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The Preventive Approach of Biocompounactives (3): A Review in Recent Advances in Cereals and Some Animal-Based Foods

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Abstract: Biocompounactives are compounds which have 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. They contain chemicals that are found in small quantities in plants and certain foods (such as fruits, vegetables, nuts, oils and whole grains); and they have actions in the body that can promote good health. All scientific studies confirm that a varied and balanced diet is a factor in protection against cancer, cardiovascular disease (CVD), diabetes, osteoporosis, obesity and high cholesterol. The philosophy that food can be a health promoting beyond its nutritional value is gaining acceptance in the public arena and among the scientific community as mounting research links diet/food components to disease prevention and treatment. In this work, we complete the discussion of the preventive approach of biocompounactives, and opportunities that present bioactivity of cereals and some animal-based foods phytochemicals to prevent many chronic diseases. As well, we finish discussing some challenges related to the evaluation of biological activity by some studies presenting important limitations that must be considered before using data types in the interpretation and extrapolation of phytochemicals bioactivities to Humans.

Keywords: Biocompounactives, Bioactive Compound, Phytochemicals, Cereals, Animal-Based Foods, Functional Foods, Healthy Diet, Nutraceuticals

1. Introduction

Biocompounactives are compounds which have 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 [1-4].

The importance attached to benefits of food on health has never been so high before [5]. Indeed, over the past two decades, there has been a growing interest in the potential benefits of natural compounds on human health [6], and if we except the genetic, ecological, physiological and botanical studies on food; research on the bioactive potential has experienced a veritable boom during the first decade of the twenty-first century, and took an accelerated rates over the beginning of the second decade, in a way that the research carried out during the past five years (2010-2014) on the majority of foods are equal or superior to the work done during all the previous decade (2000-2009) [3-4].

Noting that prevention is a more effective strategy than is treatment of chronic diseases [7], the philosophy that food can be health promoting beyond its nutritional value is gaining acceptance within the public arena and among the scientific community as mounting research links diet/food components to disease prevention and treatment [5, 8].

Interest in food composition has expanded beyond the nutrients to include bioactive compounds consumed in the traditional foods, which may help to prevent many chronic diseases that can coexist with malnutrition and undernutrition [9]. Recent trends in the functional food market suggest that products with multiple health benefits become more and more popular [10] and dietary bioactive compounds have become another quality indication [11].

In this work, we complete the discussion of preventive approach of biocompounactives (part 3), and opportunities that present bioactivity of cereals and some animal-based foods phytochemicals to prevent many chronic diseases. As well, we finish discussing of some challenges that face the good investment of biocompounactives.

2. Food Biocompounactives Opportunities

The concept of a healthy diet is considered an aspect of good and healthy practices. The observations in social behavior and archaeological discoveries lead researchers to notice that the longevity and healthy life, away from the high incidence of myocardial infarction and cancer, are caused by good habits of feeding [12].

Biocompounactives are members of a large class of organic molecules that are widely distributed in the plant kingdom and, as such, are an integral part of the daily diet of humans [13]. They are non-essential natural ingredients in, or derived from, plant, animal or marine sources, which have the ability to modulate biochemical, physiological and metabolic processes in the human body, while exerting beneficial effects beyond basic nutritional functions [14-16].

Until 2013, it was estimated that more than 8000 phytochemicals have been identified in foods [17]. All these bioactive food components are mostly found in whole grains, fruits and vegetables [18, 19], but a large percentage still remain unknown and need to be identified before we can fully understand the health benefits of phytochemicals in whole foods [18].

The phytochemicals may be classified into carotenoids, phenolic compounds, alkaloids, nitrogen compounds and organosulfur compounds. But the most studied of these biocompounactives are phenolics and carotenoids [20].

Recent investigations show that food biomolecules that contribute to human health can be found particularly in glycosylated, esterified, thiolated or hydroxy forms. These bioactive compounds display their health benefits in metabolic activity associated with several diseases [19].

So the important role that biocompounactives can have in health is related to the intake of these compounds, which, in turn, strongly linked to the high consumption of fruits, vegetables and unrefined grains [21].

Table 1 and 2 constitutes, respectively, a review on major biocompounactives and bioactivities studied for cereals and some animal-based foods that present enormous opportunities for human health.

Table 1. *Bioactivity of dietary biocompounactives (Cereals).*

Cereals	Bioactivities studied	Biocompounactives	References
Barley *Hordeum sp.* (Poaceae)	Inhibit metastasis of colon cancer *in vivo* Antiproliferative activity Inhibit oxidative DNA damage Reduce diabetes risk Neuroprotective Effects & Immunomodulatory Protecting human brain cells Cholesterol-lowering effect Reduce the risk of developing diabetes type 2	Flavanols Tocols (tocotrienols) Soluble dietary fiber (β-glucans & arabinoxylans) Phytosterols Alkylresorcinols Lunasin	[22-47]
Corn / Maize *Zea mays* (Poaceae)	Induce apoptosis of liver tumors Protection against colon cancer Antimutagenic activity Protection against DNA damage in certain blood cells Lower risk of macular degeneration and cataracts Reduction of blood cholesterol	Carotenoids (Lutein & Zeaxanthin) Flavonoids (cyaniding, pelargonidin) γ-tocopherol Ferulic acid Phytosterols	[48-67]
Oat *Avena sativa L.* (Poaceae)	Normalize intestinal transit Normalize blood glucose and insulin Prevention of type 2 diabetes	Polyphenols Soluble fiber (beta-glucan) Insoluble fibers	[22, 68-74]
Rice *Oryza sp.* (Poaceae)	Induce apoptosis of breast cancer cells and several cell tumors in humans Prevent breast and colon cancer in humans Reduce the incidence of oral and colorectal cancers Inhibit cancer cell invasion & antimutagenic activity Antitumor properties *in vitro* and in animals Control diabetes type 2 Lower blood pressure Neuroprotective, anti-inflammatory, anti-atherosclerosis & hypocholesterolemic effects Prevention of gastric ulcers in animals Treat mild to moderate diarrhea	Flavonoids : Anthocyanins (cyanidins, malvidin, peonidin & pelargonidin) Alkaloids (oryzadine) α-Tocopherol, α- and β-tocotrienol Ferulic acid & coumaric acid Oryzanols / Tricin / Lectins Soluble fiber	[30, 75-113]

Cereals	Bioactivities studied	Biocompounactives	References
Rye *Secale cereale L.* (Poaceae)	Preventing breast, skin and colon Reduce the risk of cardiovascular disease in men Reduce the risk of heart attack and stroke Control diabetes type 2 Prevent oxidation of LDL cholesterol	Phenolic acids Flavonoids (isoflavonoids) Carotenoids (lutein & β-cryptoxanthin) Tocopherols Lignans enterolactone Alk(en)ylrésorcinoles Soluble fiber (β-glucans & arabinoxylans) Lunasin	[114-139]
Wheat *Triticum sp.* (Poaceae)	Potential antioxidant & anti-carcinogenic Inhibit human LDL Protection against cardiovascular disease, diabetes & obesity Maintain proper bowel function	Alkylresorcinols insoluble fibers Phytosterols & Polycasanols	[23, 24, 114, 140-155]

It remains to be noted that the major health role of cereals biocompounactives is linked to a number of factors like other foods. These phytochemicals are mainly found in whole grain and unrefined cereals [21, 156] with a different distribution among species, and among parts or tissues of the same plant.

Generally, the content of phytochemicals in foods can be influenced by variety, environment and conditions of growth, maturity stages and harvesting factors [157-160], but little information is available on the influence of cultivation factors or genotype [161], while the impact of harvesting techniques and storage phytochemicals began to be explored in relatively recently [162]. The most studies on the application of food phytochemicals are limited to the examination of their bioactive efficiency [163].

For tocols (e.g.), tocopherols are ubiquitous in all plants and in almost all the green parts of the plant, while tocotrienols are present only in a range of independent groups of plants, and are found almost exclusively in seeds and fruits [164-168] and especially in the fraction of the bran and germ of cereals [169-171], which suggests different functions for tocopherols and tocotrienols in plants, and consequently, different probable bioactivities.

Table 2. *Bioactivity of dietary biocompounactives (Animal-based foods).*

Animal-Based Foods	Bioactivities studied	Biocompounactives	References
Egg	Lower breast cancer risk in perimenopausal women Build and restore human somatic cells Prevent macular degeneration related to age Improve cognitive function Enhance the immune activity of leukocytes Activities: antibacterial, antiviral, anti-hypertensive & anti-inflammatory	Carotenoids (lutein & zeaxanthin) Choline Ovotransferrin	[185-199]
Honey	Anti-proliferative and apoptotic effects Protection against breast cancer Solve problems: cardiovascular, glycemic & gastrointestinal Inhibit about 60 species of bacteria Activities: antiviral, antifungal & anti-inflammatory	Flavonoids (apigenin, Pinocembrin, kaempferol, quercétrine, hesperidin, rutin & pinostrobine) Phenolic acids Tocopherols Vitamin C Fibers	[40, 200-221]
Milk	Reduce cardiovascular risk Immunomodulator Influence nerve networks Antitumor properties Anti-inflammatory, Anti-hypertensive & Antimicrobial activities	Lactoferrin α-lactalbumin & α-casein β-lactoglobulin β-carotene Sphingomyelin	[222-242]
Fish Shellfish	Reduce the risk of Alzheimer's disease Good immune, circulatory and hormonal functions Reduce the incidence of arthritis Activities: antimicrobial, anti-inflammatory & anti-cancer	Carotenoids (Astaxanthin) Omega-3 fatty acids: Eicosapentaenoic acid (EPA) & Docosahexaenoic acid (DHA) Sterols Complete proteins	[243-265]

Another example is that of lignans, which are present in a long range of plants of different families (more than 55 families) [172, 173], and in which the total content of lignans varies between cereal species, as well as in same species based on genetic differences and environmental conditions [174]. Rye has a high content of plant lignans among cereals [128, 175, 176]. These biocompounactives have beneficial biological effects [177, 178]. They have been suggested to induce a wide range of biological effects such as antioxidant, antitumor, antiviral, antibacterial, insecticidal, fungistatic, estrogenic and anti-estrogenic and protect against coronary heart disease [128, 173, 179-181], diabetes [182, 183] and recently an activity against HIV-1 replication *in vitro* [184].

3. Challenges of the Preventive Approach of Biocompounactives

Biocompounactives contain chemicals that are found in small quantities in plants and certain foods (such as fruits, vegetables, nuts, oils and whole grains), they have actions in the body that can promote good health [156].

The dose or the amount of food needed to trigger a clinically apparent reaction generally varies between individuals and even in the same individual over time. It also depends on metabolic differences, the concomitant use of drugs, the freshness of food and their preparation [266].

It is true that many phytochemicals such as polyphenols, carotenoids and organosulfur and nitrogen compounds, are thought to be involved in the prevention and treatment of many diseases, including some cancers, cardiovascular diseases, diabetes , degenerative diseases, inflammation, infections, psychotic diseases, ulcers, macular degeneration, ... etc. [267-269]. But, how manifest this mutual interaction between the different biocompounactives and biological systems? and what are the main factors that can affect the physicochemical properties of bioactive compounds in biological systems?

The diversity and complexity of biocompounactives, alone, make the study of all these compounds and understanding their mechanisms of action a very difficult mission. While many critics emerge to highlight, and draw attention to, some details relating to the study of bioactive compounds [4].

The key question is whether a purified phytochemical has the same health benefits as a whole food or a mixture of food where the phytochemical is present. Liu RH (2003) proposes that cumulative and synergistic effects of phytochemicals are responsible for their powerful antioxidant and anticancer activities, and the benefit of a diet is attributed to the complex mixture of phytochemicals found in whole foods [7].

Besides that most studies are conducted with isolated bioactive components, and in addition to take into consideration the possible synergistic effect produced by various bioactive compounds; one must keep in mind that most of the studies are performed *in vitro* or *in vivo* in cell lines or biological models, which means that the concentration used is higher than is actually present in the sources of these compounds [270, 271].

So, the major problem for evaluating the biological activity is that these studies present many challenges in the interpretation and extrapolation to humans [4]. Indeed, there are important limitations that must be considered before using data types to support activities of some phytochemicals that “promote health” and interpreting an experiment to prove the effectiveness of a product [270]. These limits include observational and epidemiological studies, and research through the use of cell lines and animal models [4, 270].

3.1. Observational and Epidemiological Studies

There are two main types of observational and epidemiological studies: retrospective case-control studies and prospective cohort studies [272-274]. Both types of studies depend on food assessment through, for example, food frequency questionnaires that depend on accurate recall of the diet, which is a challenge in itself. Epidemiological and observational studies suffer from two major problems [270]:

- First, they can provide a relative estimate, as opposed to absolute risk, which can give a misleading impression of health benefits.

- Second, the choice of the control group is complex and difficult, especially as diets are often highly correlated with other lifestyles, attributes, and socioeconomic status. Other confounding factors may influence and complexing results obtained, leading to difficulties in the interpretation of epidemiological studies.

If we take the example cited of lignans; several epidemiological studies have been conducted on associations between concentrations of enterolignans in biological fluids (blood, urine, semen, prostatic fluid), and chronic disease risk [179, 275, 276]. High concentrations of serum enterolactones were associated with a reduced risk of some cancers (breast, ovarian, endometrial, thyroid, prostate, glioma, stomach) and cardiovascular diseases [277-282]. But also several studies found no association or totally gave conflicting results, pointing out, for example, the increase in breast cancer risk with high consumption of secoisolariciresinol and matairesinol [277]. This situation has sparked debate on the role of enterolactones [283].

In contrast, and further epidemiological and observational studies used to determine priorities for public health through scientific methods by pursuing epidemiological transitions and their propagation; each study method present, beside its drawbacks, many advantages which these studies appear effective. The practical value of produce quick results, or study rare outcomes with minimal funding may outweigh the limitations. In addition, there is a permanent development of scientific formulas to improve the efficiency of epidemiological studies, and find new study designs as alternatives less affected by methodological limitations [273, 284-286].

Thus, to provide convincing evidence of the promotional activity of certain chemicals, epidemiological data are often supplemented by findings from experimental studies on cellular and animal models. However, these studies present many challenges in the interpretation and extrapolation to humans [270].

3.2. Cell Cultures

Recall that the compounds in the systemic circulation, to which the cells are exposed, are different from those obtained directly from plant and wherein cellular models are frequently exposed *in vitro* [4]; there are also many practical issues, such as maintaining the conditions and modeling appropriate environment *in vitro* exposure of bioactive compounds, including those that are lipophilic.

The characteristics of the cell culture technique can also affect the representativeness of the cells response as is the situation *in vivo*. This is because the cells in culture are not maintained under hypoxic conditions and are cultured in the absence of blood circulation of origin, which supports the growth but also major circulating factors such as molecules signaling and hormones. In addition, the intrinsic characteristics of the cells culture can also be problematic in the understanding of the bioactivity. These cells generally exhibit significant changes in physiological and biological properties, such as loss of contact inhibition, and alterations in biochemical functions related to cell cycle checkpoints (e.g. the ability to proliferate indefinitely). Further, a homogeneous type of cell culture is very distant from the *in vivo* situation, where the original tissue exists in the presence of several other types of neighboring cells and cooperates with them through paracrine signaling [270].

But from another point of view, the cellular models offer an attractive and ethics alternative of animal experimentation for the initial efficacy and mechanistic studies [287-290]:

- They can provide an indication of the biological activity of the phytochemical in question, which can be used to design experiments on animals with the smallest number of animals needed to test hypotheses about the bioactivity.
- The main advantage of using *in vitro* cell models is practical convenience, such as ease of cultivation, their relatively low cost, moderate performance capabilities, and the existence of a wide selection of cell lines which can be used for different experiments. Moreover, it is relatively easy to modify gene expression to test specific hypotheses about the mechanisms of action of phytochemicals. These are particularly relevant experience for the initial studies on the understanding of disease prevention mechanisms by plant products.
- Culture of homogeneous cell lines isolated from different tissues offers the simplicity and the ability to observe the effects of dietary factors in well-defined and well-controlled environments. This allows better reproducibility of responses within an experiment and in replication between experiments.

Taking again the example of tocols, the study of breast cancer proliferation conducted on cell lines showed high inhibitory activity of tocotrienols in comparison with the tocopherols, whose γ- and δ-tocotrienol exert highest inhibitor effects. These results were attributed to preferential absorption of tocotrienols by these cells [2, 291, 292].

One method to avoid problems caused by the absence of a representative microenvironment is to make the cultivation of whole tissues *ex vivo* by organ/tissue culture. Culturing member maintains the structural and functional characteristics of the biological tissue of interest *in vivo*, which overcomes the single homogeneous cell culture limitations. However, the tissues show a very short life and are therefore not suitable for longer experiments. The availability of the tissue is also a problem that prevents their use in a medium for analysis of biological effectiveness high throughput. Nevertheless, they can be useful for understanding the biochemical processes in response to plant secondary metabolites [270].

3.3. Animal Models

Although animal models in prevention studies are chosen because they have similar characteristics to the illness of the survey; the main limitation is that they never have identical morphological, physiological or biochemical characteristics. In addition, differences in the development of the immune system, activation and response to the challenge between rodents and humans will inevitably affect the translation of the replies to humans. For example, the mouse model of colon cancer APCmin, widely used in cancer prevention studies, differs of Human that tumors are frequently found in the small intestine, which is rare in humans, as opposed to the colon itself. Another important limitation of studies in animal models, particularly relevant to the nutritional research, is the difference between human and rodents in the absorption and metabolism of phytochemicals, because of the difference in the speed of the bloodstream proportionally to the organs and important differences in the quantity and characteristics of the substrate of some CYP (Cytochrome P450). For example, after ingestion, small animals have faster gastric emptying, which affects absorption (10min in rodents against 1h in the fasting state in humans), and therefore makes the identification of human equivalent dose from a study on animal models a challenge [270].

In contrast, a wide variety of animal models is used to attempt to recapitulate human disease. Indeed, these models have several advantages, which the principal are [293-297]:

- The high degree of orthology between models and humans. For example, the proportion of orthologous genes between mouse and a single identifiable ortholog in the human genome is about 80%, which makes the mouse an ideal model for studying environmental and genetic manipulation rarely feasible in humans.
- The small size and the short life cycle of some models make them loans at a rapid breeding, and, therefore, the possibility of numerous studies in a relatively short period. Preclinical experiments on animal models can thus be performed in relatively short periods, allowing the chronic study of the response of a disease to dietary manipulation and provides invaluable pharmacological, toxicological and biological information that may predict the clinical efficacy of biocompounactives.
- Genetic homogeneity between the models and the lack of influence of variable environmental factors during the experiments also facilitate studies. In addition, it is possible to perform a complete analysis of disease response by proteomic, transcriptomic and metabolomic analysis, crucially on pre- and post-mortem at a time. This analyzes made models a precious tool in deciphering the molecular mechanisms involved in the response to phytochemicals.

Polyacetylenes are examples of bioactive metabolites that were previously considered undesirable in plant foods due to their toxicity, but thanks to recent studies conducted both in cell lines and in animal models; these biocompounactives have showed important biological activities, such as antibacterial, antifungal, antiallergenic, anticancer, anti-inflammatory and reduces platelet aggregation. These effects represent pharmacologically useful properties by which polyacetylenes can be used to develop antibiotics in addition to their positive effects on human health [2].

4. Conclusion

All scientific studies confirm that a varied and balanced diet, with minimal physical activity, is factor of protection against cancer, cardiovascular disease, osteoporosis, diabetes, obesity and high cholesterol. True that these diseases do not depend exclusively on food, they are also influenced by genetic factors, but if we cannot choose our ancestors, we can choose our food and organize our lifestyle [298]!

In the first part of this review, we have presented opportunities that contain some most common vegetables and legumes, with discussion of challenges relating to (i) radical reversal dietary habits and how to provide science to the public, (ii) methods of food processing that may affect the content, activity and bioavailability of biocompounactives in foods, and (iii) allergic reactions of some food-borne phytochemicals that are responsible for a variety of symptoms and disorders in human body [3].

In the second part, we focused on studies that have been conducted on biocompounactives of common fruits, and opportunities that present bioactivity of these phytochemicals to prevent many chronic diseases. As well, emphasis was placed on some challenges that face the good investment of biocompounactives, especially bioavailability and bioefficacy; with discussion of some improvement approaches for these factors, like (i) molecular modeling, (ii) nanotechnologies and (iii) biocatalysts [4].

In this last part, we completed the discussion of preventive approach of biocompounactives and opportunities that present bioactivity of cereals and some animal-based foods phytochemicals to prevent many diseases; and we finished discussing some challenges related to the evaluation of biological activity by (i) observational and epidemiological studies, (ii) cell cultures and (iii) animal models. These studies present important limitations that must be considered before using data types in the interpretation and extrapolation of phytochemicals bioactivities to humans.

Despite challenges described above, different studies have very important benefits. But in all cases, significant efforts are needed to increase the number of clinical studies which are still limited, and, therefore, provide irrefutable evidence of the benefits of bioactive compounds in humans [299].

Experimental studies in humans are an important link between the epidemiological studies and studies in cell culture and animal model systems. They are based on intermediate parameters related to the risk of disease using biological markers that also contribute to providing an overview of mechanisms of action of bioactive constituents in humans. At the same time, these studies are, in turn, limited by the sensitivity and specificity of these biomarkers, access to biological samples, and the logistics of conducting human studies [300].

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