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Minireview

Evolution of modern age drug discovery of lipopeptides and computer-aided drug discovery in India

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The endeavor has been attempted to present a review on the evolution of modern age drug discovery in India. The contribution of next generation therapeutics options microbial metabolites and the computational drug discovery aspects to the global market from India have been represented. Microbial metabolites such as lipopeptides and peptide therapeutics are gaining worldwide importance due to their multiple applications as broad-spectrum antimicrobial, antiviral, anticancer properties *etc*. Due to the surge of microbial resistance, tumor resistance, and ongoing pandemic due to constantly mutating corona virus, there is a need to develop next-generation therapeutics options from natural origin, less toxic to the environment, and have higher specificity towards target. Small molecule therapeutics are certainly less specific towards cancer targets hence the cytotoxicity is a major issue in cancer treatment while drug resistance due to the mutations are coming as challenges every day for drug discovery researchers. Microbial lipopeptide reserves a sweet spot in between the small molecule inhibitors and peptide therapeutics because of their amphiphilic compounds consist of a fatty acid side chain and a cyclic peptide moiety of hydrophilic nature. The computational drug discovery approach accelerates the drug discovery process due to the advancement in supercomputer facilities provided by various funding agencies such as the Department of Biotechnology (DBT) and the Department of Science and Technology (DST) in India. The current review article is focusing light on the research contribution of Indian Scientists and Govt. of India in the field of lipopeptide-based research and applications of Computer-aided drug discovery.

Keywords: Antimicrobial resistance, Computer-aided drug discovery, Evolution of drug discovery, Lipopeptides, Microbial metabolites, Role of Indian pharmaceuticals

Introduction

Indian civilization is very rich in natural medicine from the ancient era. It is one of the most abandoned civilizations in the world that has a fully developed system for traditional medicine. According to the WHO (World Health Organization), 80% of population of the developed countries still believe in traditional medicine. Though the modern medicine has also found its niche in India. The new formulations are appearing more frequently in India. Medicinal chemistry efforts are going with a significant amount on various natural therapeutics in an attempt to discover novel and more potential leads. The first synthetic drug developed in India through a modern approach was Urea Stibamine by UN Brahmachary in 1922 for the treatment of visceral leishmaniasis. In the early 20th century leishmaniasis was one of severe health burdens in India and it was a life-saving drug for a greater section of the population. In history, it was a second developed drug against infectious disease after the discovery of Salversan (Syphillis) and it was discovered before sulfa drugs or penicillin. The first drug developed in India *i.e*., urea stibamine is still being used in various countries in modified forms[1].

Competitive Market

The Indian pharmaceutical market was sharing 5% of the Indian market and the global pharmaceutical market was 95% in 1969. The current report of 2020 suggests a reverse, where Indian pharma has an approximately 85% share with a 15% global share. During the last 50 years after the independence, Indian pharmaceutical firms have gained success in terms of fulfilling the domestic needs and leading the landscape of global pharmaceuticals as well. Already, India is contributing more than 20% by value of the generic market globally, with over 40% of Indian products by volume of US drugs. The crisis of COVID-19 has provided an opportunity for the pharmaceutical industry of India to participate as a major contributor to global healthcare. India has the potential opportunity to play an important role as the 'pharmacy of the world'[2].

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Increased research

The Indian pharmaceutical sector is at the cusp of the design and development of novel compounds for the treatment of various diseases at scale. Various molecules are under clinical trials by Indian firms. Development of new drugs incurs huge costs and the government also needs to provide investments with sufficient profits for new compounds while holding the accountability of the firms for the production of new drugs from India and the world.

Currently, the prices for Indian medicines are the lowest in the world. Additionally, the research conducted by IIM-Ahmedabad revealed data for 2011-2018 on 108 compounds that the affordability and accessibility have not increased by price control. Hence, there is an urge to finetune the pricing policy for drugs to generate sufficient surplus to put into the invention of new drugs while maintaining the reasonable price levels along to facilitate the affordable healthcare[2].

In the above context, the R&D of Indian pharmaceuticals can be boosted by the government by implementing the accelerated and streamlined testing and regulatory pathways for the drugs under development. A long-term thrust can be provided to Indian pharmaceuticals by increasing the overall innovation in the R&D. The major recommendations to enable the moves are encouraging the R&D outcomes and expenses, increasing the funds available for R&D and generating a closed process of cooperation amongst the public research institutions such as CSIR labs, IITs, and NIPERs with private research labs[2].

The pharmaceutical industry of India is a strategic industry for the country, using advantage in scale as gained $37 billion for the year 2019-2020, it was a 1.5% direct and 3% indirect contribution to GDP. This is an industry with a global reach and is an earner of foreign exchange of annually over $10 billion. The Pharma sector has the capability to do for India as it was done by IT sector in 1990s and 2000s. This is the moment that can trigger to accelerate the movement to become the 'Pharmacy of the world'[3].

Foundation of current era drug discovery: Evolution of drugs

The discovery of synthetic drugs through chemical methods were started heralding from the early 1900s, it was the foundation of pharmaceutical industry. Various drugs were mined through research and underwent manufacturing but most of them were therapeutic purpose drugs instead of disease cure. The beginning of 1930s was the period when screening of natural compounds, their isolation and the active ingredients of natural origin caught the attention. The active compounds are generally the synthetic version of natural compounds. The synthetic forms which are known as new chemical entities go through various tests and iterations to ensure their effectiveness, potential and safety. In the later phase of 1970's, product development from recombinant DNA technology by utilizing the cellular and molecular biology information, the biotechnology industry was commenced and together with pharmaceutical industry along with the knowledge of mechanisms of disease cause have made possible the use and development of drugs. The research results of Human Genome Project in 1990s to early 2000 have opened a plethora of opportunities to develop drugs for specific disease-causing target sites[4].

Drug discovery from microbial origin

Microorganisms are one of the prominent sources of natural compounds and produce an enormous number of primary metabolites. Bacteria contribute significantly in the various sphere of lives of plants, human and veterinary. Natural biomolecules obtained from microbes have proven value in pharmaceutical, agriculture, nutrition and healthcare. Primary metabolites of microbes such as peptides, organic acids, alcohol biosurfactants (lipopeptides) and enzymes are used in pharmaceuticals and nutrition as well as for industrial commodity production through biotransformation. While organic compounds are extracted from plants are secondary metabolites. Furthermore, microbes and their metabolites play an inevitably significant role in the development of sustainable agriculture as well, hence act as chief recycler for environment[5,6]. As per the reports from BCC (Business Communication Company), the global market for microbial products was estimated to be USD 143.5 Billion in 2014 and with the CAGR (Compound annual growth rate) of 8-9% is projected to reach USD 250 Billion in 2025. India secures a under top 6 position following, North America, Europe, China, Japan, Middle East and Africa in utilizing microbial product in industrial market. The bigger size of healthcare market represents the importance of microbial metabolites in biopharmaceutical market[6].

The very first commercial production from microbes was reported in back 1750. The serendipitous invention of penicillin in 1929 by Fleming is a classic example of exploring microbial products for medicinal purpose. It has drawn the attention of scientists to investigate the medicinal properties of microbial products to combat the life-threatening diseases. During the World War II the mass production of antimicrobial therapeutics by surface culture methods till 1960's, is known as golden age of antibiotics. The derived microbial products are inevitably used to cure and control the infectious diseases in role of antibiotics, immunosuppressants, antiparasitic agents, cholesterol-lowering drugs, antitumor and antithrombotic *etc*[7]. In this communication, we are precisely reviewing the role of microbial metabolites like lipopeptides and computational drug discovery approaches and their evolutionary status in Indian pharmaceutical market.

The global threat from microbial resistance (AMR)

The microbial resistance has aroused as a serious threat to the global healthcare which requires immediate attention in long term by the developing of next-gen therapeutics. The current therapeutics have limitations to curb the menace because of the microbial ability to evade the mechanism of drug action. Majorly, small molecule drugs are used for antimicrobial therapy. The current trend from the drug discovery reveals a surge in peptide therapeutics as candidate drugs as they offer inevitable advantages comparative to small molecules. The last decade, suggests many success stories of peptide-based drugs and have gained FDA approval as well (Food and Drug Administration). This success is attributed with selectivity, specificity, efficacy, less immunogenicity, less cellular accumulation and high penetration ability into cells and tissues. Keeping the enormity of antimicrobial resistance (AMR) in consideration, microbial peptides are a viable alternative over current therapeutic strategies. Microbial peptides give an abundant opportunity to develop semi-synthetic peptides. They also possess with a broad-spectrum antimicrobial activity and have ability to curb the microbial resistance mechanism[8].

Microbial lipopeptides as promising drug candidates

Lipopeptides are microbial metabolites majorly produced from *Bacillus* genus bacteria. *Bacillus*species are known as the microbial factory for the production of lipopeptides. These are amphiphilic compounds which are composed of a hepta to deca amino acids containing cyclic peptide moiety which is attached to fatty acid chain of C13 to 15. Due to the presence of varied length fatty acid chain, lipopeptides are found with hydrophobic property as well the hydrophilic property due to the cyclic peptide. The amphiphilic nature of these compounds poses them into the category of biosurfactants, which are of various applications into pharmaceutical, food, cosmetics and processing industry[9]. One of the prominent applications of lipopeptides are their medicinal property which is ranging from broad-spectrum antimicrobial, antifungal, antiviral, anticancer, antithrombotic, antiobesity *etc*. Surfactin, iturin and bacillomycin are the major class of lipopeptides which have been explored extensively for their properties in cancer research, antimicrobial resistance and crop protection in agriculture[10]. Lipopeptides were first reported with the octapeptins family of cyclic lipopeptides in 1970's that is after the independence of India. At that time, the reports on antibiotic activity of octapeptins against polymyxin-resistant microbes caught the attention. In the last 50 yrs of research various scientists have explored their applications. The advent of the drug-resistant of Gram-negative bacteria has provoked their rediscovery. The discovery of polypeptide antibiotic polymyxins was done in 1947 and soon it was introduced into the medical field in 1950s. Over the 10 yrs, various pharmaceutical research and academic groups performed extensive research and applied programs of medicinal chemistry to discover novel lipopeptides with potential efficacy and improved safety profiles[11].

Extensive chemical usage for controlling plant pathogens have also disturbed theecological balance of soil inhabiting microbes, this led the occurrence of resistant pathogenic strains, contamination to ground water and obvious human health risks. This was one of the ecological challenges faced by plant pathologist and microbiologists to develop environment friendly alternatives to the chemical pesticide to overcome the crop diseases[1]. The continuous increase in drug resistance of bacteria has provoked an urge to develop safer antimicrobial molecules such as lipopeptides for the clinical applications along with daily products and food preservation as well. The demand for lipopeptides surging due to their multiple applications in human welfare. The first lipopeptide antibiotic was approved by USA in 2003 with trade name Cubicin for Daptomycin. It is the first cyclic lipopeptide

approved by FDA for the treatment of severe skin and blood infections of Gram-positive bacteria. The lipopeptides have been reported with annual US revenue of more than USD 1 billion and their use have got approval in over 70 countries. Bacteria from *Bacillus* genus are potential microbial factory for the large-scale production these active biomolecules[12].

Indian scientists have extensively reported lipopeptides since early 90s for their various applications. Dr. R. K. Sen *et al*., have explore marine lipopeptide iturin for the potential anticancer activities against breast cancer. The efficacy of marine lipopeptide were reported in MCF-7 cell lines. Khemraj Meena *et al*., have reviewed over the applications of lipopeptides and suggested the wide applications of surfactin as anticancer, antiviral, immunosuppressant, antifungal, antimicrobial, anti-obesity and anti-thrombolytic agents. M. Kanlavavattanakul *et al*., has written on the role of lipopeptides in cosmetics industry[13]. S. M. Mandal have reviewed the controlling the microbial infection through lipopeptide therapeutics[14]. R. Sen *et al*., and group have conducted studies on the genetics, biosynthesis aspects for optimized production of lipopeptides[15]. J. Satya Eswari *et al*., have reported various computational studies to decipher the mechanism of action of lipopeptide based antibiotics[12]. Biolarvicidal and vector control applications are reported by P. K. Mittal *et al*[16]. Sivapathasekaran *et al*., performed anticancer studies on marine lipopeptides and reported notable outcomes from India[17]. Antiadhesive activity of microbial surfactant are explored by R. Sen and group. The isolation, structural evaluation and antifungal activity of novel lipopeptide kannurin K. Ajesh *et al*. I. Geetha *et al*., studied mosquito pupicidal activity od *Bacillus subtilis* metabolites[18].

Synthetic lipopeptides are used widely in vaccine as adjuvants which facilitates the enhanced immune response. Lipo-Nter, a novel adjuvant is a recombinant lipopeptide derived from bacteria is capable to induce antitumor activity as compared to synthetic lipopeptides. Surfactin is a principal representator of the lipopeptide family produced by *Bacillus subtilis.* The remarkable surface-interfere and membrane-active properties of properties exerts numerous biological responses leading to the notable achievements in healthcare and biotechnology. These properties make it a potential drug candidate to resolve various global issues in healthcare, medicine and environmental protection[10].

Inclusive coverage of evolution in computer-aided drug design

Computer-aided drug discovery is revolutionary paradigm for pharmaceutical and medicinal research. The accomplishment of human genome project in 2003 has bombarded with increased therapeutic targets to discover new drugs. At that time, the development of crystallographic and spectroscopy techniques along with high-throughput purification of proteins have contributed in structural resolution details for proteins and receptor-ligand complexes. Such advanced strategies allowed computational methods to permeate into the various aspects of modern drug discovery[19], such as molecular docking, virtual screening, hit identification and lead optimization methods. As compared to the traditional *in vitro* and *in vivo* experimental techniques for high-throughput screening (HTS), virtual screening is a direct and rational approach for drug discovery and novel drug design and incurs effective screening and low cost.

In structure-based drug design, the most important method is molecular docking is utilized since the early ages of 1980s[20]. Various algorithm-based programs were developed for to conduct molecular docking experiments. This has made molecular docking one of the unavoidable applications in medicinal research. Various successful applications of molecular docking have been reviewed and published and the comparative studies to evaluate the performs of the software programs were conducted[21]. The *in silico* expression for computational methods for simulating drug discovery was first used in 1989[1]. In the era of drug discovery, it is an indispensable workflow as the various stages for novel drug design provides greatest opportunity with cost effectiveness and less time-consuming. The entire drug development process takes 12-15 years with approximately USD 15 billion which is seen to be accelerated by *in silico* techniques through speeding up the design and discovery with reduced expensive experimental efforts[19,20].

Drug Discovery Research in Indian Public Funded Organizations

Many laudable initiatives have been takes by various scientific government departments such as NMITLI (New Millennium Indian Technology Leadership Initiatives) and OSDD (Open Source Drug Discovery) by CSIR (Council of Scientific and Industrial Research. BIRAC/BIPP (Biotechnology

Industry research Assistance Council/Biotechnology Industry Partnership Programme by DBT (Department of Biotechnology) Govt. of India, which have aimed to bridging the gap between the private industries and public funded research institutions through the collaborative programs for drug discovery. Such collaborative drug discovery programs in public funded organizations have resulted in the invention of novel formulations and important lead compounds. Twelve new drugs have gotten the DCG India (Drug Controller general) approval from Central Drug research Institute Lucknow (CSIR-CDRI) itself. AN antimalarial synthetic molecule from endoperoxide family is undergoing clinical trial phase I. A synthetic molecule S002-333 and S007-867 for cardiovascular disease, have been developed as potential inhibitors targeting collagen induced platelet aggregation and adhesion for therapeutic applications for the treatment of coronary artery disease (CAD) and thrombotic cerebral stroke. The collaborative research of CSIR-IIIM Jammu and Cadila pharmaceuticals have discovery a novel combination drug Risorine.8 for Tuberculosis (TB) in 2009. These are the few of the examples. Figure 1 is depicting the market share of Indian pharmaceuticals. The research in protein and peptide therapeutics has progressed towards clinical phase trials in India. The initiatives have been taken for biggest challenges to develop drugs for neglected diseases due to the small market size in financial terms. The new approach has been established to conduct the research on new molecules targeting neglected disease through open-source mode. OSDD program from CSIR is a team from consortium of India to attain partnership with global platform with the vision of providing affordable healthcare for developing world though creating a global platform where the intelligence and best of minds can come together to collaborate with collective endeavour to resolve the complicated issues associated with the discovery of novel therapeutics for neglected tropical diseases such as malaria, tuberculosis, leishmaniasis *etc*[1].

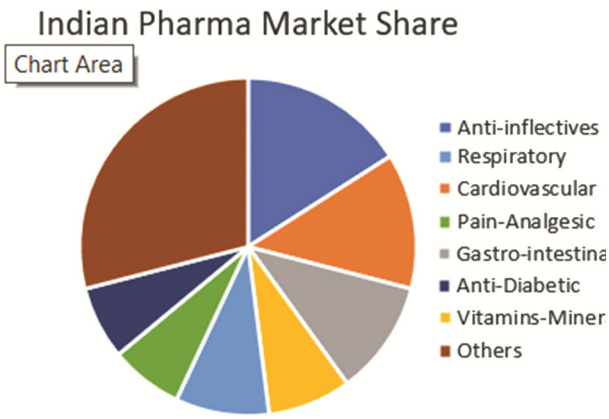

Fig. 1 — Indian pharmaceutical market share

Conclusion

In this review article, an endeavour has been made to provide evolutionary development of drug discovery form India and the status at global platform. From early development of traditional medicine to modern drug discovery age has portrayed India as one of the leading contributors in pharmaceutical research. The modern drug discovery incorporates the discovery of novel next-generation therapeutics such as peptides and lipopeptides, that which also from the natural origin and microbial origin along. This is facilitated by the modern computational drug discovery facilities provide by various government research institutions of India. The drug discovery fraternity of India caters to numerous demands, access and affordability. On the other hand, manages a plethora of life-threatening diseases, few of them are less prevalent in other countries such as tuberculosis. The generic industry has facilitated India using self-sufficient manufacturing capability for the drugs which not under patent. Although, the only single larger barrier which lags India is, being able to provide access to healthcare for under patent drugs. It is also unlikely, that in the near future, the scenario will also be managed as affordability.

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Conflict of interest

All authors declare no conflict of interest.

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