/kg (117**)**. Three flavonoids were isolated from *Cynanchum acutum,* quercetin 3-O-β-galacturonopyranoside, quercetin 7-O-β-glucopyranoside and tamarixtin 3-O-β-galacturonopyranoside, these compounds were found to exhibit significant antidiabetic activity (118).

1.6.8- Antiulcer activity:-

Ulcer is a commonly occurring disease in developed countries and its occurrence is emerging with increase in modernisation of living standards. It has been reported that phenolic compounds protect against gastric cancer. Similar to aspirin, acylated flavonoids may transfer their acyl group to the side chain hydroxyl group of serine in the active site of COX (119**)**. Flavonoids glycosides of *ocimum basilicum* decreased ulcer indexand thus inhibit gastric acids in aspirin-induced ulcers (120).Quercetin, Kaempferol, rutin when administered intraperitoneally (25-100 mg/kginhibited dose-dependent gastric damage produced by ethanol in rats (121). Also β-Hydroxy ethyl rutosides, gossypin, naringin, naringenin and (+)-Cyanidanol-3 were shown to exhibit anti-ulcer activity. 3-Methoxy-5,7,3',4'-tetra hydroxyl flavan (Meciadanol), a congener of (+) cyanidanol-3 exhibited significant anti-ulcer activity in pylorus ligated rats, restraint ulcers and gastric mucosal damage induced by aspirin models . Quercetin, kaempferol, morin, myricetin and rutin were reported to inhibit the mucosal content of platelet activating factor (PAF) in a dose dependent manner suggesting that the protective role of these substances may be mediated by endogenous PAF (122).

iv)*Phoenix Sylvestris*

Scientific name: *Phoenix Sylvestris*

Common name: Wild Date Palm, Toddy Palm, Sugar Date Palm

Silver Date Palm.Taxonomy is depicted in the following Table

Table 1.1:Taxonomy of Phoenix Sylvestris

Kingdom	**Planate- Plants**
Subkingdom	Viridiplantae
Superdivision	Embryophyta
Division	Tracheophyta
Class	Magnoliopsida
Order	Arecales
Family	Arecaceae
Genus	Phoneix
Species	Phoenix sylvestris

Palm is native to India and southern portions of Pakistan. In both countries, it occurs in areas where there is sparse vegetation mainly composed of scrub species and along flat lands where monsoons occur.

Though slow growing, it can reach heights of up to 50 feet and grows well in areas of the United States where temperatures do not fall below 15°F. Leaves are pinnately compound and blue-green, and they can grow to 10 feet in length. Leaflets can reach approximately 18 inches long and grow opposite to one another on the rachis in such a way that the entire leaf looks flat. The petiole, or stem that attaches the leaf to the trunk, is 3 feet long and armed with spines. Young trunks bear triangular shaped leaf scars (the place where leaves once attached to the trunk) that become more diamond-shaped with age. On older trees, aerial roots tend to be present at the base of the trunk. Yellow inflorescences can reach lengths of 3 feet, are heavily branched, bear small white blossoms, and grow among the leaves. The oblong fruits are 1 inch long and occur in orange clusters, turning dark red to purple when mature.(123)

Phoenix Sylvestris

Phoenix Sylvestris

1.8- Aim of work

This work was aimed :

-to extract fixed oil and flavonoids from target species.

-to isolate flavonoids from palm pollen using different chromatographic techniques, including column chromatography and sephadex filtration .

-to Identify isolates using: UV, ^{1}H NMR,^{13}C NMR

-to analyze extracted oil by GC-MS.

- To evaluate antimicrobial potential of crude extract.

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