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Drug discovery and development: A historical overview, current challenges and perspectives

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ABSTRACT

The evolution of drug discovery has proceeded for decades. The process has involved the invention of new theories, technologies, disciplines and medicines. These advancements play significant roles in drug discovery today as well as in the future. In this review, the important achievements of ancient Egyptian, Greek, Arabic, Indian, and Chinese medicines were discussed. Then, the development of key concepts, theories or technologies as well as breakthroughs in drug discovery research has been reviewed. Lastly, the current outlook and obstacles in drug discovery studies have been discussed in this article. This review provides an understanding of drug discovery research from a historical perspective and current contexts.

Keywords: *Drug discovery; history; contemporary; perspectives and challenges*

INTRODUCTION

Drug discovery has existed for almost as old as human history, it started with serendipitous discovery and gradually evolved into a process that was strongly based on scientific evidence and involved multidisciplinary studies. A historical perspective on drug discovery offers a deeper understanding of the drug discovery process. It is important in sharpening the vision of the present as well as the future of drug discovery research. In the past 20 years, reviews on the transformation of drug discovery have been scarce. Umashanka & Gurunathan (2015) provided a brief view of the transition from traditional drug discovery to modern drug discovery and particularly emphasised the protocol involved in drug development, Drews (2000) reviewed the impacts of molecular biology on drug discovery development while Gershell and Atkins (2003) focused on the pivotal technologies in the drug discovery process. On the other hand, Villoutreix (2021) presented challenges of drug discovery after the COVID-19 pandemic (Drews, 2000; Gershell & Atkins, 2003; Umashankar & Gurunathan, 2015; Villoutreix, 2021). Most papers reviewed drug discovery in specific areas, subject matters, methods, or applications including natural products drug discovery, peptide drug discovery, the role of nanobiotechnology in drug discovery, computational approaches in drug discovery

and antiviral and antibacterial drug discovery, etc (Campbell et al., 2017; George et al., 2022; Henninot et al., 2018; Katz & Baltz, 2016; Moffat et al., 2014; Ong & Gasser, 2022; Pettersson & Crews, 2019; Totura & Bavari, 2019; Tse et al., 2019). Review on the development of drug discovery research from the past to the present is scarce, and the relevant information can mostly be found in books. The books authored by Gerald (2013), Sinha & Vohora (2018), and Hill & Richards (2021) are some of the examples that discussed general drug discovery and development (Gerald, 2013; Hill & Richards, 2021; Sinha & Vohora, 2018).

In this paper, we reviewed drug discovery from historical perspectives and highlighted some achievements in the past. The contemporary drug discovery and the challenges faced in research today were also discussed in the present paper.

Drug discovery in ancient time

Some studies have reported Paleolithic humans knew about using bitter plants with poison or psychotropic plants for self-medication (Hardy, 2021). Around 10,000 years ago, the human race settled from nomad life and grow their plants for food, setting off the agricultural evolution that brought civilization as well as plagues of infectious diseases (Abbo et al., 2022; Hill & Richards, 2021). In the ancient past, there was no system of medicine, the primary source of medicine for the treatment of diseases was plants which were mostly discovered by chance. Some of the "drugs" discovered were without medicinal value such as alcohol and tea, while some others are harmful and addictive such as cannabis and opium (Gerald, 2013). The functions of plants as medicines were transmitted verbally or engraved on caves and the practices were greatly affected by the cultures and religions (Pina et al., 2010; Poduri, 2021).

Egyptian medicine

Egypt is one of the ancient civilizations and has developed in many fields including medicine. The practices of Egyptian medicine can be found in a few documents such as Ebers Papyrus which was produced in 1536 BCE (Hallmann-Mikołajczak, 2004). It is one of the oldest medical documents that recorded some disease conditions and the use of 328 ingredients that originated from plants to produce 876 prescriptions (Metwaly et al., 2021).

Greek medicine

At around 500 BCE, the Greeks transformed the superstitious beliefs in medicine by introducing empirical-rational-based medicine, under the influence of Greek philosophers such as Empedocles and Pythagoras (Pitman, 2014; Pearce, 2016). Hippocrates is a Greek physician who is renowned as the 'Father of Medicine'. He created the Hippocratic Corpus which was completed together with other physicians of his time. The Hippocratic Corpus included around 130 medicines and influenced the Galenic medicine (Pitman, 2014). In the first century of CE, another Greek physician Pedanius Disocorides systematically documented 500 plants used as drugs in De Materia Medica which laid the foundation of homoeopathic medicine (Gerald, 2013; Yildirim, 2013).

Arabic medicine

During the Golden period of Arab science (9th to 13th century), translation projects were implemented by the rulers and those collections of books from Greek, Roman, Persian, Indian, Chinese, Syrian, and other countries were translated, studied, and modified into Arab (Masic et al., 2017; Amar & Lev, 2017). Hippocratic and Galenic medicines were adopted and modified by Arabic physicians based on their studies and experience (Masic et al., 2017). The practices and development of medicine blossomed with the rise in the civilization of Arabs, for example, they set up the first apothecary in history and built a hospital with an apothecary that operated independently (Masic et al., 2017). Besides, Al-Biruni who is a Muslim scholar, produced a book named "Saydanah Fit-Tibb" which defined the role of a pharmacist. These developments planted the root of the pharmacy profession (Masic et al., 2017).

Ayurvedic medicine

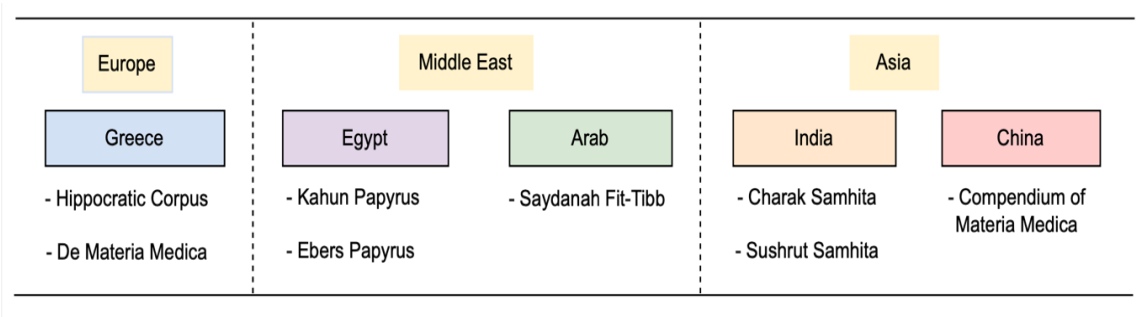
Ayurveda is the most popular medicinal system in India, it is also known as 'the science of life', and has been established since the 2nd century BCE (Patwardhan & Khambholja, 2011). It is a sophisticated ancient medicine that developed a treatment based on products, diet, lifestyle, and environment (Poduri, 2021). The books Charak Samhita and Sushrut Samhita recorded the categories, properties and pharmacology of over 700 plants in Ayurvedic medicine (Patwardhan & Khambholja, 2011). It involves the use of plant and animal products, minerals and metals in treatment as well as the knowledge of collection, preparation, and storage of those materials (Patwardhan & Khambholja, 2011).

Traditional Chinese medicine

In China, the use of herbs and materials that originated from other natural resources has been the main practice in Traditional Chinese Medicine (TCM) since the Eastern Han Dynasty (AD 25 – 220) (Chang, 2016; Zhu & Woerdenbag, 1995). Chinese medicine was developed from trial and error to the establishment of systematic herbal medicines (Sun et al., 2020). A few documents of TCM were produced and the most famous compilation was 'Compendium of Materia Medica' or "Ben Cao Gang Mu" (Chang, 2016; Zhu & Woerdenbag, 1995). Now, the TCM comprises more than 11,000 documentary herbs which can be categorized based on tastes and four properties, as well as the site of action (Chang, 2016; Xu et al., 2018). The herbal formulation in TCM and the herbs' interaction were studied based on the herbs' taste, properties, site of actions, and seven relations theory (Chang, 2016; Pan et al., 2022).

Figure 1

Ancient medicine records produced in different nations, including Greece, Egypt, Arab, India, and China.



In Asia, Chinese medicine from China and Ayurveda medicine from India are among the oldest practising medicine in the world and both medicines are still popular in China and India today. (Jaiswal & Williams, 2016; Chang, 2016). From ancient times until the 17th century, natural resources believed to have beneficial values continued to be discovered. Coffee was found to relieve migraine and help in digestion in 800 BCE. On the other hand, coca was discovered in 1532 and was used to relieve pain and feelings of starvation (Gerald, 2013). Coca was one of the ingredients in Coca-Cola, a drink which was first introduced in 1885 (Gerald, 2013). The drink was reformulated in 1907 and the coca leaves were decarbonised before being used in the formulation. Furthermore, one famous plant that was discovered in 1639 was cinchona bark which was used to treat malaria fever (Gerald, 2013). In 1681, ferrous sulfate was found to have a therapeutic effect on iron deficiency illnesses (Gerald, 2013).

Drug discovery from the 18th century to 19th century

Highlights of drug discovery research from the 18th century to 19th century

This section remarks on some of the important drug discovery events from the 18th century to the 19th century (Figure 2).

Drug discovery in the 18th century

In the 18th century, the practices of clinical trials and preventive medicine were started when James Lind reported his study on the prevention of scurvy with his established first controlled clinical study in 1753 which founded the concept of scientific testing on drug efficacy (Gerald, 2013; Hill & Richards, 2021). In 1796, the first vaccine was born when an English physician Edward Jenner used cowpox to immunize people for the prevention of smallpox which eventually led to the eradication of smallpox diseases in 1979 (Gerald, 2013). In the same year, homeopathic medicine was founded by Samuel Hahnemann (Gerald, 2013).

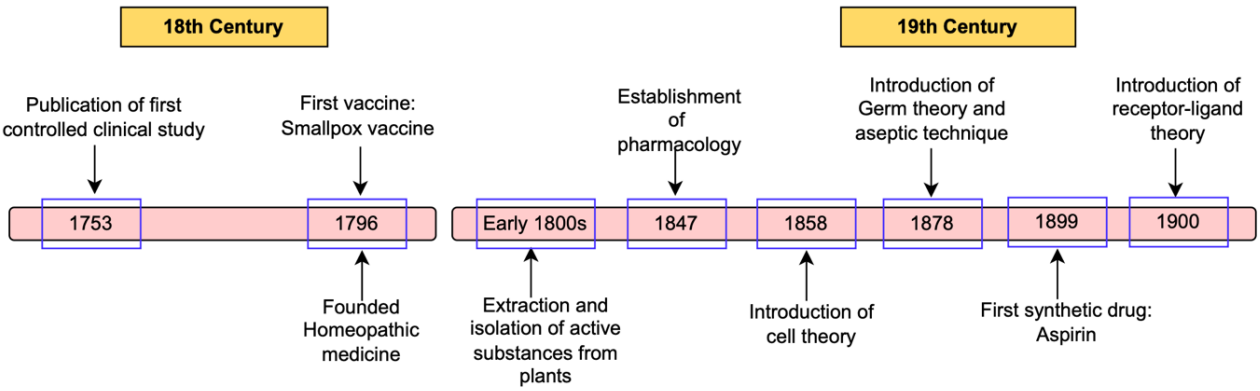
Drug discovery in the 19th century

In the 19th century, the advancement of chemistry allowed the extraction and isolation of active substances from herbal plants bringing drug discovery to small molecule drug discovery (Figure 2). In the early 1800s, important active substances such as alkaloids, morphine, quinine, and atropine were first extracted and isolated from the plants (Gerald, 2013). Morphine is still the most effective painkiller for severe pain today. In the interim, the advance of synthetic chemistry led to the production of Aspirin, the blockbuster drug derived from salicylic acid extracted from the plant and is still one of the most widely used drugs in the world. Aspirin was marketed as an analgesic in 1899 and was effective in relieving pain and anti-inflammation. In 1982, owing to the antiplatelet effect of aspirin, it was repurposed for use in cardiovascular disease and more functions of aspirin are still under study (Jourdan et al., 2020; Gerald, 2013). Progress in biomedicine was also observed in the 19th century. A new

discipline known as pharmacology was founded by Rudolf Buchheim in 1847, to understand the physiology of organisms and relate it to therapeutics (Hill & Richards, 2021). 11 years after the establishment of pharmacology discipline, German pathologist Rudolf Virchow proposed cell theory which strengthened the knowledge in biology, cell pathology and medicine (Buja, 2021; Hill & Richards, 2021). Loius Pasteur is a chemist who discovered the science of isomers and stereochemistry and in 1878, he proposed the germ theory which played an important role in the development of vaccination and sterilization or aseptic technique in medicine (Tan & Rogers, 2007). Another important achievement in the late 19th century was the introduction of receptor-ligand theory by Paul Ehrlich which boosted the development of chemotherapy (Valent et al., 2016). This also created interest in the ligand-receptor approach or target-directed drug discovery and those methods are still applied today.

Figure 2

Highlights of drug discovery research from the 18th century to the 19th century.



Drug discovery since the 20th century

Highlights of drug discovery research since the 20th century

This section highlights some of the important drug discovery events since the 20th century. Drug discovery approaches advanced significantly in the 20th century (Figure 3).

Isolation of therapeutic substances from non-plant sources

Drugs that did not originate from plants started to be produced. In the early 20th century, heparin isolated from dog's livers and insulin from dog's pancreas were used to treat blood clots and severe diabetes respectively. Antibiotic drugs such as penicillin, ciclosporin, and tacrolimus were isolated from the fungus while streptomycin and tetracyclines were isolated from soil bacteria (Clardy et al., 2009). Penicillin is the first antibiotic drug discovered by Alexander Fleming in 1928 has saved numerous lives. Later, the successful elucidation of penicillin structure subsequently produced many other structure-related antibiotics such as ampicillin. Penicillin remains one of the most commonly used antibiotics today (Gerald, 2013; Pina et al., 2009; Yip & Gerriets, 2022). In the 1880s, acetanilide was discovered to be able to diminish fever, however, it was also found to cause hematotoxicity. The discovery of acetanilide led to the synthesis of phenacetin in 1913 and was used as an antipyretic in the first few decades of the 20th century (Brune et al., 2015). In around 1948, the metabolites of Phenacetin were analysed and it was found to produce toxic anilide. On the other hand, one of its metabolites was found to be a reactive compound known as acetaminophen or paracetamol, which became a blockbuster antipyretic after its introduction in 1953 (Brune et al., 2015; Gerald, 2013). Acetaminophen is still one of the most widely used drugs today (Gerald, 2013).

Cell therapy

In 1906, the first direct blood transfusion between humans in surgery was conducted successfully signifying the start of cell therapy. In 1939, the first bone marrow transplantation to cure aplastic anaemia was conducted and initiated studies in therapy using bone transplantation (Henig & Zuckerman, 2014). After a few decades of efforts, the first bone transplantation between an unrelated donor and recipient marked another success of cell therapy (Henig & Zuckerman, 2014). In 1981, the murine embryos were used to produce the first stem cell and the potency of stem cells in cell therapy has been studied intensively until now (Hamon & Hauser, 2019).

Computational drug discovery

Before the 1950s, the discovery of drug compounds was through indiscriminate screening of a large number of natural or synthetic compounds. Together with the advancement of organic synthesis and the concept of drug actions, rational drug design started to be adopted in drug discovery research in the 1950s (Adam, 2005). This was followed by the introduction of the quantitative structure-activity relationship (QSAR) around the 1960s (Danhof et al., 2018; Van Drie, 2007). Meanwhile, medicinal chemistry continues to progress in drug discovery. In the early 1980s, the publication of the article "The Next Industrial Revolution: Designing Drugs by Computer at Merck" in Fortune magazine captivated high attention of researchers in computational aided drug design (CADD) (Gershell & Atkins, 2003). In the 1990s, combinatorial chemistry was first introduced and large libraries of small molecules can be generated for high-throughput screening (Gershell &Atkins, 2003). A large number of compounds in the screening libraries were found failed to identify promising drugs, instead combinatorial library is more practical when a small library focuses on certain scaffolds and adoption of hit-to-lead optimization methods together in drug discovery (Gershell & Atkins, 2003). CADD had successfully brought a few drugs to approval which included captopril for hypertension (1981), dorzolamide for glaucoma (1995), Saquinavir for HIV (1995), ritonavir and indinavir for HIV (1996), zanamivir for influenza virus (1999), and Aliskiren for hypertension (2007) (Śledź & Caflisch, 2018; Talele et al., 2010; Vemula et al., 2023).

Development of recombinant DNA

Discoveries of restriction enzymes started in the 1950s and the first experiment was conducted in 1971 (Felice et al., 2019). This set off the development of recombinant DNA and transformed the chemistry-based drug discovery industry (Bose & Bose, 2022; Gershell & Atkins, 2003). This enabled the production of the first peptide-based drug, Humulin or human insulin in 1982. Since then, not only peptide-based drugs but biological drugs also have been produced such as trastuzumab (Herceptin), which is a monoclonal antibody made in 1998 (Gershell & Atkins, 2003; Wang et al., 2022).

Molecular biology directed drug discovery

One of the biggest contributions to molecular biology and drug discovery research is the initiation of the Human Genome Project (HGP). The idea of HGP was conceived in 1984, then the project was commenced in 1990 and took 15 years to finish and eventually launched a post-genomic era (Hood & Rowen, 2013; Woollard et al., 2011; Yan et al., 2015). The HGP has benefited many sectors more than what scientists had expected of it when initiated the project as it has led drug discovery research to a new paradigm shift. Along the way, it set off the application of "big data" science, fostered the development of omics technologies and the advancement of multi-disciplines such as computational and mathematics (Hood & Rowen, 2013; Woollard et al., 2011). The understanding of biomedical sciences has also been improved and steered the drug discovery research perspective to systems biology which the drug is developed and evaluated not only from its structure but also from its action mechanisms as well as its effect on interactions within biological systems. Besides, HGP also aided in identifying new potential targets for diseases which eventually drifted the phenotypic drug discovery to target-based drug discovery (Swinney & Anthony, 2011). Another breakthrough in molecular biology-directed drug discovery is the advancement of gene therapy in recent years. Gene therapy has come a long way from the failure of its first clinical trial in 1988 and finally attained success in the treatment of haemophilia B in 2011. The fundamental problems of gene therapy have been solved since then. From 2011 to 2020, the number of approvals for gene therapy products reached 16 (Alhakamy et al., 2021). Nevertheless, small-molecule drugs are still important in drug discovery. A study in 2021 reported that small molecules are still holding around 90% of the market share (Makurvet, 2021). Recently, their roles have been expanded with the development of new modalities. The functions of small molecules as RNA targeting molecules, protein-protein interaction inhibitors, antibody-drug conjugates compounds, PROTACs, etc are under study (Beck et al., 2022; Danhof et al., 2018). On top of that, they are also developed as molecular probes to investigate biological systems (Klaus Pors, 2011; Triggle, 2007).

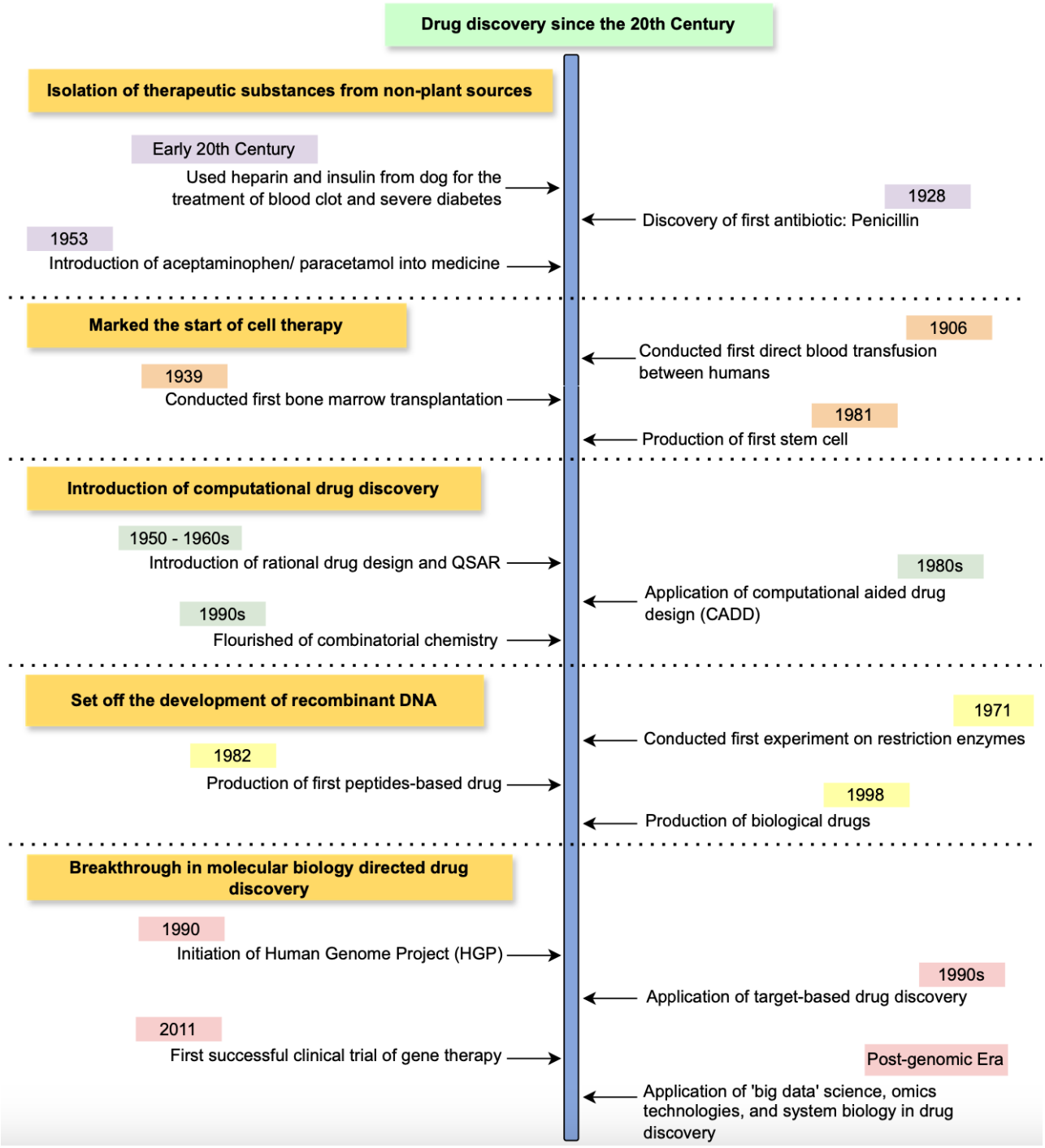
Drug regulation

The drug discovery and development in the 19th century had started industrialised leading to an increase in drug trading and problems such as false labels or unsafe medications. To tackle the problems of unsafe medications, the Pure Food and Drug Act was approved in the United States in 1906 and the Bureau of Chemistry was founded which changed to the Food and Drug Administration (FDA) in 1930 (Gerald, 2013). In addition, the unprecedented successful drug discovery in the 20th century has experienced two major drug disasters which have shaken the drug regulation systems in many countries and resulted in a more stringent drug regulation today. The first disaster was the production of elixir sulfanilamide using toxic diethylene glycol as a solvent in the preparation which caused the death of patients in the United States and led to the approval of the Federal Food, Drug, and Cosmetic Act in 1938. Since then, the test for drug toxicity and FDA approval has become compulsory

before being marketed (Gerald, 2013). Another disaster happened in 1957 in countries including the United Kingdom, Canada, Africa, Australia, Japan, and Europe due to thalidomide. Thalidomide was marketed as a sedative to treat nausea and morning sickness during pregnancy however caused severe birth defects and affected approximately 10,000 children. It was then banned in 1961 (Gerald, 2013; Kim & Scialli, 2011). The early strengthening of drug regulation in the US has prevented the same disaster in the country and until now FDA rules and regulations have become the golden standard reference for drug regulation. In 1997, the FDA approved direct-to-consumer advertisements which included disease-awareness ads and product-claim ads to ensure the public has some basic understanding of the medicine they use (Gerald, 2013).

Figure 3

Highlights of drug discovery research since the 20th century



Current challenges and perspectives in drug discovery

The evolution of technologies in recent years does not correlate positively with productivity in drug discovery. It was reported the research and development cost in drug discovery has increased dramatically but the rate of

drug approval clinically remained stagnant (Belleli et al., 2015; Romano & Tatonetti, 2019). The low productivity and efficiency in drug discovery and development can be caused by several factors including the complexity of the diseases under study, inadequacy of knowledge in new research fields and cutting-edge technologies, and lack of innovation in drug discovery studies (Figure 4).

Complexity of the diseases

Easy diseases such as hypertension have been solved previously. Research today faces the challenges of solving more complicated and difficult diseases such as rare genetic diseases, diseases that involve multi-targets and the increasing cases of antimicrobial resistance as well as the emergence of new and recurring viruses infections (Li et al., 2022; Romano & Tatonetti, 2019; Sun et al., 2022; Triggle, 2007). Besides, diseases associated with ageing such as neurodegenerative disease, cardiovascular diseases, metabolic diseases etc, pose another challenge with the increasing ageing population (Li et al., 2022).

Knowledge gaps in new research fields and the use of cutting-edge technologies

Studies also reported more efforts are required to fill the knowledge gaps in the application of cutting-edge technologies to better translate drug actions and disease mechanisms in preclinical research as well as the clinical level (Malandraki-Miller & Riley, 2021; Romano & Tatonetti, 2019; Swinney & Anthony, 2011; Swinney & Lee, 2020; Vasan et al., 2023). The recently arising technologies such as omics technologies and continuously improving understanding in molecular biology would help to uncover the functions of biological systems and develop new study models which would precisely illustrate the interactions networks of the biological systems and produce effective therapies for those complex diseases (Danhof et al., 2018). The revolution of "big data" science, computer techniques and technologies, as well as structural biology, has improved the competency of computer-assisted drug discovery and turned it into an effective tool in drug discovery research (Frye et al., 2021; McPherson & Gavira, 2014; Ou-Yang et al., 2012; Schaduangrat et al., 2020).

Insufficiency of study in new human proteins as drug targets

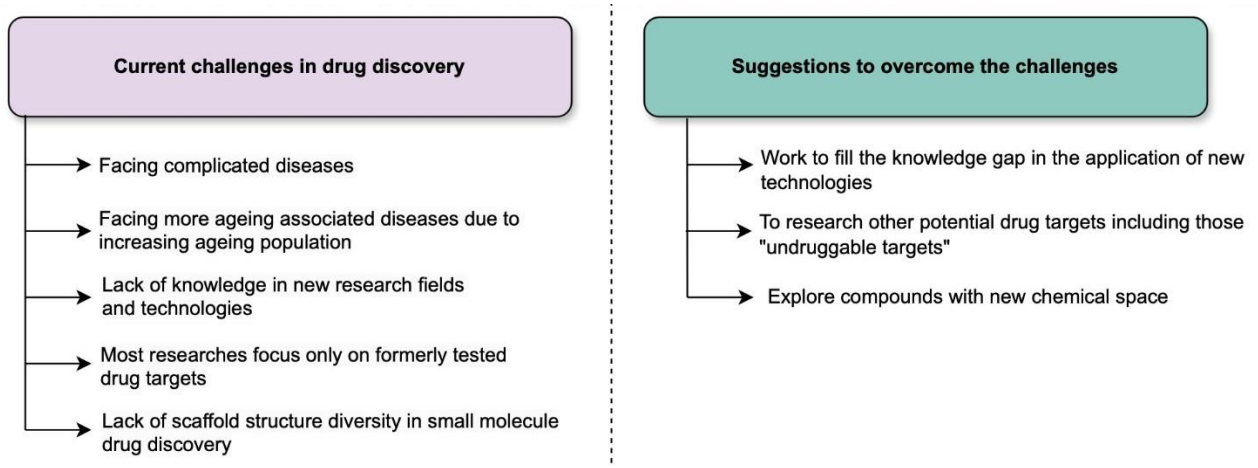
Although 95% of the human genome has been uncovered and many new drug targets have been identified, only 12% of human proteins were studied in clinical trials (Vasan et al., 2023). This showed that most of the research was still focusing on formerly tested drug targets and lack of innovation. Some studies encourage researchers to seek potential from validated targets or even those that are identified as "undruggable targets" (Danhof et al., 2018; Swinney & Anthony, 2011).

Challenges in small molecule drug discovery

Small molecule drug discovery seems to reach a bottleneck due to a lack of scaffold structure diversity between the approved and developing drug compounds and there is a need to explore compounds with new chemical space (Romano & Tatonetti, 2019).

Figure 4

Challenges in current drug discovery and the suggestions to overcome them



CONCLUSION

The search for therapeutic drugs has revolved from a mystery and serendipitous findings to empirical exploration and now it has established as a field with extensive scientific research. Modern drug discovery research is an interdisciplinary and comprehensive process which requires unceasing efforts and cooperation between different agencies including the government, academia, and industries.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization of this paper. The writing and visualisation of this paper were performed by Chai Xin Yu and Chau Ling Tham contributed to the supervision of the production of this article.

ETHICS APPROVAL

Not applicable.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this work.

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