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Review

# From covalent bonds to eco-physiological pharmacology of secondary plant metabolites

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ABSTRACT

Despite the availability of numerous drugs and other therapeutic modalities, the prevention and cure of over- and under-nutrition triggered metabolic and other disease states continues as a major challenge for modern medicine. Such silently progressing and eventually life-threatening diseases often accompany diverse spectrum of comorbid psychiatric disorders. Majority of the global population suffering from metabolic diseases live in economically developing or underdeveloped countries, where due to socioeconomic, cultural, and other reasons, therapies may be unavailable. Evidence from preclinical, clinical, and epidemiological studies of numerous structurally and functionally diverse secondary metabolites of plants suggest that many of these could be promising therapeutic leads for the treatment and prevention of malnutrition-associated diseases and mental health problems. The review discusses the potential therapeutic uses of secondary plant metabolites and their bacterial and mammalian catabolites based on their bioactivity profiles, with special emphasis on their modulating effects on gut microbial ecology and physiological stress responses. Based on concepts in medicinal chemistry and pharmacology considerations that evolved during the author's interactions with David Triggle, secondary plant metabolites may represent an alternative and economically feasible approach to new drugs.



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## 1. Introduction

In 1966, I had the great privilege to be one of the very first Indian postdoctoral students working with David Triggle. In my close to 50 year association with Professor Triggle, he was a constant source of surprise based on his remarkable knowledge, ideas, and thoughts on the future of medicinal chemistry, and also by his outstandingly original suggestions, advice, and critical comments on the chemistry and pharmacology of bioactive molecules in the context of pharmaceutical research and real world challenges.

As a graduate student in India, I had synthesized several 2-chloroethylamino substituted amino acid derivatives as well as other small molecular weight natural products that were potential anticancer drug leads. Up until then, the ability to practically interrogate the receptor was in its infancy, and 3D structures of DNA were unknown. While drafting my Ph.D. thesis, I had come across one of David Triggle's early publications dealing with structure-activity studies using alkylating drugs and bioactive agents to better understand receptor structure and function and to design cytotoxic and other drug leads with higher specificity and longer duration of action [1]. Therefore, I wrote to him inquiring about the possibility of getting a postdoctoral fellowship.

After reaching Buffalo, it was a great surprise for me to note that unlike professors and mentors in India, my post-doctoral mentor spent many of his working hours sharing bench work and space with his students and assistants, and often helping them to solve synthesis, isolation, and purification problems. Unlike the small synthetic chemistry laboratories in India I was acquainted with, the Buffalo lab was large with an abundant supply of chemicals and other facilities, where many others from other medicinal chemistry research groups were also working. Only once in a while did Professor Triggle ask us to come to his office for lessons, advice, consultation, discussions, etc.

On one such occasion in 1968, I received from him my very first book on autonomic pharmacology [2], and also had my very first medicinal chemistry lessons dealing with the synthesis of structurally rigid analog of a neurotransmitter, which could be helpful for better understanding of the structure and function of their receptors. Noting that azetidine-3-ols could represent structurally rigid analogs of the β-hydroxylated ethylamine moiety of acetylcholine, noradrenaline, and adrenaline, he inquired whether I would be interested in synthesizing using a theoretically possible synthetic route he had in mind. Although I did eventually synthesize, purify, and reconfirm the structure of a few such molecules [3–4], for personal reasons I had to return to my hometown in India during early 1970s, where I became involved in the synthesis of alkylating derivatives of some well-known bioactive secondary plant metabolites, and their structurally rigid analogs.

Until 2003, Professor Triggle and I met each other only occasionally in the context of international pharmacology meetings held outside USA and India and once in a while we had exchanged letters. During these interactions, Professor Triggle always took the time and interest in discussions on diverse experimental pharmacological problems of common interest. I thus continued to profit enormously from his input and timely comments on my working hypotheses on the therapeutic possibilities offered by electrophilic or covalently binding secondary plant metabolites. On one such occasion in 1981, he advised me to learn some electrophysiology so as to assess whether some of the secondary plant metabolites I was working with had effects on the function of calcium and other ion channels. Prior to this, I had only evaluated these metabolites in animal models and had believed that *in vitro* bioassays were of little value for understanding the mechanism of action of polyvalent bioactive molecules. Following his suggestion, I soon found out that many of the molecules we were studying had a broad spectrum of effects not only on diverse ion channels, but also on neurotransmitter receptors and enzymes. As several of them were considered as bioactive constituents of medicinally used plant extracts, attempts were made to better understand the possible pharmacological interactions between them. Observations made during these efforts, eventually led to the concepts of standardized and concentrated extracts, which could be easily patented, and therefore could be of interest to herbal pharmaceutical industries. Although this concept is still widely used by many such industries around the globe, and now well accepted also by IUPAC and health authorities in most countries, questions concerning the appropriate bioactive constituents, doses and treatment regimen necessary for obtaining health benefits from any given plant extract remain unanswered or at best can only be speculated on.

### 1.1. The ethics of health care in the developing world

Professor Triggle and I first met in India in 2003, when we discussed ethical and moral questions dealing mainly with availability, affordability, and accessibility of drugs and nutrients in India, and also with drug discovery and development possibilities in India and other developing countries. These and related questions now affecting almost all countries were nicely formulated and discussed by him [5]. Two of these questions critical to academic, government and nonprofit organizations sponsoring research laboratories in India and other developing and underdeveloped countries are: "*How do we handle the fact that one billion people are overweight and obese while one billion are undernourished*?" *and* "*drugs for poor people are often considered to be a bad investment*?".These questions deal with malnutrition-associated health problems that are associated not only with the socioeconomic and cultural backgrounds in different countries, but also with the obsessive and inappropriate uses of the neoclassic economic theory of "eat or be eaten"[6] driven by the pharmaceutical, agricultural, food and associated industries. Although these questions cannot be directly answered by the efforts of medicinal chemists, pharmacologists, and physiologists, the efforts of the latter to better understand the roles of inappropriate food choices and eating habits in regulating human health will certainly have impact on the policies and commercial interests of those industries now causing numerous socioeconomic and nutritional status associated health problems for the global population in the 21st century.

### 1.2. The microbiome

David Triggle has also noted that "*Nous sommes tous des bacteries* " and that the development of our personal physiology and pathology can be deeply influenced by our microbiome and we in turn influence the microbial ecology through our diet, environment, and agricultural practices [7]. Analogous to the behaviors of globally expanding pharmaceutical and other industries, bacteria also try to proliferate and colonize every ecological space and also adapt themselves to their environment which supplies their own food as well [8]. Depending on the genetic background and metabolic demand of themselves and their hosts, both parties can either benefit or become sick as the result of the symbiotic coexistence. The latter not only dictates the availability and quality of food for all living organisms but also, almost all other products necessary for the survival of terrestrial plants and animals that supply human food. Since farm animals, like human beings, also depend largely on plant-derived food and their gut bacterial colonies are involved in food digestion, growth and well-being, it is apparent that more rational answers to the