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An insight into the future potential of natural products chemistry: A comprehensive review

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Abstract
This review emphasises the enduring significance and contributions of natural products chemistry in advancing both the physical and biological sciences. It emphasises the interdisciplinary nature of this field and how it has led to the emergence of new avenues, providing innovative applications, valuable insights, a strong foundation, a broad perspective, and a visionary outlook for the future. The article intricately highlights the potential developments in biomedical research, health, nutrition, and other closely related sciences. It touches upon some of the emerging trends within natural products chemistry, discussing their impact on the broader scientific landscape. Furthermore, it highlights core developments, innovative techniques, methodological advances, and potential applications, and how these contribute to the advancement of science as a whole, with a particular focus on natural products chemistry. It then concludes by shedding light on the ongoing progress and developments in various aspects of natural products chemistry, their economic and scientific implications, contemporary objectives, future prospects, and impending goals.

Keywords: Drug Discovery, Immunopharmacology, Natural Products Chemistry, Separation Techniques

Introduction

There has been a remarkable resurgence in the interest surrounding natural products and their chemistry, which has profoundly seen various scientific disciplines, technological advancements, and economic activities being impacted in recent times. This renewed enthusiasm follows a period during which the subject had lost some of its appeal, with several factors contributing to this decline, including a lack of prioritisation, limited access to precise tools and techniques, resulting in hindered progress, waning interest from scientists, outdated analytical equipment, and a shortage of comprehensive academic and industrial programs. Additionally, inadequate financial resources for research and development further impeded the advancement of this enthralling knowledge area.

This decline affected several key aspects

1. Advancement of knowledge: The understanding of their impact on the physical and biological sciences, their interrelation with broader disciplines, and their economic implications suffered greatly.
2. Technological progress: The fields of analytical, biotechnical, and pharmaceutical sciences experienced significant impediments for a considerable period of time.
3. The discipline's validity: Its outreach and role as a modern research tool in chemical sciences for various applications were compromised.
4. Advances in mechanistic understanding: There were setbacks in comprehending biotic and abiotic processes, the environment, ecosystems, and the study of natural products and metabolites.

However, the renewed interest has now fostered a fresh understanding of natural products and their chemistry and has since led to advancements in various aspects, including purification, characterization, structure determination, functional analysis, inter-relational chemical and metabolic dynamics, and diverse pharmacological applications. These advances have contributed significantly to the field, resulting in an unprecedented growth in our knowledge of complex natural products and their implications.

Exploring finer details of the ecological nature of natural resources and their impact on the generation of constituents, as well as their variations in design and diversification, has broadened our understanding of their involvement in the biomechanics of cellular and ultra-cellular processes. This, in turn, has opened up new horizons for research and broader applications in the chemistry of terrestrial species and marine organisms (Atanasov *et al*., 2015) [1]. Notably too, the emergence of alternative therapies, increased interest in ethnobotanical herbs, nutraceuticals, the pursuit of technical products, and the discovery of new drugs and their templates, as well as advances in chemical ecology, genetic profiling, biomechanics, marine chemistry, and plant-microbe symbiosis, have rejuvenated and accelerated progress in the field. Recent discussions on research priorities and reports of natural product isolation from diverse ecosystems, identification of active constituents in traditional remedies, and the search for new compound templates have expanded the search for novel chemical entities and target templates for structurally and pharmacologically diverse bioactive compounds (Li and Vederas, 2009) [16].

The primary role of natural products as a reservoir for solutions in structure, function, reactivity, pathway identification, synthetic route generation, and other chemical challenges in phytochemistry, marine chemistry, chemical ecology, microbial chemistry, functional biochemistry, and macromolecular chemistry has been substantiated (de Smet, 1997; Berman and Flanery, 2001; Kayne, 2002; Fowler and Stepan-Sarkissian, 1983; Fowler, 1993; Scheuler, 1995; Lachance *et al*., 2012; Cordell and Colvard, 2012, Busch *et al*., 2012; Nguyen *et al*., 2008). This reinforces the notion that the discipline continues to play a pivotal role in the future development of chemo-biological, pharmaceutical, health, life sciences, and biotechnology (Newman and Cragg, 2009; Yao, 2004) [20].

Drug discovery

Natural compounds have historically played a pivotal role in pharmaceutical research, with a substantial portion of pharmaceuticals being either derived from natural sources or developed as semi-synthetic derivatives thereof, estimated at approximately 40% (Jacob, 2009) [12]. Early medicinal breakthroughs, including aspirin, digitoxin, morphine, quinine, and pilocarpine, were primarily based on the clinical, pharmacological, and chemical exploration of traditional medicines, largely sourced from plants (Butler, 2004) [32].

The conventional procedure for the research and development of pharmaceuticals based on natural products typically commences with the selection of living organisms for investigation, using various selection methods. Following this, extracts are prepared and empirically assessed for their biological activity through in vitro and/or *in vivo* experiments. Active extracts then undergo a series of iterative steps involving fractionation and further biological activity assessment until individual bioactive compounds are isolated. These isolated compounds have their chemical structures either confirmed or determined through spectroscopic analyses. The traditional methodology has been enhanced by the inclusion of dereplication tools that rely on integrated techniques, which involve the real-time coupling of chromatographic separation instruments with spectrometers such as UV, MS, and NMR. In addition, in vitro bioaffinity assays have been combined with classic chemical deconvolution techniques to expedite the identification of bioactive compounds.

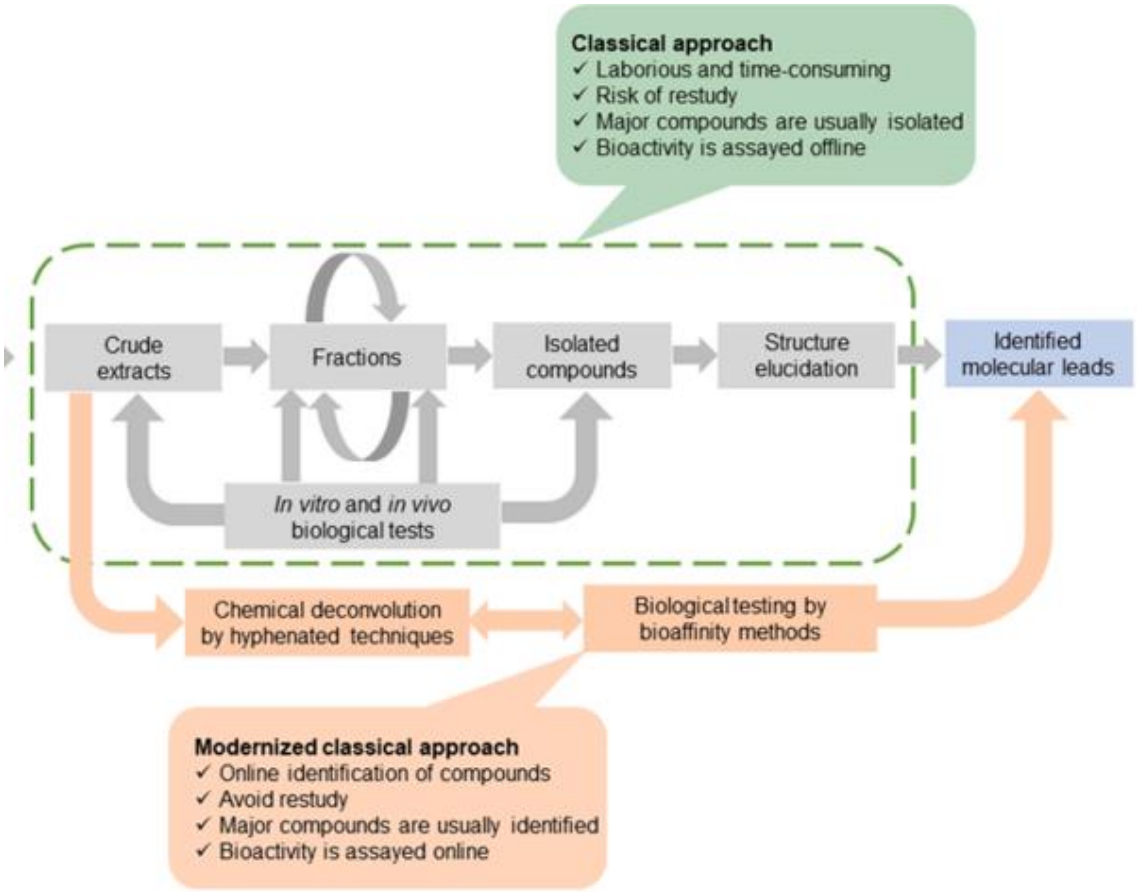
Despite the emergence of alternative drug discovery methodologies, natural products continue to contribute significantly to the discovery of new clinical candidates and therapeutic agents (Butler, 2004) [32]. These compounds remain a noteworthy reservoir of novel drugs, particularly in therapeutic domains related to anticancer, antihypertensive, anti-infective, immunosuppressive, and neurological diseases. A subset of these natural product-based candidates has advanced into clinical trials or even reached the pharmaceutical market (Butler, 2004) [32].

Therefore, in addition to being a proven and important source of drug leads, natural products derived from drugs also contribute significantly to the profitability of many companies.

Natural products research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs by the pharmaceutical industry (Patwardhan *et al*., 2004) [21]. These approved substances, representative of very wide chemical diversity, continue to demonstrate the importance of compounds from natural sources in modern drug discovery efforts (Chin *et al*., 2006). In addition, natural products, containing inherently large-scale structural diversity than synthetic compounds, have been the major resources of bioactive agents and will continually play as protagonists for discovering new drugs. Drug discovery from medicinal plants has mainly relied on biological activity guided isolation methods which have led to the discovery of important drugs (Lahlou, 2007) [33].

The role of natural products in therapeutics has been thoroughly examined and evaluated (Lahlou, 2007) [33]. Natural products typically possess pharmacological or biological activities that make them valuable in pharmaceutical drug discovery and design.Interestingly, even when it is possible to synthesise these compounds entirely, they are still considered natural products. They can be derived from various sources, such as terrestrial plants, marine organisms, or microorganism fermentation broths. Extracts obtained directly from these sources are often unprocessed and contain a wide array of unique and structurally diverse chemical compounds.

Notably, not all natural products can be effectively recreated through chemical synthesis, with many of these substances having intricate structures that make large-scale synthesis difficult. This category includes essential drugs like penicillin, morphine, and, in the past, paclitaxel. These compounds can only be sourced from their natural origins, a process that can be labour-intensive, time-consuming, and economically challenging, while also posing sustainability concerns for the resources involved. Another challenge arises from the fact that isolated natural product compounds often exhibit distinct properties compared to their original natural sources, which have synergies and can combine. A typical example being antimicrobial compounds with compounds that stimulate various pathways of the immune system.



(Cherry *et al*., 2022)

Fig 1: The conventional natural product-based drug development process begins with organism selection using various strategies. Extracts are prepared and empirically screened for bioactivity through in vitro and/or *in vivo* tests. Active extracts then undergo iterative steps of fractionation and bioactivity assessment until individual bioactive compounds are isolated, and their chemical structures are verified through spectroscopic analysis.

This traditional approach gained speed by integrating dereplication tools, employing hyphenated techniques that link chromatographic separation devices with UV, MS, and NMR spectrometers. In vitro bioaffinity assays were also combined with classical chemical deconvolution methods to expedite the identification of bioactive constituents.

Synthetic and Semi-synthetic drugs

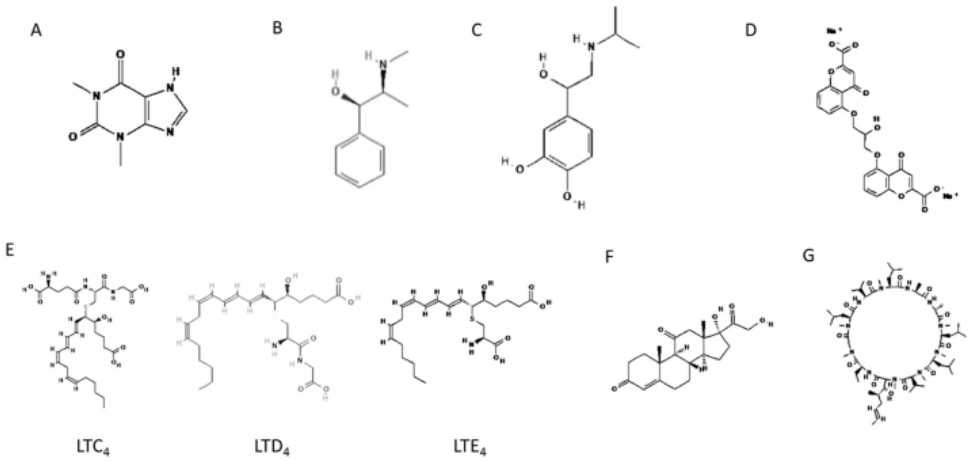
The introduction of synthetic compounds as pharmacological agents established the fundamental principles of contemporary drug development in a more systematic and rational manner. Natural products and their derived pharmaceuticals held sway until the 1980s, accounting for more than one-third of the pharmaceutical landscape. Subsequently, synthetically derived medications gained prominence, constituting approximately half of all pharmaceuticals, while the remaining half continued to rely on compounds sourced from natural materials.

Nonetheless, concerns regarding purported adverse effects and perceived toxicities, coupled with the demand for advanced infrastructure and facilities, strict regulatory compliance, and specialised expertise in the design and large-scale production of semi-natural and purely synthetic drugs, contributed to the expansion of phytochemical and marine-derived medications at a consistent rate. This expansion was concurrent with the development of drug templates tailored to various biological activities. In recent times, the synergy of synthetic methodologies with naturally-derived pharmaceutical compounds and drug templates has significantly propelled the field of natural products chemistry forward. This synergy has underscored the essential interplay between molecular connectivity and structure-activity relationships (SAR), particularly within the context of various natural templates, notably those pertaining to anti-cancer and anti-biotic drugs. Researchers from diverse institutions worldwide have made substantial contributions to this endeavour, as documented by Lal *et al*. in 2013 [15].

Until recently, the global perspective on natural products predominantly considered them as prophylactic agents, nutraceuticals, food supplements, herbal remedies, or complementary and alternative medicinal options. However, the pursuit of safer and more effective drugs from natural sources has gained momentum due to the varying degrees of adverse side effects associated with synthetic drugs used in the treatment of genetic, lifestyle-related, occupational, and chronic diseases. Notably, this shift in perception and appeal has been driven by the immense potential inherent in nature's offerings.

These natural products have traditionally formed a significant component of the pharmacopoeia for tribal populations around the world. This wealth of traditional medicinal knowledge has created opportunities for systematic exploration, including bio-assay guided fractionation and activity localization within the active constituents. Additionally, it has spurred endeavours in the development of synthesis, semi-synthesis, and drug design, all based on the templates provided by natural products. The creation of semi-synthetic analogs of natural products has enabled intricate

modifications of structural features while leveraging insights from SAR and QSAR. This modification can enhance the inherent drug-like characteristics for biological activity without necessarily disrupting the initial molecular template. One notable outcome of this approach has been the ability to cross over from the original natural product templates in terms of clinical significance, generating entirely new biological activities through comparisons, predictions, and the utilisation of in silico activity predictors. Natural products have further served as a viable starting point for generating substances with improved therapeutic efficacy, sometimes unrelated to the known biological functions of the original natural material. Key contributions in this direction have been made by researchers such as DeCorte (2016), Banwell (2008), Galloway *et al*. (2009), Kombarov *et al*. (2010), and Tanaka *et al*. (2009).



(Cherry *et al*., 2022)

Fig 2: Chemical Structures of early natural product-derived drugs. A – Aminophylline (theophylline derivative; B – Ephedrine; C – Isoproterenol; D – Sodium cromoglycate; E - LTC4, LTD4 and LTE4; F – Cortisone; G- Cyclosporin.

The place of natural products in immunopharmacology

The significance of immunopharmacology using natural products is of paramount importance in addressing noncommunicable diseases (NCDs). NCDs encompass a broad spectrum of ailments, including cardiovascular diseases, cancer, chronic respiratory conditions, diabetes, neurological disorders, and various chronic inflammatory pathologies. Research has unequivocally demonstrated the involvement of the immune system and inflammatory processes in most NCDs, which happen to be the leading causes of mortality and morbidity on a global scale (Furman *et al*., 2019).

Concurrently, communicable diseases (CDs) are significantly reliant on immune system responses, but the potential effects of natural products in this regard remain underexplored. The disparities in susceptibility to both CDs and NCDs between affluent and disadvantaged populations are starkly evident. Hence, the role of immunopharmacology in the developing world is instrumental in advancing healthcare.

However, it's worth noting that the Global Burden of Disease (GBD) report published by Goulda *et al*. (2019) has illuminated a demographic shift occurring in numerous sub-Saharan African nations, mirroring the increasing prevalence of NCDs observed in countries like India. This demographic transition poses a growing challenge to healthcare systems in low- and middle-income countries (LMICs), which have traditionally concentrated on combating infectious diseases and maternal/child mortality. In this context, the availability of affordable and reliable immunomodulatory and anti-inflammatory medications becomes imperative. These medications will play a pivotal role in achieving the United Nations' Sustainable Development Goal 3.4, aimed at reducing premature deaths between the ages of 30 and 70 by one-third due to the four major NCDs.

Presently, a wide array of immunomodulators is at our disposal. This spectrum ranges from conventional glucocorticoids, which continue to be widely employed and have demonstrated their efficacy in significantly reducing mortality among severe COVID-19 patients, to a diverse selection of monoclonal antibodies extensively used in treating chronic inflammatory conditions (Schett *et al*., 2019). More recently, checkpoint inhibitors have emerged as a groundbreaking advancement in cancer immunotherapy, capable of enhancing the immune system and curing patients with end-stage cancer. This remarkable discovery was recognized with the Nobel Prize in Physiology or Medicine in 2018, awarded to Tasuku Honjo and James Allison (Kroemer and Zitvogel, 2021) [30].

Nonetheless, a major impediment to the widespread adoption of biologics in LMICs is their exorbitant cost. The potential global market for innovative and established natural product immunotherapies is substantial, and their utilisation could lead to significant cost savings, ultimately improving patient access to these treatments. The ensuing sections will provide insights into the array of immunomodulating agents already available from various natural sources, laying the foundation for further exploration of these resources for the development of novel drugs that target the immune system.

Separation Techniques and Structure Elucidations

The advancement of finer separation, assaying, and detection techniques has played a pivotal role in propelling the field of natural product research forward. The adoption of stable and chemically non-reactive methods for isolation and purification, as demonstrated in studies by Kloss *et al*. (2013) [13], Donia *et al*. (2011a) [8], Schmidt and Donia (2009) [22], Freeman *et al*. (2012) [9], Taylor *et al*. (2007) [26], and Tianero *et al*. (2012) [25], coupled with improved technologies, has led to the discovery of minor-yield products on an unprecedented scale. Overcoming the challenges posed by secondary

metabolite mixtures, molecular associations, polarity-based mixtures, and the influence of biological molecules on preservation, including ionic and non-ionic interactions and deposits, particularly in marine products, has required intricate chemical conjugation and the understanding of physicochemical phenomena, as highlighted by Bedir *et al*. (2002) [3].

The development of analytical techniques in isolation and structure determination has enabled the exploration of the vast and biodiverse natural resources and products for their novel structures and bioactivities, as exemplified in the work of Berkov *et al*. (2014) [4]. The increasing use of non-conventional chromatographic techniques, including Flash chromatography, UHPLC (Ultra High-Pressure Liquid Chromatography), MPLC (Medium Pressure Liquid Chromatography), electrokinetic chromatography, droplet countercurrent, supercritical fluid chromatography, and circular chromatography, alongside gel filtration techniques, has unravelled many mysteries in the fields of detection, isolation, purification, instant constituent screening or dereplication, and chemical profiling and fingerprinting of natural products from diverse sources, as reported by Nielsen (2014), Stege *et al*. (2011) [23], and Hu *et al*. (2010).

In a recent development, a neural network-based descriptor model has been created to predict the chromatographic sequence of natural compounds in a gradient chromatographic procedure. This innovative approach, described by Hou *et al*. (2016), has proven to be highly successful in facilitating the identification of compounds within chromatographic fingerprints, opening new possibilities for compound analysis in this context.

Biochemical Systems, Physiological Processes, Biosystematics, and Chemistry of Natural Products

Biochemical interactions in physiological settings, the progression of reactions, and the implications on the production of response-mediated phytochemicals, secondary metabolites, molecular structures, ion-clustered molecular systems, as well as ionic and non-ionic entities are of paramount importance. Understanding the physiological impact on biogenesis, cellular signalling, and the roles of channels in natural product entities of varying sizes and properties, alongside other targeted chemicals, is best achieved by delving into the biochemical framework. This approach opens possibilities for designing the production of specific plant-based chemicals in tandem with microbial bioengineering to enhance metabolite production. Such understanding should consider the varying physiological roles across different organisms and species.

Experimental release of formed templates within cellular systems and drawing parallels with interdisciplinary science instances can provide valuable insights into these interactions. This knowledge is pivotal for advancing pathways at different stages of natural and induced natural product production in various biochemical and biogenetic settings. Moreover, this understanding can be applied to different levels, including interactions between drugs and receptors and xenobiotic substances in both *in vivo* and in vitro conditions.

The field of cell-based signalling assays plays a critical role, with a focus on their activators, as indicated by McCulloch *et al*. (2009). Additionally, the involvement of TRP (Transient Receptor Potential) channels and natural products in bioactivity and drug discovery, as explored by Appendino *et al*. (2008) and Pillon and Fogliani (2009) [31], has garnered attention. Further developments concern bioactivity enhancements, as discussed by Singh *et al*. (2015), and the intricate mechanisms governing inter- and intra-molecular interactions of different chemo-biological entities within natural biosystems, a field rapidly evolving with implications for various related subject areas.

Exploring the mechanistic pathways in physicochemical and biochemical processes, along with identifying and utilising channels, as mentioned by Marko (2003) [18] and Mori (1997) [19], and understanding their role in biomechanisms, will shed more light on the comprehensive understanding of natural products in these areas. This, in turn, will facilitate the comprehension of various biological factors influencing biogenesis, biosynthetic plans, drug likeness, drug discovery, drug action, pharmacodynamics, ADME (Absorption, Distribution, Metabolism, and Excretion), and the synergy observed in biological activity evaluations across a spectrum of contexts.

Computational procedures and data mining

The rapid advancements in the ever-expanding fields of plant sciences and natural products chemistry necessitate cutting-edge technological progress in computational methods, data mining, and data management. To harness the potential of these developments, such as drug discovery, and to comprehend their broader impact on interdisciplinary sciences, including medicine and veterinary medicine, we must enhance our capabilities for information storage, data mining, retrieval, and ensure the safe and ethical handling of generated data.

Chemical insights are increasingly setting new challenges for bioinformatics and the management of computational resources, with significant contributions from natural products chemistry and chemists. Prediction tools and strategies for understanding various interactions in natural resources, including their potential pathways, biomechanical properties, software development, and other computational methods, offer tremendous promise for the future (Lopez-Perez *et al*., 2007; Nakamura *et al*., 2014; Huang *et al*., 2007) [17, 11].

Conclusion

The significance of natural products as valuable resources for scientific and economic advancement cannot be overstated. These compounds, originating from biochemical processes and physiological conditions, encompass a wide range of applications, from designer foods and their constituents to ecological and environmental investigations. Furthermore, they include secondary metabolites resulting from unusual biosynthesis pathways, marine products, and revisions of traditional herbal uses and ethnobotanical knowledge in underdeveloped regions. Collectively, these contributions have played a pivotal role in changing the negative perceptions surrounding natural products.

Natural products have emerged as versatile building blocks for diverse technical-grade products, offering a preferred avenue for economic gains. They serve as indispensable tools in scientific endeavours, particularly in the field of phytopharmaceuticals and biomedicine.

The advancements in natural products chemistry have not only expanded scientific knowledge but have also led to technological breakthroughs. These advancements have been driven by both direct and indirect influences on other

scientific disciplines, such as the physicochemical sciences, medicine, and various bio- and techno-industrial technologies. As a result, they have significantly contributed to economic growth over the years.

The field of natural products has harnessed the benefits of traditional and local technologies and resource procurement methods, adding to its significance. This discipline's enduring contributions, spanning over a century, have played a pivotal role in the development of chemistry, medicine, and technology. They have also fostered interdisciplinary collaborations, especially in biology, biochemistry, microbiology, chemical ecology, and life sciences. The role of natural products chemistry is ever-expanding, offering promise and opportunities in biochemical, ecological, and medicinal domains. This field holds the potential to provide innovative solutions for understanding and addressing various natural phenomena. It continues to inspire new questions and challenges, further driving scientific exploration.

The future holds great promise for natural products chemistry, with emerging trends and deeper insights into its interplay with the natural and biological sciences. This synergy extends to biotechnology, drug discovery, pharmaceutical sciences, genetics, and chemical ecology. These developments are poised to lead to new avenues for economic and technical growth, solidifying the field's importance. In the current landscape, as the chemical, biochemical, and chemical ecology fields evolve, and commercial research and development expand, the potential for discovering novel phytochemical-based food products, drugs, and other chemically viable items remains significant. Amid economic uncertainties, the advancements in science, technology, and economic progress are closely intertwined with the contributions of natural products chemistry and its researchers. This field is increasingly gaining recognition and importance at various levels.

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