PharmacologyOnLine
Archives • 2021 • vol.3 • 1313-1319

Drug Discovery in the New World

Saif Aldeen Jaber[1*]
[1]Faculty of Pharmacy, Middle East University, Amman, Jordan

*corresponding author email address (sjaber@meu.edu.jo)

Abstract
The demands for novel chemical compounds to be used as therapeutic agents are increasing every day. These demands have been motivated by many reasons such as the emerging of new diseases and infections, plus the advances in the instruments used for analysis. The increasing incidence of multi-drug resistant microbes, which cause deathly infections is one of these reasons that are boosting the field of discovering new chemical compounds that can overcome these infections. Furthermore, life-threatening diseases, such as cancer and microbial infections are playing important role on keeping drug discovery processes moving on.

Drug discovery can be accomplished by three different pathways depending on the source, type and classes of compounds. The first pathway of discovering new bioactive compounds is by exploring various natural sources. These chemical compounds are produced by both macro and microorganisms through different biosynthetic routes. While the second pathway is by computer-based drug design (CBDD), where the chemical compound is designed *in-silico* by a computer software to fit and interact with a specific active site or receptor. Finally, there is the utilisation of combinatorial chemistry, where libraries are produced by large number of synthesised compounds to be tested against specific targets, then followed by data analysis for the most potent drugs between the various congeners.

Keywords: *natural products, drug discovery, antibacterial, anticancer, antidiabetic.*

Introduction

Recently, pharmaceutical companies and research centres have been interested in employing the 2nd and the 3rd pathways (CBDD and combinatorial drug discovery) of drug discovery by involving new technologies such as 3D X-ray crystallography, drug-docking, and computer-based tools in their favour [1]. However, computer-based drug design and combinatorial drug discovery have been facing difficulties as well. These difficulties involve the need for knowledge on the mechanism of elucidating target receptors [2]. In addition, most of these chemically-synthesised compounds pose many side effects and environmental concerns [3]. Even more, the high cost to discover novel compounds and marketing them later are adding more pressure on these pathways of drug discovery [4].

2 Natural source for drug discovery

Natural products (NP) are chemical compounds produced by a living macro or microorganism, such as animals, plants, seaweeds, bacteria and fungi. Plants are the biggest source of natural compounds between all sources. Even though, marine sources, especially marine endophytes, have yielded many of the biologically active secondary metabolites [4-6].

Natural products are divided into two groups of compounds that include primary and secondary metabolites. Primary metabolites such as glucose, amino acids and some fatty acids are compounds produced by living organisms and are essential for its life cycle and its physical activity. Whereas secondary metabolites are low or high molecular weight compounds that are produced by the organism to adapt to a specific situation or environment and are produced by a gene translation process. [7, 8].

Records on the utilisation of natural products date back before 2600 BC by using oils of *Cupressus sempervirens* and *Commiphora* species (myrrh) [9]. These oils were used by people in Mesopotamia for the treatments of cough and inflammation [9]. The Eber papyrus from 2900 BC is an Egyptian pharmaceutical record of 700 plant-based drugs ranging from many drug formulation such as gargles, pills, infusions, to ointments [10]. In addition, in 1100 BC, the Chinese Materia Medica had documented 52 prescriptions. Furthermore, Shennong Herbalrom from 100 BC recorded 365 drugs, and the Tang Herbal at 659 AD recorded 850 drugs [9]. All therapeutic preparations mentioned before were produced from a plant source. On the other hand, microorganisms have also been used before as a source of natural medicinal preparations. A first example is the fungus *Piptoporus betulinus*, which grows in birches, it was incorporated in charcoal to be used as an antiseptic and disinfectant [11]. In addition, *P. betulinus* strips were earlier used as corn pads for staunching bleeding [12]. A second example is *Agaricus campestris* found in the Caribbean, which was reported to be used for throat cancer by stewing the fungi in milk [13]. Furthermore, lichens have also been utilised such as *Usnea dillenius* that was used for scalp diseases, and sold as an ingredient for anti-dandruff shampoo while it was also described to treat sore eyes in Ireland [14]. Many famous examples of medicines based on traditional basis or natural products are still being used nowadays. A famous example is the anti-inflammatory agent, acetylsalicylic acid which was derived from the natural product salicin isolated from the willow tree [15]. As well as, opium poppy which produced the commercially and clinically important analgesic drug morphine [15]. Another example of a drug based from a natural source is the cardiotonic glycoside digitoxin isolated form *Digitalis purpurea* L., and it could be traced back to Europe in the 10th century, but was only discovered after 1700 to improve cardiac conditions, especially with patients facing heart failure [15]. Likewise, quinine drugs isolated from

Cinchona succirubra Pav. were used for many diseases such as malaria, fever, indigestion, mouth and throat diseases as well as cancer [15]. Additionally, L-histidine derivative of pilocarpine isolated from *Pilocarpus jaborandi* have been used for the treatment of different glaucoma cases [15]. Finally, the antibiotic penicillin isolated from *Penicillium* mould was the beginning of the golden era of antibiotics to treat microbial infections.

Combinatorial drug discovery

Combinatorial drug discovery involves the generation of huge numbers of structurally diverse compounds from different chemical groups, which are called compound libraries. Such libraries would catalogue compounds according to their physicochemical properties such as, solubility, permeability, type of interaction, easiness of formulation and fitting with the binding cavity of the targeted enzymes [16]. Active chemical compounds would be categorised on their biological activity and mechanism of action [16]. Combinatorial chemistry was introduced in the 1980's during the invention of Geysen's multi-pin technology[17]. The compounds in the libraries can be screened by two ways, as follows:

Virtual screening is based on computer simulations, by predicting the interaction between compounds and a target receptor or structurally-related compounds [16]. Virtual screening can be done by three methods that included molecular docking, pharmacopeia mapping and quantitative structure-activity relationship [16]. The major problem with virtual screening is the inability to exclude real biological activity testing of these compounds [16]. Virtual screening is fundamentally done in a dry lab environment.

Experimental screening is accomplished in a wet lab [16]. The invention of the high-throughput screening (THS) made the screening methodology easier and faster, in which hundreds of thousands of compounds coud be tested providing a real-time result in a short period with least effort [16]. Even though, there is a time advantage through THS, it actually still needs plenty of time to set-up and its considered to be more time consuming than virtual screening [16].

Structural information provided by the different libraries on molecular binding between compounds and receptors guided the rational selection for the best compounds in the library, which lead also to affect the design of the library [18]. Many examples on combinatorial drug discovery were found to be successful. For instance, plasmid relaxation assay was used from a solution phase library [19]. This afforded the discovery of an antiprotozoal compound (such as, fluorophenyl ethers) against *Leishmania donovani* with no toxicity to the normal mammalian cells [19]. Another example is the OBOC peptidomimetic library [20], that utilised a cell binding assay for $\alpha_4\beta_1$ integrin ligand screening and generated the development of the drug LLP2A-alendronate for the treatment of osteoporosis [20]

Computer-based drug discovery (CBDD)

Computer-based drug discovery and development processes has been getting more implementable, extensive, and popular [21]. Many names are used to describe computer-based drug discovery, such as computer-aided molecular design (CAMD), computer-aided molecular modelling (CAMM), rational drug design, in-*silico* drug design and computer-aided drug design [21]. Computer-based drug discovery (CBDD) involves the following objectives:

1- To streamline drug discovery and development process using computing abilities [21].
2- To provide a strong source of chemical and biological information about the legends and/or targets, which would aid in the identification and the optimisation of new drugs synthesis [21].
3- To eliminate compounds with low interest for further drug development due to their inept physicochemical and biological properties, such as (absorption, distribution and metabolism) and (excretion, toxicity and biological activity) respectively [21].

The increased interest in CBDD had pushed companies to upgrade the needed software to be specifically used for drug design and identification of molecular targets coupled to a publicly available database to target protein structure [21]. Furthermore, this improvement in the software led computer companies to improve their hardware power and sophistication [21]. Biological activity testing of the selected compounds would be done in two ways similar to combinatorial drug discovery, which would either be by virtual or real-time screening [21]. CBDD has been enrolled in important pathways for drug discovery as presented in the workflow shown in Figure 1.2. The advantage of using CBDD over a natural source and combinatorial chemistry for drug discovery is the ability to increase the hit rates for novel compounds [22]. In addition, CBDD has a higher capability to predict the biological activity on a molecular basis along with the plausible derivatives that would enhance the biological activity of the selected compounds [23].

Many drugs and mechanisms of actions have been discovered using CADDD with potent bioactivity against specific target like the discovery of Tip60 [24]. Another example of CADDD was the using of virtual screening of thymidine monophosphate kinase inhibitor, as antitubercular agents by Gopalakrishnan et al., 2005 [25].

Acknowledgments

The author is grateful to the Middle East University (MEU), Amman, Jordan, for the financial support granted to cover the publication fee of this research article.

References

1. Muller, B. A., Imatinib and its successors–how modern chemistry has changed drug development. *Current pharmaceutical design* **2009,** *15* (2), 120-33.
2. Barry, C. E., 3rd; Blanchard, J. S., The chemical biology of new drugs in the development for tuberculosis. *Current opinion in chemical biology* **2010,** *14* (4), 456-66.
3. Strobel, G.; Daisy, B., Bioprospecting for microbial endophytes and their natural products. *Microbiology and molecular biology reviews: MMBR* **2003,** *67* (4), 491-502.
4. Alvin, A.; Miller, K. I.; Neilan, B. A., Exploring the potential of endophytes from medicinal plants as sources of antimycobacterial compounds. *Microbiological research* **2014,** *169* (7-8), 483-95.
5. Sarker, S. D.; Nahar, L., An introduction to natural products isolation. *Methods in molecular biology (Clifton, N.J.)* **2012,** *864*, 1-25.
6. Harvey, A. L., Natural products in drug discovery. *Drug discovery today* **2008,** *13* (19-20), 894-901.
7. Nisa, H.; Kamili, A. N.; Nawchoo, I. A.; Shafi, S.; Shameem, N.; Bandh, S. A., Fungal endophytes as prolific source of phytochemicals and other bioactive natural products: A review. *Microbial pathogenesis* **2015,** *82*, 50-9.
8. Harvey, A. L.; Edrada-Ebel, R.; Quinn, R. J., The re-emergence of natural products for drug discovery in the genomics era. *Nature Rev Drug Discov* **2015,** *14* (2), 111-29.
9. Cragg, G. M.; Newman, D. J., Biodiversity: A continuing source of novel drug leads. *Pure Appl Chem* **2005,** *77* (1), 7-24.

10. Dias, D. A.; Urban, S.; Roessner, U., A historical overview of natural products in drug discovery. *Metabolites* **2012,** *2* (2), 303-336.
11. Swanton, E., Economic and folk lore notes. *Trans British Mycol Soc* **1914,** *5*, 408-409.
12. Swanton, E., Sussex County Magazine. *Eastbourne: TR Beckett* **1932**.
13. Hatfield, G., *Country remedies: Traditional East Anglian plant remedies in the twentieth century*. Boydell Press: Woodbridge, 1994.
14. Zavarzina, A.; Zavarzin, A., Laccase and tyrosinase activities in lichens. *Microbiology* **2006,** *75* (5), 546-556.
15. Süntar, I., Importance of ethnopharmacological studies in drug discovery: role of medicinal plants. *Phytochem Rev* **2019**, 1-11.
16. Liu, R.; Li, X.; Lam, K. S., Combinatorial chemistry in drug discovery. *Current opinion in chemical biology* **2017,** *38*, 117-126.
17. Houghten, R. A., General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc Nat Acad Sci* **1985,** *82* (15), 5131-5135.
18. Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J., Combinatorial synthesis—the design of compound libraries and their application to drug discovery. *Tetrahedron* **1995,** *51* (30), 8135-8173.
19. Marcon, L.; Battersby, B. J.; Rühmann, A.; Ford, K.; Daley, M.; Lawrie, G. A.; Trau, M., 'On-the-fly'optical encoding of combinatorial peptide libraries for profiling of protease specificity. *Molecular bioSystems* **2010,** *6* (1), 225-233.
20. Guan, M.; Yao, W.; Liu, R.; Lam, K. S.; Nolta, J.; Jia, J.; Panganiban, B.; Meng, L.; Zhou, P.; Shahnazari, M.; Ritchie, R. O.; Lane, N. E., Directing mesenchymal stem cells to bone to augment bone formation and increase bone mass. *Nature Med* **2012,** *18* (3), 456-62.
21. Kapetanovic, I., Computer-aided drug discovery and development (CADDD): in silico-chemico-biological approach. *Chemico-biological interactions* **2008,** *171* (2), 165-176.
22. Sliwoski, G.; Kothiwale, S.; Meiler, J.; Lowe, E. W., Computational Methods in Drug Discovery. *Pharmacol Rev* **2014,** *66* (1), 334-395.
23. Abagyan, R.; Totrov, M.; Kuznetsov, D., ICM—a new method for protein modeling and design: applications to docking and structure prediction from the distorted native conformation. *J Comput Chem* **1994,** *15* (5), 488-506.
24. Gao, C.; Bourke, E.; Scobie, M.; Famme, M. A.; Koolmeister, T.; Helleday, T.; Eriksson, L. A.; Lowndes, N. F.; Brown, J. A., Rational design and validation of a Tip60 histone acetyltransferase inhibitor. *Sci Rep* **2014,** *4* (1), 5372.
25. Gopalakrishnan, B.; Aparna, V.; Jeevan, J.; Ravi, M.; Desiraju, G., modeling, A virtual screening approach for thymidine monophosphate kinase inhibitors as antitubercular agents based on docking and pharmacophore models. *J Chem Inf* **2005,** *45* (4), 1101-1108.

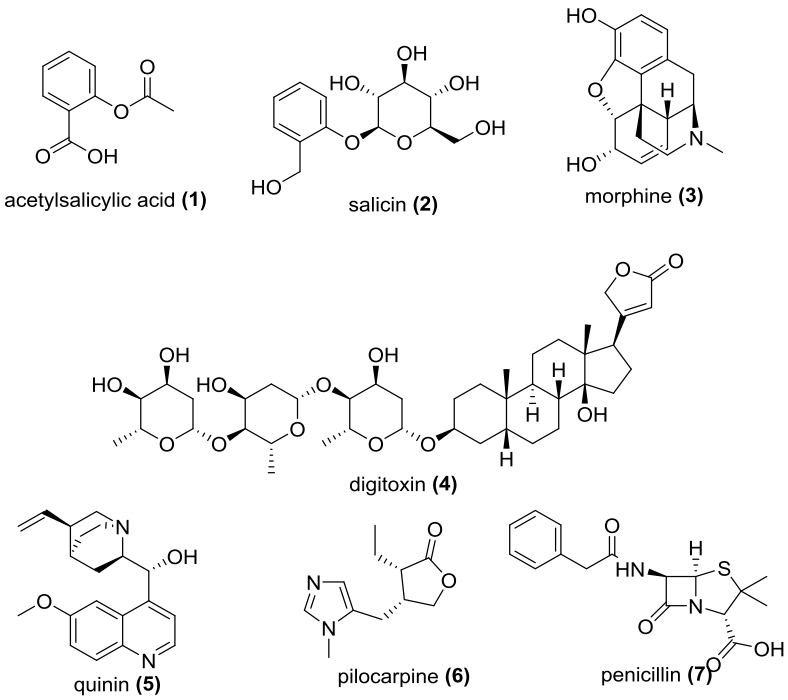

Figure 1.1: Important compounds isolated from natural sources. **(1)**: acetylsalicylic acid, **(2)**: salicin, **(3)**: morphine, **(4)**: digitoxin, **(5)**: quinin, **(6)**: pilocarpine and **(7)**: penicillin.

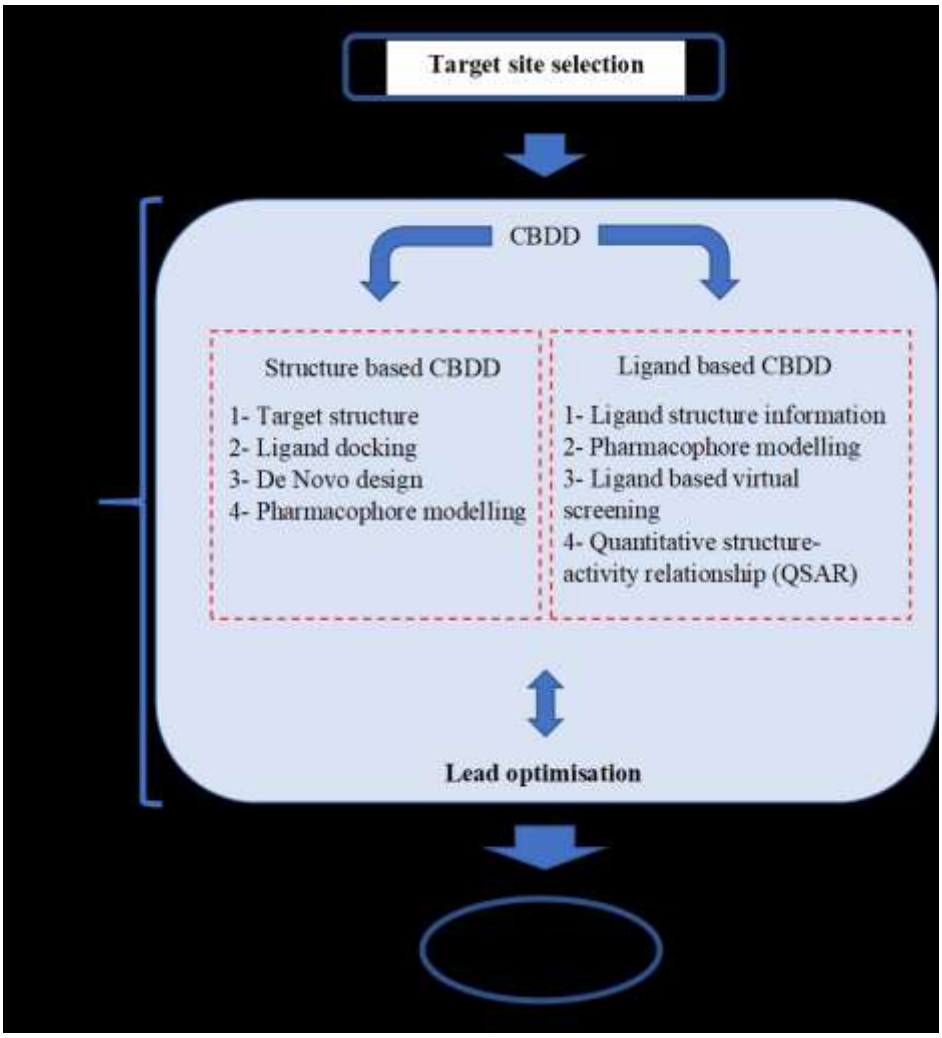

Figure 1.2: CBDD position in drug discovery process flowchart[25].