Summary

The flavonoids similarly to the other phenolic substances are secondary products of the plant metabolism. Their basic role is the defence of the plant cell from different damaging agents such as UV light, fungi, viruses, insects and oxygen free radicals. Laboratory and epidemiological studies have proved their wide-range chemical, biological and biochemical effects. Their beneficial action is unquestioned in preservation of health and prevention of diseases. The author of the review article presents the chemical structure, biochemical effects of the most frequently studied flavonoids, their metabolism and bioavailability, the flavonoid intake of the population, and their beneficial effects in various disorders and diseases.

Introduction

Bioflavonoids (BFs) are a large, exceptional group of natural plant components, all very similar in chemical structure. Bioflavonoids are an ubiquitous group of non-toxic biologically plant active principles. They belong to a larger group of compounds called polyphenols, which are presently perhaps the most interesting components of our diet. The up to now discovered number of polyphenols and bioflavonoids totals around 5,000. During the past three decades much has been learnt about their application in medicine. Numerous extensive studies have been published, which are exclusively concerned with this interesting group of compounds.

History

Bioflavonoids became the focus of attention in 1936 when the Nobel Prize laureate Albert Szent-Györgyi and colleagues discovered that the crude extract of vitamin C obtained from green pepper (paprika) and lemon juice is much more effective in the treatment of guinea pigs suffering from scurvy than the purified form of ascorbic acid (1). Further analysis of the lemon extract resulted in the isolation of “citrin”, which, as we know it today, is a mixture of bioflavonoids. Szent-Györgyi, the discoverer of bioflavonoids, called these substances “vitamin P” because of their capacity to decrease the permeability of the capillaries, in other words, increase capillary resistance. Not long after being discovered it was proved, both experimentally and clinically, that when it is removed (extracted) from food does not result in any sign or syndrome characteristic of P vitamin deficiency (avitaminosis P). [NOTE: by the definition as a vitamin is considered a substance whose absence from the diet causes specific symptoms because it cannot be synthesized by the body, and therefore it must be taken from food sources]. Consequently, in 1950 the Food and Drug Administration (FDA) proposed to replace the term ‘vitamin P’ used for the compounds mentioned above, by the term bioflavonoids. At present, on the recommendation
of RDA (Recommended Dietary Allowances) Committee of the FDA in the USA bioflavonoids are considered more as pharmacological agents than dietetic components (2, 3).

Whatever their official status is, the fact remains that bioflavonoids are ubiquitous, non-toxic compounds of plant origin, which greatly affect numerous diseases in humans, and we can be certain only of the fact that their presently still unknown properties will be investigated and discovered in the future.

Our world abounds in polyphenols. They are the basic chemicals of fruit pigments, berries and wine – ranging from deep red to blue or purple or white in the white spongy inner covering of the citrus fruit peel (pericarpium). On the other hand the yellow colour often comes from carotenoids. In the autumn the magnificent colours of deciduous forests originate mainly from the polyphenols and bioflavonoids, which become visible only when the green pigment – chlorophyll – passes away. In the opinion of experts of the field, the ubiquity of bioflavonoids is a proof of the exceptionally significant role that they play in the world of plants (plant kingdom). The role of bioflavonoids in plants is multi-faceted. One of them is that they give colour to the plant (the flower and the fruit), which is, no doubt, very important in the process of pollination. It has been proved that the right colours attract the right kind of insects to the right petals. Another important role of the bioflavonoids is their capacity to protect the plants from the environmental stresses, such as: ultraviolet radiation, ozone, etc. This protective function of the polyphenols and bioflavonoids is most likely due to their antioxidant role. In addition many bioflavonoids produce an antibacterial and antifungal effect, which is by no means any less important than the previously mentioned functions. There is scientific evidence that bioflavonoids also regulate the transport of plant hormones termed auxins, which control the growth and the development of plants. In this respect quercetin possesses the most powerful activity.

Polyphenols can have a bitter, acrid and sometimes even sweetish taste. By their functional characteristics they act as astringents, bactericides and viricides, and have deleterious effect on many other microbes. Polyphenols also contribute to the taste of coffee (caffeic acid), tea (catechins), wine (resveratrol), bananas and vanilla, as well as to the pungency of black pepper (bioperine) and hot peppers (capsaicin). Polyphenols are used for tanning animal skins, protect food from unwanted oxidation and they turn the fruit into a rusty brown colour once it has been sliced.

Nevertheless, the most extraordinary contribution of polyphenols is their role in the prevention and cure of diseases in humans. The chemistry of the polyphenols is very complex indeed, yet it needs to be worked out for the sake of a better knowledge of their versatile effects. The inherent complexity of natural (vegetable) products is the consequence of the many thousand organic compounds which they contain: the bioflavonoids, phenols, terpenes, karotenoids and alkaloids – to mention the ones which have been identified and isolated until now. This process is not simple, yet the task of identifying their biological function is an even more complicated one.

VITAMIN P – THE OTHER SIDE OF ASCORBIC ACID:

The Rest of the Vitamin C-complex

As it was mentioned earlier, many years ago, scientists viewed vitamin C as one whole vitamin and nothing else. But then Dr. Albert Szent-Györgyi, a Nobel Laureate (1937, for his discovery of ascorbic acid) turned up the first evidence of other factors associated with it that clearly showed the evidence of a vitamin C complex rather than just one nutrient alone.

Dr. Szent-Györgyi used what he later called some „intuitive guesswork” to identify these other factors as flavonoids. “I felt very strongly that this substance had to be a vitamin,” he stated in a 1977 interview, “so I decided to call it ‘vitamin P’ for want of something better.” Later, in 1950, the biochemist B. L. Oser coined the term bioflavonoid, which expanded the classification considerably. Szent-Györgyi’s original understanding of his newly discovered flavonoids had been limited to numerous plant pigments known as the flavonols and flavones. Eventually both words were synthesized down into just one, flavonoids. But when Oser came along, he felt there was a
pressing need for a more specific term that would define those flavonoids that exhibited biological activities of some kind; hence was born in his fertile mind the word bioflavonoids.

In the same year this word came into being, the Joint Committee on Biochemical Nomenclature of the American Society of Biological Chemists and the American Institute of Nutrition adopted a firm resolution recommending that Szent-Györgyi’s “vitamin P” no longer be used. They claimed, in effect, that “studies have failed to substantiate these claims” of its being a vitamin. Furthermore, they insisted that “the identity of a substance of a vitamin nature had not been fully established” by the man. The New York Times even ran a front page story describing “vitamin P” as being “perfectly useless”. However, just because American Scientists pooh-poohed Szent-Györgyi’s claims, the same did not necessarily hold true for many other countries, especially those in Europe and Scandinavia, where even today the term “vitamin P” still remains very much alive within the medical and nutritional communities.

Rediscovering Vitamin P

Citrus fruits are a major source of those bioflavonoids that do the body the most good, namely the methoxylated kind. Their highest concentrations are always in the inner peel or white portion, with far lesser amounts in the juices and edible parts of the fruits themselves.

Oranges (Lat. Citrus Aurantium L. var. dulcis; Citrus sinensis Gall.), lemon (Lat. Citrus Limonum Risso; Citrus medica var Limonum L.), mandarin, (Lat. Citrus reticulata), and grapefruit (Lat. Citrus paradisi) are a rich source of white coloured bioflavonoid. The inner soft, white pulp of the peel of the citrus fruits (agrums) has no scent and hardly any taste. When peeling the fruit this layer is discarded.

CLASSIFICATION SYSTEM OF POLYPHENOLS

If the objective of a classification is simplicity (and this seems to be a good starting point when dealing with such a complex material) – polyphenols can be classified into two basic groups: bioflavonoid and non-bioflavonoid polyphenols. (4,5)

Non-bioflavonoid polyphenols

The members of this polyphenol subgroup are organic acid derivatives (mostly benzoic acid, and cinnamic acid, after cinnamon). In addition, various other classes of phenolics are known, such as: xanthones, coumarins and naphthoquinones, which are important components of fruit extracts and have proved to be very beneficial in clinical medicine.

Cyanidin and the other anthocyanidins can be recognized by their unique property that they absorb light in the range of 475 – 560 nm (nanometres), which explains their colours ranging on the scale between nuances of reddish-purple, blue and violet. Their absorption spectrum is without rival among the natural bioflavonoids and polyphenols, and this must be the explanation for the unique role that they play in various diseases – for example the beneficial effect of anthocyanidin in bilberries (European blueberries, Lat. Vaccinium myrtillus) on the night vision (1). The so called aurones absorb the visible range of the spectrum scale between 370 – 430 nm and have golden yellow colour (hence the term aurones). They are important, together with other yellow coloured flavonoids and carotenoids for the functioning and regeneration of the eye pigments, especially in the region of the macula lutea (yellow spot). This spectrum of visible light is most present at day-time, therefore its physiologic role is in the daylight vision. (4, 5)

Division of polyphenols into subclasses

The polyphenols are divided into several subclasses based on three distinct characteristics. They are their degree of: hydroxylation, polymerization, and conjugation with carbohydrates or other molecules (4, 5).

The presence of the hydroxyl groups is of great importance in the chemical structure of polyphenols, since the efficacy of their anti oxidative effect depends on the hydroxyl group. The scavenging effect of the polyphenols on the free radicals, is well known from the antioxidant ac-
Without entering into details, we can state that regarding their biological effects the most interesting ones are the first two classes, namely the hydroxybenzoic and the hydroxycinnamic acid, respectively, which are the most significant natural polyphenols discovered up to the present.

In this system there are six fundamental groups which differ in the number of carbon atoms (Table 1). Some classes are further divided into subgroups. Without getting into too much detail, you can see several classes we have yet not mentioned, including the hydroxybenzoic acids and hydroxycinnamic acids (e.g., ferulic acid) which contribute to the bulk of the monophenols found in nature.

**Coumarines**

Coumarines can only be found in certain species of plants and that in low concentrations. Academic medicine has been using them since a very long time as indispensable anticoagulant drugs. They are antagonistic to K-vitamin dependent coagulating factors (II. VII. IX. and, X.), in other words, they inhibit the synthesis of the functionally full valued factors (biologically active forms) of the pro-thrombin complex. Another feature of the coumarines, which made them “famous”, is that they are one of the ingredients of certain rat poisons. It is surprising that compared to some of the other polyphenols, coumarines have found such wide application in clinical medicine since their therapeutic doses are only slightly under the toxic values.

**Xanthones**

According to another system of classification, there are six basic groups of compounds, which differ in the number of carbon atoms they contain (Table 1). Some of these classes are divided further into subgroups.
Xanthones are an interesting class of compounds whose medicinal qualities are presently being extensively investigated and tested. Results obtained so far indicate that xanthones promote an anti-allergic and anti-asthmatic activity and also an inhibitory activity on the aggregation of platelets (7). These properties make the xanthones in effect similar to bioflavonoids. This kind of overlap in physiological effects can account for the analogous medical application of a great variety of plants (for example, inflammation, allergy/asthma, heart diseases, etc.).

Biological studies on the xanthones obtained from the fruit of the tropical tree Garcinia mangostana L. (Clusiaceae), regarded as “the queen of fruit,” have demonstrated interesting biological activities. Studies have been conducted to examine the anticancer properties of the extracts or xanthones obtained from the fruit hulls of this plant species against colon preneoplastic lesions, DNA topoisomerases I and II, human leukemia, hepatoma, lung and gastric carcinomas and human breast cancer. Our interest has been focused on the isolation of structurally interesting prenylated xanthones and the biological activities of intermediates at various stages of fruit maturity. In our previous study, the isolation of 17 xanthones including three new xanthones, mangostenol and mangostenones A and B, from the green fruit (14-week maturity stage) of this plant and their antituberculosis activity were already described. In a continuation of this work, the EtOAc-soluble extract obtained from the young fruit (7-week maturity stage) of G. mangostana was subjected to a chemical investigation leading to the isolation and structural elucidation of three new prenylated xanthones, mangostenones C, D and E in addition to 16 previously reported xanthones, thwaite-sixanthone, demethylcalabaxanthone, garcinone B, compound, b-mangostin, 8-desoxygartanin, gartanin, garcinone E, the major metabolite a-mangostin, mangostinone, the second major metabolite g-mangostin, mangostanol, mangostatin, garcinone, garcinone C and the third major metabolite 11-hydroxy-1-isomangostin. We here report on the structural elucidation of the three new compounds and the in vitro cytotoxic activities of xanthones listed against three human cancer cell lines, epidermoid carcinoma of the mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187).

Three new prenylated xanthones, mangostenones C, D and E together with 16 known xanthones, were isolated from the young fruit (7-week maturity stage) of Garcinia mangostana. The structural elucidation of the new compounds was mainly established on the basis of 1D and 2D NMR and HR-MS spectroscopic analysis. Compound C showed cytotoxic properties against three human cancer cell lines, epidermoid carcinoma of the mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187), with IC50 values of 2.8, 3.53, and 3.72 mg/ml, respectively. Among the isolates, a-mangostin, the major metabolite, exhibited the strongest activity against the BC-1 cells with an IC50 value of 0.92 mg/ml, an activity greater than that of the standard drug ellipticine (IC50 1.46 mg/ml). A-mangostin also showed the highest activity against KB cells, while gartanin displayed the strongest activity against the NCI-H187 cells at the respective IC50 values of 2.08 mg/ml and 1.08 mg/ml.

Chrysin or or flavone X

Although oestrogen is known as a female hormone, and testosterone is known as a male hormone, in reality men produce a small amount of oestrogen, and women produce a small amount of testosterone. In both men and women, testosterone is basically broken down into oestrogen. In fact, one of the problems with men taking supplements to enhance testosterone levels to build muscle, is the possibility that the result will be higher levels of oestrogen, which will have a feminising effect. This is not exactly what the average body builder has in mind.

Chrysin, also known as flavone X, inhibits aromatase, an enzyme responsible for breaking down testosterone into oestrogen, thereby helping to maintain higher testosterone levels. There are few human studies on chrysiné however, European Olympic athletes who took 1 to 3 grams of chrysin reportedly experienced a 30 per cent increase in testosterone.

Bioflavonoid Types

What replaced vitamin P in the USA was the fancier term, bioflavonoid, of which there are a great many in nature. But, as it turns out, relative-
ly few of them show any clinically useful activity in human beings. Such activity, we now know, depends on whether a particular bioflavonoid contains certain chemical constituents known as hydroxyl- or methoxy- groups. A hydroxyl group is made up of one atom of oxygen and one of hydrogen. On the other hand, a methoxy group contains one atom of oxygen, one of carbon, and three of hydrogen. Most consumers do not realize it but there are sharp differences in activity between hydroxylated (hydroxy-containing) bioflavonoids and methoxylated (methoxy-containing) bioflavonoids.

Knowing how they differ from each other, helps us to better appreciate what we should be taking into our bodies for specific health needs. The most common bioflavonoids in food plants are hydroxylated. Some of these, which are helpful in preventing cataract formation in the eyes, are: quercetin, myricetin and kaempferol. Hydroxylated bioflavonoids also have an antioxidant activity helpful in preserving foods.

Methoxylated bioflavonoids occur almost exclusively in citrus fruits. In his early research, Szent-Györgyi and his associates isolated two, hesperidin and erioctyiol, from lemon extract. Interestingly enough, such citrus-derived bioflavonoids are more active in the body than the hydroxylated ones coming from ordinary food plants. Besides this, the citrus kinds are more resistant to degradation in the intestinal tract, which means they are more readily absorbed from the gut.

One other thing has become more apparent in recent years. It usually takes twice as much of the hydroxylated bioflavonoids to do the same jobs that the methoxylated ones can do better. A case in point is the common bioflavonoid quercetin, which readily occurs in spices like cloves, dill, onion, and pepper, in medicinal herbs such as boneset, elder flowers, and hawthorn berries, and in natural beverages like black and green tea. Quercetin exhibits antibacterial properties in spite of being hydroxylated. But so does nobiletin, a methoxylated bioflavonoid that is always present in the inner white part of the peels of grapefruit, lemon, lime, oranges, and tangerines. But you have to use at least twice as much of the herbs, spices, and tea to get rid of a bacterial infection within or on the outside of the body, whereas just half of the same amount of citrus materials would be required to do the same task!

This is why it is important to do some careful label reading before you ever purchase any brand-name vitamin C product or a bioflavonoid formula of any kind. Because regular food plant bioflavonoids that are hydroxylated are cheaper to obtain, many vitamin manufacturers like to use them over the citrus or methoxylated bioflavonoids, which are more costly to extract. If the label doesn’t specify citrus bioflavonoids, then do not buy it.

Renaissance of the Bioflavonoids

As it was mentioned previously, in 1950 a group of orthodox scientists effectively quashed the matter of bioflavonoids gaining any legitimacy for a vitamin P status. Then, in 1968, the Food and Drug Administration (FDA) withdrew the rights of pharmaceutical companies to distribute and doctors to prescribe bioflavonoid preparations. In effect, the FDA declared that these were utterly worthless and totally ineffective in people “for any condition” whatsoever.

However, this didn’t stop consumers from purchasing bioflavonoid products at their favorite health food stores or nutrition centers. Consumers mainly took them because of scientific evidence indicating that these vitamin P factors help to sustain ascorbic acid’s own antioxidant activity within the system. Moreover, it was later determined that vitamin C is able to protect at least one of these bioflavonoids from oxidation, namely quercetin. Recent research is showing a real “key and keyhole” relationship between the bioflavonoids and vitamin C in much the same way that all of the vitamins of the B complex are interrelated. Hence, there is now a pretty strong case to be made for a vitamin C-complex, just as there has been for many years for the vitamin B-complex.

Beginning in the early 1980s, the popularity and acceptance of the bioflavonoids by consumers and scientists alike really started in a big way. From an abstract taken from a review article in a 1984 edition of the journal Trends in Pharmacological Sciences, a great amend to bioflavonoids
was given: “Naturally occurring [bio]flavonoids have potent anti-allergy, anti-inflammatory, and anti-viral activity. Since they are common dietary constituents the question arises, are they natural biological response modifiers?” (bold letters given by the author of this review article). Knowing the rather bizarre history of vitamin P, the opposition against them for many years, there were still some scientists dedicated enough and willing to spend their research time and dollars to continue investigating the bioflavonoids. It was the gradual outpouring of their combined findings presented to consumers by an eager media that finally resulted in their gaining their much-deserved and prominent place in modern medicine and nutrition.

The Vitamin C-Complex, citrus bioflavonoids: Key Bioflavonoids

At present count, there are an estimated 5,000 bioflavonoids, which belong to a more diverse group of chemical compounds known as polyphenols. They are present in just about all plants in the pigments that give food plants and herbs their notable colours. Coloured fruits and vegetables are particularly high in bioflavonoids, especially those that are emerald green, golden yellow, vivid orange, brilliant red, or royal purple.

Of this vast number, however, a mere handful or few hundred are believed to possess biological characteristics that may be useful to the human body in various ways. In citrus species alone, well over 70 different methoxylated bioflavonoids are known to reside, yet just a few are known to have therapeutic significance. The same holds true with the more common, hydroxylated kind so abundant in nature.

The very best way to obtain the majority of them is by consuming the plants they appear in. The only notable exceptions to this would be the supplementary use of rutin (50 mg), hesperidin (100 mg), and quercetin (25 mg) or any of these together with citrus bioflavonoids in a mixed formula product (400 mg) of some kind, usually termed as citrus bioflavonoid complex.

Bioflavonoids as potent nutritional agents

Plant polyphenols – a brief review

A large difference exists in polyphenol composition between different types of plants. Agrumes (citrus fruits) are abundant sources of flavones and flavonones, while berries, such as blueberry, red grapes, and pomegranates are very rich in anthocyanidins. Tea is known for its high levels of catechins.

The distribution of bioflavonoids in the different parts of the plant also varies. Fruits and berries mainly contain bioflavonoids which are equally distributed throughout the skin and flesh of the fruit. This is why plums, cherries, and raspberries are of uniform colour. On the other hand, in some other fruits, for example apples, flavonoids are almost exclusively found in their skin.

Each plant and fruit has its own specific mixture of polyphenols.

Polyphenols in wine

Red wine is well-known for its anti-aggregation effect on platelets (the ability to block platelet aggregation), the primary cause of the intra-arterial thrombus (clot) formation. These wine-types are exceptionally rich in anthocyanidins as well as catechins (approx. 200 mg/l of each type of substances). Red wines on average contain about 1300 mg/l of phenols altogether, which means about six times (600%) more than white wines (25 mg/l on average) (8). What is even more important, 82% of all the polyphenols present in red wine are bioflavonoids and related compounds, whereas in white wine this percentage is only approximately 14%. Tannins which give the distinctive aromas (somewhat tarry taste) of the red wines are represented on average 550 mg/l, whereas in white wine there is an average of 5 mg/l (that is, 110 times more in red wine!) (6). Every good oenologist (vintner) knows that upon standing (ageing) the quantity of anthocyanidins drops from 200 to 20 mg/l, and this drop is manifested in a visible change in colour from crimson/purple/violet to brownish-red. In fact, the essence of making a high quality red wine more or less lies in avoiding the oxidation of the anthocyanidin pigments into an unwanted brownish colour, which does not only affect the aesthetic quality but the biological quality of
the wine, too (8). The polyphenols listed above, and the resveratrol (a stilbene) are the explanation for the so called “French paradox”. Red wine, the fermented beverage containing all these compounds is responsible for this phenomenon. Namely, medical investigators became attracted to red wine after discovering that the French, who love to indulge in foods rich in fats and sugars, still somehow manage to have the world’s lowest rates of heart disease, heart attacks, and strokes.

**Polyphenols in green tea**

The polyphenols found in green tea have lately become highlighted in the medical news due to their anti-cancer activity. The phenol components make up about 30% dry weight of the fresh, unprocessed tea leaves. The majority of these polyphenols are catechins of which the most important ones are: epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate. The only difference worth mentioning among them is the complexes which the phenols form with gallic acid, a polyphenol with a well known strong antioxidant activity. [NOTE: The gallic acid, an excellent metal-chelating and antioxidative popyphenolic compound of the green tea) or to be more precise its salts such as propyl-gallate, – are often used as additives in soft drinks and other food products to prevent their oxidation].

However, the flavour of the commercial tea products stems, not from the catechins, but from their oxidative products called theaflavins generated during the processing (fermentation) of tea leaves. Processed tea also contains another group of related molecules termed thearubigins.

**Turmeric (Lat. Curcuma longa)**

Curcuma longa is a perennial plant whose rhizome has long been used for medicinal purposes and as a colouring agent for foods. The powder called turmeric, contains curcumin – a polyphenol composed of two ferulic acid molecules linked together, chemically termed diferuloylmethane. Turmeric contains two curcumin derivatives. The therapeutic uses of curcumin, are very similar to those of many flavonoids, cyanidin included. In an experimental study (published in the Journal of the American College of Nutrition) administration of curcumin prevented cancer development in the 68% of the treated animals. Curcumin is a potent anticancer compound which can retard cancer at both the initiation and promotion phases –just like cyaniding and many other bioflavonoids. Moreover curcumin shares many of the same mechanisms of action, namely the antioxidant effects, stimulation of drug-metabolising enzymes like the glutathione-S-transferases, and increased levels of glutathione in liver and other tissues.

Curcumin has well documented anti-inflammatory effects in a variety of animal models. Two main mechanisms of action are inhibition of lipoxygenase and antioxidant effects. Not surprisingly, cyanidin and many other bioflavonoids exhibit, also powerful anti-inflammatory activity with identical mechanisms of action. Two double-blind, clinical trials of curcumin supplements (in arthritis and postoperative inflammation) documented its therapeutic usefulness. The doses used were 120 and 1 200 mg/day/person.

The list of medical applications common to curcumin and flavonoids is a long one, and includes: protection against chemically induced liver damage, improvement in the lipid profile of blood, reduction in the extent of platelet aggregation, antimicrobial effects, and immune stimulation.

**Polyphenols as we experience them through our tasting-buds**

Polyphenols can evoke quite a wide variety of tastes in humans. Tartness of red wine and teas, for example is lately being associated with the lipid-normalising actions of these “healthy drinks” [tartness: Hung. = fanyar iz; Serbian = oporkast ukus].

Bitterness is also one of the common tastes of plants, which can be caused by several, different compounds, such as: alkaloids, terpenes, and amino acids, but mainly is due to polyphenols.

In wine and cider, bitterness has been ascribed to the proanthocyanidin polymers of a relatively small size, called proanthocyanidin oligomers (like glucose oligomers).

Astringency means a contracting and tightening action. [Astringency: Hung. = összehúz, fogat elvásol; Serbian = skuplja, grči, utrne zube]. It is related to the presence of proanthocyanidins of larger molecules, the so called proanthocyanidin polymers (like starch in the glucose polymer ana-
logy above). These large polymers are tannins, plant extracts originally used to convert skin into leather. [Tannins: Hung. = cserzőanyagok; Serbian = jedinjenja za štavljenje kože]. The mechanism of tannin’s action is based on of tannins capability to interact with proteins, or more precisely on their action to precipitate proteins in water-based (aqueous) media. This means that if tannins are placed in a glass containing milk, whey or casein (milk protein), the protein would precipitate (fall down to the bottom of the glass).

Bitterness and astringency correlate inversely: while astringency increases with the polymerization of proanthocyanidin oligomers, at the same time, bitterness diminishes with the loss of the smaller proanthocyanidin molecules (oligomers).

**Differences and similarities between polyphenols and bioflavonoids**

Is there a difference between polyphenols and bioflavonoids? The answer is both yes and no.

YES: it is true that most bioflavonoids have a characteristic ring structure – the 2-phenylchromanene ring – which defines them as a group. Polyphenols do not have this chemical characteristic, since any polyphenol with such a ring structure would, by definition be a bioflavonoid.

NO: Although chemically different, the physiological actions of polyphenols are quite similar to those of bioflavonoids. Their physiological actions directly influence health and disease processes, and, therefore is not surprising that they are used in clinical practice interchangeably. For example, cyanidin the main anthocyanidin pigment in nature – is a member of bioflavonoid group, whereas curcumin is a representative of the polyphenols. However, the therapeutic uses of curcumin are, virtually identical to those of cyanidin, and many other flavonoids (as inhibitors of cancerogenic processes).

**Absorption and metabolism of polyphenols**

This is a relatively unknown area, and it definitely needs further extensive research. Since polyphenols are so ubiquitous in the world of plants it should be expected that they are well represented in our everyday diet. In the case of a well-balanced, mixed diet, the daily intake of polyphenols is assessed to be in the well-developed countries of the West and the USA about 1,000 mg/day per person. Half of this amount is absorbed in the gastrointestinal tract, and the rest is metabolized through the intestinal microflora. Different flavonoids show different sensitivity to the effects of the microbial enzymes (of intestinal flora), the least sensitive among them being the metoxy flavonoids of the citrus fruits (agrumes) (9).

One of the first stages in the process of polyphenol absorption is the breaking-up (cleaving) the flavonoid-glycosoide bond since most of the bioflavonoids present in food are in their glycone forms. The enzymes responsible for this process are not found in human gastro-intestinal secretions, but they come from the enzymes produced by the eubacterial flora (friendly bacterial content) of the intestines (10). The metabolism of bioflavonoids by bacterial enzymes results a whole series of metabolic products. Some of them continue to be very useful compounds, because they have beneficial physiological or medicinal properties. Important class of molecules produced in this way are two organic acids: the phenylpropionic and phenyl-acetic acid. They inhibit the growth of a substantial number of various microorganisms. A similar effect is well recognized on behalf of phenyl-gamma-valerolactones (another class of bioflavonoid metabolites). After being absorbed, the blood transfers the bioflavonoids into the tissues in order to be utilized, but prior to their catabolism or excretion they are re-conjugated in the liver either with sulphates or glucuronates.
Besides of the facts described above, the most interesting relationship discovered until now, is the one existing between bioflavonoids and ubiquinone (Coenzyme-Q10, CoQ10). The sequence of events is as follows: one of the metabolites formed during the enzymatic decomposition of bioflavonoids performed by the intestinal bacteria is the para-hydroxy-benzoic acid (pHBA). [NOTE: it’s cousin, para-amino-benzoic acid, PABA is a B-complex-like nutrient]. It has been confirmed that this organic acid is used in various tissues (e.g., leukocytes) as a basic substance in the process of endogenous biosynthesis of the coenzyme Q10 (10). In essence, para-hydroxy-benzoic acid is the main portion (the business end) of the CoQ10 molecule. It maintains the primary or active part of the reduced CoQ10 or the ubiquinol molecule, which is responsible for its powerful antioxidant activity. The realization of this fact seems to be of utmost importance, and it gives rise to speculations that bioflavonoid supplementation might stimulate the endogenous production of CoQ10 (ubiquinol) of the human body, which after the age of 35-40 usually rapidly slackens (but is it a physiological rule or necessity?).

Types of Bioflavonoids

According to their structure twelve classes (structural classes) of bioflavonoid have been until now identified and new structures are being reported at ever-increasing rate. These structural classes are the following: flavans, flavones, flavanones, flavanols, flavanolols, isoflavons, leucoanthocyanins, chalcones, dihydrochalcones, aurones, anthocyanidins, and catechins (13).

Bioflavonoids in plants

The ubiquitous presence of bioflavonoids in the plant kingdom is, one of the most important mechanisms of action of herbs. Extracts or other herbal preparations almost always contain bioflavonoids of some sort, and in many cases the active component has been shown to be a bioflavonoid.

Berries are very rich in anthocyanins. European blueberry (bilberry) (Lat. Vaccinium myrtillus), for example contains blue -coloured bioflavonoids (anthocyanidins) which have been well documented to possess anti-allergic and anti-inflammatory activities.

Citrus fruits on the other hand, contain high levels of flavones and flavonones

Ginkgo biloba or Maidenhair contains flavoglycosides (flavonoids linked to a sugar, named rutin) which are believed to be responsible for its pharmacological activities.

Milk thistle (Lat. Sylibium Marianum) contains a bioflavonoid called sylmarin, which displays a great healing effect in treating liver disease, particularly in alcoholics.

Prominent characteristic of plant flavonoids is the variety of isomers of a single bioflavonoid found within each species.

In black raspberry [Hung. = szeder; Serbian = kupina] for example, the primary anthocyanin is cyanidin, or more precisely its six isomers. The underlying reason for such a variety of isomers is not yet known, but is currently under investigation.

Biochemical effects of bioflavonoids

Bioflavonoids promote a wide spectrum of biochemical activities, many of which directly influence the state of health or disease. Their principal biochemical activities are listed in Table 2.

1. One of the primary effects of natural bioflavonoids and polyphenols is the neutralization of the free radicals, that is, their antioxidative activity. Furthermore, bioflavonoids capable of chelating certain metallic ions known to have pro-oxidative effects (iron is one of them, turning ferrous form (Fe2+) in the ferric (Fe3+) state, and thus reduce their potential to generate free radical chain reaction. Several laboratory tests have demonstrated that the majority of bioflavonoids manifest a certain degree of antioxidative activity, and some are quite powerful in this respect. The protective, anti-oxidative effect of various bioflavonoids on plasma lipoproteins was tested, by the measurement of the intensity of a hydroperoxide–induced lipid peroxidation (11). The strongest protective effect on plasma lipoproteins was exhibited by quercetin, and catechin. The intensity of the anti-oxidative effect the two bioflavonoids mentioned, almost equalled that one of the well known antioxidative food preservatives, the butylated hydroxytoluene (BHT) (11). In this respect, other bioflavonoids, namely morin, rutin and naringein, have manifested a weaker protective effect. Researches on various models have
shown that bioflavonoids and polyphenols generally protect living organisms against oxidative damages (12).

2. The second significant biochemical effect of polyphenols is that they inhibit the enzymes of the so-called lipoxygenase-enzymatic circle, which converts arachidonic acid (AA) into leukotrienes (LTs), the well-known mediators of allergic and inflammatory reactions. The studies have indicated that quercetin, fisetin, rutin, morin, caempherol and silymarin are the most active compounds regarding their inhibitory action on the lipoxygenase activity (14, 16).

3. The bioflavonoids mentioned inhibit two enzymes generally associated with asthmatic and allergic reactions, namely the calcium dependent ATP-ase and cAMP-phosphodiesterase (17,18). This enzymatic duo (tandem) works together in order to inhibit the release of histamine from the tissue mastocytes and basophilic granulocytes. Thus, in fact they prevent the start of a biochemical chain-reaction triggering off every form of the early type hypersensitivity reactions such as the anaphylactic shock and various types of allergy. The third, but by no means less important biochemical mechanism of flavonoid activity relates to the inhibition of cAMP-phosphodiesterase enzyme. The inhibition of cyclic adenosine monophosphate (cAMP)- phosphodiesterase leads to the increase of intracellular cAMP level. A high level of cAMP in cells containing high quantities of histamines blocks the process of degranulation and, consequently the release of histamine from the histamine-rich cells. The net effect is the prevention or reduction of the histamine release (18). (NOTE: Teophyllin, a conventional bronchodilator used also as an anti-asthmatic drug has a similar effect).

4. The fourth mechanism of action exerted by the bioflavonoids observed in research studies has been – the inhibitory activity of bioflavonoids on protein-kinase C. This enzyme is a very important regulatory enzyme which stimulates the eleration of histamine during the complex series of events known as degranulation of histamine-rich cells (19). The most powerful protein-kinase C inhibitors are the following bioflavonoids: quercetin, fisetin and luteolin, and they seem to be efficient in the prevention and treatment of allergic reactions, as well.

Bioflavonoids also play a role in stabilizing collagen – an extremely important structural protein, which influences vascular diseases, cancer development and its spread. Anthocyanins, especially those extracted from blueberry and grape, are very active in collagen stabilization.

5. In addition, studies have also shown, that bioflavonoids inhibit the enzyme reverse transcriptase, which is used be RNA-containing viruses (such as the AIDS virus) for replication. The importance of this is obvious: bioflavonoids might prevent (inhibite) viral replication due to inhibition of this important viral enzyme.

6. Bioflavonoids inhibit the enzyme aldose reductase, which is intimately involved in cataract formation. Of over forty flavones tested and found to be active, quercetin and quercetrin exhibited the greatest inhibitory effect on aldose reductase activity, and consequently the most efficacious protecting effect against the development of cataracts.

Bioflavonoid Contributions to Good Health

It may be helpful at this point to mention in passing some of the health contributions generated by bioflavonoids within the human body.

Reduce Heart Disease Risk. In evidence of some clinical studies, vitamin P factors can reduce a person’s risk of developing heart disease later in life. Bioflavonoids in general seem to protect “bad” (low-density lipoproteins or LDL) cholesterol particles from oxidation (this is a chemical process that makes cholesterol’s effect more deadly on blood vessel walls). Vitamin P helps reduce the tendency of blood platelets to clot. Likewise, it strengthens arteries and capillaries in the heart; this, in turn, helps avert the disease process.

Protect Against Cataract Development. Body enzyme systems occasionally go awry. One example may be seen in the activity of aldose reductase, an enzyme involved in the formation of cataracts in diabetics and in those with the metabolic disorder galactosemia.

Some years ago researchers working out of the National Eye Institute’s Laboratory of Vision Research in Bethesda, Maryland tested bioflavo-
Bioflavonoids on partially purified rat lens aldose reductase. They also tested them on intact rat lenses, culturing the lenses in a medium rich in cataract-producing sugar (sorbitol). In both tests, they discovered the bioflavonoids to be exceptionally potent inhibitors of the enzyme, capable of as much as 80 percent inactivation of the enzyme. This phenomenal action was evidenced even in the lenses that should have been highly cataract-prone because of the culture medium. In an old issue of Science journal (188:1215) they suggested that bioflavonoids could be very “useful in preventing the onset of diabetic or galactosemia cataracts.”

**Better Stress Management.** Scientists know that a certain amount of vitamin C is always stored in the adrenal cortex for immediate use when stress activity within the system rises. But ascorbic acid is not alone there since its many accompanying bioflavonoids are added to this reserve as well, alongside with vitamin B5 (the anti stress vitamin, panthotenic acid). Without a full and active complement of the entire vitamin C complex, the adrenal cortex is less able to cope with stress.

**Avert Capillary Bleeding.** Bioflavonoids protect blood vessels against fragility and abnormal permeability (leakage). They increase the strength of tiny capillaries. When this happens, easy bruising, surface blood vessel damage, varicose veins, and bleeding gums are averted for the most part.

People who bruise easily or have pinpoint-size red blotsches under the skin (purpura), those subject to periodic nosebleeds, women experiencing heavy menstrual bleeding or recurrent miscarriages, and individuals afflicted with hemorrhoid will all benefit from ample citrus bioflavonoids like rutin and hesperidin.

**Curb Heart Attacks and Strokes.** The May 1997 issue of Harvard Men’s Health Watch, a monthly newsletter published by Harvard Medical School, included highlights of several medical reports that are part of a growing body of evidence that shows the value of bioflavonoids in helping to curb the risk of heart attacks and strokes in men. The article opened by noting that “eating apples and other foods high in bioflavonoid may indeed reduce a man’s risk of heart attack and stroke.”

The following four studies were then cited as evidence of this:

- A 1993 report mentioned 805 men between 65 and 84 years of age being examined for their intake of bioflavonoid foods. Those who ate the most enjoyed the lowest incidence of coronary artery disease, as well as having a 58 percent lower risk of cardiac death than those consuming only minimal amounts of bioflavonoids.

- An investigation printed in 1995 reviewed the link between bioflavonoids and heart disease in 16 different population groups of middle-aged men in seven nations. Where bioflavonoid intakes were high, coronary artery disease was extremely low.

- Two separately published studies in 1996 followed the health benefits of bioflavonoids in some 5,500 people. The first investigation tracked the effects of dietary vitamin P in 2,748 men and 2,385 women for 26 years. People of both genders who consumed the most bioflavonoids invariably had the fewest heart attacks and deaths from heart disease. In men especially, a high intake of dietary vitamin P correlated with a 22 percent reduction in mortality rate.

- The other study involved 552 male participants only, who entered the 15-years-long evaluation program when they were between 50 and 69 years of age. Results were astonishing to medical investigators: Men with a high intake of bioflavonoids had a 73 percent lower risk of stroke and heart attack!

The Harvard Medical School newsletter article concluded by naming those vitamin-P foods that best corresponded to each type of health problem. The simple table below helps us to illustrate this better.

<table>
<thead>
<tr>
<th>Heart Attacks/Heart Disease</th>
<th>Stroke</th>
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<tr>
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**Help for Varicose Veins.** Varicose veins afflict about 25 percent of the populations of industrialized nations; the ratio of women over men suffering from this disorder usually runs around 5 to 1. Those who are middle-aged or older are most often at highest risk for developing this disease of the venous system.
Varicose veins are twisted, swollen veins near the surface of the skin. Vein varicosity usually occurs when weak or defective valves distributed along the walls of the veins permit blood to flow backward instead of in a normal forward pattern; the accumulation of stagnant blood within a vein can also make this happen. Sometimes chronic obstruction of the veins may produce varicosity. Varicose veins generally appear in the legs, though they also occur within the anus, where they are known as hemorrhoids.

Typical symptoms include the usual enlarged, swollen, knotted clusters of purple veins. Sometimes swelling in the legs due to fluid accumulation in muscle tissue takes place. There may also be an aching or a sensation of heaviness in the legs. Sometimes the skin may itch directly over the affected veins. In more advanced cases, skin discoloration and ulcers on the inner aspect of the ankles may occur. Periodic fatigue is not unusual. Symptoms in women always seem to be worse during their menstrual periods.

For several decades now, a number of German doctors have routinely treated tens of thousands of cases of varicose veins with herbs rich in bioflavonoids. One of those who helped to pioneer this beneficial therapy was the late Rudolf Fritz Weiss, M. D. His medical training was highly unusual: He studied medicine and botany together at the University of Berlin and began his practice of internal medicine in 1922. In 1961 he retired from clinical practice and focused his efforts entirely on bringing folk herbal remedies into a more scientific and medical setting.

Two of his more notable accomplishments in this direction were the founding of a still-published medical journal, Zeitschrift für Phytotherapie and a wonderful medical text, Lehrbuch der Phytotherapie (Stuttgart: Hippokrates Verlag GmbH, 1974). For the more severe cases, Dr. Weiss preferred using intravenous injection of certain herbal extract preparations. But he wasn’t hesitant to recommend these same items used in tea or capsule form for less serious cases. The herbs he utilized are all rich in vitamin P factors and help to, as the put it, “tone up the vascular walls” for each vein so as to reduce most of the varicosity.

His three favorite herbs for treatment of venous system diseases like varicose veins were horse chestnut (not to be confused with edible sweet chestnut), yellow sweet clover, and (in the closing years of his medical practice) ginkgo biloba.

MEDICAL APPLICATION OF BIOFLAVONOIDS AND POLYPHENOLS

Allergy and asthma

The most studied and documented potency of bioflavonoids is that they inhibit allergic reactions (20-40). Khellin is a bioflavonoid extracted from the plant khella (Amni Visnaga L.). This extract is a really strong inhibitor of the histamine release and of the synthesis of leukotrienes (LTs). It also, prevents increased capillary permeability and acts as a mild bronchodilator. In asthmatic patients an imbalance between the leukotrienes (LTs) and prostaglandines (PGs) has been found to the advantage of the former.

In order to improve the broncho-dilatory (relaxing) effect of khellin, a whole series of synthetic compounds have been made. One of the more successful ones is disodium chromoglycate (Chromoline™) which has proved very efficient both in the prevention of the asthmatic attack, and of its severity. Carefully controlled clinical studies have verified the quoted therapeutic activities of Chromoline™. It is produced under various names depending on the manufacturer, and is considered presently to be the standard medication used in the additional treatment of asthmatic attacks, allergic rhinitis and allergic reactions of the gastrointestinal tract. The synthetic form of khellin, i.e, disodium chromoglycate exhibits the identical mechanism of action as the natural one: it inhibits calcium dependent ATP-ase (17, 25). The synthetic drug is much more expensive than the extract obtained from the khella plant, but all natural extracts have the same disadvantage, namely, they are difficult to standardize and even more difficult to patent for clinical application.

Histamine-release inhibitors

Fewtrell and Gomperts have in their researches used activated tissue mastocytes to which they added at first very low and then increasing con-
centrations of various bioflavonoids. They found that even the low concentrations of *quercetin, fisetin* and *miricetin* prevent the release of histamine, and that this activity increases parallel to the increase of dosage, i.e., their beneficial effect is dose-dependent. This property of bioflavonoids to prevent histamine release from the mast cells and basophilic granulocytes is mainly based on the inhibition of the earlier mentioned enzyme – the calcium dependent ATP-ase. The blockage (inhibition) of this enzyme impedes the calcium ion transport across the cell membrane, thus preventing the increase of intracellular calcium, necessary for the histamine release from the depot-granules (17, 36). Theoretically, this mechanism of action is much more superior to the mechanism of antihistamines, which is the blocking of the H1-receptors on the target cells to bind free (already released) histamine.

**Antimicrobial activity**

There is yet another area where bioflavonoids can be applied, and that is in combatting infectious disease, especially disease caused by viruses. Studies on animals and *in vitro* studies have given solid proof (evidence) of the anti-microbial protective action of bioflavonoids, but they have not yet been tested as a mono-therapy in the cure of infections in humans.

Numerous laboratory techniques and studies confirm the antiviral effect of many bioflavonoids. Beladi and associates (41) have studied the *in vitro* effect of several bioflavonoids: *quercetin, luteolin, morin, physetin, procyanidin*, and others on the following viruses: *herpes simplex, pseudorabies, parainfluenza, polyovirus and adenovirus* (41). Of all the compounds studied, *quercetin* proved to be the most effective. Vrijssen and colleagues using *in vitro* studies compared the effects of *quercetin, luteoline* and *2-methylquercetin* on the polyovirus (42). Their results also proved *quercetin* to be the most efficacious but it had to be protected from oxidation by *ascorbic acid* alias vitamin C to maintain its antiviral property. There are several other studies which demonstrate the strong antiviral activities of quite a number of bioflavonoids.

The biological mechanisms of bioflavonoid activity have not yet been fully revealed. As a possible mechanism of their anti-viral action – inhibition of viral protein synthesis and consequently, the viral replication is contemplated (43). There have also been some speculations indicating direct anti-viral activities (45). This direct anti-viral effect of the polyphenols is most likely based on their capability that under conditions of a high partial pressure of the oxygen, using the complex enzymatic system of the cells they exert a *protective cellular effect*, whereas the same mechanism *burns* (kills) the simple organisms. In other words under the same condition their action is *viricidal*. A much more fundamental action of bioflavonoids is in the stimulation of certain branches of the host’s immune response, to be precise, the activation of Thymus dependent cytotoxic (CD8+) lymphocytes (TCLs). This type of immunity is known as a *cell-mediated immunity* (CMI), playing a central role in protection against the *obligatory intracellular pathogens – viruses, fungi, chlamydia, mycobacterium tuberculosis, leprosy, and some parasites* (45).

Studies which have proved the protective activity of polyphenols against viruses *in vivo* are – as always when we want to extrapolate data from experimental studies and apply them on humans – of much greater importance. Veckenstedt and colleagues, researching into the effects of *quercetin and morine* on Mengo-virus induced encephalitis (the virus which causes inflammatory brain disease in mice), have found that oral application of both bioflavonoids resulted in a strong antiviral activity with 30-50% higher rate of survival among the treated animals. The effects were shown to be dose-dependent, (46). The effective doses of bioflavonoids were ranging 30 to 40 mg/kg BW/day which, in humans equals the doses of 2-3 g/ to the total BW /day. This amount of bioflavonoids equals to that which people consume on a sound diet by eating vegetables and fruit every day, therefore it cannot be considered as a mega-dose. Since the animals had been subjected to a massive viral infection (challenge study), those animals which were not given bioflavonoid protection after having been infected, died within two weeks, at the latest. In humans it is expected that lower doses of bioflavonoids may suffice, since in clinical conditions the viral infection is never as massive as under experimental conditions, and the period of latency is long. References (46, 48) give detailed...
data about studies, conducted on animals, which indicate that polyphenols and bioflavonoids definitely manifest an antiviral activity.

According to experimental data bioflavonoids also affect the human immunodeficiency virus (HIV, AIDS-virus). Namely, it has been proven that numerous flavonoids inhibit the enzyme named reverse transcriptase (RT) inherent to HIV, which is able to force the host’s DNA to surrender to the genetic information coded by the viral RNA (putting it plainly, to make DNA out of RNA). It is well-known that retro-(ONCO-RNA) viruses instead of DNA contain RNA and the enzyme reverse transcriptase which they use in the process of viral replication and the spreading of the infection. In a research carried out on reverse transcriptase (Apple and colleagues) it was found that quite small quantities of various flavonoids efficiently inhibit the enzyme (49). The remarkable fact is that the same researchers also noted that bioflavonoids, not only successfully inhibit reverse transcriptase in vitro, but can also inhibit retrovirus induced cancer-growth in infected animals. This result confirms that bioflavonoids effectively can block retroviral infections (49). Data obtained from the trial using a trihydroxylflavone called “baicalein” reveal that it is also a very powerful inhibitor of a number of different kinds of reverse-transcriptase enzymes, including the one inherent to HIV (50).

Further, there are pieces of evidence that polyphenols can increase the percentage of T-helper cells and at the same time lower the percentage of T-suppressor cells in the peripheral blood of humans. In a study conducted by Par and his colleagues, 14 patients with a chronic, active viral hepatitis underwent a cyanidine supplementation trial, which resulted in the already mentioned beneficial effect, i.e., the satisfactory quotient between T helper/T suppressor cells (70:30) (51). This capacity of polyphenols, that they can inhibit the reverse transcriptase activity and simultaneously improve the ratio between the subclasses of T cells in the peripheral blood, calls for further research into their potentials in the treatment of patients infected with HIV virus.

Clinical researches in the field of treatment of patients affected with viral infections have not yet been conducted. Literature has only couple of studies published on this topic, but both studies have used bioflavonoid together with vitamin C to which they are organically bound in nature (52, 53). In the latter study (53), for example, patients infected with virus herpes simplex (causing herpes labialis) were given either a complex bioflavonoid formula together with 600 mg vitamin C, or just a 600 mg vitamin C, or placebo (600 mg lactose), respectively. The results showed that the combination of bioflavonoids plus vitamin C was the most effective. It shortened the time-course of vesiculation from 9.7 days in the placebo group to 4.2 days in the treated group. Naturally, one could criticize this study and say that it did not show the viricidal activity of bioflavonoids since vitamin C, a proven viricidal agent was also present. Nevertheless, it is important to stress out that the bioflavonoid and vitamin C duo are naturally complementary; producing a synergistic effect within the body, since in nature they are also bound together. Nevertheless, it is necessary to conduct objective, double-blind cross-examinations exclusively with bioflavonoids, in order to obtain valid results concerning solitary actions of bioflavonoids.

In addition to the antiviral effect polyphenols and bioflavonoids affect bacteria and fungi, too. It has been known for a long time already that vegetarian foodstuff contain effective antibacterial materials which, in fact, during the last fifteen years or so, have been proved to be polyphenols (54). For example, from time immemorial nuns have been recommending cranberry (Lat. Vaccinium macrocarpon) as a curative for the infection of the urinary tract, although they had no knowledge of its active principles. Marwan and Nagel have recently documented that cranberry extract is effective against Pseudomonas fluorescens and Saccharomyces Bayanus, and what is even more important, they have revealed that the red pigments – proanthocyanins and flavonols – are the principal antimicrobial factors in that extract (55, 56). Apart from the already described mechanisms, bioflavonoids are partly metabolised in the gastrointestinal tract into certain organic acids such as phenyl-acetic and phenyl-propionic acid, which also can produce a strong anti-microbial activity against a whole range of various microorganisms. Similar effects have also been detected using a different class of flavonoid metabolite – the phenyl-gamma-valerolactons.
Conclusion

- There is already ample evidence for a prophylactic and/or therapeutic effect of natural biologically active and supplementary polyphenols and bioflavonoids in allergy, some ocular disturbances, one among them the diabetic cataracts, asthma, inflammation generally, infectious diseases, alcoholic hepatitis and other liver diseases, and cardiovascular diseases, as well.

- The interest for the investigations in the field of polyphenols and bioflavonoids is still alive, very much. One area of investigation, of scientific interest is neurology. Unusual flavonoid belonging to the subclass “biflavonoids” (*not to be confused with bioflavonoids!) – namely chrysin and amentoflavone- have been identified as ligands for benzodiazepine receptors. Additionally, administration of chrysin proved effective in blocking seizures (the tonic-clonic kind) showing, that chrysin is active not only in vitro, but also in vivo.

- It has also been shown, that bioflavonoids are effective against the toxic effects of some snake venoms, by inhibiting the hyaluronidases contained in the venom. Hyaluronidases are enzymes which break down hyaluronic acid, a major constituent of connective tissue. Studies in vivo discovered that bioflavonoid treatment increases the survival rate in animals injected with lethal doses of snake venom.

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