Developmental Therapeutics: Review of Biologically Based CAM therapies for Potential Application in Children With Cancer: Part I

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Summary: This article is a review of the status of biologically based complementary and alternative medicine (CAM) therapies that have potential anticancer activity with a focus on those agents that may be active in childhood cancer. The review presented in 2 parts includes the descriptions of the mechanisms that underlie their effects, the manner by which these agents are identified and evaluated and discussion of some of the limitations of current research. The first part introduces the topic of biologically based CAM therapies. The discussion includes a description the discovery biologically based products for cancer, the classification of these compounds and their use from the perspectives of the Ayurvedic and traditional Chinese medicine systems. Issues associated with evidence-based research of compounds used in these practices are addressed. The second part focuses on preclinical and clinical studies of specific herbs or natural products and their bioactive constituents that demonstrate potential in cancer therapeutics. Turmeric, mistletoe, green tea, ginseng, mushrooms, and micronutrients are representative of compounds that exert their effects through mechanisms attributed to specific chemical classes. The section concludes with a discussion of status of clinical trials of biologically based CAM therapeutics for cancer and the future direction of research.

Key Words: biologically based therapies, cancer, ayurveda, traditional Chinese medicine, terpenes, polyphenols

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Biologically based therapies in the form of substances found in nature such as botanicals, foods, vitamins, or other natural products have been used over the course of millennia by traditional medicine systems that include Ayurvedic medicine and traditional Chinese medicine (TCM). In some respect it is ironic that these therapies are considered by modern Western medicine as alternative when in fact they enjoy rich historical traditions that form the basis for many modern medical therapies. In fact, more than 50% of pharmaceuticals including cancer therapies are derived in whole or in part from botanicals.1,2

Western medicine is founded on the principles of the scientific method and as such validation of these therapies requires an evidence-based approach. This is in no way impugns the important role or challenges the efficacy of traditional therapies which are used by 80% of the world’s population living in developing nations; it is simply a recognition that Western medicine requires a different form of validation. Although the scientific method does not preclude the study of such therapies, a bias against biologically based complementary and alternative medicine (CAM) therapies, in fact CAM therapies in general seem to be a mainstay in medicine. This prejudice contrary to the precepts of the scientific method that seems to take its cue from authority rather than observation may have its roots in the separation of science from philosophy and the humanities in the 20th century. This dichotomy does not exist in many traditional medicine systems. However, for more than a decade there has been a growing recognition of the potential of many traditional biologically based therapies as demonstrated by the burgeoning body of evidence-based research in the peer-review medical literature as evidenced in major bibliographical databases such as MEDLINE and Cochrane Library.3

The biologically based component of CAM practices comprises a substantial part of this research that includes, but is not limited to, botanicals, functional foods/nutraceuticals, and dietary supplements such as vitamins, minerals, fatty acids, amino acids, and proteins. The prevalence of the biologically based CAM practices is difficult to ascertain because there is no clear consensus of what constitutes these practices. For example, the terms functional foods and nutraceuticals are often used interchangeably or as subcategories of one or the other. In this review, functional foods are considered to be foods that in addition to being nutritious contain natural, bioactive chemical compounds that have health promoting, disease preventing, or medicinal properties. These may include polyphenols, phytoestrogens, fish oils, carotenoids, phytosterols, and soy isoflavones. Nutraceuticals are products that are isolated or purified from these foods and prepared in pharmaceutical forms.4,5 On the basis of 2002 data, the annual market for dietary supplements and functional foods/nutraceuticals in the United States was estimated at $40B and increasing at a
rate of 6% per year. The prevalence of use of these products in adults is up to 47% in children about 10%. The rate is much higher in cancer patients, ranging from 50% to 76.7% in adults and 16% to 20% in children.

Clearly, biologically based CAM practices are quite prevalent in adults and to a lesser degree in children treated for cancer. Consequently, it is essential to gain knowledge of these therapies, their potential impact on cancer and their interactions with conventional cancer therapies. This is an arduous task owing to the tremendous diversity of botanicals, functional foods, nutritional supplements, and other natural products used in CAM, particularly viewed in the context of various traditional medicine systems. This review focuses on a narrower range of biologically based therapies, particularly botanicals and nutraceuticals because they have more frequently been the focus of translational research and randomized controlled trials (RCTs). Because even this narrowed focus entails a vast array of botanicals and natural products as potential candidates for cancer therapies, an attempt is made to consider them within a framework in which to evaluate these therapies.

DISCOVERY OF BIOLOGICALLY BASED THERAPIES FOR CANCER

Over the past 50 years systematic drug discovery and development have yielded an extensive repertoire of chemotherapeutic agents for the treatment and management of cancer. However, there remains a continued need for additional agents because many common malignancies are resistant to available antineoplastic agents. The current strategy of drug discovery involves the use of high-throughput chemistry and high-throughput screening of large numbers of candidate compounds derived from combinatorial chemistry techniques, thereby creating entire libraries of potentially bioactive molecules including peptides, oligonucleotides, and other small organic molecules. This paradigm of drug discovery has been indispensable in attempting to keep pace with the ever growing number of drug targets for many diseases including cancer, identified through the greater understanding of the genome, proteome, and metabolome. However, the efforts of classical, combinatorial, and new techniques of drug discovery such as rational drug design (computer modeling of potentially active molecules) have not met expectations. First, the identification of new bioactive molecules has not kept pace with the discovery of new drug targets and secondly, most of the molecules that have been synthesized do not have useful pharmacologic properties. For these reasons this powerful paradigm of drug discovery is at crossroads. Because of this shortfall of chemical compounds to match targets, the pharmaceutical industry has been turning to traditional sources of bioactive molecules with enormous diversity, viz. botanicals which ironically were the primary source of drugs in Western medicine in the preorganic synthetic chemistry era.

This trend of moving from combinatorial organic chemistry or other techniques toward bioprospecting is being adopted by a growing number of pharmaceutical firms. This transition toward bioprospecting acknowledges the shortcomings of the current drug discovery methodologies and the existence of vast sources of as yet untapped natural resources. Natural ecosystems such as rain forests, marine ecosystems, and botanicals in general are akin to a myriad of chemical laboratories where each species has for millions of years synthesized various chemical compounds for purposes of defense against predators and disease as part of the process of natural selection.

As the pharmaceutical industry considers this more traditional form of drug discovery, it is still questionable whether random bioprospecting will achieve the goal of more compounds directed at molecular targets associated with cancer and other diseases. Already this approach has generated promising new cancer chemotherapies; Homoharringtonine (Harringtonia cephalotaxus), Flavopiridol (Amoora rohituka), 4-Ipomeanol (Ipomoea batatas), and Elliptinium (Bleekeria vitensis) in addition to the current repository of plant-based cancer chemotherapeutics. However, the problem with a random approach to bioprospecting is that randomly selected natural products have a similar chance of containing a chemical compound with specific activity directed against any one target as any other compound. Considering the enormous expense of bioprospecting, the fact that less than 5% of plant species and less than 1% of marine and microbial sources have been screened and the relatively poor yield of effective and safe therapies some are questioning the validity of this approach. The problems however lie not in the concept of bioprospecting but in the inefficient methods employed. Two methodologies that offer the promise in making bioprospecting more efficient are ecochemistry and ethnobotanical chemistry.

The evolutionary links between the different taxa in nature provide the basis for the discovery of common metabolic pathways. During the course of evolution, nature has used metabolites derived from intermediary metabolism to guide the production and subsequent development and specialization of secondary metabolites (not required for growth or development) for the defense against pathogens and control of diseases. This is in contrast to primary metabolites such as carbohydrates and lipids that are involved in the process of building and maintaining plant cells. The recognition that these secondary metabolites act on the same targets within a given Kingdom has given rise to the science of ecochemistry.

Therefore, secondary metabolites produced by plants or animals have an advantage compared with compounds synthesized by combinatorial chemistry because they are by definition biologically active. In contrast, chemicals obtained by combinatorial chemistry (stochastically synthesized) need to be subjected to
large-scale high throughput technology to detect potential bioactivity. The resulting synthetic organochemical libraries have a low yield of medically useful compounds with as few as 1:10,000 compounds used in phase 3 clinical trials. In other words, a much higher proportion of natural secondary metabolites will reach the clinical phase.\textsuperscript{14–16}

Examples of this approach are the cyclic derivatives of squalene an open-chain 30-carbon isoprenoid molecule found in plants, animals, and microbes. These derivatives are known as triterpenes and are members of a larger class of compounds known as terpenes that are primarily secondary metabolites with numerous functional roles. Terpenes, found in all living organisms, are the largest and most diverse class of natural low-molecular weight compounds (>30,000).\textsuperscript{17,18} A large subset of terpenes, cyclosqualenoid intermediary metabolites exist in nature of which many have been evaluated. Considering only a subset of these compounds, triterpenoids which have related structures to steroids, a large proportion have been shown to possess anticancer and anti-inflammatory activity.\textsuperscript{17,19}

The understanding of the evolutionary development and biology of secondary metabolites in plants and other natural products offers an opportunity for a more directed approach to drug discovery than the stochastical approach as combinatorial chemistry alone. However, there are still a large number of potential compounds to be evaluated. The efficiency of this process can be further enhanced by acknowledging the contribution of indigenous and traditional knowledge in the process of medical discovery (rather than only drug discovery) of compounds to treat cancer and other diseases.

The ethnobotanical approach to drug or medicine discovery provides an opportunity for a purposeful and targeted evaluation bioactive compounds that may play a role in cancer therapy. There are several reasons that suggest this approach to be far more efficient and likely to produce effective therapies. Cultures that have a long standing medicine tradition as found in Asia, Central and South America by virtue of their access to botanically diverse areas such as tropical rain forests and geographic stability over thousands of years have through selective and long-term use identified the most effective and least toxic plants; in essence, large scale clinical trials.\textsuperscript{20} By understanding how botanicals are used, for what ailments and the context of the traditional system they are used, the search for potential biologically based anticancer or other therapies becomes exceedingly efficient and is becoming more and more a strategy of many pharmaceutical companies. Given the enormous cost (hundreds of millions of dollars) and substantial time (as long as decades) of developing even a single drug via the methodology of combinatorial chemistry with high through-put screening, it is of little wonder that the pharmaceutical industry has adopted this far more directed approach to drug discovery. This perspective therefore has placed biologically based CAM on a firm footing which seems to have come full circle and provides a framework within which to view natural products used in cancer therapy.

**CONTEXT OF ETHNOBOTANICALS IN TRADITIONAL MEDICINE**

Botanicals and natural products used in traditional medicine systems though potential sources for pharmaceuticals, differ in significant ways beyond their manner of discovery. Unlike synthetic pharmaceuticals which generally consist of a single type of molecule, many ethnobotanical compounds demonstrate additive or synergistic actions at single or multiple sites.\textsuperscript{21,22} This principle has its basis in the functional role of secondary metabolites that are associated with survival of plants. In the context of plant defense, the synergistic or additive effects directed at multiple targets confer protection against a wide range of predators or pathogens and reduce the chance these organisms will develop resistance or an adaptive response. This concept may be fundamental to the beneficial actions of medicinal plants.\textsuperscript{21}

Traditional systems of medicine have been practiced effectively as state of the art at the time for thousands of years by all of humanity. However, the terminology used by these systems to describe the functioning of the human body and the nature of disease have not been adequately related to modern Western medicine and science. Consequently, this has been an impediment to the general acceptance of healthcare practices in such systems as Ayurveda and TCM.\textsuperscript{23} A brief perspective of these two ancient systems with a focus on cancer therapy and correlation of their concepts to those of Western medicine will help to provide a context in which to understand and evaluate biologically based CAM therapies and hopefully overcome biases against them.

**AYURVEDIC TRADITION**

Ayurveda is a holistic medical system that originated in India at least 3000 years ago. Ayurveda is a Sanskrit term derived from the word Ayus which means life and Veda which means knowledge. The simple meaning can thus be considered as the knowledge or science of life. However, life has a deeper meaning than the biologic definition in Western science. It includes in addition to the physical element (body), mental (mind), the senses and spiritual (soul) aspects, their relationships with each other and the Universe in its totality.\textsuperscript{23,24}

Whereas an in depth discussion about Ayurvedic medicine is beyond the scope of this article, it is nevertheless important to understand the framework in which botanical or other biologically based therapies are used. One of the cornerstones of Ayurveda is the concept of tridosha which involves the regulation or balance of the 3 fundamental biologic energies of all living systems, or doshas that govern physical structure and function. According to Ayurveda, the tridoshas: vata, pitta, and kapha are responsible for all physiologic and psychologic processes.\textsuperscript{23,25,26} Furthermore, all physical characteristics, emotional tendencies, and mental
capacities can be understood within the tridosha framework. Although all individuals consist of each of these biologic energies, the proportions vary which leads to different constitutional types, propensities for diseases and consequently individualized treatments are required to bring the doshas back into a state of balance. 23,25

Although these concepts may be unfamiliar to Western medicine, this very intricate system of medicine has correlates to more familiar concepts of physiology and biochemistry as they govern processes at a macroscopic, microscopic, and molecular level. The dosha vata, governs motion and activity and as such is responsible for physiologic process of the body such as circulation, respiration, activities of the nervous system and at a cellular level, and functions such as ion transport and cell division. Pitta governs metabolism or biochemical reactions and energy exchange and kapha governs the structure and cohesion of the body whether they are macroscopic as with anatomic structures or molecular as with intracellular matrix or cell membranes. 23,25,27 At this level there are clearly commonalities between the 2 systems. However, the concept of disease in Ayurveda arises from imbalance of the doshas and those functions that they govern. The diagnosis and treatment of disease is focused on recognizing the nature of this imbalance and individualizing the treatment to restore it. Thus, unlike Western medicine, “one size does not fit all.” Clearly, in Ayurveda and similarly in TCM, the concepts of balance and imbalance do not have precise correlates to the more mechanistic biochemical or molecular concepts. In Ayurveda and TCM, diseases are viewed in a more holistic paradigm involving patterns of illness relative to constitutional differences of individuals and the matching of therapy to restore balance rather than employing one-to-one maps.

Ayurveda does include a concept of cancer and disease in general and includes biologically based as well as other treatment modalities. 28 Because a diagnosis is understood in terms of the nature of a disease state rather than the name of a disease it is not possible to draw a one-to-one correlation between types of cancer as is understood in Western medicine. Nevertheless, there are common general features. The pathogenesis of neoplasia in Ayurveda follows a general 6 stage sequence of disease pathogenesis. Causative factors including diet and environmental exposures which if uncorrected leads to the accumulation of one or more doshas somewhere in the body. This leads to biochemical derangements that ultimately lead to cellular disturbances, and ultimately tissue and organ system abnormalities. In terms of carcinogenesis, Ayurveda recognizes the evolution of a tumor in the true sense of a swelling with the successive development to neoplasia, malignancy, and local and distant metastasis. 23,28 These concepts seem to have similarities to the modern concept of carcinogenesis: initiation, promotion, and progression. What is paramount to this sequential model of pathogenesis is the concept that there are multiple opportunities for intervention. In fact the term used in Ayurveda to describe this sequence, sakhriyakala, may be interpreted as “6 times for action.” This perspective of the entire natural course of the disease from its early, reversible stages through intermediate stages of manifestation and symptoms, to advanced stage with potentially irreversible complications has significant parallels to Western medicine. 25,28

Treatment of neoplasia in Ayurveda is not only directed at the tumor but also includes the use of immune-potentiating or immunomodulatory therapies, micronutrients and nutrition-promoting agents because cancer is often associated with immune dysfunction and because normal tissues are in competition with the cancer for nutritional support. The focus on improved nutritional status, immunity microcirculation, etc. is considered essential as are biopurificatory therapies that allow medications and nutrients to more effectively reach their targets.

Botanical or herbal therapies have long been a major part of the treatment of disease including cancer in Ayurvedic medicine. However, there is a perception that these botanical therapies have not been evaluated in human or in vivo trials. In a recent review of 166 species of botanicals used in Ayurveda, 43% had at least one or more human study and 62% had one or more animal study. 29 Although a significant number of these studies lack sufficient rigor as required by standards of evidence-based medicine, the review clearly demonstrates the broad interest these compounds have generated and the potential for more stringent evaluation.

Although the description of cancer in Ayurveda is somewhat vague, it is important to note that many botanical compounds used to treat cancer have in translational and clinical studies demonstrated cytotoxic anticancer activity. However, many studies follow a standard pharmacologic efficacy model (efficacy is proportional to drug concentration) and did not take into consideration the need for alternative models to evaluate indirect immunologic or nutritional-based mechanisms for cancer treatment. Such approaches are considered in a later section.

**TCM**

TCM, also an ancient and complete medical system used to diagnose, treat, and prevent disease, has been known for at least 3500 years. 24 TCM has evolved over the centuries, to include acupuncture and herbal medicine. However, the basis of TCM involves fundamental concepts of Chinese ancient philosophy: Qi, yin-yang, and the 5 elements (water, fire, wood, metal, and earth). Qi is considered to be the basis of all phenomena, physical or nonmaterial and explains the interrelatedness of the entire Universe. Applied to the concept of medicine it addresses the physiologic and biochemical interactions in the body and environment in a manner reminiscent of the tridosha system in Ayurveda. 24,30 The principle of yin-yang stems from the belief that any object is a unified whole composed of complementary yet opposing qualities creating a duality. TCM has identified yin and yang
qualities to each system of the body and to constitutional aspects of an individual or jing. The 5 elements in Chinese philosophy relate to an explanation of the composition and phenomena of the physical world. In medicine, these define the 5 systems of the body or Zang-Fu organs which are also linked to each other and the body as whole through the meridian system. The correlates between TCM and Western medicine are less clear than with Ayurveda. However, these 3 concepts can be viewed as defining human physiology at some level.

Two primary branches comprise TCM: acupuncture and herbal medicine. Each approach is focused on restoring balance and the choice of either or both is based on the nature of the disease. Acupuncture, which has gained wide acceptance in the West, is based on the concept of Qi which circulates through the body via meridians which connect internal and external organs and connective tissues. By stimulating certain points on the surface of the body reached by meridians through techniques such as acupuncture, massage, or moxibustion (burning an herb near the skin), the flow of Qi can be regulated, thus restoring balance of physiologic or biochemical functions.

Consequently, the pathogenesis of disease in TCM may be seen as resulting from an antecedent cause that produces a disturbance in Qi and thus an imbalance of the yin-yang of an organ or system. Therefore, disease in TCM is a process similar to the concept of satkriyakalas. The therapeutic approach in TCM as with Ayurveda not only focuses therapeutic intervention on a specific organ or pathogen but on the attempt to restore balance or homeostasis of the whole body. Therefore, an understanding of the various yin-yang attributes of organs, individuals, and recognition of its imbalance is key to determining the nature of the therapeutic intervention.

Chinese herbal medicine is a sophisticated and complex system on the basis of empirical observations that have been refined over the centuries and categorizes clusters of symptoms and signs that may benefit from specific herbal formulas. Herbs are classified in 2 major categories: the first refers to temperaturelike characteristics of the herb, viz. hot, warm cold, neutral, and aromatic. The second refers to the taste property of the herb, viz. sour, bitter, sweet, spicy, and salty. Practitioners of TCM prepare combinations of herbs whose properties are matched to the complementary properties of specific conditions that can influence the yin-yang properties of the body in specific ways that lead to the restoration of balance. This approach acknowledges the concept that the breakdown of homeostasis involves different factors including the individuals own constitution or jing and specific stressors of varying duration. Ultimately, the stressors are viewed as inducing imbalances that manifest in symptoms and disease. Therefore, there is typically no one-to-one correlation with a disease state as understood in Western medicine which along with the relative paucity of stringent RCTs may explain why it may be less widely appreciated. This individualized approach is however not without parallel in Western medicine. Current research has increasingly demonstrated important relationships between nutrients, genes and outcomes, concepts that are embodies in a recently introduced field of nutrigenomics. In part, this field acknowledges the importance of genetic polymorphisms in the interplay between biologically based therapies and their use in treatment of diseases including cancer. In a recent epidemiologic study of breast cancer incidents in women who consume green tea, the incidence was significantly lower in women with a less active form of the gene catechol-o-methyltransferase which inhibits certain antioxidants. Although these concepts require more study, they support in principle (though with a different rationale) of the individualized approach to the treatment of cancer practiced in systems such as TCM.

The extensive permutations of stressors and constitutional attributes lead to the plethora of herbal preparations used in TCM. Consequently, Chinese herbs are frequently used in combinations for various reasons including enhancement of their efficacy and minimization of the toxic side effects of principal component. Because Chinese herbs are mostly used in combinations, the number of herbal prescriptions used is extensive. This state may be appreciated by considering the fact that the Chinese pharmacopoeia lists several thousand different herbal substances not to mention the more than 11,000 herbal formulae described in Chinese and Korean literature.

The status of clinical trials of Chinese herbal compounds, including single and multiple preparations is not unlike that of Ayurvedic compounds, that is, there are relatively few high quality clinical trials. The Chinese literature contains numerous with estimates of more than 10,000 RCTs published in Chinese journals. However, there are significant concerns about the quality of these studies. There is little doubt that there is great value in exploring the therapeutic opportunities associated with these compounds, but it is equally clear that these therapies must be subject to rigorous evidence-based methods.

The foregoing discussion demonstrates that the rich and ancient traditions of Ayurvedic and Chinese medicine are not in conflict with Western medicine; rather they offer a complementary view of the treatment of the whole individual such as cancer and restoring a state of balance. The difficulty in embracing these concepts in part lies in the different “languages” which often lack meaningful translations because of cultural overlays. However, this should not dissuade us from seeking a common ground upon which to satisfy the requirements of the Western system of medicine and introduce the experience of thousands of years of botanical therapies by billions of people. This will require a broadening of our perspective with respect to novel approaches to RCTs that adhere to the precepts of the scientific method and rigorously evaluate traditional biologically based therapies. New approaches to well designed RCTs are being considered which importantly include quality control or...
standardization of preparations, the evaluation of side effects and the potential for herb-drug interactions.

FORMULATIONS USED IN TRADITIONAL MEDICINE

Inconsistencies of herbal preparations in many cases may well be at the core of the variable results attributed to often poorly controlled studies. Part of the problem is the complexity of preparations and inherent synergies of some constituents of even single botanicals. Plants contain hundreds of constituents with many at low concentrations. For example, a common herb such as ginger is recognized to have 477 constituents; clearly this is a challenge for standardization.37 Further complicating the matter of consistency are the multiple factors that affect the various plant constituents including the source (wild or cultivated), temperature, light exposure, water, nutrients, methods of collection, storage, drying, age, transport conditions, etc. These factors therefore represent a major challenge to standardization.38 There are also factors that affect the quality, safety, and efficacy such as the methods of extraction, and contamination with environmental pollutants, heavy metals, and microorganisms.38,39 This problem can be convincingly illustrated by considering the variability of only a small number of constituents in a well-known and comprehensively studied herb, viz., ginseng. Considerable product-to-product variability was demonstrated in the concentrations of total eleutherosides and ginsenosides of 25 different commercially available ginseng products. The variation of total ginsenoside concentrations was 15-fold in powder preparations and 36-fold in liquid preparations whereas the total eleutheroside concentrations varied 43-fold in powder preparations and >200-fold on liquid preparations.40

Although relatively few RCTs have addressed these concerns, the problem is tractable because of recent advances in the technology of cultivation, isolation, purification, and structure determination.38 The principles inherent in these new methods acknowledge it is not feasible to standardize all constituents of plants; however, it is possible to reduce the variables by standardizing the cultivation and collection procedures and focus the quality control monitoring the major secondary metabolites in each plant. It is equally important to screen for various types of toxins or other contaminants.

The enormous complexity of the biochemistry of traditional botanicals raises a fundamental dilemma from the perspective of Western medicine regarding the identification and evaluation of compounds for the treatment of cancer and other disorders. From the perspective of traditional medicine systems, the complexity of botanicals whether singly or in combinations underlies the balance, efficacy, and safety attributed to these therapies.37 This seems to diverge from the Western pharmaceutical approach of a single or small number of molecules in cancer treatment. There is validity to both approaches and they can be reconciled. An important key is recognizing the appropriate context for each approach. Secondly, although it is essential to respect the traditional medicine systems it is equally important to translate an understanding of the perspective of traditional botanicals onto the Western scientific frame of reference to evaluate potential opportunities for cancer therapy. In this manner botanicals and/or constituents used in traditional medicine for cancer may be subjected to rigorous standardization, in vitro and in vivo evaluation and unlimitedly well designed RCTs. This will help to moderate the cultural overlays of these compounds and take advantage of the millennia of empirical selection.

ESTABLISHED COMPOUNDS USED IN TRADITIONAL MEDICINE FOR THE TREATMENT OF CANCER

An extraordinary number of botanicals have been recognized and used in traditional medicine. Between Ayurveda and TCM alone at least 10,000 plant species with medicinal potential have been recognized in Asia.44,39 Although this is less than the estimated 265,000 flowering species on earth, this is a formidable number, particularly when considering in addition the many more associated secondary metabolites.20 Fortunately, there are far fewer classes and subsets of metabolites which define chemical classes with structural features that frequently share affinities for specific targets, though with varying efficacy. For example, many triterpene compounds tested, in particular pentacyclic triterpenes, have demonstrated anti-inflammatory activity through COX-2 inhibition which may also have a role in cancer therapy or chemoprevention.17,41

Bioactive metabolites studied from traditional medicine include a number of classes, for example, terpenes, polyphenols, alkaloids, polysaccharides, glycoproteins, etc. Plants contain multiple metabolites with varying concentrations and many metabolites are found in a variety of plants which implies some may have more than one source. Although metabolites may have similar effects on a particular molecular target associated with a disease process, some may impact multiple targets. Discerning the activities of secondary metabolites and the biologically relevant concentrations requires some form of extraction from the plant source and subsequent purification. Typically, these extracts are studied to determine the spectrum of biologic activity including anticancer and anti-inflammatory activity.41 Through this process, an understanding of the biologically active constituents of traditional botanicals is developed. This will result in improved standardization of natural extracts containing these compounds and the identification of compounds alone or in combination as pharmaceuticals or nutraceuticals.

Many of the bioactive constituents of therapeutic botanical compounds fall into 2 broad categories: terpenes and polyphenols. Many botanicals contain constituents from each of these classes. Each of these classes consists of a number of subclasses which share
chemical and biologic properties. This perspective helps to translate the empirical foundations of traditional herbal medicine systems into the framework Western science while removing the randomness attributed to the current pharmaceutical approach to drug discovery. Understanding of botanical constituents selected by traditional medicine in this way will also aid in understanding the value of natural combinations of constituents in the prevention of disease and the rational selection of purified extracts or molecules for the treatment of disease, in particular cancer. Some of the more promising compounds and combinations in these groups are discussed in a subsequent section.

**TERPENES**

Terpenes which are perhaps the most widespread group of natural products are known to play a role in traditional herbal remedies and are under investigation for antibacterial, antineoplastic, and other pharmacologic effects. They are universally present in small amounts in living organisms, where they play important functions in membranes and other biologic activities. Terpenes are hydrocarbons resulting from the combination of several isoprene units (C5H8). Oxygen containing terpenes are terpenoids which are derivatives of terpenes. Isoprene is formed naturally in plants and animals and is generally the most common hydrocarbon found in the human body. As a structural motif for terpenes it is widely present in the natural environment at low concentrations and is also common in low concentrations in many foods.

Terpenes/terpenoids are classified by the numbers of isoprene units: monoterpenes-oids (10 carbons, 2 isoprene units), sesquiterpenes-oids (15 carbons, 3 isoprene units), diterpenes (15 carbons, 4 isoprene units), triterpenes-oids (30 carbons, 6 isoprene units) up to tetraterpenes-oids (40 carbon, 8 isoprene units). Terpenes and terpenoids may also be classified by the number of cyclic structures they contain. Examples of commonly recognized terpenes include diterpenes (taxol and retinal), triterpenes [squalene, the precursor for all steroids (including cholesterol and hormones)], and tetraterpenes (β-carotene and lycopene).

Because of the broad spectrum of biologic activity of terpenes, especially triterpenes, there is growing interest in the evaluation of triterpenoid extracts in the treatment of cancer. Several triterpene compounds that have recently appeared in the literature in preclinical studies suggest potential therapeutic opportunities. Betulinic acid, boswellic acid, ß-sitosterol, ginsenosides, squalene, ursolic acid, oleic acid, triterpenoid saponins, amorin, and synthetic derivatives of these compounds are among the growing numbers of these compounds evaluated in preclinical and some clinical studies. Botanicals and natural products that contain these and other terpene derivatives in addition to demonstrating a variety on anticancer mechanisms also possess antiinflammatory activity through selective COX-2 inhibition. This consistent relationship has led to speculation that there is a mechanistic relationship between carcinogenesis and inflammation that can be further explored.

**POLYPHENOLS**

Phenolic compounds (polyphenols) are receiving considerable attention in medicine because of the growing epidemiologic evidence of the association of polyphenolic food consumption and of disease prevention. Additionally, approximately 1000 basic in vitro and in vivo animal studies dealing with polyphenols have been published from 2000 to 2004. The role played by this class of compounds may in part be attributed to the fact that they are reducing agents or antioxidants and thus help the body manage oxidative stress, clearly an important factor in carcinogenesis and other diseases. Polyphenols, like terpenes represent one of the most abundant substances in the plant kingdom with at least 8000 chemical structures identified. Polyphenols are characterized chemically according to the number of carbon atoms in their skeleton thus defining the various classes: phenolic acids, xanthones, flavonoids, etc. Although 10 classes of polyphenols have been defined, the majority are either simple phenols or flavonoids.

Common polyphenols with potential implications in cancer therapy and chemoprevention include resveratrol (grapes), quercitin (broccoli, onions, and tea), curcumin (turmeric), genestein (soy), and epigallocatechin (green tea) and their sources.

Like the terpenes, a significant number of polyphenols may not have any relevance to human health or the treatment of disease. This is attributed to the fact that in relatively few is the assessment of the antioxidant capacity of these compounds biologically (as opposed to purely chemically based) based on in vitro or in vivo studies. Furthermore, many studies do not consider the pharmacologic concerns such as bioavailability or delivery to a specific tissue. Research into polyphenolics and their natural sources has largely been focused on the direct antioxidant effects in relation to cancer; however, there is evidence that polyphenols impact carcinogenesis through indirect antioxidant mechanisms and other molecular mechanisms entirely.

Flavonoids are the most common and widely distributed plant polyphenol. These compounds share a common diphenylpropane (C6–C3–C6) structure which consists of 2 aromatic rings linked through 3 carbons that form variably oxygenated heterocycles which defines several flavonoid subclasses: flavones, flavonols, isoflavones, anthocyanins, flavonoids, proanthocyanidins, and flavanones. Although the focus on polyphenols in the study of cancer can be substantially narrowed, there are several important considerations that impact their study. First, many less well-characterized polyphenols are derived from modifications such as polymerization of flavonoids or other polyphenols that occur during
ripening or food processing. This issue, elsewhere addressed, is problematic with respect to the use reproducible natural sources that contain polyphenolics for clinical or preclinical research. Secondly, a broad range of chemical and biologic factors affect the bioavailability of polyphenolics. Polyphenols may be glycosylated, acetylated, hydrolyzed, or form acid esters. These chemical properties can significantly impact the bioavailability of these compounds. This further underscores the importance of clearly defining the source or starting materials used in clinical studies and perhaps evaluating serum metabolites as an end point to correlate to mechanism of action or efficacy.

**OTHER CLASSES OF COMPOUNDS**

Although terpenes and polyphenols represent 2 of the broadest classes of phytochemicals, medicinal compounds include constituents from other classes. Extracts and whole herb preparations contain active compounds from a variety of other classes including alkaloids, glycoproteins, polysaccharides, and glycosides. There are also instances when some of the compounds share chemical structural properties from more that one of these classes as in the case of glycosylated polyphenols and terpenes.

Consideration of the diverse chemical properties of these compounds is important because the structural or chemical feature give way to their biologic activity. To some extent this is apparent in the case of the polyphenols with regard to antioxidant properties. However, it is equally important not to be too rigorous or mechanistic in applying these concepts because many compounds have multiple mechanisms of action that are totally unpredicted from knowledge of their chemistry. Not to mention the difficulty in factoring in the synergistic effects of combinations of constituents as hitherto discussed. Furthermore, activities from distinctly different classes of compounds may be similar just as compounds from the same class may possess divergently different biologically activities. It is therefore, in this context that the following discussion of more well documented herbal compounds should be considered.

**REFERENCES**


