Editorial

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Insights into Research on Natural Products

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Small, naturally derived molecules are important targets of drug research and development and are models of chemical synthesis. Such molecules accounted for over 60% of the approved drugs and pre-New Drug Application candidates from 1989 to 1995 (*1*). Of the top 35 ethical drug sales worldwide, drugs derived from natural products accounted for 24% in 2001 and 26% in 2002 (*2*). Drug research and development is gaining insights from research on natural products, a new trend that combines traditional methods with new techniques in life science. In addition to research seeking to discover natural compounds through use of isolation techniques and structural determination methods, research to identify new sources of natural compounds and classify their functions and research to modify the structures of those compounds by biosynthetic or chemical manipulation will definitely expand the field of natural product chemistry.

New Sources of Medicines — Natural products were originally small molecules derived from higher plants and microorganisms on land. Plant endophytes and marine organisms represent the dominant source of compounds of pharmacological interest. Ecteinascidin 743 from *Ecteinascidia turbinata* has been developed into an antitumor agent while ω-conotoxin MVIIA from cone snails has been developed into an analgesic, and numerous metabolites have been evaluated in clinical trials (*3*).

Manipulation of Secondary Metabolite Biosynthesis — Organisms biosynthesize specific secondary metabolites catalyzed by gene-regulated enzymes. Elucidation of the pathways of biosynthesis has allowed scientists to manipulate the production of metabolites or increase molecules of interest by either supplying alternative substrates or by artificially altering those organisms. Modifying organisms to improve secondary metabolite production has been an effective means of increasing various natural products and producing vast amounts of specific constituents. The *ttmM* gene, for instance, encodes a C3' hydroxylase in the biosynthesis of tautomycin. Artificial inactivation of this gene has yielded a mutant SB6005 bacterial strain, and fermentation of this strain has yielded three new 3'-deshydroxy tautomycin derivatives (*4*).

Chemical Synthesis — Chemical synthesis of a complex natural product from simple chemicals is a challenge because of the instability, multiple functional groups, multiple stereocenters, and complex framework of target structures (*5*). This challenge has encouraged chemists to identify efficient methods for and strategies of synthesis and has thus encouraged the development of organic chemistry. A large number of molecules and their derivatives have been synthesized, increasing their potential for development into drugs. The synthesis of camptothecin and its derivatives is a topic of great interest in order to establish high-yield strategies and identify potent anti-tumor agents with low toxicity. The camptothecin derivatives topotecan and irinotecan have been approved by FDA and belotecan has been marketed in Korea; some derivatives are in different phases of clinical studies (*6,7*). Chemical synthesis

has now become an active branch of research on natural products. Taxol, epothilone derivatives, and tubulin-targeting drugs have also been synthesized, but they still have a ways to go until they are ready for commercial use.

Biomimetic Synthesis — Nature is an outstanding 'chemist' that promotes highly efficient reactions under different conditions and in a regio- and stereo-selective manner in order to produce complex secondary metabolites. Like of nature's students, biomimetic synthesis prepares natural metabolites by mimicking nature's steps of biosynthesis. Important reactions in biosynthesis such as the Diels-Alder reaction, cyclization of isoprenoids, and oxidative coupling of phenols have been widely used to synthesize natural products (*8,9*).

Learning How Organisms Function — The official goal of research on natural products was to identify bioactive compounds for use in treating human diseases, and this research did not bother with the physiological functions of these compounds in target organisms themselves. However, this research now seeks to determine why such compounds exist and what significance they have. A typical example is resveratrol, a stilbene known for its cardioprotective and chemopreventive effects in humans (*10*). Resveratrol is essentially a toxin produced by several plants in response to infection or other stresses (*11*).

Nature knows best. Natural molecules produced by natural organisms will have greater biological significance as they are used in drug development. Future research on natural products will be multi-disciplinary, including fields such as phytochemistry, organic chemistry, microbiology, pharmacology, chemical ecology, and molecular biology.

References

1. Cragg GM, Newman DJ, Snader KM. Natural products in drug discovery and development. J Nat Prod. 1997; 60:52-60.
2. Butler MS. The role of natural product chemistry in drug discovery. J Nat Prod. 2004; 67:2141-2153.
3. Molinski TF, Dalisay DS, Lievens SL, Saludes JP. Drug development from marine natural products. Nat Rev Drug Discov. 2009; 8:69-85.
4. Ju J, Li W, Yuan Q, Peters NR, Hoffmann FM, Rajski SR, Osada H, Shen B. Functional characterization of *ttmM* unveils new tautomycin analogs and insight into tautomycin biosynthesis and activity. Org Lett. 2009; 11:1639-1642.
5. Peterson EA, Overman LE. Contiguous stereogenic quaternary carbons: A daunting challenge in natural products synthesis. Proc Natl Acad Sci U S A. 2004; 101:11943-11948.
6. Butler MS. Natural products to drugs: Natural product derived compounds in clinical trials. Nat Prod Rep. 2005; 22:162-195.
7. Cragg GM, Newman DJ. A tale of two tumor targets: Topoisomerase I and tubulin. The Wall and Wani contribution to cancer chemotherapy. J Nat Prod. 2004; 67:232-244.
8. Bulger PG, Bagal SK, Marquez R. Recent advances in biomimetic natural product synthesis. Nat Prod Rep. 2008; 25:254-297.
9. de la Torre MC, Sierra MA. Comments on recent achievements in biomimetic organic synthesis. Angew Chem Int Ed Engl. 2004; 43:160-181.
10. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: The *in vivo* evidence. Nat Rev Drug Discov. 2006; 5:493-506.
11. Adrian M, Jeandet P, Bessis R, Joubert JM. Induction of phytoalexin (resveratrol) synthesis in grapevine leaves treated with aluminum chloride ($AlCl_3$). J Agric Food Chem. 1996; 44:1979-1981.

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