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EDITORIAL

# Current Trends in the Chemoprevention of Cancer

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In the latter part of the last century, we have witnessed the development of pharmaceutical agents for the treatment of human malignancies. During this development, active agents have been discovered from the bounties of nature, as well as from the hard work of synthetic medicinal chemists who have developed a synthetic chemical library of thousands of compounds. In recent years, we have also witnessed the discovery and synthesis of novel targeted agents for the treatment of human malignancies, some of which have shown excellent therapeutic superiority over conventional chemotherapeutic agents. However, we have not fully exploited what nature can offer in terms of novel agents. Such agents alone may not be sufficient as superior therapeutic agents, although "natural agents" (dietary agents) are by definition non-toxic, which could be very useful for sensitization of drug-resistant tumor cells to the existing conventional therapeutics. Moreover, such natural agents could also guide medicinal chemists toward the synthesis of targeted analogs, which could become novel therapeutic agents for the treatment of human malignancies, especially for solid tumors, in the 21st century.

Throughout history, natural products have afforded a rich source of compounds that have found many applications in the field of medicine (1,2). The partially explored dense tropical rainforests and colorful coral reefs in the ocean have long been a source of promise for novel agents in the fight against cancer and other diseases. To capture some of nature's potential gifts as anticancer agents since 1960, the Natural Products Branch (NPB) of the Developmental Therapeutics Program of the National Cancer Institute (NCI) has devoted itself to finding these chemicals by setting up a repository of plant and animal samples from around the world (3–6). The NCI Natural Products Repository currently houses some 170,000 extracts from samples of over 70,000 plant and 10,000 marine organisms collected from over 25 countries, as well as over 30,000 extracts of diverse bacteria and fungi. This repository is considered to be the source of novel compounds to add to the 500,000 compounds envisaged for the NIH Roadmap Molecular Library (7–12).

After over 40 years of screening these extracts, critical anticancer arsenal drugs have been developed. The fleet is led by the flagship drug Taxol, which has been approved by the FDA for the treatment of several human malignancies. Many other drugs originally discovered from nature have also been approved by the FDA, including camptothecin and its analogs (topotecan and irinotecan), vinblastine and vincristine, and the microbial-derived anthracyclines, such as doxorubicin and the bleomycins (7–12). Several other promising compounds are currently being tested in clinical trials against cancer and other deadly chronic diseases. Interestingly, it has been estimated that over 60% of the current anticancer drugs are derived in one way or another from natural sources, and, thus far, natural product chemistry has proved superior to combinatorial chemistry (13).

Over 20 new drugs launched on the market between 2000 and 2005; they originated from terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates. These clinically approved substances, representative of very wide chemical diversity, together with several other natural products or their analogs are undergoing clinical trials, and they continue to demonstrate the importance of compounds from natural sources in modern drug discovery efforts. The

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large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products, especially flavonoids, coumarins and indoles (9,10,14), and increasing evidence suggests that natural compounds are superior for further drug development (15–18).

To keep abreast of emerging and rapid advances in the synthesis, characterization and biological testing of many agents coming through the drug pipeline and by exploitation of rich natural sources, it is becoming important to document emerging focused research that has been going on in the laboratories of chemists, medicinal chemists, biochemists, cell biologists, molecular biologists and others. In an attempt to report recent advances, we have compiled a series of review articles and research articles for this theme issue of *Pharmaceutical Research*. These articles, which focus on specific and novel classes of compounds derived from both natural resources as well as from the tables of synthetic medicinal chemists, could become a new resource for the rapid development of agents that could be not only useful but also superior to the currently available conventional chemotherapeutics for the management of human malignancies.

This special theme issue of *Pharmaceutical Research* is composed of a series of review articles starting with the review article written by Dr. Rajendra Mehta, which describes the perspectives and history of chemopreventive-related compounds found in nature. This review is followed by a series of other articles focusing on a specific class of natural products and compounds, such as apigenin (Dr. Sanjay Gupta), resveratrol (Dr. S. M. Hadi), and the structure-function relationship of resveratrol and its analogs (Dr. Thomas Szekeres). In addition, there are articles on bitter melon for its cancer chemoprevention efficacy (Dr. Ratna Ray) and on targeted alterations in Polo-like kinase by chemopreventive agents (Dr. Nihal Ahmad). In addition, the article by Dr. Young-Joon Surh summarizes the role of Nrf2-Keap1 signaling as a potential target for chemoprevention of inflammation-associated carcinogenesis, and I offer a commentary on the need for clinical trials to test natural agents protecting lymphocytes against TNF-alpha-induces activation of NF-κB. Two articles focus on diet: Dr. Rajvir Dahiya explores the relationship between microRNAs (miRNAs) and prostate cancer, and Dr. Yiwei Li offers a comprehensive review on the regulation of miRNAs by natural agents, an emerging field in cancer chemoprevention research. Dr. Hasan Mukhtar concludes the review articles with a very comprehensive look at how some of these chemopreventive natural agents could be delivered using nanoparticles.

In addition, this theme issue offers original research articles documenting specific findings that have never been reported elsewhere in the literature. These articles focus on different agents as well as different tumor systems, such as the effect of polyphenon E and EGCG on lung tumorigenesis by Dr. Ming You and the biochemical role of Diallyl trisulphide in prostate cancer by Dr. Shivendra Singh. Articles on the chemopreventive role of resveratrol in hepatocarcinogenesis by Dr. Anupam Bishayee and the role of grape seed proanthocyanidins in skin cancer by Dr. Santosh Katiyar are followed by Dr. Gary Wood's research on the anti-melanoma effect of Vorinostat in combination with EGCG. The notion of sensitization of cancer cells to conventional therapeutics by natural agents is explored by Dr. Gilda Hillman, who shows that natural agents are superior to isolated active compounds. Dr. Hasan Mukhtar reports here for the first time the *in vitro* and *in vivo* effect of white cocoa tea against prostate cancer, and Dr. Gary Stoner offers research on multiple berry types preventing esophageal cancer. An interesting article on the new era of chemoprevention comes from the group led by Dr. Ramzi Mohammad reporting for the first time the activity of thymoquinone and its synthetic analog in pancreatic cancer. Dr. Zhiwei Wang concludes the research articles by reporting the specific role of FoxM-1 transcription factor in mediating the effects of many natural agents, such as isoflavone and other flavonoids.

Emerging evidence clearly suggests that novel therapeutic strategies must be developed for killing cancer cells that are the root cause of tumor recurrence. Therefore, focused research on elucidating the expanding role of chemopreventive agents not only for primary prevention of cancer, but also for the prevention of tumor recurrence, and further assessing the role of these natural agents for sensitization of cancer cells to conventional therapeutics is warranted. If we succeed, then we may witness the application of newer agents for the treatment of human malignancies with better survival outcome because such strategies would be able to eliminate not only tumor cells but also cancer stem cells (CSC) that are becoming important in drug resistance and are believed to be the root cause of tumor recurrence. Therefore, targeted elimination of CSCs or cancer stem-like cells that are often found in the remnants of tumors after conventional therapies by newer agents would be an important step toward eradicating the root cause of tumor development and progression, which will certainly improve the overall suffering and survival of patients diagnosed with cancers.

In conclusion, natural products play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases, especially cancer. In order for natural product drug discovery to continue to be successful, new and innovative approaches are required. Some of these new approaches may include exploitation of our emerging

knowledge in "omics," searching for natural compounds in the environments that have not been efficiently mined in the past, and applying new screening technologies. However, much of nature remains to be explored, particularly the marine and microbial environments, and the interplay of these sources leaves no doubt that a host of novel, bioactive chemotherapeutics awaits discovery and should be found in order to serve humanity at large.

## INTERVIEW WITH DR. FAZLUL H. SARKAR

*What do you think holds the key to your success as a cancer research scientist?*

It is difficult to measure success; however, if I have achieved anything at all, it would in part be due to my training not only as a basic scientist but as a translational researcher. The success is also due to perseverance, hard work and being surrounded by students and colleagues of superb quality, and finally due to unconditional love and support from my family, without which success would not have been realized.

*What do you consider to be your key research accomplishments?*

My greatest accomplishment includes my diversified research contributions in multiple solid tumors, bringing basic research findings to the clinic, and bringing the concept of sensitization of cancer cells to conventional therapeutics by natural agents that are classically known as chemopreventive agents. In addition, the novel design and chemical synthesis of small molecules derived from the chemical structures of compounds found in nature is a major accomplishment, which is just beginning to be appreciated as a novel drug discovery platform for anticancer agents.

*What was the turning point in your career?*

My molecular biology training at Memorial Sloan Kettering Cancer Center (MSKCC) and the exciting, scientifically rich environment at MSKCC within the close proximity of Rockefeller University and Cornell University School of Medicine surrounded by Nobel Laureates was the most important turning point for my career.

*Who are the individuals who most influenced your research career?*

There are many individuals, such as the scientists who discovered oncogenes and tumor suppressor genes in the early 1980s. Also, my mentors and professors, especially those at MSKCC, had a significant influence on my career. The unconditional love of my sweetest wife, my dearest life partner, and my friend: Arifa, and the support of my children: Sarah, Sanila and Shaan, significantly influenced my career because without their love, sacrifice, and support, my dream to become a successful cancer research scientist would not have been possible.

*Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does this mean cutting-edge science will not likely be featured in the pharmaceutical research?*

It is true that scientists are under enormous pressure to publish research papers in high impact journals. However, publishing special topics and innovative review articles combined with innovative approaches should improve the impact factor of *Pharmaceutical Research*, which would certainly attract cutting-edge scientific articles in this specialty journal for all drug discoveries.

*Where are the fields of cancer chemoprevention and natural products for cancer treatment going? How do the articles in this theme issue fill the gap?*

Although this is a challenging question, the article by Dr. Mehta articulated where the field is going. However, it is important to note that "natural products" are a multi-billion dollar market, and we as scientists are burdened with the responsibility to prove the role of natural chemopreventive agents, not only for primary prevention, but also for the prevention of tumor progression and/or treatment of human malignancies. To that end, the review articles along with selective research articles presented in this theme issue highlight our current knowledge, filling the gap between research and the practical use of natural agents for targeted intervention. The future seems very bright, not only for the use of single or combination of natural agents for cancer prevention and therapy, but for the use of natural agents and their synthetic analogs, which would be the key to success in winning the battle against cancer.

*What are the challenges for cancer chemoprevention, and how can they be overcome?*

There are many challenges, such as educating cancer research scientists who are trained with tunnel vision to open the door as visionary scientists accommodating the emerging knowledge on the role of natural chemopreventive agents toward the prevention and treatment of cancers. In addition, cutting-edge basic science research must continue with recruitment of clinicians for appreciating the enormous potential of natural agents in the field of

cancer so that they can conduct novel clinical trials. Most importantly, none of these is possible without funding, which should remain the focus of advocacy groups in lobbying congress for increasing funding in the field of chemoprevention research.

*What is the key to developing successful collaborative relationships between basic cancer scientists like yourself and more applied pharmaceutical/drug delivery scientists who can help in product development?*

I believe that one of the keys is to educate scientists from different disciplines to see what is out there beyond their own horizons. This could be accomplished by novel cutting-edge articles, such as those presented in this theme issue, for larger audiences in the scientific community. In addition, partnering with individual scientists from different disciplines with a common goal to cure cancer is possible by designing and successfully funding multi-investigator-initiated proposals, program projects and other projects by bringing academic institutions, industries and legislative bodies together with a common goal.

*What is your philosophy of educating graduate students?*

Education and proper training of graduate students, who are the future of humanity, should remain the highest priority. However, we need to build the structure that will provide hopes for a brighter future, and we must train graduate students in multi-disciplinary scientific fields, such as basic science, drug discovery and formulation, and partnership training with clinicians, so that ideas from the laboratory bench can be translated to the clinic. This would be the key for our success in winning the battle against human malignancies.

*What are the challenges facing cancer research and development?*

There are many challenges, such as the lack of well-trained, young graduate students and junior faculty and the lack of funding for conducting multi-disciplinary research for rapid development of agents from the desk of the basic scientists to the hands of pharmaceutical scientists. In addition, the lack of mechanisms for funding the rapid development of agents for pre-clinical toxicity studies and the mechanism of expedited approval of IND from the FDA are the major challenges in cancer and drug development.

*What is the place for collaboration with industry in academia?*

In the past, there has been an active partnership between academia and the industry; however, with increasing financial pressure due to the current economic condition on both academia as well as industry, now is the time that may be more fertile than ever before to foster collaborative research which will eliminate duplication of efforts in basic research and drug discovery. I therefore believe that robust and active collaboration between academia and industry must be developed in order to find a new arsenal to win the battle against human malignancies.

## REFERENCES


1. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. J Nat Prod. 2007;70:461–77.
2. Newman DJ. Natural products as leads to potential drugs: an old process or the new hope for drug discovery? J Med Chem. 2008;51:2589–99.
3. Douros J, Suffness M. New natural products of interest under development at the National Cancer Institute. Cancer Chemother Pharmacol. 1978;1:91–100.
4. Douros J, Suffness M. The National Cancer Institute's natural products antineoplastic development program. Recent Results Cancer Res. 1980;70:21–44.
5. Douros J, Suffness M. New natural products under development at the National Cancer Institute. Recent Results Cancer Res. 1981;76:153–75.
6. Douros J, Suffness M. New antitumor substances of natural origin. Cancer Treat Rev. 1981;8:63–87.
7. Wall ME, Wani MC, Taylor H. Isolation and chemical characterization of antitumor agents from plants. Cancer Treat Rep. 1976;60:1011–30.
8. Wall ME, Wani MC. Antineoplastic agents from plants. Annu Rev Pharmacol Toxicol. 1977;17:117–32.
9. Wall ME, Wani MC, Manikumar G, Abraham P, Taylor H, Hughes TJ *et al.* Plant antimutagenic agents, 2. Flavonoids. J Nat Prod. 1988;51:1084–91.
10. Wall ME, Wani MC, Manikumar G, Hughes TJ, Taylor H, McGivney R *et al.* Plant antimutagenic agents, 3. Coumarins. J Nat Prod. 1988;51:1148–52.
11. Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J Am Chem Soc. 1971;93:2325–7.
12. Wani MC, Ronman PE, Lindley JT, Wall ME. Plant antitumor agents. 18. Synthesis and biological activity of camptothecin analogues. J Med Chem. 1980;23:554–60.
13. Wang HK. Plant-derived anticancer agents currently in clinical use or in clinical trials. IDrugs. 1998;1:92–102.
14. Wall ME, Taylor H, Perera P, Wani MC. Indoles in edible members of the Cruciferae. J Nat Prod. 1988;51:129–35.
15. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life Sci. 2005;78:431–41.
16. Chin YW, Balunas MJ, Chai HB, Kinghorn AD. Drug discovery from natural sources. AAPS J. 2006;8:E239–53.
17. Cragg GM, Grothaus PG, Newman DJ. Impact of natural products on developing new anticancer agents. Chem Rev. 2009;109:3012–43.
18. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Discov. 2005;4:206–20.

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