

Natural Product Research: An Immense Hope and Sustainability in Present Time

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Abstract

Natural Product-based drug discovery and development represent a complex, composite and innovative endeavour. It demands a highly integrated interdisciplinary approach and combined proactive participation with all. Several locking and unlocking phases are involved in natural product-based research with a significant number of approaches, explanations, and interpretations. But, the major area of concern needs to be improved. The only way to eliminate all these difficulties by meaningful investigation and rational approaches. The true ambience and encouragement of the natural product-based research still lacking here. It can be possible to overcome with these efforts like positive vision (Focus), innovative culture adaptation (Technology), reducing the knowledge gap (Wisdom) and indeed to change our old mindset and ethos. A few points are highlighting here.

Keywords

Ayurveda, Biopharming, Conflict of interest, Drug Discovery, Natural Product Research, Traditional Chinese Medicine

Introduction

Who can predict that the best natural products-based drugs have been already discovered? Have Nature's chemicals been exhaustively investigated and is the discovery redundancy too large to be pursued? Even though, the breath and momentum of natural products-based research remain impressive and the unprecedented interest of this has been taking place around us, because the beauty of natural product sciences is that it can be performed by several approaches, as far as it is a good-quality science. Certain situations may not merit or encourage to imbibe the natural product-based research here. The reason behind this, a lack of considerable entrepreneurship and non-empathic behaviors of the certain sectors are responsible directly or indirectly for rig the situations.

If you want, looking at the present 'scenario' under the 'microscopic resolving lens' with an open eye, the picture will be different from the Indian perspective as compared to global in the above-mentioned sector. A country like India, which does not belong to the fast-track economic growth zone but a sustainable economy and futuristic prospect always be a beacon of hope, needs immediate attention with intense collaboration with the Private-Public partnership module (P2P) to overcome the situations. Undoubtedly, these kinds of liabilities should bear out by the Govt authority in the right way to take an arbitrary decision (judgmental), introduce firm and conducive policies and sector-wise implementations.

The pathetic situation is now none of the big Pharmaceutical or Biotech companies especially in the health care sector are not paying to heed much attention or not doing any accountable effect to uplift and revitalize these sectors like pharmacognosy/phytochemistry and natural product-based research. Probably as the saying goes- to breathe with oxygen from nature is much beneficial always, rather than artificially breathe in with oxygen, except in case of emergency. When we have enormous resources, a huge amount of fauna and flora are remaining for exploration, then why we are skeptical, hesitate to invest financially and showing our impatience towards natural product-based research, herbal medicine, phytopharmaceuticals, and herbal-nutraceutical or nutraceutical based on natural products etc. It's because we are not focused and low-risk takers apart from these, a mammoth generic and synthetic medicine production houses/lobby play a game-changing role in the pharmaceutical business which has directly or indirectly cast a dark shadow on it. Die-hard dedication in any field of research is always encouraging and if this firm motivation leads to cultivating industrial mobility and contributing towards the country's economic growth and incremental GDP, it must be a welcome stride for all of us. It ought to be the stepping stone for any country to achieve its immense prosperity (i.e., socio-economic benefit and development).

The truths are more or less same everywhere either in India or global. Drug companies stray from their original mission of discovering and manufacturing useful drugs and instead become vast marketing machines with unprecedented control over their own fortunes. The bitter truth is that drug companies funnel the bulk of their resources into the marketing of products of dubious benefit. Meanwhile, as profit soar, the companies brazenly use their wealth and power to push their agenda through Govt agencies,

Regulatory bodies and academic medical centers. When markets fail to generate socially adequate investments in basic research to discover new medicines and for this reason, governments are globally the principal funders and organizers of this type of research. But the development of promising molecules into final products occurs largely under the auspices of multinational companies (MNCs) operating under the imperative of maximizing exchange value. As a consequence, funding for research to development drugs for diseases affecting mainly the poor in low and middle-income countries (LMICs) is dwarfed (i.e., insignificant) by funding of research focused on the diseases and conditions predominant in wealthy markets. Just quoted one example in 2010, the MNCs contributed about \$500 million to this type of R&D, out of total R&D spending by top 50 global companies alone of more than \$100 billion [1]. Indian companies are far behind among the race. We cannot afford as such or as much as a developed country like USA, UK, France, Germany etc., can do. All these countries are investing or funding a huge amount of money to eke out potentially sustainable research as a mission for 'long vision', because, they have different apprehension, liberal attitude, not believe in artificial involvements for easy popularity or introduce tricky business modules to convert quick hefty returns. At least they are paying full respect and attention to a versatile area of research irrespective of any field of research or any new discipline. I am sure, in India, no one is disrespecting our natural or traditional based research but truly, no one even least bothers to take care or nurture it also, or any kind of encouraging activity is not visible in our surroundings, except academic enticement. Few are there, but they are not enough and not doing the remarkable things, for say, I anticipate beyond of this. One such example is "Ayurveda" which is indigenous and had a glorious past but gradually faded away with time. It became more popular in western countries rather than India, the originator; because of its 'holistic approaches'.

There is an urgent need to validate basic principles as well as drugs used in the Ayurvedic system of medicines with the help of advanced research methodology. If, we want Ayurveda integrates well with conventional medicine then researchers should work in line to enhance the core competency of Ayurveda without compromising its fundamental principles and advancements [2]. In a world where western medicine dominates, it's all too easy to say traditional and alternative medicines as a bunch of pseudoscience. However, as research into these alternative systems of medicine continue some time ago. The scientific community and consumers alike must remain open minded to the potential wisdom and efficacy of traditional system like Ayurveda. Often times, there's a reason why these practices have stood the test of time. As we continue to investigate traditional practices like Ayurveda in medical treatment and health promotion studies. Perhaps in the not-too-distant future, a cluster of new compounds may be come up from natural sources which have real promising effects in a clinical setting [3].

Why termination of Natural products-based research by companies?

Most of the generic players are not interested in drug discovery programs because their stakeholders are expecting unrealistic double-digit growth which can be possible to channelize through generic products. After all, a large number of patented and off-patented drugs are in a queue. Besides this, drug discovery is always a risky business venture. Most of the big pharmaceutical companies are encumbered by extensive litigation's, involves in competitive marketing, bearing huge financial crisis due to large sum of acquisition cost [4] besides this, if any firm actively participating in research and development works and fortunate enough to producing any new molecules for any therapeutic indication but, getting an approval to become a cumbersome job for them from any regulatory agencies like FDA, CDER, EMAR etc. The things have been echoed in the published journal 'Despite unprecedented investment in pharmaceutical research and development, the number of new drugs approved by the USFDA remains low'. In the past 60 years, the pharmaceutical industry has delivered over 1,220 new drugs that have played an important part in improving public health and extending life expectancy by an average of 2 months each year [5]. Eventually, it was also reported, 45 new drugs were approved by US FDA in 1999, only 21 were approved in 2010, 35 in 2011, 39 in 2012, 45 in 2015, 46 in 2017, 59 in 2018 – 2019. Stringent norms have been followed in the approval process without compromising the safety and quality which has indeed led to efficacious drugs coming up in the market. The R&D model that has powered that success, however, is showing signs of fatigue: costs are skyrocketing, breakthrough innovation is ebbing, competition is intense and sales growth is flattening. This cluster of symptoms has often foretold major disruption in other industries.

Other factors: Conflict of Interest -

Two decades back, the prevailing sentiment was swirling in many pharmaceutical companies that natural products sources are a difficult effort with a high probability of duplication, that is, the result may be a known compound that cannot be patented. Assuming less than 1% of microorganisms are easily cultured and perhaps fewer than 15% higher plant species have been examined for bio-activity. Certain insects and other animals have been targeted for specific bio-activity, such as toxins but are not generally subjected to HTS screening. It concluded that biological resources are available throughout our surrounding, but access and examination are problematic especially if there is pressure for a short time frame for the discovery of new leads [4].

Universal Legal Acceptance -

Convention on Biological Diversity (CBD), ecological and legal consideration and 'bioprospecting' leads [6] to unfavorable situations for drug discovery through Natural resources especially in plants, which have tremendous biodiversity and wildcrafting nature found across the global territory.

Broad Spectrum Technical Complexity-

Common incompatibility of natural products with HTS requires sophisticated instrumentation, appropriate methodological adaptations and understanding (i.e., statistical considerations to determine the threshold at which a compound is recognized as an active compound) [7]. Natural products identification process are slow and complicated, because of complex chemical structure (i.e. Presence of numerous oxygen-containing substitution and chiral centers, total synthesis become great difficulties and time-consuming) therefore, to determine or pin down its precise molecular mechanism of action is really a challenging task, and very often it has been proven failure due to lack of coordination between multidisciplinary researchers, otherwise, a lot of discrepancies are observed between the non-equilateral teamwork. The resultant effect ultimately come out with much ado about nothing.

Bearable expenditure:

After conducting extensive clinical studies, data generation and interpretation process - 'combo package' is very costly, tedious, and time-dependent until and unless a linear correlation found out from *in vitro-in vivo* studies. Launching these episodes successfully requires an enormous expenditure and powerful propaganda which is quite tough for a medium or small size company furthermore, it's not possible without a quantum of favouritism, proactive involvement, or any sort of persuasion evolve out from the big pharmaceutical companies. If this was not the case then perhaps the scenario today would have been quite different. It is a matter of willingness and passionate approach of companies towards the betterment of mankind. Nevertheless, they are not doing any charity as they are gaining notable wealth and fame in return. Some well-funded research laboratories (*viz.* renowned Universities) are doing a great job in the field of research, unfortunately, they are at the penultimate stage - looking for a 'saviour' who should come forward to rescue them.

The ambiguity or inexactness of patentability:

According to a new guideline imposed by the US Patent and Trademark Office like "Guidance for determining subject matter eligibility of claims reciting or involving laws of nature, natural phenomena & natural products". A marked difference should prevail between a 'novelty', 'obviousness' and 'descriptions'. Further, it became too complicated, when the Supreme Court introduced the 'Mayo versus Prometheus theory'. Now the major issue crops up about the ambiguity in patenting or exact interpretation of patentability. Industries are neither interested nor want to be involved in such a complicated business [7],[8].

Way to develop a renewable interest in natural product-based drug discovery

What are the prominent steps we should follow enhance, and accelerate drug discovery from natural sources? The first thing, several interlocking phases of exploration of natural sources can be considered such as, access to the biological resource, to find out useful activity needs appropriate screening of that resources, analysis of the structure of the key compounds first and deprioritization others with less focused diversification, generation of analogues for optimal activity not likely other synthetic compounds libraries which has similar generation strategies, overlapping issues and nonlinear correlation between potency vs kinetics (i.e. pharmacokinetics).

If you want diversity-oriented bioactive compounds with different chemical scaffolds, certainly the plant kingdom is the right choice for now [9]. A huge number of plant compounds are not well investigated pharmacologically [4]. According to the International Union for Conservation of Nature (IUCN-2015) listed down approximately 310,000 plant species among them few are endanger [7]. Now the time has come to explore them potentially. A search was made related to 'diversity of the origin' in natural compounds, based on an extensive survey report (published data) reveals that plants are still the main source of 'new' natural compounds therefore, natural chemistry is more advanced than organic chemistry and requires substantial amounts of effort [10].

The knowledge about traditionally used medicines (like Ayurveda, CHM, Kampo) or ethnic medicine (*viz.* Dai medicine, Tibetan medicine, Yi medicine, Miao medicine and Naxi medicine) based on ethnopharmacological concepts should utilize as much as possible at urgent basis before going to disappear its flavour forever. TCM is far ahead [11] as compared to Indian and western chapter because, it had been conceptualized the traditional wisdom and evaluated them (i.e., natural-based compounds, extracts etc.) scientifically through evidence-based studies before induced them into the modern system of medicine (i.e., mainstream) therefore, its usages were adopted or found in China Health Care system [12],[13].

Drug discovery strategies based on natural products and traditional medicines are re-emerging as attractive options. Drug discovery and development need not always be confined to new molecular entities. Rationally designed, carefully standardized, synergistic traditional herbal formulations and botanical drug products with robust scientific evidence can also be alternatives [14]. Bridging Ayurveda with evidence-based scientific approaches in medicine, paving the way for drug discovery approaches [15]. Genome-wide analysis correlates Ayurveda Prakriti (nature of the body in terms of *dosha*), DNA barcoding was recently used to test the authenticity of herbal products etc., are the new approaches for innovations [16].

The advent of novel technology including state-of-the-art techniques in bioinformatics, cheminformatics, and knowledge engineering or semantic (i.e. relating to human interpretable meaning) for data-driven drug discovery from natural products become more evident nowadays[17], therefore, we should know how Cheminformatics is functioning; the invention of entirely new approaches for predicting the bioactivity of the molecules, it can be either direct measures of chemical activity (e.g. Chemical constants, reactive

groups or ADME measurement), or indirect measures (e.g. structural motifs, compound class membership, or other higher-order observations). The well-advanced research communities are adopting these tools-Quantitative Structure-Activity relationships (QSAR) studies, molecular Docking and dynamics, computational mutagenesis, and Library construction to find the hit to lead more precisely. Similarly, Bioinformatics that cover anything related to biological functions (i.e., organism producing the compounds) of potential drug candidates, including sequence-based characteristics, interactions with body structure (metabolites, proteins, cell, tissues, etc.), pathway perturbations, and toxicity, among others. Multi-omics and high-throughput sequencing are also major areas within bioinformatics [11].

Other approaches like genetic and metabolic engineering to increase in *planta* production of key metabolites (i.e., metabolon formation) of medicinal interest for Plant and microorganism etc., therefore, 'Biopharming' is a favourable option for pharmaceutical development now. For example, sweet wormwood is a rich source of terpenoids and terpene precursors. Using *Agrobacterium tumefaciens*-mediated transformation, the taxadiene synthase gene from *Taxus* was used to express the taxane biosynthetic pathway in sweet wormwood. Due to competition for FPP between the taxane biosynthetic pathway and the artemisinin biosynthetic pathway, taxadiene was produced at the expense of artemisinin. However, as the plants matured and FPP was no longer limiting, metabolic flux shifted, and the transgenic plants produced artemisinin at levels comparable to that of the wild type. Interestingly, the production of both compounds caused no significant decrease in the vitality of the plants or dried biomass. Moreover, the highest accumulation of each compound was segregated between plant organs, with artemisinin concentrated in the leaves and taxadiene in the stems. This spatial separation suggests that sweet wormwood could be employed for the dual bioproduction of both [18].

Artificial intelligence (AI) will become a fundamental aspect of, and the basis for, effective natural product research especially for 'eco pharmacognosy's which, was developed as both a philosophy and a practice, from which the necessity for a 'medicines security' strategy evolved, means; analyzing the need for sustainable medicinal plants in an emerging, ageing population model would therefore seem to be an important global research area for developments and corporations to collaboratively develop accessible (sustainable and affordable) products to meet future patient requirements as part of a large program of embracing medicines security as a policy issue[19].

Concluded remarks

It is fundamentally true that any approach towards discovery has its inherent difficulties and biases but, in the end, shows complimentary contentment. The low success rate of drug discovery requires a paradigm shift for innovative drug development strategies. Many individual efforts have been proven unsuccessful or failure, whereas the larger collective effort increases the odds of creating a successful therapeutic. Ultimately, the contradictions within the current drug discovery/development paradigm may be unresolvable and require a 'scientific revolution' in which completely new and noncumulative ideas are established and implemented to solve contemporary challenges. If we narrow down all the challenges, they are 1) organizational effectiveness; 2) significant knowledge gaps; 3) partnership/collaborative mindset; 4) key stakeholder interest; 5) reforms regulatory and patent system; 6) social and/or political changes, including more emphasis on care than cure and /or on prevention [5],[20],[21],[22]. Perhaps It could be the major reason for increasing the acceptance of the society for natural based products. Naturally occurring compounds, - known as 'natural product' a wide variety of structurally complex natural products- have had a long-standing role in the process of drug discovery and pharmaceutical industry [13], [23]. Therefore, innovative drug discovery from natural products will potentially increase the success rate of new therapeutic moieties, the resultant effects of this several blockbuster medicine/drugs have been evolved out from time to time from natural product-based research and discovery. Hope, the sequel would be continuing in future also if natural products-based research gets back its sovereignty and 'glorious past'. Henceforth, we can assume drug discovery and natural products is not the end of an era, it is an endless frontier in the future. It is a collective effort by all; researcher, academicians, entrepreneurs, industrialist and overall Govt agencies of the country should provide a tremendous support to imbibe the natural product-based research to become more sustainable things at present timeframe.

Abbreviations

GDP: Gross Domestic Product

FDA: Food and Drug Administration

CDER: Center for Drug Evaluation and Research

EMAR: Electronic Medication Administration Records

HTS: High throughput screening

CHM: Chinese Herbal Medicine

ADME: Adsorption, distribution, metabolism, and excretion

Kampo: Traditional Japanese Medicine called as Kempo.

FPP: Farnesyl diphosphate

Conflict of interest: This article contributes evidence based facts and author's own perceptions therefore, author declare no conflict of interest.

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