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Botanicals and translational medicine: A paradigm shift in research approach

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The gain in new knowledge with regard to understanding the underpinnings of many disease states has allowed for testing of effective prevention and treatment strategies. For example, it has been definitively established, at least in well-controlled clinical research settings, that the onset of type 2 diabetes can be delayed with effective lifestyle and/or pharmaceutical interventions [1–3]. Given new knowledge of molecular targets, there are now pharmaceutical agents that are commonly used as effective treatment strategies for glycemic control, lipid disorders, hypertension, and other cardiovascular disease states [4–6]. Additionally, recent insights on the interrelated physiological processes for the development of obesity and study of its onset have yielded new marketed products for its management [7,8]. In large measure, the pharmaceutical agents currently on the market and available to clinicians have undergone a systematic, lengthy, and rigorous testing process as mandated by the FDA to ensure efficacy, evaluate interactions, and to establish a favorable risk–benefit ratio. The well-characterized approach to drug development begins in the basic laboratory, extends to preclinical research, advances to early and late human phase testing, then proceeds to evaluate the “real-world” health outcome of the discovery. Despite the “checks and balances,” the concern for the process is the length of time to bring a discovery to market. An additional concern remains, in many cases, as to what agent works best in certain populations and essentially, how efficacy is “translated” to real-world settings given the concerns of adherence, compliance, socioeconomic issues, etc, that often may not be addressed in an academic setting. At this next step, new research approaches such as “comparative effectiveness” studies are required and represent the last stage in “translation” [9].

As just outlined, “translational medicine” and the phases of drug development are well known and generally effective, but are highly time-consuming and costly. The term *translational medicine* can be defined to consist of several phases [10,11]. Phase 1 translation (T1) research seeks to move basic discovery into a candidate health application. Phase 2 translation (T2) research assesses the value of T1 application and extends studies into larger populations. Phase 3 translation (T3) is the practice-oriented stage and relies on dissemination and implementation research to address relevant clinical questions. Finally,

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Phase 4 translation (T4) research involves incorporating findings from T1 to T3 to policy research. The four phases are expected to overlap and provide feedback loops to allow integration of new knowledge. In many ways, this process is appropriate to drug discovery and has served us well despite the fact that the process is time-consuming. However, it is not clear how the process works for other products, such as dietary supplements, especially those containing phytochemicals and whole botanical extracts. This is a critical issue as this market continues to grow at alarming rates. Specifically, we have known for years that alternative strategies, e.g, nutritional supplementation with over-the-counter botanical agents, are extensively practiced by a large number of individuals either to treat and mitigate symptoms noted with chronic diseases or to generally maintain health [12]. We also recognize that the supplements are frequently consumed without advice from a medical provider. Given the unknown interactions between bioactives and known pharmaceuticals, this remains a huge concern. Thus, even today, there remains a paucity of scientifically controlled clinical studies for the majority of botanical supplements. Most botanical supplements have not been evaluated for the effectiveness of any individual bioactive(s) and have not had definitive pharmacokinetic and pharmacodynamic studies performed. There is no clear guidance on their properties with regard to potential drug interactions. Moreover, the precise cellular mechanism of action of most bioactives has not been studied. Thus, considerable controversy has existed, and will continue to exist, regarding the routine use of most supplements on human health unless a paradigm shift in the approaches to the study of botanicals becomes commonplace.

In this regard, significant progress is being made for botanical research and is clearly being driven by the Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine at the National Institutes of Health (NIH). In brief, we can state the process truly started in 1999 with the development and funding of a botanical research initiative with major research institutions in the United States [13]. The Botanical Research Centers Program (BRCP) was the most visible activity of the initiative; and the program was intended to advance the spectrum of botanical research activities ranging from plant identification to early-phase clinical studies, with preclinical research encouraged as the primary focus of center activities [13]. At the current time, the NIH funds five Dietary Supplement Research Centers focused on botanicals [14]. Each center has a thematic focus with high potential for being translated into benefits for human health. As of early 2014, both the Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine have published a Request for Applications for continuation of this program, which appears also to provide the required focus on understanding some fundamental aspects of botanicals. Specifically, there is a focus on “botanicals as they relate to resilience or health maintenance” [15]. As such, rather than wait until onset of disease state and then propose treatment with botanicals to interdict the pathophysiologic processes, it is our current research focus that botanicals may provide resistance to the tissue dysfunction secondary to exposure to an obesogenic environment, and thus can promote resiliency to the development of metabolic dysfunction at the whole body level.

Given this emphasis on relevant studies of botanicals, we are pleased to provide this special volume, a collaborative project of the major institutions that comprise our NIH funded Botanical Research Center (Pennington Biomedical Research Center of the Louisiana State

University System and the Department of Plant Biology and Pathology of Rutgers University). The overall goal of the Botanical Research Center is to provide a comprehensive evaluation of botanicals in addressing the pathophysiologic mechanisms that lead to the development of insulin resistance and the metabolic syndrome. Attainment of our goal will not only allow for specific investigation into the underlying mechanisms of this condition, but will provide the necessary data for future clinical trials for botanicals designed to intervene in the process. Thus, the articles in this volume result from work supported by the NIH BRCP and address fundamental gaps in botanical research. For example, several of the articles focus on method developments that address novel approaches to enhancing bioactive bioavailability [16] or provide a novel method to evaluate substrate metabolism in target tissues [17]. In addition, the volume also provides an overview of how plants considered as herbal remedies in specific cultures, specifically the population of South Louisiana of French descent, are now validated as to their medicinal properties [18].

One of the more exciting lines of investigation featured in this supplement is the role that botanicals have to modulate the intestinal microbiota [19]. There is an incredible amount of new data implicating the gut microbiota in contributing to health or disease state of the organism. The interaction of botanicals and microbiota is almost completely unexplored. Thus, it is exciting that a manuscript published in this journal appears to be one of the first to report a specific botanical–microbiota interaction. Finally, articles are presented that evaluate botanicals on specific muscle metabolism and a possible role in sarcopenia [20]. We present articles on the role of botanicals in altering glucose and lipid metabolism in both skeletal muscle and liver [21,22]. We report the role of botanicals on modulating adipose tissue function [23] and an exciting line of research on how botanicals may modulate central nervous system functions [24]. Taken together, the data provides a solid foundation for future studies designed to enhance maintenance of health for humans and resistance to disease states (termed *resiliency*) and thus may be potentially useful in attenuating the progression of many factors related to the development of metabolic syndrome.

This special issue of *Nutrition* would not have been possible without the funding of the BRCP by the NIH. Clearly, there has been a paradigm shift in the study of botanicals, and this shift is necessary to inform the medical community and patients alike on effectiveness and use of a specific bioactive or to discourage use of a specific botanical based on ineffectiveness or even adverse effects. We hope you enjoy reading this issue as much as we have enjoyed conducting the research. In our opinion, these studies represent the rigorous and careful science that is greatly needed for the study of botanicals.

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