The Evolutionary Insights in Drug Discovery

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Abstract

Drugs play a vital role in the betterment of humanity; remedies are discovered to treat diseases to eliminate suffering. This chapter will give a deep insight into how drugs are discovered, from a long era ago to modern times, computational and targeted therapies. The chapter begins with a historical touch, initiating from the traditional remedies to step into new pharmacology; both are included in a scientific discipline. By including evolutionary principles, such as natural selection and resistance mechanisms, scientists have revolutionized the discovery and improvement of drugs, specifically in addressing hurdles like resistant antibiotics and disease emergence. Antimicrobial resistance is one of the biggest and most serious threats to human and animal health worldwide. The contribution of natural products from microorganisms, plants, and animals is considerable, ensuring their importance in therapeutics such as paclitaxel and artemisinin. The discovery of drugs has achieved improvement from typical traditional methods to innovative modern phases, which include principles of evolution, computational approaches, and technological enhancement. The role of natural products is still leading to the reduction of suffering and improvement of health quality.

Keywords: Drugs, Pharmacology, Antibiotics, Disease control, Natural resources

Cite this Article as: Anisa, Shehzadi F, Noor A, Zafar L, Iqbal A, Moavia U, Raza MQ and Asmat-ullah, 2025. The evolutionary insights in drug discovery. In: Farooqi SH, Kholik K and Zaman MA (eds), One Health Horizons: Integrating Biodiversity, Biosecurity, and Sustainable Practices. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 258-265. https://doi.org/10.47278/book.HH/2025.244

A Publication of Unique Scientific Publishers

Chapter No: 25-035

Received: 13-Feb-2025
Revised: 31-March-2025
Accepted: 13-Apr-2025

Introduction

A drug is a chemical substance used to treat diseases and produce biological effects on living organisms (Elshafie, 2023). Our body and brain are affected by these drugs which also cause mood swings or changes in feelings. Drugs also affect our mental and physical state. In most common diseases treatments such as cancer drugs are used. The combination of drugs works well together to enhance their effect but sometimes they counter one another in ways which reduces the desired effect (Caminero et al., 2010).

Evolution helps us understand ourselves and the surrounding world. So, evolutionary thinking is increasingly being incorporated into other disciplines involving environmental science, conservation biology, human health, agriculture, and natural resource exploitation. Evolutionary principle plays a vital role as they help in understanding the differences and their responses and the fact that how will we change our environment in to order meet these differences (Nanglu, 2023).

History

Drug discovery involves a long history. They belong to the beginning of human culture. In ancient times the treatments were discovered through nature by using animal and plant extracts for the treatment of diseases. Modern drugs were discovered in the 19th century. In the development of new medicine, macromolecules were used (Hughes et al., 2011; Mohs and Greig, 2017; Villoutreix, 2021). For small molecule drug discovery, the Food Drug Administration (FDA) from 1999 to 2008 recommended the phenotype screening approach. This approach is more productive than target-based approach. From the FDA approved (1999 to 2013) first-in-class drugs, 78 were identified through target-based approach, 25 drugs were discovered through a chemocentric approach and 33 drugs were found in the absence of target based approach (Jorge et al.,2014). Pernicious anemia is a serious inherited autoimmune disease that is usually fatal. In the case of this disease, we observe the symptoms and research on it. We find the patient ate different foods, and one food, liver, helped to reduce the symptoms. And use of vitamin B12 and many drugs for the treatment of this disease (Rees, 2005). In modern times, there are three main periods in drug discovery. Due to advancements in genetics and molecular biology, many significant changes have occurred in biomedical research. During 1970 and 1980, drug discovery was revolutionized. Many drugs are discovered and approved in the 1950s (Scannell et al., 2012).

Evolutionary Principles in Drug Discovery

A process through which new entities in drugs are identified is known as drug discovery, using a combination of experimental, translational, and clinical models (Zhong and Zhou, 2014; Xiao et al., 2015). Despite new advancements in biotechnology, drug discovery is still a very long process. Drug development and discovery includes pre-clinical research not only on cellular-based animal models but also on human trials (luu et al., 2013). The most important issue “Drug Discovery Principles Related to Evolutionary Insights” was focused on the basics like modern drug discovery and evolution.

Evolution in Drug Development

1. The Ebola Epidemic happened in West Africa in 2014, believed to have caused more than 11,000 fatalities. Gaurav Chopra and co-authors developed CANDO (Computational Analysis of Novel Drug Opportunities). It was based on the hypothesis that drugs work by interacting with multiple functional protein targets to create a molecule-molecule interaction so, the CANDO platform was beneficially used to produce a high range of drugs for Ebola virus treatment (Chopra et al., 2016).
2. Wei Xiao Jinyi Xu and their co-workers designed and produced a new series of furoxan-based nitric oxide donor hybrids from the commercially available molecule oridonin (Li et al., 2016).
3. Malaria is also one of the principal diseases, particularly in Asian countries. So, the need for anti-malarial agents eventually rises in these countries. For this purpose, quinoline compounds were discovered to act as anti-malarial bodies (Guo et al., 2016). Evolutionary therapy typically focuses on competition for spaces and resources. There are two general principles

a) **Resistant population growth:** is subjected to evolutionary forces and therefore can also be controlled by changing its fitness on that of competing population.

b) **Evolving population:** in only case adopts the local and current environmental selection forces, so they can never anticipate the coming future (Fletcher et al., 2010).

So, the emergence of new technology of resistant pathogens in response to solution procedures by drugs and particularly their invisibility when the drug is discontinued is the evolutionary process that is very casual to many pathogens (Pia et al., 2011). Evolutionary principles are also now routinely incorporated into medicine and agriculture. Basics rules and regulations are also present in thermodynamics and target binding of drugs, within the context of drug discovery. It is also highlighted that combining different antibiotics leads to drug interaction synergistically and antagonistically. Usually, these interactions offer opportunities for drug discovery. Generally, principles usually enable the predictions of cellular responses to the combination of drugs. Overall, the conceptual and technical foundation for the evolutionary design of potent drug combinations is currently developing (Tobias et al., 2015).

Stages for Drug Identification

1. In the first stage, the research is done on disease mechanisms and targets (e.g., protein).
2. The second stage is the drug discovery stage, where scientists search for molecules, then research finding new molecules, and then find the disease symptoms and make strategies for cure.
3. In the third stage, researchers would take a potential action for investigating drug toxicity levels in lab research to evaluate the effect. It is also known as the preclinical stage.
4. The fourth stage is the clinical stage in which researchers find drugs for humans.
5. The last stage is the drug safety monitoring process in which the investigated drug is approved whether it is applicable for market use or not (Hughes et al., 2011; Mohs and Grieg, 2017; Gashaw et al., 2012; Villoutreix, 2021; Kandi and Vadakedath, 2023).

Natural Products as Evolutionary Inspirations in Drug Discovery

Human diseases are treated by natural products that are obtained from animals, plants, and microorganisms. These basic resources are never going to be out of work at all, but there can be the most probable chances of modification. Few natural products as drugs describe in Table 1.

Table 1: Natural products as drugs

Natural Products	Source	Drugs	References
Alkaloids	Plants (e.g., Opium poppy)	Morphine, Vinblastine	(Vadhel et al., 2023).
Flavonoids	Fruits, Vegetables	Quercetin, Rutin	(Taylor and Groteworld, 2005).
Terpenoids	Tree, Herbs	Paclitaxel, Artemisinin	(Rodriguez et al., 2017).
Polyketides	Bacteria, Fungi	Erythromycin, Tetracycline	(Peirú et al., 2005).
Peptides	Microorganisms	Cyclosporine, Bacitracin	(Maeda et al., 2011).
Phenolic	Plant extracts	Resveratrol, Curcumin	(Lantto et al., 2009).
Steroids	Animal, Plants	Cortisone, Diosgenin	(Barrueto et al., 2006).
Glycosides	Plants (Foxglue)	Digoxin, Ouabain	(Barrueto et al., 2006).

Microorganisms

Microorganisms play a basic component in the formation of drugs. Secondary metabolites are obtained from microbial genomes. Each microorganism at least serves in the production of 50 drug-related compounds. The beneficial products obtained include antibiotics, anticancerous agents, and immunosuppressants. In addition to these, antivirals, anthelmintics, enzyme inhibitors, nutraceuticals, polymers, surfactants, bioherbicides, and vaccines have been commercialized (Demain, 2014).

Regrettably, in the past 20 years, there have been no significant efforts put into discovering natural products. The reasons include costly clinical trials, the need for considerable time to become generic, and resistance in the organism against the antibiotics. Besides the lack, of modern technology, which works in discovery, is getting advanced, like combinatorial chemistry of natural product scaffolds, findings in biodiversity, genome mining, and systems biology (Demain, 2014). Penicillin was the first antibiotic discovered in 1925 and then formally introduced by Fleming, Chain, and Florey in 1945 (Bruner et al., 2023).

Currently, more than 120 of the most important medicines used are obtained from terrestrial microorganisms (Shaaban et al., 2012). A greater portion of bioactive metabolites is used in medicine, agriculture, and industry but more than that is serving for therapeutic purposes, herbicidal activity, growth promoting agents, and other biochemical tools (Clardy et al., 2006). In the present times, unexplored microbial

resources such as actinomycetes (Ceniceros et al., 2017). Marine ecosystems and microorganisms associated with plants, mammals, and invertebrates from marine and terrestrial habitats are taken into consideration (Agarwal et al., 2017). Besides these, the most important currently used antibiotics are obtained from cultivable microorganisms, but yes, a tiny fraction can be cultivated in routine laboratories (Stewart, 2012).

Plants

Afterlife came into being, plants also acted as natural resources for remedies and health care (Okigbo et al., 2009). In the beginning, plants in the form of powder, tincture, infusions, teas, inhalation, and other forms serve as medication (Chaachouay et al., 2020). It varies from disease to disease in terms of administration and doses (Avery and Hains, 2017). Various disciplines of scientific study and different methods have contributed to drug discovery from medicinal plants. Botanists and plant ecologists identified the plant of interest (Balunas and Kinghorn, 2005). Plants after processing through factories converted into final products, which are used for future medication and treatment (Paul and Ma, 2011). As recently the work on drug plants has deepened, the active ingredient in plants is separated initially. At the beginning of the 19th century, morphine was isolated from *papaver somniferum* (Brook et al., 2017; Yuan et al., 2016). In the field of drug medicine, digitoxin, cocaine, pilocarpine, and codeine served remarkable (Klebe, 2025). Initially, these compounds were deeply studied for their medicinal usage and are still now acknowledged for their therapeutic use. Apart from the old findings in the current day, it is also an ongoing event in the identification of medicinal plants. the new compounds are identified, analyzed collected processed, and then commercialized (Ernest et al., 2010). Scientific searches for medicinal plants play a crucial role in the discovery of drugs. Each of them has different pharmacological aspects. Paclitaxel, which is taken from *Taxus brevifolia*, is used in the treatment of lung, ovarian, and breast cancer. A derivative of *Artemisia annua*, known as artemisinin a traditional Chinese herb, is used to cure malaria and is resistant to many drugs (Katiyar et al., 2012). Silymarin from the resources of *silybum* is used to treat hepatic disorders and digitoxin is used to cure cardiac disorder which includes congestive heart failure (Shakya, 2016). Cocaine was the first anesthetic drug to be identified, usually used as local anesthesia, and pilocarpine, obtained from the jaborandi plant, can stimulate salivation and precipitation (Rates, 2006). Usually most of these early drugs, like digitoxin and quinine, are still used in contemporary medicine; these drugs have significance over a range of time (Balunas and Kinghorn, 2005).

Moreover, scientists continuously separate and describe pharmacologically active substances from flora, resulting in the discovery and identification of more substances with the same medicinal benefits. The whole procedure includes a detailed study of the structure, mode of action, and possible medicinal purposes of these substances. The continuous flow of investigation highlights, the importance of nature as a good source of bioactive compounds that are contributing to the creation of new medications and treatments in current medicine. The developmental approaches in drug discovery have been standardized; remedies from plants also identify analytical marker biomolecules (Chin, 2006). Pharmaceuticals obtained from plants are the most probably creative application of biotechnology to create drugs from plant resources that are medically contributing to plant sources are efficient and cost-reasonable. And a safe alternative to conventional procedures using microbial fermentation or cell culture. Therefore, drugs obtained from plants are more convenient for patients in terms of medication and quick access (Subramoniam, 2014).

Animals

Venom: A Complex mixture of compounds usually composed of inorganic salts, small organic molecules, polypeptides, and higher molecules such as proteins and enzymes that help in animal defensive action (king, 2011). It has been years where animal toxins serve as drugs due to high selectivity and specificity for their target molecule (curry and piccolo, 2006). Apart from a large number of studies on the use of venom, the successful case is rare (Harvey, 2014). According to the studies from 2000 to 2003, just 1453 new drugs were approved by the US Food Administration (kinch et al., 2014) but among them, a very small number are inspired by animals (Harvey, 2014). When it comes to the success of drugs in animals' captopril is always mentioned, an antihypertensive drug approved in 1980 (smith and vane, 2007). In 1950 angiotensin converting enzymes were identified and obtained from Brazilian viper snake. Venom from bees and wasps are also providing therapeutic uses. Melatonin and Apamin peptides are the most common in this group. Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use are melittin, apamin, and mastoparan (Moreno and Giralt, 2015).

Molecular as Evolutionary Inspiration

The lives of cancerous patients have now improved when the treatment is developed from cytotoxic chemotherapy to molecularly targeted medication. The use of antiestrogen and antiandrogen as treatment of prostate and breast cancer that are caused by the corresponding hormones. The discovery of Tran's retinoic acid added success in the treatment of acute promyelocytic leukemia, the addition of Tran's retinoic in drugs is considered beneficial when treating acute promyelocytic leukemia, which happens due to the translocation of the RAR retinoic acid receptor gene, supporting small chemicals to target pathogenic-causing defects in clinics (Mahadiet al., 2022). After that, ABL inhibitors are considered pioneer medications for creating small molecule theory to treat specific patients, in the case of chronic myeloid leukemia, where translocation BCRABL drives malignancy and survival improved dramatically (Druker et al., 2006).

The success and improvement in small molecule medication is followed by a series of examples, which include the vascular epidermal growth factor (VEGFR) kinase inhibitor sorafenib in renal cancer; the EGFR/ERBB2 inhibitor lapatinib for ERBB2-positive breast cancer; and the kinase growth inhibitors gefitinib and erlotinib and the epidermal growth receptor (ERFR) in the patient with non-small cell lung cancer (Workman et al., 2012). The therapy of patients in late-stage, castration-resistant prostate cancer is most likely to be affected as a result of the inhibitor abiraterone, which causes testosterone to be inhibited (de Bono et al., 2011). In addition, vemurafenib and cricotinib are inhibitor protein kinases (Kwak et al., 2010). Protein-based therapeutics, particularly antibodies, are always a considerable improvement over small molecule drugs; these drugs also contributed to the high success rate of identifying pathogenic agents to cause cancer-addicted cells (Weinstein 2008). Some antibodies, like the monoclonal antibody trastuzumab in ERBB2 "Erythroblastic Oncogene B2 receptor tyrosine kinase 2" positive

breast cancer and anti-ERBB2, are also included (Slamon et al., 2001). Mostly notable improvements made can also bring advancement in diseases like NSCLC and melanoma; there are few treatment options available (Yap and Workman, 2012). Still, in some cases, treatments are not available, and even provision is frustrating with a very low rate of success (DiMasi and Grabowski, 2007).

Antimicrobial Drug Resistance (AMR)

One of the biggest threats to human and animal health worldwide is antimicrobial resistance (AMR). When antimicrobial medications are used on humans or animals, resistant germs develop and spread, and this problem is exacerbated by overuse or misuse. Thus, it is crucial to continue using effective antimicrobials for the benefit of human and animal health and to preserve them for as long as possible (Founou et al., 2021) the development of new antimicrobials has not kept pace with the spread of AMR. This is because only a small number of new agents have lately received approval for usage, and the process of finding new drugs and conducting clinical trials for new antimicrobials takes a long time. As outlined in our last analysis, these circumstances drive efforts to create substitutes for conventional antimicrobials (Chang et al., 2014). AMR's effects include higher morbidity and mortality rates as well as challenges or impossibilities in treating infections (prestinaci et al., 2015; de Kraker et al., 2016). It is expected that 10 million people will be affected by 2050 AMR if this issue is not resolved (Mancuso et al., 2021).

Mechanism of AMR

Two degrees of resistance are present in AMR: cellular and community-level resistance (Penesyan et al., 2015). Both internal gene mutations and horizontal gene transfer (HGT) of resistance determinants from other microbes contribute to the development of cellular resistance. Community-level resistance is the ability of a group of bacteria to withstand environmental stress that individual cells cannot. Antimicrobial resistance may rise as a result of such tolerance (Penesyan et al., 2015). For instance, germs in a biofilm can develop resistance up to 1000 times greater than their planktonic counterparts, creating difficulty in curing biofilm-associated infections clinically. (Lebeaux et al., 2014b; Penesyan et al., 2015). The existence of persister cells is the primary mechanism now put out to explain such tolerance. Bacterial persistence is the ability to evade the deadly effects of antibiotics by going into a physiological state where the antibiotics do not kill them (Maisonneeuve and Gerdes, 2014).

Additionally, resistance at the cellular and community levels can work in concert to significantly increase the microbial population's overall AMR shown in Figure 1 (Penesyan et al., 2015).

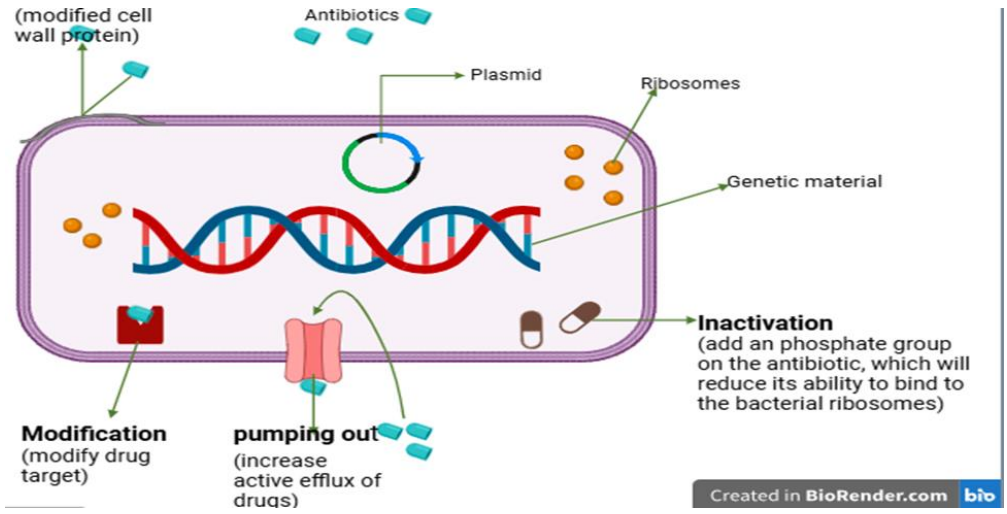

Fig. 1: Mechanism of Antimicrobial Resistance

Approaches to Address AMR

AMR Global Plan of Action

To counter to AMR in a "One Health" manner, the WHO, in partnership with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE), formed the GAP on AMR on May 2015 during the World Health Assembly, the leaders of this meeting committed to their nations creating multisectoral national (WHO, 2015). Countries subsequently pledged to put the NAPs into effect when they were formed and assisted AMR. In order to combat AMR, the GAP on AMR focuses on five goals

1. Raising awareness and understanding of AMR through effective education, training, and communication;
2. Strengthening the body of knowledge and evidence through research and surveillance.
3. Lowering the incidence of infection through effective measures for infection prevention, sanitation, and hygiene
4. Optimizing the use of antimicrobial medicines in human and animal health
5. Developing the economic case for sustainable investment that considers the needs of all countries and increases investment in new medications, diagnostic equipment, vaccines, and other services (WHO, 2015). To monitor AMR, conduct additional research, and slow its spread, stakeholders in human, animal, agricultural, and environmental health must work together globally (Earnshaw et al.,2013).

AMR National Action Plan

Many nations worldwide have created the NAPs on AMR to address AMR in accordance with the GAP on AMR (Lota et al., 2022 and Boon et al., 2017). Countries use these NAPs to keep in check AMR using a "One Health" approach, and they were created based on the goals

established by the GAP on AMR (Karp et al., 2017). Since the GAP on AMR has five objectives, the majority of NAPs on AMR have been created with these five goals in mind. Health" approach and they were created based on the goals established by the GAP on AMR (Karp et al., 2017). Since the GAP on AMR has five objectives, the majority of NAPs on AMR have been created with these five goals in mind. Some nations used a One Health strategy to address AMR and built their NAPs following the GAP on AMR (Chua et al., 2021). Theoretically, nations that have created and executed their NAPs are required to carry out assessments to track their progress and efficacy in reducing AMR (Chua et al., 2021). Countries that have successfully executed their AMR NAPs have so far made good strides toward lowering AMR and its effects. Implementing their NAPs on AMR may be difficult for LMICs due to a lack of funding and capability (Shabangu et al., 2023).

Encouraging International AMR Collaboration

Encouraging international cooperation on AMR is essential to tackling its pressing public health risks (Stewart et al., 2019; Veepanattu et al., 2020). Governments, medical professionals, researchers, and international organizations must work together to address the worldwide issue of AMR. Programs such as the GLASS and the GAP on AMR offer a framework for tracking and dealing with the problem globally. (WHO, 2021). By encouraging international cooperation, we can combat AMR together and ensure that antimicrobial medications continue to be effective for upcoming generations (Villanueva et al., 2022).

The Effect of Genetics on the Evolution of Pathogens

Bacteria, inheritance works in a very complicated way. Unrelated people can exchange DNA; a process known as "horizontal gene transfers", and many people have plasmids, which are DNA molecules that are physically distinct from an organism's genomic DNA and may multiply on their own (sun et al., 2019). These plasmids frequently carry important genes, including those associated with antibiotic resistance. Depending on how it is transmitted, a gene's evolutionary history will determine the environment it has encountered; a gene on a plasmid will have been in different species and settings than a gene on a chromosome. As a result, the specifics of genetics determine a gene's fitness and selective forces. For many pathogens (bacteria, viruses, etc.), the process leads to connected complications (Lerminiaux and Cameron, 2019).

The fundamental biology of pathogen reproduction can have a significant impact on evolutionary dynamics, also for the relatively ordinary mutation process. Dynamic pathogen model evolution has mostly overlooked the molecular- and cellular scale processes by which infections replicate their genomes and produce new infectious particles, despite considerable research in virology and microbiology. According to recent theoretical models, the release of offspring virions through budding or bursting various genome replication mechanisms and the way proteins and genome are combined during virion assembly all produce a considerable impact on host which cause new strain to emerge (Pearson et al., 2011; Loverdo et al., 2012; Loverdo and Lloyd-Smith, 2013). Testing and extending this emerging corpus of ideas through comparison is a significant problem.

Conclusion

Drug discovery had earlier largely stemmed from chemical modification of natural products; they introduced a more rational approach based on the understanding of fundamental biochemical and physiological processes. By considering evolutionary principles such as natural selection and resistance mechanisms, drug research and development have undergone tremendous change. Pathogen genetic exchange promotes co-infection, which increases immunological escape and adaptation. Because bacteria and viruses share resistance genes, this makes drug resistance more complicated. Drug discovery and addressing issues like antibiotic resistance and emerging illnesses depend on an understanding of host-parasite interactions. Natural compounds with therapeutic value include artemisinin and paclitaxel. Addressing global health issues and increasing efficacy are two benefits of using evolutionary ideas. To combat the challenges in drug discovery, an increasing number of researchers and pharmaceutical companies recognize the benefits of utilizing computational techniques.

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