

Betalains, polyacetylenes and tocopherols as biocompoundactives: A concise review for enriching the bioactivity concept

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Abstract: Bioactive compound is “a compound which has the capability and the ability to interact with one or more component(s) of the living tissue by presenting a wide range of probable effects”. In a previous study; we discussed the bioactivity concepts and we used, for the first time, the term of “biocompoundactive” to more simplify the use of bioactive compound/component in relation to their physicochemical and biological properties (e.g. chemical structure, bioavailability...etc.). The aim of this work is to prove different concepts discussed about “bioactivity” by giving some chosen examples (betalains, polyacetylenes and tocopherols) that demonstrate different bioactivities of these biocompoundactives. Betalains, polyacetylenes and tocopherols are generally not categorized like the known classes of phytochemicals (phenolics, alkaloids, and terpenes), but exhibit important bioactivities such as antioxidant, antimicrobial, antifungal, anticancer, anti-inflammatory, neuroprotective and radioprotective properties... etc.

Keywords: Biocompoundactive, Bioactive Compound, Betalains, Polyacetylenes, Tocopherols, Phytochemicals, Food Components, Healthy Diet

1. Introduction

Bioactive compound is a compound which has the capability and the ability to interact with one or more component(s) of the living tissue by presenting a wide range of probable effects. These compounds are experiencing a growing interest in wide range of applications: geo-medicine, plant science, modern pharmacology, agrochemicals, cosmetics, food industry, nano-bio-science... etc. This is a very promising area in full development, which has resulted in research works more and more numerous, designed to diversify the resources of bioactive compounds and improve their salvage pathways or synthesis [1].

The majority of bioactive compounds belong to one of a number of families, each of which has particular structural characteristics arising from the way in which they are built up in nature (biosynthesis) [2]. Based on their biosynthetic origin, phytochemicals can be divided into several

categories: phenolics, alkaloids, steroids, terpenes, saponins, etc. [3, 4]

Natural products and secondary metabolites formed by living systems, notably from plant origin, have shown great potential in treating human diseases such as cancer, coronary heart diseases, diabetes and infectious diseases [5, 6]. Phytochemicals are natural and non-nutritive bioactive compounds produced by plants that act as protective agents against external stress and pathogenic attack [7]. They could also exhibit other bioactivities such as anti-mutagenic, anti-carcinogenic, antioxidant, antimicrobial, and anti-inflammatory properties [8].

In a previous study; we discussed the bioactivity concepts and we used, for the first time, the term of “biocompoundactive” to more simplify the use of bioactive compound in relation to their physicochemical and biological properties [1]. Here, we try to give some chosen examples to enrich the concepts already discussed, and this by:

(a) Betalains those are nitrogen compounds like alkaloids, but function as colorants replacing anthocyanins (flavonoids) in plants, and which have a significant bioactivity as described above. This example revealed the complexity of biocompounactives and their roles;

(b) Polyacetylenes that were considered undesirable in plant foods due to their toxicity, but now highlighted important biological activities. This is a good example to prove that the bioactivity includes negative and positive effects both in relation with physicochemical properties;

(c) Tocols that constitute a subfamily of natural vitamin E which was excluded, as vitamin, from bioactive compounds by some authors [9, 10]. Here, we prove the other points of view [11, 12] by demonstrating different bioactivities in relation to their physicochemical and biological properties.

2. Betalains

Betalains are a class of water-soluble nitrogen-containing pigments derived from tyrosine that are found only in a limited number of plant lineages, including the order of Caryophyllales (15 families and 8600 species) where they replace anthocyanin pigments, and in some fungi such as basidiomycetes [13, 14].

Some betalains have a stronger coloring capacity than anthocyanins. Interestingly anthocyanins and betalains are mutually exclusive and never have both been found in the same plant. Betalains include betacyanins (purplish red) and betaxanthins (yellow-orange) [15-19].

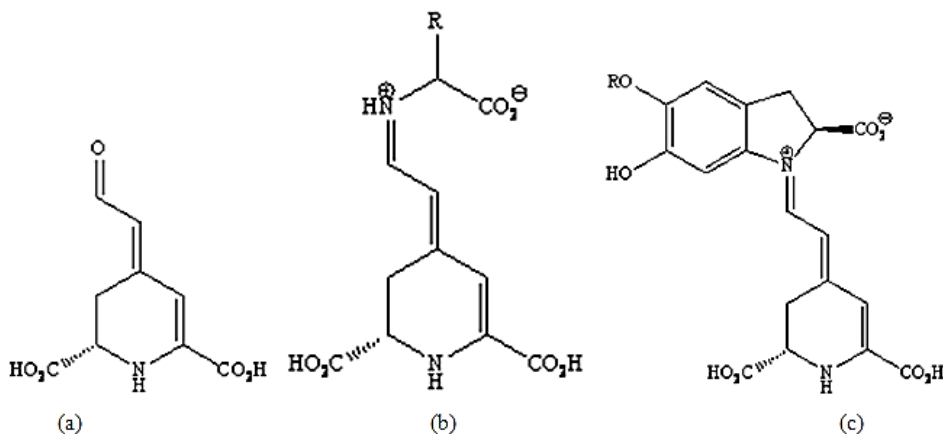


Figure 1. General structures of betalains [13, 39-41]. (a) Betalamic acid. (b) Betaxanthins: R = side chain of the amino acid or amine. (c) Betacyanins: R = H (bethanidine); R = Glucose (bethanine).

2.3. Uses and Bioactivity of Betalains

Like other phytochemicals (anthocyanins, carotenoids and chlorophylls), betalains are used as coloring substances in the low acid food processing because of their wide pH stability (pH 3-7), or in fruit preparations, dairy products, ice creams, confectionery, soups, sauces, beverages and drinks [14, 17-19, 23, 32, 42], and to adjust or correct a color change or discoloration of the food during processing or storage [43].

Betalains are also reported for their antiradical properties

2.1. Sources of Betalains

These compounds accumulate in flowers, fruits and vegetative plant tissues [13, 20] where they play important physiological roles, such as protection against damage caused by injury and bacterial infiltration, optical attraction for pollination and seed dispersal, and protection against UV radiation [21].

The main edible sources known of betalains are red beet [22-26], prickly pear (cactus) [27, 28], chard [29], amaranth grains or leaves [30], pitaya (dragon fruit) [25, 31-33], ulluco tubers (*Ullucus tuberosus*) [34] and djulis (*Chenopodium fromosanum*) a native cereal in Taiwan [19, 35-37].

2.2. Chemical Structure of Betalains

Betalains are not chemically bonded to anthocyanins (or flavonoids in full). Each betalain is a glycoside which comprises a sugar and a colored portion. The 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. 1) [19, 38].

The betacyanins contain a cyclo-3,4-dihydroxyphenylalanine residue (cyclo-DOPA), while betaxanthins contain various amino acids and amines with various conjugates bethanidine (acylglucosides and glycosides) [13].

and exhibit strong antioxidant activity [14, 27, 31, and 44]. They may also contribute to anti-inflammatory activities [45], in the inhibition of lipid oxidation and peroxidation [22, 46] and have anticancer effects against human liver cells [47].

3. Polyacetylenes

Polyacetylenes are a group of bioactive compounds widely distributed in the Apiaceae and Araliaceae families [48]. These are examples of bioactive secondary

metabolites that were previously considered undesirable in plant foods due to their toxicity [49].

Polyacetylenes are considered defensive compounds within the plant, and many studies show their regulation in response to abiotic and biotic stress [50]. Some of these secondary plant compounds may function as free radical scavengers and osmo-protective [51].

3.1. Sources of Polyacetylenes

Over 2000 polyacetylenes are known, among which the majority were isolated from higher plants [52]. These phytochemicals are mainly found in vegetables of the Apiaceae family including carrots, celery, fennel, parsley and parsnip, all of which contain small amounts of the group bioactive aliphatic C17-polyacetylenes [53-56].

In carrots, for example, profile polyacetylenes contains three main polyacetylenes: falcarinol the falcarindiol and falcarindiol-3-acetate, among which the first two received much attention (Fig. 2) [53, 55, 57, and 58]. The falcarindiol has been identified as the main responsible for the bitter flavor compound in fresh and stored carrots [49, 55, 59, and 60]. For parsley and celery, polyacetylenes which have been elucidated are falcarindiol, 8-O-methylfalcarindiol and panaxydiol, while falcarinol was not detected in parsley but exists in celery [53].

3.2. Chemical Structure of Polyacetylenes

Acetylenic natural products include all compounds with a carbon-carbon triple bond or alkynyl functional group. While not always technically accurate, the term “polyacetylenes” is often used interchangeably to describe this class of natural products, although they are not polymers and many precursors and metabolites contain only a single acetylenic bond. These compounds tend to be unstable, succumbing either to oxidative, photolytic, or pH-dependent decomposition, which originally provided substantial challenges for their isolation and characterization [60].

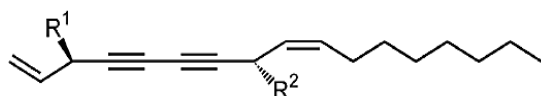


Figure 2. Structure of aliphatic polyacetylene [52, 54]. *Falcarindiol*: $R1 = R2 = OH$ and *Falcarinol*: $R1 = OH$, $R2 = H$

3.3. Bioactivity of Polyacetylenes

Slight variations in polyacetylene structure result in extreme variations in biological activities. [61]. Recent studies have highlighted important biological activities both in cell lines and in small animal studies, such as antibacterial, antifungal, antiallergenic, anticancer, anti-inflammatory and reduces platelet aggregation [52-54, 58, 62-69]. These effects represent pharmacologically useful properties by which polyacetylenes can be used to develop antibiotics in addition to their positive effects on human health [52].

Since the highlighting of possible biological relevance of polyacetylenes, studies were conducted to evaluate the effect of different factors on the levels of polyacetylenes. The majority of these studies have examined the effects of storage and conventional treatment on the levels of these biocompoundactives [58, 63, 70-73], and the influence of genotype, some extrinsic factors and spatial tissue distribution in these bioactive compounds [49, 53, 57, 58, 63, 66, 74, 75]. For example, it was observed that peeled carrots contain up to 50% less faltarindiol [66].

4. Tocols

Tocols include two groups of compounds: tocopherols and tocotrienols, which are also collectively known as the tocochromanols [76-78]. They are lipid-soluble molecules that belong to the group of vitamin E compounds and are essential in the human diet and health [76, 79]. The tocolds (Vitamin E) are synthesized exclusively by photosynthetic eukaryotic and other photosynthetic organisms, such as cyanobacteria [76, 80].

Tocols consist of four members each of tocopherols and tocotrienols [81]. Vitamin E is a generic term for the eight tocols. These include four tocopherols (α , β , γ and δ -tocopherol) and four tocotrienols (α , β , γ and δ -tocotrienols) (Figure 3) [77, 81-85]. The most abundant and active form of vitamin E isoforms *in vivo* is α -tocopherol; but recently, the role of other forms received renewed attention [84].

4.1. Sources of Tocols

Tocols are natural antioxidants found mainly in vegetable oils, nuts, peanuts, almonds, olives, and beans; with relatively low levels in fruits and vegetables [86-90] as peppers, peas, cabbage, kiwi, avocado, plums and berries [91-94]. Generally, leaves and other green parts of plants are rich in tocopherols, while mostly tocotrienols are present in the fraction of the bran and germ of cereals (such as barley, wheat, maize and oat) [79, 95, 96].

Even when tocopherols and tocotrienols are present in a plant, they are not necessarily found in the same tissue, which suggests different functions for tocopherols and tocotrienols in plants. Tocopherols are ubiquitously present in all plants and in almost all plant parts, while tocotrienols are only present in a range of unrelated plant groups and are almost exclusively found in seeds and fruits [76, 97-100].

4.2. Chemical Structure of Tocols

Tocopherols and tocotrienols are lipid-soluble bioactive compounds that contain a phenolic-chromanol ring (chroman head group) linked to an isoprenoid side chain with 15-carbon, which is either saturated (tocopherols) or unsaturated (tocotrienols). Greek letters α , β , γ , and δ are added as prefixes to denote the number and positions of methyl groups linked to the chroman head (Figure 3) [76, 80, 101].

In addition, the phytol side chain of the tocopherols has three chiral centers at positions 2, 4', and 8', which can be either in the R- or S-conformation, giving rise to eight different stereoisomers (RRR, RSR, RRS, RSS, SRR, SSR, SRS, and SSS) for each tocopherol. RRR- α -tocopherol has the highest bioactivity and is also the most abundant in human blood and tissues [80-82, 101-103]. Tocotrienols possess only the chiral stereocenter at C-2 and naturally occurring tocotrienols exclusively possess the (2R,3'E,7'E) configuration [104, 105].

The individual stereoisomers are not interconvertible in the human body [106]. The chirality of these molecules should be taken into consideration when we have to evaluate the activity of a compound in biological studies or clinical trials. If one enantiomer has the desired effect on the body, another may have no effect or an adverse effect [81, 107].

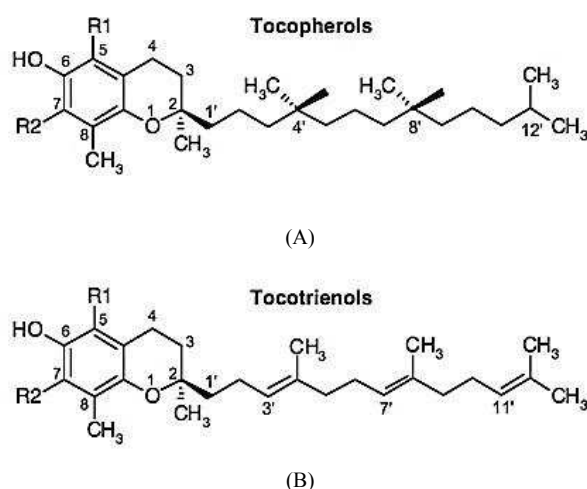


Figure 3. Structures of tocopherols (A) and tocotrienols (B)[108-110].

4.3. Bioactivity of Tocols

This unique structure enables the vitamin E to perform various functions, especially anti-oxidative, with greater efficacy [83]. Some evidence suggests that the potency of the antioxidant effects, and bioactivity in general, may differ between natural or synthetic source of tocopherols (vitamin E) [80, 82]. The excellent antioxidant activity of the tocopherols is mainly due to the capacity of their heterocyclic chromanol ring system to donate the phenolic hydrogen to lipid-free radicals [76].

Recently, other biological activities of Vitamin E, assumed to be unrelated to their antioxidant properties, have been reported. These include roles in cell signaling, gene expression, immune response and apoptosis [82, 83, 101, 111], in addition to reducing the risk of cardiovascular disease, cancer, and neurodegenerative diseases such as Alzheimer's disease [76, 77, 82, 112, 113]. However, there is some controversy about the optimum range of vitamin E intake for health benefits [88].

From a health point of view, at the moment there is a great interest in the natural forms of tocopherols, because they are considered promising compounds able to maintain a

healthy cardiovascular system and satisfactory blood cholesterol levels [80]. Yoshida Y. *et al.* (2007) [84] summarized the differences among α , β , γ and δ -tocopherols and tocotrienols; specifically regarding their radical-scavenging efficacies and their protective effects against cell toxicity, in particular for the prevention and treatment of disease.

Current developments in vitamin E research clearly indicate that members of the vitamin E family are not redundant with respect to their biological functions. As illustration, the tocotrienol subfamily of natural vitamin E possesses powerful neuroprotective, anticancer, and cholesterol-lowering properties that are often not exhibited by tocopherols [80, 109, and 114].

In tocotrienols, indications show that the different isomers of tocotrienols exhibit distinct activities and have various applications: α -tocotrienol was highly effective in the brain for cerebral ischemia, and γ and δ -tocotrienol exhibited strong anticancer activities, with radioprotective properties for γ -tocotrienol [115].

For example, the proliferation of human breast cancer cell lines was suppressed by tocotrienols. The higher inhibitory potency of tocotrienols, as compared with tocopherols, was attributed to a preferential uptake of tocotrienols by these cells. In all cases, γ and δ -tocotrienol exert the highest inhibitory effects [82, 109].

As for tocopherols, and addition of their antioxidant functions that prevent the propagation of free radical reactions, they have recently attracted much attention clinically because of their potential to be very useful drugs, and have been widely studied for their anti-aging, anticancer, anti-atherosclerotic, anti-carcinogenesis, and anti-allergic effects [83, 108]. However, the molecular basis of the action of tocopherols is still an enigma. The α -tocopherol appears to be involved in gene regulation, while the γ -tocopherol appears to be very effective in the prevention of cancer related processes [82]. It is also shown that in food, γ and δ -tocopherol are more potent antioxidants than α -tocopherol [116]. Although, β -tocopherol has similar antioxidant properties as α -tocopherol. The presence or absence of the methyl group at position 5 in the chromanol structure determines the mode of action of tocopherols [82].

Described effects of α -tocopherol are undoubtedly anti-inflammatory and should, in consequence, be anti-atherosclerotic and anti-carcinogenic [82, 116]. In cultured cells, δ -tocopherol is the most toxic tocopherol. This toxicity has been associated with the induction of apoptosis [82]. In addition, recent epidemiological, experimental and mechanistic evidence suggests that γ -tocopherol may be a more potent cancer chemopreventive agent than α -tocopherol [85].

In another side of interactions, biocatalysts bacteria are expected to convert exogenous lipophilic food ingredients to their glycosides soluble in water. In tocopherols case for example, this characteristic reaction (glycosylation) has converted α - and δ -tocopherols to tocopheryl glycosides, thus improving their bioavailability and pharmacological

properties as food additives having an effective anti-allergic activity [108].

It should be noted, at the end, there are many literature data having positive or negative results on the same biological activity [80], which often opens debates on topics, and sometimes debates on interpretation of the same activity proved positive or negative.

5. Conclusion

In the end of this concise review, we reaffirm that a biocompounactive:

- a) may be of natural or synthetic origin ;
- b) may present a wide range of positive and/or negative effects in one or more component(s) of living tissue; and this, according to several factors, which are usually linked to three major changes:
 - i. Biocompounactive itself: we confirm here that slight variations in chemical structure result in extreme variations in biological activities.
 - ii. Subject involved in the biocompounactive use, and
 - iii. Manner of using the biocompounactive (dosage, alone or mix ... etc.).
- c) The bioactivity can manifest whatever the natural source of bioactive compound: food or non-food, integrated into an essential nutrient or not. But once such compounds provoke a biological activity, we consider them as non-essential [1].

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