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NATURAL PIGMENTS-A MEDICINAL PERSPECTIVE

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ABSTRACT: Pigments are present in all living matter and provide attractive colors and play basic roles in the development of organisms.. This review presents the basic information about pigments focusing attention on the natural ones; it emphasizes the principal plant pigments:flavonoids, carotenoids and betalains. Special considerations are given to their pharmacological activity .Several works are mentioned which have demonstrated the potent antioxidant activity of flavonoids and other pigments , which has been associated with protection against degenerative diseases.Our main focus is the pharmacological properties of some natural pigments,their sources and main hurdles in using them as medicines.

KEY WORDS: color, carotenoids, flavonoids, betalains, food, antioxidant.

INTRODUCTION

Pigments produce the colors that we observe at each step of our lives, because pigments are present in each one of the organisms in the world, and plants are the principal producers. They are in leaves, fruits, vegetables, and flowers. Also, they are present in skin, eyes, and other animal structures; and in bacteria and fungi. Natural and synthetic pigments are used in medicines, foods, clothes, furniture, cosmetics, and in other products. The melanins act as a protective screen in humans and other vertebrates, and in some fungi melanins are essential for their vital cycle. A lot of pigments have a well-known pharmacological activity in sickness such as cancer and cardiovascular diseases, and this has stressed pigment importance for human beings. Some natural pigments has remarkable antioxidant activity, which is important in the development of their functions such as scavenging of radicals and disease treatment and prevention.

CLASSIFICATION

Pigments can be classified by their origin as natural, synthetic, or inorganic. Also, pigments can be classified by taking into account the chromophore chemical structure as: (a) Chromophores with conjugated systems: carotenoids, anthocyanins, betalains, caramel, synthetic pigments, and lakes.

(b) Metal-coordinated porphyrins: myoglobin, chlorophyll, and their derivatives.

PHARMACOLOGICAL EFFECTS OF NATURAL PIGMENTS

1.FLAVONOIDS: Flavonoids are phenolic compounds with two aromatic rings bonded by a C3 unit (central pyran ring) and divided in 13 classes based on the oxidation state of the pyran ring and on the characteristic color: anthocyanins, aurons, chalcones, yellow flavonols,flavones, uncolored flavonols, flavanones, dihydroflavonols, dihydrochalcones, leucoanthocyanidins, catechins, flavans, and isoflavonoids. Figure1 shows some flavonoid structures.

Several reports have shown the antioxidant activity of flavonoids. Rutin inhibited malonaldehyde formation from ethyl arachidonate by 70% at the level of 0.125 μmol. With ethyl linoleate, naringin, galangin, and rutin exhibited dose-related activities and showed inhibitions of 30% at 0.5μmol.

It has been pointed out that the major mode of flavonoids as antioxidants is in their ability to scavenge free radicals, and that hydroxylation of the B-ring is an important contributor to such activity.

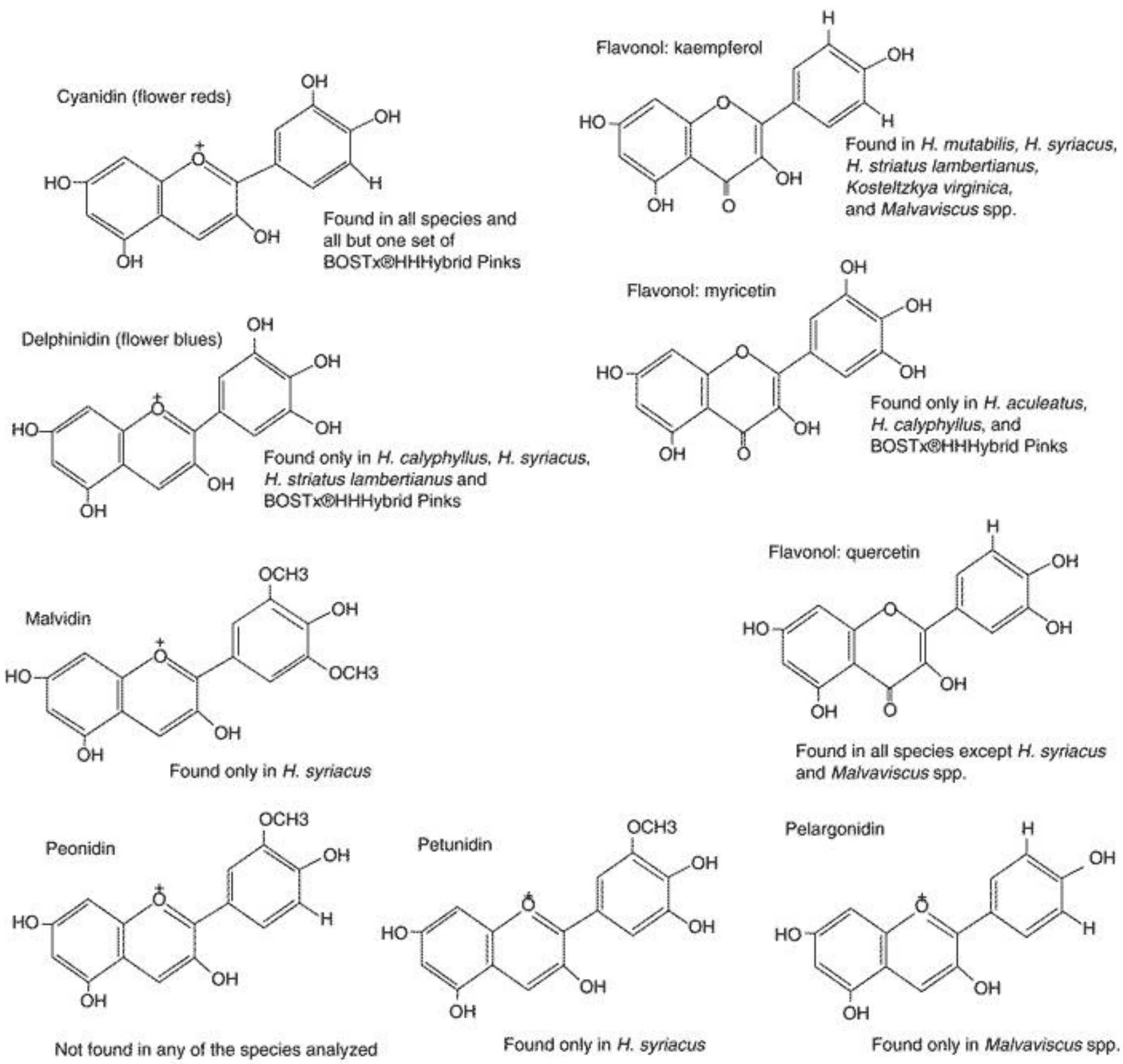

Fig.1 Structure of some flavonoids

In particular, hydroxyl groups at the 3′- and 4′- positions of the B-ring exhibited the highest antioxidant activity, but it was lower than the observed with BHT[24]. It was shown that luteolin has good antioxidant activity , and it was suggested that C2-C3 double bond and C4 keto group seem to be essential for high antioxidant activity (quercetin > (+)- catechin). Also, it was shown that aglycone flavonoids are more potent antioxidants. However, luteolin did not show quality antioxidant activity, and quercetin and other flavonoids were better.

TABLE 1: Pharmacological Activities of Some Flavonoids[1,11]

Flavonoid	**Activity**
(+)-Catechin, 3-O-Metil-(+)-Catechin , naringenin	Against ulcers
Naringenin	Antimicrobial and antifungic on skin
Proanthocyanidins	Astringent for digestive system, diuretic, cardiac tonic, in the treatment of high blood pressure
Rutin, silibin	Against disorders of the respiratory system
Butrin, isobutrin	Hepatic disorders and viral hepatitis
Chisin, floretin, apigenin, quercetin , kaempferol, baicaelin	Antiinflammatory
Epicatechin	Against diabetes
Genistein, kaempferol, sophoricoside	Antifertility
Galangin	Activity against Staphylococcus epidermis
Quercetin, morin, procyanidin, pelargonidin	Antiviral

The antioxidant activity of wines has also been evaluated, and it has been reported that almost 96% of the activity can be explained by the content of catechin, *m*-coumaric acid, epicatechin, *cis*-polydatin, and vanillic acid, showing higher correlations with several flavonoids (catechin, myricetin, quercetin, rutin, epicatechin, cyanidin, and malvidin 3-glucoside). Wine flavonoids also show a good peroxynitrite scavenging activity.

It has been clearly established that flavonoids in natural products (e.g., grape, soybean, peanut, wine, tea) have a good antioxidant activity. In some instances a better activity than in the commercial antioxidants has been determined. Additionally, flavonoids contribute to the protection and/or regeneration of antioxidants. It has been suggested that the flavonoid action is by trapping free radicals. Flavonoids are antimutagenic that can reduce the atherogenesis and the risk for strokes, and that are modulators of arachidonic acid metabolism. This last point involves flavonoids in many metabolic processes[11].

Interestingly, flavonoids are ubiquitous of plants and a person can consume up to 1 g of them. This quantity implies that flavonoids can reach pharmacological concentrations in the organism. Thus, it is interesting to point out that many flavonoids have assigned pharmacological activities (Table 1), and that many medicinal plants are known and used by their flavonoid content. Moreover, it has been determined that flavonoid structure has the responsibility of a large part of the activity. Also, it has been shown that different substitutes give a molecule with an specific polarity that permits the presence of privileged bonds in the active sites[1]. This characteristic could have a relation with the antioxidant activity From an acetone extract of the root bark of *Ormosia monosperma* several flavonoids were isolated, and it was observed that 2,3-dihydroauriculatin showed a moderate activity against oral microbial organisms such as *Streptococcus mutants, Porphyromonas gingivalis,* and *Actinobacillus actinomycetemcomitans*, each at 6.3 μg /ml. From *Ononis spinosa* subsp. *Leeiosperma*, two flavonoids with biological activity were isolated. Spinonin showed a moderate activity against *P. aeruginosa* and higher activity was obtained with ononin against β-hemolytic *Streptococcus* (minimal inhibitory concentration or MIC = 25 μg/ mL). It was shown that some flavonoids (isorhamnetin, rhamnetin, and quercetin) diminished the total serum cholesterol levels when rats were fed with these compounds. In view of the relatively low toxicity ofquercetin and related antitumor activity, its use as an anti-cancer drug seems feasible[2].

Flavonoids have been involved in the inhibition of several individual steps related to the thrombosis process, and one of the most active compounds was the biflavonoid hinokiflavone. Other biflavonoids (e.g., amentoflavone, agathisflavone, robusta-flavone) showed activity against the human immunodeficiency virus (HIV) reverse transcriptase (HIV- 1 RT). It was concluded that the presence of an unsaturated double bond at C-2, C- 3 and three hydroxyl groups at C-5, C-6, and C-7 positions were prerequisites for inhibition of RT[18].

The estrogenic activity of isoflavonoids has been reported, and 7-isopropoxyisoflavone is now sold on the market (‘Osten’ from Takeda Chemical Industries, Ltd.) as a therapeutic drug for osteoporosis. One of the main flavonoids in teas is scutellarein, which has been used as a diuretic, antiinflammatory, and antiasthmatic drug[14]. . Additionally, it has been suggested that a glucose moiety in the flavonoid structure plays an important role for its activity[14]. Flavonoids have also been proposed in the treatment of obesity.

2.CAROTINOIDS

carotenoids are compounds comprised of eight isoprenoid units (ip) whose order is inverted at the molecule center(FIG.2). Carotenoids are classified by their chemical structure as: (1) carotenes that are constituted by carbon and hydrogen; (2) oxycarotenoids or xanthophylls that have carbon, hydrogen, and, additionally, oxygen

Many diseases, such as cancer and strokes, involve oxidative processes mediated by free radicals. Carotenoids, by their antioxidant effect, can show benefits in such diseases. Carotenoids are an integral part of membranes. Carotenes are immersed in membranes, but xanthophylls showed a variable membranal position, polar groups in xanthophylls affect their position and mobility. Consequently, carotenes are able to react efficiently only with radicals generated inside the membrane.

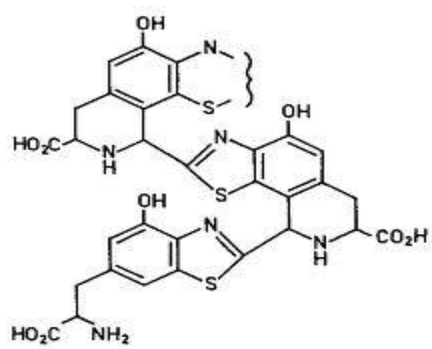

Fig.2 Structure of a carotenoid

While zeaxanthin, with their polar groups aqueous exposed, is able to react with radicals produced in that zone. Additionally, it has been suggested that carotenoids influence the strength and fluidity of membranes, thus affecting its permeability to oxygen and other molecules.

Also, it has been determined that carotenoids have a remarkable effect in the immune response and in intercellular communication[3,8,13]. There exists evidence of the effectiveness of β-carotene in the treatment of certain kinds of cancer, for example, smoking related cervical intraepithelial neoplasia and cervical and stomach cancer[8]. More than 600 carotenoids are known, and 50 of them are consumed in meals to be transformed into the essential nutrient vitamin A. After their absorption, these carotenoids are metabolized by an oxidative rupture to retinal, retinoic acid, and small quantities of breakdown products. Carotenoids are transported by plasma lipoproteins. Vitamin A is required in the vision process, epithelial maintenance, mucose secretion, and reproduction[20,21]. It has been established that retinoids affect many biological process, such as cellular proliferation, differentiation, and morphogenesis. Additionally, retinoids have been used in treatments of certain kinds of cancers and some dermatological activities.Moreover, it is mentioned that a diet with deficiencies in vitamin A or supplemented with an excess of retinoic acid could induce teratogenesis. It was suggested that different combinations of retinoids produced different pharmacological responses in the specificity and potency in cancer therapy[9]. Retinoic acid induces the response of proteins associated with damage by ultraviolet light in F9 and NIH3T3 cells. However, this induction does not show a correlation with the repairer of DNA damage]. Currently, the effect of retinoic acid in arthritis treatment is controversial It was proposed that negative effects of alcohol consumption during fetus development could be caused by the inhibition in retinoic acid synthesis, catalyzed by alcohol dehydrogenase, which conduces to a failure in function of retinoic acid receptor (necessary for normal development).

Retinoic acid (RA) has also been related to the aging process.Prostaglandins are substances that have been involved in several physiological process, and in particular prostaglandin D2 has been involved in the endogenous sleep promotion, modulation of several central actions (regulation of body temperature, release of the luteinizing hormone), etc.

carpenter et al. observed that mixtures of canthaxanthin with low-density lipoproteins (LDL) inhibited macrophage formation from human monocytes. It was explained that all evaluated carotenoids show good antioxidant activity, and observed differences are caused due to their activity at different levels.It was concluded that antioxidant activity depends on the particular system: radical, carotenoid, microenvironment, etc. Thus,

diets with carotenoid mixtures are recommended instead of having just one particular carotenoid. Carotenoids have been considered that provide benefits in age-related diseases, against some forms of cancer (in especial lung cancer), strokes, macular degeneration, and cataracts. On the other hand, it is clear that carotenoids in association with other components of fruits and vegetables seem to have a protective effect against some chronic diseases and precancerous conditions. Additionally, in some studies β-carotene was supplied to smokers, and it was found that cancer mortality indexes were higher in smokers than those supplied with β-carotene[21]. It has been signaled that a combined supply of β-carotene, α-tocopherol, and selenium reduces stomach cancer mortality.

Carotenoids protect lab animals of UV-induced inflammation and certain type of cancers. Historically, carotenoid supplementation has been used in the treatment of diseases produced by light sensitivity, which are usually hereditary. Lutein and zeaxanthin have been considered as protective agents against aging macular degeneration and senile cataracts[21]. Also, it has been suggested that β-carotene suppress the increment of hormones related to stress syndrome.

Nowadays it is thus premature to give final conclusions regarding the potential role of carotenoids in the therapeutics of degenerative diseases. However, the consumption of fruits, vegetables, and fortified foods with antioxidants is encouraged[8].

3.BETALAINS

Chemically, betalain definition embraces all compounds with structures based on the general formula shown in (Figure 3); therefore, they are immonium derivatives of betalamic acid. Betalains are water-soluble nitrogen-containing pigments, which are synthesised from the amino acid tyrosine into two structural groups: the red-violet betacyanins and the yellow-orange betaxanthins. Betalamic acid, is the chromophore common to all betalain pigments. The nature of the betalamic acid addition residue determines the pigment classification as betacyanin or betaxanthin .

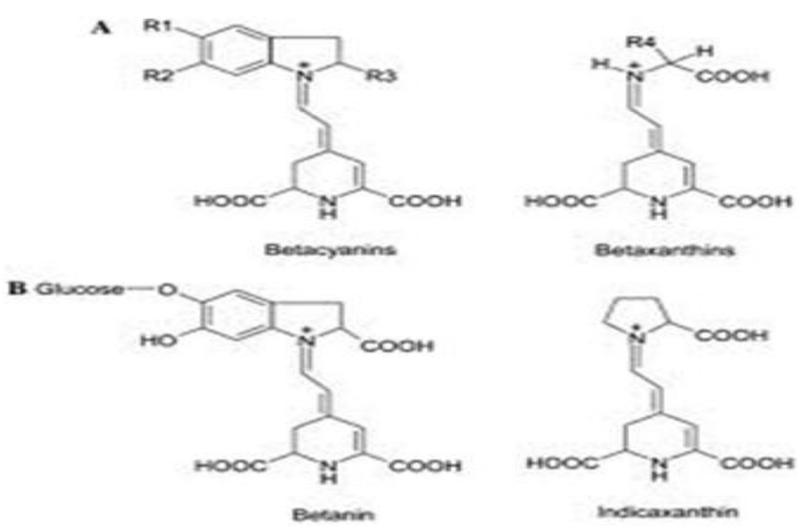

fig.3 structure of some betalains

Betanidin is the basic structural unit of most of the betacyanins, followed by its C15 epimer, the isobetanidin. In a strict sense, betalains do not belong to alkaloids because they are acidic in nature due to the presence of several carboxyl groups. Although structurally related to alkaloids, betalains have no toxic effects in the human body, as can be shown by the fact than they are present in considerably high amounts in certain foodstuffs, such as red-beet, prickly pear fruits and *Amaranthus* seeds. Therefore, betalains represent a safe natural alternative to some synthetic color additives that are currently in use. Interestingly, there is no upper limit to the recommended daily intake.

Several works have demonstrated the potent antiradical scavenging activity of betalains in vitro [10,15,4,25,5]. Kapadia et al. (1996) showed a significant inhibitory effect of beetroot towards skin and lung cancer in mice. Years later, Kapadia et al. (2003) demonstrated the efficacy of betanin for long-term local suppression of skin and liver tumours induced by different chemical carcinogens in mice. Kanner et al. (2001) reported the ability of both betanin and betanidin at very small concentrations to inhibit lipid peroxidation and heme decomposition. Tesoriere et al. (2005) showed that human red blood cells incorporate dietary betalains, which may protect the cells and avoid oxidative hemolysis. Tesoriere et al. (2004b) suggested that cactus pear fruit decreases oxidative damage to lipids, and improves antioxidant status in healthy humans. The structure–activity relationships of betalains with respect to free radical scavenging capacities were studied by Cai et al. (2003, 2005).

In a recent work, the importance of some natural pigments as nutraceutical ingredients was reviewed[19]. It was suggested that betalains like anthocyanins, β-carotene, and various vegetable and fruit extracts must be used for their potential health benefits. For example, yellow betaxanthins, in addition to their potential role as natural food colorant, may be used as a means of introducing essential dietary amino acids into foodstuffs, giving rise to an “essential dietary colorant”.

CONCLUSION

The antioxidant properties of natural pigments make them a better option for curing and prevention of diseases. There is increasing evidence that oxidative stress leads to biochemical changes, which contribute to the development of several degenerative diseases, such as cancer and cardiac diseases. Antioxidant molecules, some of which are derived from the diet, protect against the potentially injurious effects of oxidative stress. They can be used on a wide scale as an alternative for synthetic drugs. Nowadays, people have shown a clear preference for natural products, including pigments, because more nutritious and healthy characteristics have been associated with them. Moreover, one of the main problems to be solved, that all the natural pigments are not approved by FDA and European Union for consumption. Thus, many research groups are looking for new sources of natural pigments.However, these efforts have vanished, because under the current legislation the FDA or the European Union approval of new natural sources of pigments is very difficult. The reason is, that they can have some side effects.The pigment research area is very wide. So a lot of research is required to establish all the properties of these pigments and find out natural pigments with improved characteristics.

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