Cast aside for years, natural products drug discovery appears to be reclaiming attention and on the verge of a comeback

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The pharmaceutical industry's productivity continues to be dismal. This state of affairs is due to many factors, and one may have been the diminished interest in natural products drug discovery as the industry embraced promising and exciting new technologies, particularly combinatorial chemistry.

However, the tide may be turning, for three reasons. First, combinatorial chemistry's promise to fill drug development pipelines with de novo synthetic small-molecule drug candidates is unfulfilled. Second, the practical difficulties of natural products drug discovery are being overcome by advances in separation technologies and in the speed and sensitivity of structure elucidation. And third, a compelling case is being made for the intrinsic utility of natural products as sources of drug leads.

For decades, natural products have been a wellspring of drugs and drug leads. According to a recent survey by David J. Newman, Gordon M. Cragg, and Kenneth M. Snader of the <u>National</u> <u>Cancer Institute</u>

, 61% of the 877 small-molecule new chemical entities introduced as drugs worldwide during 1981–2002 can be traced to or were inspired by natural products [

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]. These include natural products (6%), natural product derivatives (27%), synthetic compounds with natural-product-derived pharmacophores (5%), and synthetic compounds designed on the basis of knowledge gained from a natural product (that is, a natural product mimic; 23%).

In certain therapeutic areas, the productivity is higher: 78% of antibacterials and 74% of anticancer compounds are natural products or have been derived from, or inspired by, a natural product. These numbers are not surprising if it is assumed that natural products evolved for self-defense. But the influence of natural products is significant even in therapeutic areas for which they might not seem relevant, such as cholesterol management, diabetes, arthritis, and depression.

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