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Science and claims of the arena of food bioactives: comparison of drugs, nutrients, supplements, and nutraceuticals

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The scientific community and lay press are participating in a heated debate over the usefulness of food bioactives when used as dietary supplements. This debate often ignores hard scientific evidence and the outcomes of proper research in either direction. Some propose that health claims should be awarded based on classic pharmacological parameters of efficacy and safety. Others suggest that a botanical history of their safe use and basic biological evidence in support of their effects should suffice to allow their marketing. The current regulatory impasse does not help solve this conundrum. It is time for scientists, regulators, and legislators to open an epistemological debate on the appropriateness of using classic pharmacological methods for substances that do not share the usual drug profiles and which are, consequently, difficult to study in humans.

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The scientific community and lay press are participating in a heated debate over the usefulness of dietary supplements.[1,2] This debate often ignores hard scientific evidence and the outcomes of proper research in either direction. Some propose that health claims should be awarded based on classic pharmacologic parameters of efficacy and safety.[3–5] Others suggest that a botanical history of their safe use and basic biological evidence in support of their effects should suffice to allow their marketing.[6] The current regulatory impasse does not help solve this conundrum (see below).

In this paper, I would like to elaborate on food bioactives and dietary supplements by underscoring their main differences from classic medicines, with which they share a somewhat "grey zone".[7] In particular, I will focus on compounds of vegetal origin that are nutritionally non-essential, considering that their dietary avoidance does not cause significant deficiency (in lay terms: what happens if you don't eat broccoli or garlic?). However, these molecules can theoretically contribute to human health *via* homeostasis maintenance and response-to-stimuli optimization, devoid of the specificity of action that is typical of pharmaceuticals.[8,9]

Given the strong ideological background that undermines what should necessarily be an impartial scientific debate, I would like to propose some food for thought to foster a constructive discussion and update regulatory frameworks.

Drugs

A drug (either synthetic, phytochemical, or produced from a biological lead) is characterized by its (a) chemical structure, (b) specific mechanism of action, (c) PK/PD (*i.e.* ADME), and (d) toxicological profile and is prescribed by balancing its indications and contraindications. Usually, the more specific a drug's interaction with a target, the more exclusive is its mechanism of action and, in turn, its effect. The pharmaceutical industry looks for and develops highly selective drugs, in terms of unique targets.[10] In short, one molecule, one target, one effect. When medicines do not mimic biological actions, they are usually inhibitors of targets (most often a proteic enzyme). The biochemical interactions between drugs and targets dictate both their therapeutic effects and toxicity, thus generating a non-linear biological dose–effect correlation.[10]

Molecular biology strongly contributes to the development of 'biological medicines' (often monoclonal antibodies) and small molecules synthesized through drug design based on the target structure.[11] Again, the latter are highly specific (and often inhibitors in nature).[12]

Often, traditional and modern drugs directly or indirectly evolve from the vegetable realm.[13] This is a consequence of the evolutionary interaction between animals, plants, and plant foods (see below). Indeed, plants synthesize a huge amount of bioactive secondary metabolites, which they use to protect themselves from environmental stress and insects.[14] Therefore, many such metabolites can be called drugs considering that they are toxic to predators. In fact, the ancient Greek

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medicinal school (φαρμακον) did not distinguish between the two functions. Digitalis[15] and atropine[16] are convenient examples.

Nutrients, supplements, and nutraceuticals

Supplements are ill-construed and their definition varies among countries and regulatory structures. For example, the FDA describes supplements as "products intended for ingestion that, among other requirements, contain a 'dietary ingredient' intended to supplement the diet".[17] The whole notion comes from the research conducted in the past century on vitamins and other nutrients and is continually updated based on basic and applied research.[18] The European Food Safety Authority (EFSA) defines supplements as "concentrated sources of nutrients (*i.e.* mineral and vitamins) or other substances with a nutritional or physiological effect that are marketed in the 'dose' form (*e.g.* pills, tablets, capsules, and liquids in measured doses)".[19]

The nutraceutical (a neologism[20] that has no current legal framework[21] and might be inappropriate) notion concerns extracts of various purities. Such extracts are obtained from food items and contain compounds with medical or health benefits, similar to the intended use of drugs, but without the approval and regulatory framework required for drugs. One suitable example is fermented red rice, which contains Monacolin K, *i.e.*, lovastatin, employed to lower blood cholesterol (and other isoprenoids derived from mevalonate).[22]

If we accept this (of the many) definition of nutraceuticals, we should also acknowledge that this term is often employed to indicate foods that contain vegetal molecules in a mixture. Such molecules/mixtures – if not essential nutrients – cannot even be termed drugs because they lack complete PK/PD data and a specific target. These molecules (or their mixtures) are sold as supplements. Although it is not too difficult to discriminate drugs from supplements that mimic essential nutrients, we should not forget that most research has been focused on the biological/health effects of non-essential yet healthy supplements. It is noteworthy that such phytochemicals do not fit the rigorous definition of drugs or nutrients.

This circumstance has been termed the "Omnivore's labyrinth"[23] and calls for a definition of the consumption of some vegetal products, based on tradition, medical habits, modern nutritional epidemiology, and basic biomedical research.

To mirror the necessary safety assessments of botanicals (which must be generally recognized as safe, GRAS),[24] a proposal introduced the concept of generally recognized as beneficial (GRAB),[25] based on basic research and aimed at underscoring salubrious aspects. In turn, the consumption of these 'beneficial' molecules is associated with that of essential molecules, *i.e.* nutrients, within the framework of an optimal and healthy diet.

Nonnutrient phytochemicals

We daily ingest thousands of phytochemicals, many of which – according to biochemical studies – are endowed with anti-inflammatory, chemopreventive, microbicidal, anti-viral, blood pressure regulatory, neurodegeneration-preventive, hypocholesterolemic, *etc*. potentials.[14] All of these effects are often superimposed; the same phytochemical might potentially protect from neurodegeneration and cardiometabolic disorders.

In addition, these molecules only rarely exhibit a dose–effect linear response and classic PK/PD might become ambiguous in this context, as opposed to the drugs situation. Therefore, the approach we take toward these relevant components of nutrition should surpass the rigorous and clear-cut concepts with which we classify nutrients and drugs and requires a more ample and complex vision: biochemical, but also evolutionistic in nature.

In the frame of biological equilibrium, vegetables (but also fungi and microorganisms) produce many secondary metabolites, among which we find molecules that help the organism avoid being eaten or killed by predatory and parasitic animals.[26] Among such molecules, some are truly toxic to predators (from viruses to animals) and some are repellents.[26] It is noteworthy that these compounds, *e.g.* spices, are often bitter and/or spicy and irritant. These characteristics have led to the ancient association between bitterness and venomousness; recently, this association has been expanded to include drugs,[27] at least among the lay public (suitable examples include Pinocchio and Mary Poppins). In folk medicine, limited amounts of bitter compounds are often viewed as "healthy", based on the hormesis concept I discuss below.

Animals (including humans) eat vegetables and, thus, ingest bioactive molecules that have been developed by plants for defensive purposes.[26] Because such molecules are an integral part of the anti-stress endogenous mechanisms of plants, they are produced in larger quantities under environmental stress conditions, *e.g.* UV irradiation, heat, and drought.[28]

The xenohormesis hypothesis posits that the consumption of such compounds by humans is beneficial in several disorders.[29–32] The notion of hormesis is pharmacological and toxicological in nature and refers to the non-linear relationship between the dose and the effect: a substance that is toxic at high doses might be healthy at lower ones.[33] From a nutritional viewpoint, the "hormetic zone" is the optimal dose range between ineffective and toxic.

If we extend the hormetic zone to include phytochemicals, we can find – at the extremities – the doses at which a vegetal molecule is only toxic or just protective. The latter situation is the one in which animals defend themselves, *e.g.* by limiting intestinal absorption or activating phase I, II, and III detoxifying enzymes. This physiological mechanism is likely evolutionary in nature and allows for minimal absorption, which triggers internal defense mechanisms. One notable example is dietary antioxidants, for which the definition of para-hormetics has been proposed.[8]

Nutritional hormesis

What has been discussed above fits very well with the concept of nutritional hormesis. The ingestion of molecules that act as electrophiles triggers the nucleophile response, in turn contributing to homeostasis *via* the redox mechanism and, hence, anti-inflammatory feedback.

Many phytochemicals currently recognized as beneficial share some chemical and biochemical characteristics, for example, they are or they act like electrophiles; then, by reacting with cellular nucleophiles (usually labile thiol groups) they activate nuclear factors connected with the nucleophilic (antioxidant) response.[8,13] Such compounds generally have antibacterial and/or antiviral activities, are pesticides, and are toxic at doses that cannot be reached *via* the oral route.[30]

In particular, plants produce molecules (pesticides) for their own defense, because they are toxic to predators.[14] The latter defend themselves by limiting absorption and activating hormetic responses. Some phytochemicals, *e.g.* secondary metabolites, contribute to human health even though they are not essential based on the definition of nutrients. Therefore, these molecules do not fit the classic and rigorous pharmacological definitions; they can be modified by organisms before they interact with targets, can have different targets depending on their concentration, and do not have a univocal pharmacological mechanism of action.

Diclofenac, for example, is an anti-inflammatory agent that specifically inhibits cyclooxygenases;[34] conversely, phytochemicals such as (poly)phenols, terpenes, and isothiocyanates exert their anti-inflammatory activities because they probably activate – through parahormesis – Nrf2, which, in turn, increases the nucleophilic tone.[8] The latter activity acts on NFκB, NADPH oxidases, and the metabolism, consequently modulating the gene expression to restore the redox homeostasis, metabolic balance, and anti-inflammatory response.

The regulatory deadlock

As discussed elsewhere by Dominguez Diaz *et al.*,[35,36] we need a specific harmonized regulation for nutraceuticals, botanicals, supplements, and food bioactives in general. Most regulatory bodies agree with the American Dietetic Association (ADA) considering the fact that the best nutritional strategy to achieve optimal health as well as reduce the risk of the appearance of chronic diseases is based on a varied diet with nutrient-rich foods.[37]

In the USA, the Dietary Supplement Health & Education Act (DSHEA) of 1994 regulates supplements *via* routes that are less onerous than those of drugs (*e.g.* see the United States *vs.* Bayer Corp., no. 07-01, 2015 WL 5822595).

Europe is witnessing a legislative vicious cycle that appears difficult to break.[38] For example, Directive 2000/13/EC prohibits health claims conducible to pharmacological ones. In plain language, the EU law remarks that it is illegal to state to consumers that a food item prevents, treats, or cures an ailment. The consequence is that the regulatory bodies are examining data that should prove 'beneficial physiological effects', while the same cannot hint at the cure or prevention of diseases. Although the current legislation protects consumers from ineffective or dangerous products, it concomitantly impedes the sales of goods that fall into these categories.

The rationale behind the prohibition of health/medical claims for foods and their derivatives (including phytochemicals and botanicals) is reasonable and laudable and aims at protecting consumers from fraudulent allegations. However, the paradox is now that EU regulations require 'beneficial physiological effects' to be proven before a food ingredient can sport a health claim. At the same time, there can be no physiological effect if that food ingredient cannot (by law) cure a disease or reduce the risk of developing one. Therefore, a vicious cycle is in place that appears difficult to break without a change of scientific paradigm.

One proposal to exit the current impasse is that of using "traditional use" to allow for health claims associated with botanicals. The prevailing definition of "traditional" is that of 15 years of usage (Article 16a(1) of Directive 2001/83/EC).

A recent and noteworthy American opinion (Civil Action no. 11-03017) concluded that the 'plaintiff's motion [omissis] is denied as moot' because, in summary, the plaintiff failed to present competent evidence that claims relating to a mixture of probiotics promoting general digestive well-being are false and misleading. In summary, this opinion makes it clear that not all consumers benefit from supplements and/or drugs and that the absence of clinical trials is not the legal standard in the case of supplements. The Federal Trade Commission underscores the difference between supplements and drugs and makes it clear that the former do not need randomized controlled trials, but, rather, accumulated scientific evidence (including basic science) is acceptable to make health claims.

In closing, it currently appears difficult to apply to food bioactives, such as phytochemicals (and their various formulations) the same legal criteria presently applied to drugs, including what is likely the major one, *i.e.*, patentability.[39,40] Hence, we probably need an epistemological debate conducive to the creation of an *ad-hoc* class, whose health allegations cannot be based on classic pharmacological routes, mostly because of costs and complexity considerations.

Conclusions

In conclusion, several food bioactives can be described as para-hormetic (=nontoxic hormetics) amplifiers of our innate ability to maintain homeostasis when challenged, while concomitantly avoiding excessive reactions. This prospect helps clarify effects that should be interpreted in evolutionistic terms, even if they might appear as pharmacological panaceas. When gatherers/hunters became farmers, their energy intake increased along with their [inflammatory] ability to fight noxious stimuli. The consequence is a lower risk of communicable diseases along with an increased risk of cancers, cardio-

metabolic disorders, and neurodegenerative diseases, possibly because of the suboptimal intake of molecules that restrain the inflammatory response.[41]

By amending diets in terms of reducing calory intake and consuming food bioactives, we could optimize the maintenance of homeostasis, a key feature of aging in health (the main goal of contemporary medicine). Therefore, in terms of scientific research, we should open an epistemological debate on the suitability of using classic pharmacological methods for substances that do not share the profile of the usual drugs and are, consequently, difficult to study in humans.[7,42]

On the other hand, regulatory and governing bodies should acknowledge these limitations and act accordingly by establishing appropriate procedures to handle the use of dietary supplements and food bioactives for health purposes.

Conflicts of interest

There are no conflicts to declare.

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