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Establishing health benefits of bioactive food components: a basic research scientist's perspective

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Bioactive food components or functional foods have recently received significant attention because of their widely touted positive effects on health beyond basic nutrition. However, a question continues to lurk: are these claims for 'super foods' backed by sound science or simply an exaggerated portrayal of very small 'benefits'? Efforts to establish health benefits by scientific means pose a real challenge in regards to defining what those benefits are, as well as how effective the foods are in justifying any health claim. This review discusses the pitfalls associated with the execution, interpretation, extrapolation of the results to humans and the challenges encountered in the dietary research arena from a basic scientist's perspective.

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Introduction

Consuming certain foods for their health-promoting properties have been in existence for over a millennium across different cultures. Yogurt and honey, for example, are recognized for their health benefits and their combination was considered "the food of the gods" in ancient India [1]. For several thousand years, use of herbs, as in traditional Chinese medicine, took into account possible food interactions as well as food combinations that enhanced the healing effects when treating specific diseases [2–4]. To date, a substantial number of studies have shown that dietary food components can impart profound beneficial effects on human health ranging from the reduction of potential risk factors to the prevention of or delay in the onset of chronic diseases [5–7]. However, despite the perceived safety, low cost and health claims attributed to diet-derived or food-derived components/compounds, the precise food components and the underlying mechanisms responsible for the biological effects remain elusive.

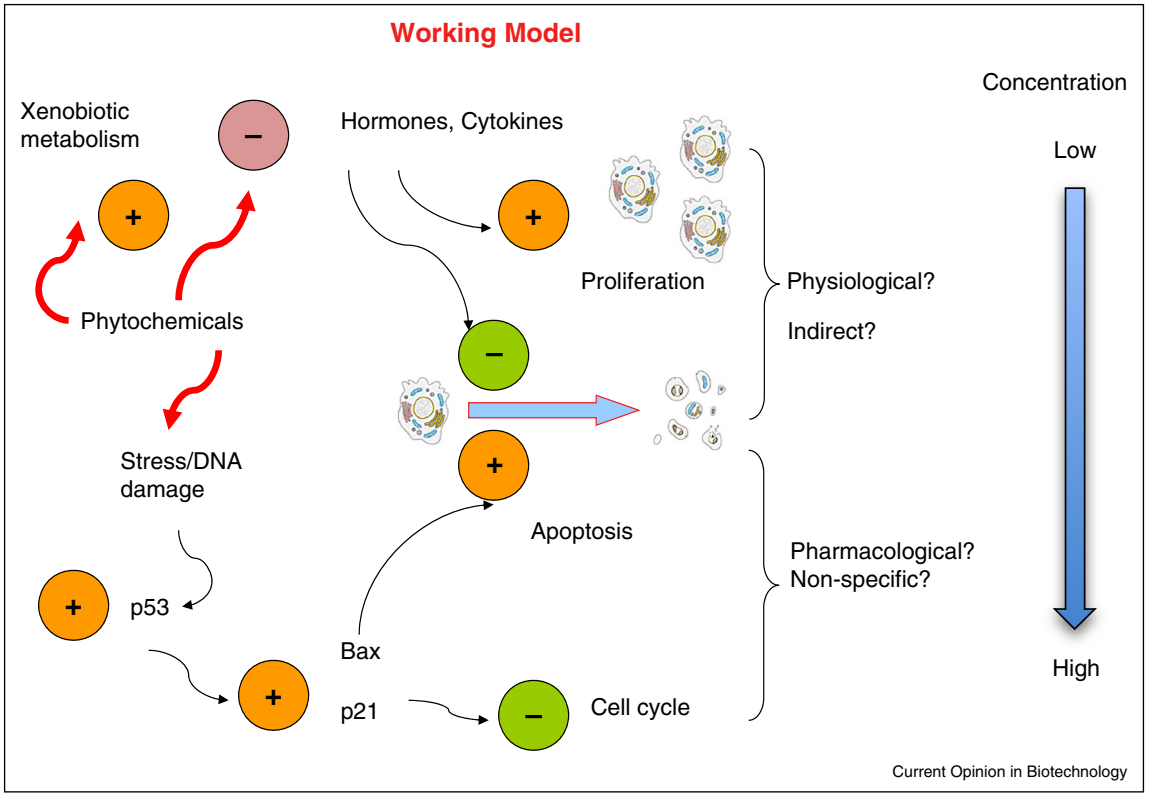
Recently, greater public health interest in bioactive food components led to attention from the regulatory and scientific community as well as the popular press. For example, a recent ad hoc Federal working group proposed a working definition: "Bioactive food components are constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, that are responsible for changes in health status." [8]. A 2013 workshop (International Union of Nutritional Sciences (IUNS)) 20th International Congress of Nutrition (ICN) held in Granada, Spain, September 15–20, 2013 and a 2013 symposium 'Are Dietary Bioactives Ready for Recommended Intakes?' held in April 21, 2013, at the ASN Scientific Sessions and Annual Meeting (Experimental Biology 2013, Boston, MA,) examined how to establish putative health effects of bioactive food components and suggested using the Dietary Reference Intake (DRI) approach that establishes nutrients requirements [9]. Recommendations for future research were also proposed [10••,11••]. However, despite a number of efforts to identify and establish the beneficial health effects of bioactive food components, the available data are often conflicting and the field of dietary research is challenged by competing interests (academic, scientific, political, consumer, industry).

The goal of this review seeks to outline, from a basic scientist's perspective, the experimental challenges encountered by scientists interested in establishing the health effects of bioactive food components. Potential experimental approaches available will be discussed to promote and facilitate the design and execution of studies that focus on food bioactives and health. Throughout the review, some of our previous work will be cited as examples to exemplify the key points we have identified as challenges.

Challenge 1. Experimental considerations for assuring quality *in vitro* data

The isoflavone genistein, a well-documented health-promoting bioactive component from soy, activates multiple cellular pathways in a concentration-dependent manner in the human prostate cancer cells LNCap and breast cancer cells MCF-7 [12,13]. The highest reported concentration for genistein in tissue/tissue fluid is at 10 μM [13]. However, the majority of studies reporting anticarcinogenic and antiproliferative properties of

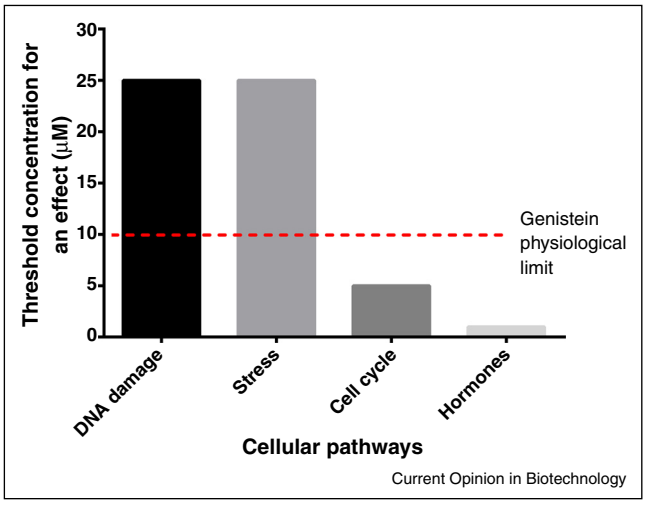
Figure 1



Schematic representation of biphasic action of phytochemicals. Hormones, cytokines induce proliferation of cancerous cells. At physiological concentrations, phytochemicals induce xenobiotic metabolism and reduce cell proliferation through inhibition of hormones and cytokines. However, at higher concentrations, phytochemicals exhibit a pharmacological effect, inducing apoptosis and DNA damage through modulation of genes involved in the p53 mediated pathways. p53; tumor suppressor p53; p21; a cyclin inhibitor; BAX; a pro-apoptotic member of the bcl-2 protein family.

genistein utilize much higher concentrations than what is physiologically relevant *in vivo*. In our laboratory, we observed using the microarray approach that low concentrations of genistein inhibits hormone-(androgen/estrogen)-induced gene expression and proliferation activities. However, at high concentrations, (>10 μM) it may be detrimental through the induction of DNA damage [14,15] (Figures 1 and 2). Another example relates to resveratrol, a phytochemical considered to possess anti-carcinogenic properties. We found that resveratrol inhibits cell growth through induction of DNA-damage-related cyclin inhibitor p21 expression in LNCaP at higher concentrations. However, at lower concentrations, resveratrol decreases prostate-specific antigen (PSA), a classic androgen-responsive prostate cancer marker [16] (Figure 3). The circulating concentration of resveratrol is less than 5 μM [16]. Hence, considering physiological achievable concentration, we concluded that the anti-androgenic/estrogenic effects may prevail over apoptosis [13]. These findings make us ponder how to ascertain the true health benefits of bioactives and caution us about the importance of how we might interpret the data. Oftentimes, scientists try to push the *in vitro*

Figure 2



Concentration-dependent effects of genistein on cellular pathways. At higher concentrations, genistein modulates DNA damage, cellular stress, while at physiologic concentrations (5–10 μM), genistein inhibits cell growth and hormone (androgen/estrogen) [13].