Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

2.20 The Role of Natural Products as Sources of Therapeutic Agents for Innovative Drug Discovery

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Glossary

Artificial Intelligence Computer-based algorithms and softwares for performing tasks that is normally associated with human brain such as reasoning, speech identification and decision making. Several aspects of AI include computer vision, deep learning and machine learning.

Bioinformatics A computer-based analysis of biological data with the aim of extrapolating such information into knowledge.

High-Throughput Screening A fast and efficient experimentation used in many areas including drug discovery to be able to discover 'drug hits' and used mainly in the area of chemistry and biology.

Machine learning A field of AI involving algorithms and statistical models used to perform tasks with no input of instructions but depends on inference and modelling.

Metabolomics The systematic evaluation of all metabolites that are synthesized by an organism within specific settings at any given time.

Proteomics A comprehensive analysis of proteins within a sample including protein mapping and the identification of proteins and their associated structure and function.

Rule of five The Lipinski's "rule of five" is a set of rules used by scientists to characterize properties of compounds that are given orally. The molecular weight of these compounds must be <500 Da, with a cLogP <5, the number of hydrogen-bond donors <5 and number of hydrogen-bond acceptors <10.

Systems biology A biological field that include tolls such as transcriptomics, proteomics, glycomics and fluxomics. The end result of such a comprehensive analysis is to be able to know the gene expression and proteins/enzymes within cells and include analyzing cellular messenger RNA, proteins and associated structures.

2.20.1 Introduction

The year 2020 started very well for many people throughout the world. The discovery and spread of the SARS-CoV-2 virus responsible for Coronavirus disease-2019 (COVID-19) changed everything. Yet it is not surprising that new viruses causing diseases are expected to emerge. In fact, the existence of many communicable and non-communicable diseases is a fact and presents several challenges in terms of finding cures to treat these diseases. The real challenge lies in finding drugs with little or no side effects. Despite advances in technology and knowledge on the causes of these diseases, they still cause significant deaths throughout the world. Drugs that can cure diseases many diseases are still in short supply or do not exist at all. Novel and innovative strategies for drug discovery are needed. In addition, the "wonder drug" strategies where one drug can cure several diseases and all people must be redefined. Nature already provides options in terms of drug discovery with many compounds still to be discovered. Already several drugs such Taxol (*Taxus brevifolia*), and antimalarial drugs such as quinine (*Cinchona* spp.), Artemisinin (*Artemisia annua*)

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have all been provided by nature (Thomford et al., 2018). Faced with the possibility of future pandemics and disease, drug discovery must take advantage of the available natural products to come up with innovative drugs.

Most plants are found on habitable land globally with a sizable amount also found in seas. Plants are sedentary and therefore require ways and strategies to overcome insults from the environment including cold and heat (Weng et al., 2012). Several plant compounds or molecules allow plants to resist insults and also be able to give off fragrances and colors. Humans have learnt that plants are a good source of medicines over a long time (Lietava, 1992). Community members with knowledge on the medicinal properties of plants were respected people and these would pass on their knowledge to others in order to ease sufferings from diseases and other ailments. Whilst there was lack of documentation in the early days, knowledge was easily passed between community members via word of mouth. The advent of writing and other recoding methods allowed knowledge on plants healing powers to be kept within communities, resulting in many people being treated using plants-based extracts (Ernst et al., 2015; Hotwani et al., 2014; Mannangatti and Naidu, 2016; McGovern et al., 2009). Thus, extracts and concoctions from plants have been used for centuries to treat different diseases, culminating in discovery of drugs for cancer and microbial organisms (Blunt et al., 2018; Chang et al., 2016; Harvey, 2008). Over the years, modern medicine has overshadowed the use of extracts and concoctions from plants human diseases treatment (Tansaz and Tajadini, 2016; Yuan et al., 2016). Recent interests in natural products and the use of medicinal plants in disease treatment stems from the lack of efficacy of purified compounds used in drug discovery (Banjari et al., 2017; Thomford et al., 2016a,b,c; Yatoo et al., 2017). In many countries worldwide medicinal plant extracts are now available over the counter or are used in combination with prescription drugs (Ji et al., 2017; Ruhsam and Hollingsworth, 2017).

Many approved drugs currently on the markets are obtained from plants and these include Paclitaxel and Morphine (Patridge et al., 2016; Wani et al., 1971). Indeed, a significant portion of drugs available in the past two decades are natural products-based or their synthetic derivatives (Carter, 2011; Newman and Cragg, 2012). In addition, several microorganisms can also provide compounds that can be used in drug discovery such as the discovery of penicillin from fungus (Li and Vederas, 2009). Many other drugs were discovered from natural products including tetracycline, artemisinin and doxorubicin. From the early days, plants extracts and concoctions were used as medicines but these are un-purified with little or no knowledge of which compounds within the extracts actually has healing powers. Over time it has been discovered that the synergistic effects of the different compounds within these extracts is the reason why they have healing power (Kiyohara et al., 2004).

The lack of standardization and the rawness of these plant-based extracts present challenge to scientists involved in drug discovery. The purification of plants compounds sometimes leads to loss of healing power and loose of therapeutic efficacy. In many cases these extracts affect biological systems in diverse ways and thus require elucidation of biological mechanisms of action. Studies on natural products and plant-based compounds is challenging as these mixtures are complex and once removed from plants or microorganisms may become altered, leading to the loss of their therapeutic activities (Leonti and Verpoorte, 2017; Li and Weng, 2017). In most cases drug discovery is based on studying single compounds whilst many diseases are complex in nature. Thus the study of single compounds for some diseases will result in failure to provide effective cures. Recent drug discovery strategies therefore also include combinatorial approaches when evaluating potential compounds. New technologies also allow scientists to use combinatorial approaches in evaluating potential compounds therapeutic properties and molecular effects in more accurate biological systems (Özdemir, 2015; Ozdemir and Hekim, 2018).

Whilst it is possible to extract all compounds from natural products, it is not possible to know the effect of every compound in an extract as some effect maybe small. In addition, some compounds found in extracts may mask the effects of other compounds. Thus, it has been suggested that the removal of compounds such as tannins may help in revealing the effect of certain compounds in extracts (Wall et al., 1996). Several strategies that can be performed to achieve this include the use of innovative extraction methods and pre-fractionation (Eldridge et al., 2002; Wu and Liang, 2010). The use of these strategies has been shown to yield better hit leads for drug development (Harvey et al., 2015; Koehn, 2008; Wong et al., 2012). For example, there is semi-bionic extraction, microwave-aided extraction, molecular distillation methods, ultrasonic-aided extraction, membrane separation method as well as supercritical fluid extraction (He et al., 2017; Williams et al., 2012; Zhang et al., 2012) and evidence show that these are efficient at extracting compounds from any source.

Furthermore, several advances in high-performance liquid chromatography (HPLC), nuclear magnetic resonance spectroscopy (NMR), microfluidics and algorithms have been utilized successfully in medicinal chemistry leading to the synthesis of analogues of many natural compounds (Thomford et al., 2018; Wang et al., 2018; Zhang et al., 2018). The use of bioreactors for example as well as microfluidics systems has led to great discoveries of compounds, with many of these compounds resulting in useful drugs or chemicals such as opium and morphine (Edwards, 2002; Manglik et al., 2012). In addition, the use of computational softwares resulted in many structural analogues of natural compounds, leading to drug discovery. Many drugs in use in clinics and hospitals have their origins to natural compounds. Recent studies have also shown that many potential drugs for diseases such as anti-cancer remedies are obtained from plants and these are obtained from African lettuce (*Launaea taraxacifolia*), as well as *Brucea javanica* (L.) Merr. (Simaroubaceae; Thomford et al., 2016c). Classical examples of drugs originating from plants include Artemisinin, which is a product from *Artemisia annua* also known as Sweet Wormwood (Tu, 2011, 2016). Furthermore, derivatives of Artemisinin are useful in treating diabetes and cancer (Lai et al., 2013; Li et al., 2017). There are many challenges associated with high throughput screening assays during drug discovery. Questions on who own the rights to plants found within certain regions and who should benefit from the utilization of local plants are some of sticky questions asked before the use of plants in drug discovery. Organizations such as the Rio Convention on Biodiversity are focussed on avoiding the over-utilization of natural sources for profit and try to address issues around intellectual property rights. A balanced view is needed when utilizing natural products for drug discovery

whilst maintaining the presence of natural species (Barbault, 2011; Li and Vederas, 2009; Salazar and Cabrera, 1996; Tollefson and Gilbert, 2012).

Contrary to traditional medicine where whole extracts of plants are used during treatment, modern science requires the purification of individual compounds from extracts and their evaluation as potential drugs. Both the use whole extracts and the purification of compounds have their advantages and disadvantages. The use of whole extracts with no purification process has the effect of producing better therapeutic effects compared to the use of individual compounds. Compounds found in whole extracts are likely to work together or in synergy to produce the desired effect. Modern medicine on the other hand requires individual compounds to be isolated and evaluated, many times making drug discovery a long and expensive adventure. The isolation of individual compounds however does not show a similar effect as three compounds within the extract are known to work in synergy (Srivastava et al., 2013; Yang et al., 2013).

A combination of innovative drug design and the use of latest technologies including artificial intelligence must be utilized to develop new drugs needed to combat current and emerging global health challenges. Among the new technologies are innovative computational and analytical methods that can be used to isolate compounds from extracts and the need to identify compounds with desired therapeutic effect. In addition, the pharmaceutical industries have to abandon the "one wonder" drug approach and instead use the combination approach as many diseases are treated using combinations of drugs anyway. The use of omics technologies will come in hand to study how combinations of compounds affect cellular genes and proteins. In addition, the development of biological models such as organoids and microfluidics will allow the proper testing of these compounds on cells and tissue. The development of computational softwares can allow the designing and testing of new compounds derived from plant extract, their synthesis and biological testing (Kim et al., 2015; Medema and Fischbach, 2015). It is not surprising that natural products will allow improved drug discovery given the vast amount of compounds that can potentially be obtained from the design of new pharmacologically important molecular products from natural products (Akbulut et al., 2015; Ludlow et al., 2017).

2.20.2 Innovative strategies for drug discovery with natural products

To succeed in coming up with new drugs, innovative as well as multidisciplinary strategies must be devised to use natural products to completely drive development of new drugs used in clinics and other medical practices. A combination of these strategies is likely to yield new drugs that can eliminate health challenges experienced today. The isolation and evaluation of individual compounds from natural products as potential drug candidates has been shown to weaken the therapeutic efficacy of these compounds as most compounds found in plants for example display synergistic effects. Thus, new methods are needed to combine and evaluate compounds for their therapeutic effects. Lately, system biology approaches have been used to guide drug discovery from natural products, helping to understand both efficacy and the lack of in several compounds (Buriani et al., 2012). This goes beyond just evaluating single compounds but looks at the complete effects of compounds on an organism of system. Evaluating the effect of compounds from natural products by looking at genomics, transcriptomics, proteomics, and metabolomics has allowed fast and efficient screening of compounds. This has led to better drug candidates. The deposition of many compounds into both public- and company-molecular libraries of potential drug candidates from natural products has led to compounds tinctures for new and improved drugs. Most pharmaceutical companies are discarding the reductionist approach of isolating and evaluating single compounds and are now realizing the need to include combination studies during drug development.

2.20.2.1 The role of genomics in natural product drug discovery

One of the most important stages of plant-based drug discovery is the need for precise identification of the species of the plant from which a compound came from. Therapeutic effects of a compound must be ascribed to the right plant species as well as location for future research on that compound. The possibility of using the wrong plant source is there and must be avoided. Different plant species have different compounds in varying amounts. Recent advances in genomic techniques has allowed the establishment of an accurate identification criteria for plants and other natural products sources (Buriani et al., 2012). For example, DNA barcoding can be used to identify different species of plants and other natural products sources and is very accurate (Ganie et al., 2015). Thus, DNA barcoding and other recent techniques can provide rapid and accurate identification of plants in comparison to morphological and other traditional methods in use currently (Ghorbani et al., 2017). Due to its accuracy and speed, DNA barcoding is now used in biodiversity inventories to identify natural products and their sources (Thompson and Newmaster, 2014) and rapid identification of herbal products (Cao et al., 2014; Mishra et al., 2016). For example plant species such as *Amaranthus hybridus* L. have been identified using DNA barcoding (Chen et al., 2017; Ghorbani et al., 2017). Whilst DNA barcoding is useful in identification of plants and other natural product sources, plant parts may have different therapeutic properties as they are exposed to different environmental factors.

Lately, it has become necessary to have natural products sources showing consistency in terms of the compounds found within. Hence, bio-farming was introduced whereby plants are grown under the same conditions until harvesting and extraction of natural products. Compounds or molecules from natural products extracted under the same conditions are then authenticated via DNA barcoding (Pulice et al., 2016). In addition genomic techniques can be used to develop markers from different plants and used in genomic chips that allow the use of high-throughput methods in the authentication of sources of natural products as well as genotyping (Buriani et al., 2012; Gantait et al., 2014). Furthermore, by using novel techniques such as microarray analysis, it is

possible to have an efficient and rapid way of analyzing transcripts (Buriani et al., 2012; Lv et al., 2017). Multiple genes can therefore be evaluated at the same time (Kiyama, 2017). This allows the evaluation of natural products' or compounds mechanisms of action as well as the molecular mechanisms through which they act.

There are several ways in which genomics aid in targeting of natural products during drug discovery. Certain cellular signaling and enzymes target specific compounds for metabolism and this can be achieved through genomic analysis. Several genome-based methods including sequencing and transcriptomic investigations have allowed the evaluation of many systems in terms of compound targeting. For example, protein modifications, the binding sites of transcription factors, methylation patterns as well as DNA structure alterations are being evaluated at genomic level (Barbosa et al., 2015; Jones et al., 2015; Nordlund et al., 2013; Zykovich et al., 2014). Many studies have identified new drug targets via the identification of deletions, insertions and copy number variations associated with cancers (Bose et al., 2017; Eckel-Passow et al., 2015; Vogelsang et al., 2012). The advent of techniques such as CRISPR-Cas9 and other new technologies has allowed unprecedented genome-wide analyses allowing several drug targets to be identified. Furthermore, new and improved public and private natural products and compounds databases has allowed high throughput screening of many compounds, shortening the time taken during drug discovery and drug designing (Fishilevich et al., 2017; Mehta et al., 2013; Simmonds et al., 2017; Yang et al., 2014).

2.20.2.2 The role of proteomics in natural product drug discovery

Proteomic analysis has emerged as a complimentary approach to genomic and transcriptomic approaches in terms of identifying and delineating the mechanisms of action of many natural products. From protein expression, function and biosynthesis cascades, proteomics can also translate to quality of the natural product under review (Bumpus et al., 2009; Martínez-Esteso et al., 2015). Advances in mass spectrometry including the use of isotope tags and in combination with two-dimensional (2D) electrophoresis can reveal protein profiles associated with natural products in a similar way to genomic data. For example, mass spectrometry was successfully used to identify Chinese herbal medicine species *Panax ginseng* as being different from *Panax quinquefolium* (Lum et al., 2002; Thomford et al., 2018). In addition, natural product biochemistry and chemistry can be investigated by mass spectrometry in order to identify both the biosynthesis and metabolic pathways associated with that product (Hung et al., 2012; Li et al., 2011). Proteomics can also be used to reveal multitarget effects of many natural product or plant extracts (Buriani et al., 2012; Lao et al., 2014).

An important task during drug discovery is the identification of target proteins of natural products before their use as medicines, to prevent deleterious effects. For example, the interaction between natural products and proteins can be studied via affinity chromatography. In most cases there is no need to modify the natural product before being used in analyses. Thus natural products are studied in their natural state, leading to the identification of the true activity and therapeutic effect. New methods including cellular thermal shift assay, can be used to stabilize the product of natural product-protein interaction. Another method, thermal proteome profiling takes advantage of target protein stability at increased temperatures. In addition, new techniques including bioinformatic analysis of how compounds bind to their target proteins can now be done easily, thanks to artificial intelligence and other methods. As a group of compounds, natural products display a great variety of biological properties as they are complex and have several known structures. In addition, natural products can also bind to many ligands. Thus, it is very important that specific protein targets of natural products be identified and studied. The potential to cause deleterious side effects is high, given their complex structures. Any natural product that is a potential drug must be evaluated for its toxicity, side effects and the possibility of having what is known as off-target effects. Affinity chromatography has been used over the years to identify target proteins and the in vivo biological properties of such proteins (Guan and Chen, 2014; Novick and Rubinstein, 2012; Rix et al., 2012; Wang et al., 2015a). In this method, the natural product is pulled-down and bound to a physical solid surface (McFedries et al., 2013). The bound protein can then be analyzed and identified via immunoblotting and mass spectrometry. The binding of a natural product to its target protein can also cause alterations to its structure and activity. Thus, methods that avoid the modification of the natural product are needed (Lee and Lee, 2016; Rix and Superti-Furga, 2009). Novel label-free methods have been developed over time to avoid natural product modifications and these new methods can evaluate the reaction between natural product and its target protein as well as the response to proteomic and thermal treatment (Franken et al., 2015; Lomenick et al., 2009). A single natural product can have several target proteins as shown through the use of label-free methods and proteomic analysis (Chang et al., 2016; Schirle et al., 2012).

One of the label-free method used to directly identify target proteins is drug affinity responsive target stability (DARTS) (McFedries et al., 2013). In this method, the differences between a bound and free- target protein when treated by proteinases is measured (Schirle et al., 2012). Over the years, successful validation of target proteins using this method has been done. For example, DARTS has been used to identify target proteins for (Lomenick et al., 2009, 2011). Low abundant proteins are however very difficult to identify using this method (Dejonghe and Russinova, 2014). In addition, a newer method referred to as stability of proteins from rates of oxidation (SPROX) can measure alterations in target proteins caused by ligand binding (McFedries et al., 2013; West et al., 2010). Methionine residues are oxidized in target proteins and this can easily be measured (McFedries et al., 2013). The natural product and its potential target protein are mixed with an oxidizing agent plus the addition of guanidinium hydrochloride. The methionine residues on the target proteins are oxidized. Peptides that are generated are analyzed for methionine oxidation via mass spectrometry. SPROX is able to identify many target proteins and has been successfully used with many compounds or drugs including resveratrol and cyclophilin A (Dearmond et al., 2011; Strickland et al., 2014). SPROX however, require high concentrations of proteins to work. A method based on the modification of SPROX referred to as stable isotope labelling with amino acids in cell culture (SILAC). SILAC is considered better than SPROX as it can identify more target proteins for

natural products (Larance et al., 2011; Ong and Mann, 2006; Tran et al., 2014; Zhang et al., 2015). However, SILAC can only identify target proteins containing methionine.

Recent methods, including cellular thermal shift assay (CETSA), can be used to evaluate the stability of the complex formed between the target protein and its ligand (Martinez Molina et al., 2013; Tang et al., 2016). In this method, proteins within lysates and cells are mixed with compound and heated (Thomford et al., 2018). Target protein and destabilized protein are separated and analyzed (Thomford et al., 2018). An alteration to the melting temperature or curves can be detected via the plotting of ligand-target interactions versus temperature. Target proteins for compounds including raltitrexed and methotrexate have been identified via this method (Martinez Molina et al., 2013). CETSA has the advantage of being able to be used with intact cells with no lysis needed. One of the major disadvantages of this method is that some target proteins may not be identified. Antibodies can be non-specificity resulting in off-target proteins being identified as false positives. An advancement of CETSA is Thermal Proteome Profiling (TPP). One of the disadvantages of TPP is that it is a very expensive method and requires a lot of labor.

Another method that can be used to validate target proteins is the use of small interfering RNA and short hairpin RNA. These methods are great ways to manipulate and functionally validate target proteins (Ho et al., 2009; Jung and Kwon, 2015). For example, by performing target protein knockdown via interfering RNA, off-target effects of natural products can be evaluated. A recent addition, the clustered regularly interspaced short palindromic repeats-Cas9 (CRISPR-Cas9) is used to investigate and potentially avoid off-target effects of natural products (Bassik et al., 2013; Shalem et al., 2014). Genome editing using CRISPR-Cas9 together with sequencing is useful to evaluate drug resistance and as a way to validate anti-cancer therapeutic agents (Kasap et al., 2014; Neggers et al., 2015).

2.20.2.3 The role of metabolomics in natural product drug discovery

One of the most innovative ways of discovering new drugs that can be used to treat the ever-increasing global health threat is metabolomics strategies in identification and evaluation of compounds. Delineating the metabolomic profiling of natural products is a way of identifying as well as the quantification of the metabolites associated with a specific natural product (Clish, 2015; Liu and Locasale, 2017). On the other hand, metabonomics is a way to measure the overall and changing metabolic changes in an organism to alterations in its biology and most importantly its genome (Nicholson and Lindon, 2008; Perez-Pinera et al., 2012; Yarmush and Banta, 2003). For some time, drug development has utilized metabolomics to identify and evaluate natural products-based metabolites. Metabonomics on the other hand include a stems biology-based approach to investigate the functions and changes of a biological system after a pharmacological effect. Thus, metabonomics tends to reveal more details about a natural product, its biological mechanism of action as well as its effect on the whole living organism.

Several well established techniques including mass spectrometry and specifically ultra-performance high performance liquid chromatography-quadruple TOF MS (UPLC-MS) has been used for metabolomic profiling of natural products, leading to revelations of new compounds demonstrating therapeutic effects (Thomford et al., 2018). For example, therapeutic compounds from plants including *Newbouldia laevis, Cassia abbreviata* and *Panax* herbs have been identified (Thomford et al., 2016a; Xie et al., 2008). Metabolomics has also been used to identify plants species and therefore maintain the quality and consistency of plant species usage. For example, the use of NMR as well as mass spectrometry has led to the authentication of several plants including *Panax ginseng* and *Panax quinquefolius* (Park et al., 2014). In most cases, metabonomics has been used to profile natural products and in so doing serve as a phenotyping tool. Metabonomics allows the evaluation of natural products and reveal both the metabolites and biology systems effect of a natural product. Most importantly, both metabolomic and metabonomics can be used to profile natural products using techniques such as NMR, mass spectrometry and UPLC, and in so doing reveal properties such as pharmacokinetic and toxicological effects of natural products and their related compounds.

2.20.2.4 The role of big data in natural products drug discovery

Generation of big and complex datasets through the use of "omics" analysis has necessitated the use of bioinformatic and computational tools for interpretation. Statistical analysis will enable the usage and application of such complex data to delineate the pathophysiological effects of natural products. In addition, information such as natural product's target specificity and molecular effects can also be revealed. Furthermore, data such as pharmacodynamics and toxicological testing of natural products and their associated compounds can be evaluated via the use of omics technologies. The use bioinformatic and computational tools has also allowed processes such as docking and virtual screening to be done easily. Advanced techniques such as machine learning algorithms are being utilized to perform virtual screening of millions of natural products and their associated compounds, allowing drug discovery costs to be reduced significantly (Korotcov et al., 2017; Oprea and Matter, 2004).

With several public and private databases available and containing millions of potential drug candidates, it is now possible to perform virtual screening of natural products and their related compounds for drug discovery. In addition, it is now possible to identify compounds with identical activity and biological effect. Generally compounds of similar structure ca be grouped together and assumed to have similar biological activity, although data does not always support this notion. If the chemical structure of a compound is known combined with knowledge of target protein can be used to map out possible interactions. By comparing the possible responses to candidature compounds, it is possible to get a gene signature for a specific candidate drug (Beck et al., 2016; Brum et al., 2015; Lamb, 2007). One of the inventions of the recent years is the connectivity map. The connectivity map associates drug gene signatures with disease-associated gene signatures, thus allowing the identification of compounds that may reverse

the disease gene signature (Beck et al., 2016; Brum et al., 2015; Lamb, 2007). The generation of large datasets is not without disadvantages. For example having large datasets can result in the loss of meaning of the data or the ability to understand it. Therefore, large datasets must be organized so as to be useful and be organized into actionable data (Awale et al., 2017; Denny et al., 2017; Ozdemir and Hekim, 2018). Some of the available data bases and sources utilized during drug discovery include ChEMBL, DrugBank and the Small Molecule Repository (Bento et al., 2014; Gaulton et al., 2017; Kruger et al., 2012).

Overall, the Connectivity Map (CMap), computational method used to evaluate compounds and molecular mechanisms of disease has been useful in drug discovery (Chen and Chen, 2008; Roos, 2001). The CMap was established in the United States of America at the Broad Institute as a database of transcriptional information of human cells treated with thousands of compounds (Beck et al., 2016; Lamb, 2007; Segal et al., 2012). The CMap allows the user to generate connections between compounds and gene expression signatures, genes and disease response. In addition, the CMap can be used to connect diseases and drugs. Studies have shown that pattern-matching analysis can be applied to natural products and their associated compounds and diseases (Brum et al., 2015; Cheng et al., 2014; Lamb, 2007).

The use of computers and electronic databases of chemicals has enabled scientists to reduce the cost of drug discovery significantly. Knowledge of natural products protein targets in addition to clinical information including patients differences in response to therapy may result in increased rate of drug discovery (Kim et al., 2016). Efficiency is one major hindrance to effective drug discovery. A dearth of proper models that are able to mimic the human body and tissues in their response to natural products or therapy is a major concern. In addition, patient heterogeneity in responding to drugs together with difficulties in analyzing some biological processes in drug studies continue to be a major hurdle to effective drug discovery (Cappon, 2011; Kaneko et al., 2011; Morford et al., 2011). Huge losses are incurred during drug discovery when potential candidate drugs fail towards or during clinical trials (Beggs and Dobrovolny, 2015; Nelson et al., 2016; Tsugawa et al., 2015). The generation and accumulation of large amounts of information with no bias and then used to generate innovative ideas is called Big Data (Gange and Golub, 2016; Greene et al., 2014; Wasser et al., 2015). The integration of Big data with chemical structures, target proteins and toxicity information has led to generation of several bioinformatic algorithms that can be used to analyze such data (Omberg et al., 2013; Reshef et al., 2011).

Cancer patients however do not display similar somatic alterations, presenting a major challenge during utilization of big data during drug discovery. This is due to differences in patients sometimes called tumor heterogeneity (Dzobo and Dandara, 2020; Dzobo et al., 2018). Tumor heterogeneity is a major cause of chemoresistance and failure during drug treatment. Another important hindrance to the use of big data is the need to reduce large datasets into specific and meaningful messages. Most importantly is the need for clinical phenotype to be integrated with genomic, transcriptomic, proteomic and epigenomic data (Chen et al., 2012; Kim et al., 2016; Ozdemir and Hekim, 2018).

2.20.2.5 The role of automation in natural product drug discovery

Worldwide, automation is considered bad as it is linked with loss of jobs as well as the idea that machines will rule over humans one day. However, currently automation has enabled humanity to do great things unimaginable some few years back. For example in drugs discovery, automation has enabled the screening of thousands of natural products and other compounds, successfully speeding up drug discovery in the process. Almost all drug discovery companies make use of high-throughput screening procedures and assays to speed up compounds analysis and evaluation (Chapman, 2003). Many synthetic compounds have been designed and synthesized with the aid of computational softwares. Computational softwares such as ADAM and EVE are useful to identify drug targets and potential drug candidates (King et al., 2009; Sparkes et al., 2010). Even with the use of bioinformatic softwares, many false positive are being recorded in terms of potential drugs. To deal with false positives as well as reduce unnecessary usage of material, new and advanced softwares are being made to allow designing of compounds and biological testing (Meanwell, 2016; Schneider, 2017). Several laboratories and companies are making use of advanced microfluidics systems that can allow the use of liquids and high temperatures during analysis of synthesized compounds as well as purification (Baranczak et al., 2017; MacConnell et al., 2017). Several ideas and new hypothesis can now be evaluated in days or even hours. New technologies such as artificial intelligence and animal models such as organoids can be integrated within the drug discovery process to allow the design and optimization of the process (Gupta et al., 2017; Merk et al., 2018; Schneider, 2017). The use of these new technologies have eliminated bias and human mistakes from the drug discovery process as well as the amount of time required for testing of candidate compounds (Eglen and Randle, 2015; Esch et al., 2015). In addition, the use of advanced models has allowed the mimicking of human tissues and diseases better than before. In practice however, new technologies and innovations have not resulted in new drugs in record time. This is partly because technologies alone cannot produce better drug candidates. Thus, whilst new technologies have reduced the amount of time needed during drug development, the use of such technologies must be sustainable in the long run (Ozdemir and Hekim, 2018; Ozdemir and Patrinos, 2017).

Compound designing is influenced by several factors including absorption, distribution, metabolism, excretion and toxicity (ADMET) properties. In addition, the activity of the final product is also important. All in all, the process of drug development is a multifactorial as well as multidimensional. Most importantly, having the right structural properties may not mean the right biological effect. Thus a balance is needed between natural product or compound activity versus properties (Schneider, 2017). This is where automation is of great help. Computational tools and automation enable drug developers to balance compound design and biological activity, whilst maintaining the needed ADMET properties. Compound designing has been done using several methods including diversity-oriented synthesis (DOS) and biology-oriented synthesis (BIOS). These new developed methods have

allowed the designing of new chemical structures (Basu et al., 2011; Burke and Lalic, 2002; Kaiser et al., 2008; Wetzel et al., 2011). A recent method is based on the function of the promising natural product or compound. Referred to as function-oriented synthesis, this method aims to recapitulate the function of drug candidate so as to obtain scaffolds that can make the synthesis of compounds easier (Schneider, 2017; Wender et al., 2015). Generators of compounds have also been automated and make use of deep learning techniques during the designing of compounds that have needed characteristics and biological activity (Merk et al., 2018; Zhu et al., 2011). Deep learning models or techniques are useful in predicting ADMET properties as well, besides the usual drug-target interactions predictions (Jing et al., 2018; Rubio et al., 2010). Deep learning softwares were used in the discovery of drugs designed based on imidazopyridine scaffold leading to the identification of ligands for G protein-coupled receptors antagonists (Schneider, 2017, 2018). By combining the use of computers and the use of microfluidics-assisted synthesis, it was demonstrated that different ligands with different binding profiles can be made (Reutlinger et al., 2014b; Schneider, 2018; Wang et al., 2015b). Through the use of microfluidics synthesis together with target prediction, compound libraries can be obtained easily (Reutlinger et al., 2014a).

For automation of compound synthesis to succeed, there is need for building blocks and derivation of chemical reactions that can give rise to a variety of by-products. The use of microfluidics enables minute volumes of starting materials to be used in compact synthesis. Together with purification of by-products during synthesis as well as final analyses of the final product has led to new models and machines that can synthesize complex structures. This is similar to the natural synthesis of natural compounds by plants or other organisms (Besnard et al., 2012; Sutherland et al., 2014). In this regard, 3D printing has played a huge role by allowing the building of microfluidic devices or structures that can use complex bioinformatic algorithms or softwares to monitor and evaluate product synthesis. By using 3D printing it is possible to custom-make microfluidics platforms specific for certain compound synthesis and function. With the addition of remote control of automated robotic synthesis can be made to run for the whole day and be more efficient (Godfrey et al., 2013; Nicolaou et al., 2016). Recently automated compound synthesis only require small amounts of building blocks in order to generate a great amount of by-products (Li et al., 2015). Continuous synthesis of compounds through the use of microfluidics can prevent batch to batch differences between synthesized compounds. Lately, it has been shown that drug oxidation by cytochrome P450 enzymes can be mimicked allowing on-chip chemo-transformations of compounds to replace metabolite identification which was done in vitro (Genovino et al., 2016; Stalder and Roth, 2013). Thus, automation of compound synthesis together with in-process evaluation and identification of by-products can transform drug discovery greatly going into the future (LaPorte and Wang, 2007). One great advantage of continuous compound synthesis with in-process evaluation of the process is the avoidance of contact with chemicals and other dangerous solutions. There is great savings in terms of reagents as microfluidics allows the use of small amounts of reagents and solutions (Brzozowski et al., 2015; Chin et al., 2009). Most traditional animal models are not good predictors of drug response in humans, the use of microfluidics and organoids can help in mimicking many human- and species-specific biological processes. New models such as organoids and microfluidics allow the generation of microenvironment that are relevant to humans and can be used over a long time (Eyer et al., 2013; Loskill et al., 2017). For example, tumor organoids mimicking human tumors have been developed (Ferrari, 2010; Zhang et al., 2017). Hindrances still exist in preventing the use of continuous flow systems and these include the danger of fluidic surfaces instability as both reagents and compounds could mix with final products. Furthermore, system clogging can occur and can be difficult to resolve as this require opening up the whole closed system.

Lately the integration of microfluidics-assisted synthesis and evaluation platforms has allowed the selection of both reagents as well as adapts in-process steps that collect and test the by-product or final product. In addition, both public and private institutions have developed networks with many reactions and pathways relevant for drug discovery in automated systems. These reactions and pathways have resulted in previously unknown routes being revealed for compound selection and synthesis (Kayala et al., 2011; Kowalik et al., 2012; Szymkuc et al., 2016). Artificial intelligence has also helped drug design by optimizing reagents use and testing of final compounds, making drug discovery a sustainable process (Baker, 2013; Lopez-Rubio et al., 2015; Wesolowski and Suchacz, 2012). Softwares and machines are able to perform hypothesis testing without the use of reagents. Many compounds can be synthesized simultaneously by machines using artificial intelligence. Criteria such as biological activity, side-effects and synthesizability can be tested using virtual compounds, saving time and money in the process. Microfluidics and artificial intelligence are therefore enabling technologies that can push drug discovery to new heights by allowing pattern recognition and compound designing (Baskin et al., 2016; LeCun et al., 2015).

2.20.2.6 The role of computer-aided drug design in natural product drug discovery

Natural products have been used to come up with synthetic compounds that have similar structures, with the hope that these new compounds can be effective drug candidates. In some cases however, these new synthetic compounds derived from natural products would have designs not suitable for drugs or would prove to be ineffective as drugs via virtual screening and therefore discarded. The existence of certain criteria regarding choosing drug leads makes it easy to decide whether a synthetic compound is good or not. For example, there is the "rule of three" and "rule of five" criteria that are usually used to choose compounds that can be taken forward during drug discovery. Many have observed that this criterion tends to be very strict, as many compounds fail the test (Congreve et al., 2003; Lipinski, 2000; Ntie-Kang et al., 2014). In contrast to computer based selection of compounds, many guidelines in use during drug designing is influenced by human bias. This has the net effect of reducing their usage and effectiveness, when used to natural products (Ntie-Kang et al., 2014; Zuegg and Cooper, 2012). Thus, lately many compounds have been selected and developed through the use of designs made by computers (Elumalai et al., 2015; Grabowski et al., 2008; Renner et al., 2009). For example, the Scaffold Hunter software was very effective in selecting designs and generating virtual designs of attractive

molecules (Wetzel et al., 2009). Reports show that some of these computer-designed molecules or compounds can retain biological activity similar to the parent compound. The Scaffold Hunter software has already been used to select, develop and identify inhibitors and activators of pyruvate kinase (Rodrigues et al., 2016). In some cases, however, the synthetic compounds derived from natural products demonstrate weak biological activity compared to the parent compound (Bon and Waldmann, 2010; Renner et al., 2009). Another computer software, the PASS software, is effective at predicting the activities of very simple structures derived from natural products as well as anti-tumor activities of many alkaloids obtained from the sea (Lagunin et al., 2000; Rodrigues et al., 2016; Stepanchikova et al., 2003).

Several compounds obtained from John wort were correctly shown to have modulating effects on enzymes including the cytochrome P450 (Rodrigues et al., 2016). Currently, many private and public bioinformatic softwares, databases and web servers are available that can be used in selection of compound structures as well as predicting their biological activities. Other softwares and mathematical models are good at predicting synthetic compound-target protein associations. Prediction of biological activity by new compounds is assumed based on similarity of new compounds to already available drugs. Similarity in structure is assumed to infer similar target and normal ligand-receptor docking. Another software referred to as the SPIDER software is able to compare different structure between new compound and known drugs and be able to predict the potential target of new compound (Reker et al., 2014; Schneider et al., 2014). For example, the prediction and eventual identification of G-protein coupled receptor ligands was done using the SPIDER software (Schneider et al., 2014). It is now common practice during drug discovery to use computational drug design and target prediction. One major hindrance to the use of computational softwares for selection of compound structure and prediction of biological activity include having prior knowledge of targets for prediction to take place. This is partly due to the fact that computer based quantitative structure activity approaches are used to explain biological activities of compounds based on their structures as well as come up with compound derivatives able to improve activity (Sliwoski et al., 2014). A huge advantage of computer-based drug designs and predictions is that optimization and biological activity prediction can be done virtually, saving reagents and avoiding contact with dangerous chemicals. In addition, the affinity, pharmacodynamic and pharmacokinetic properties of a candidate compound can be predicted virtually.

Furthermore, the toxicity of potential drug can be studied well before the compound is synthesized. Novel systems under development can predict toxicity of compounds virtually, before resources are committed towards synthesis of that compound (DiMasi et al., 2010, 2013; Hay et al., 2014; Loong and Siu, 2013). Currently, in silico methods are being used to study biological activities of many compounds, with in vitro studies confirming the results. Overall, computational strategies are able to reduce costs as well as the time taken to get drugs. Many quantitative structure-activity relationship models are being used to predict and delineate the relationship between compound structure and toxicity (Chavan et al., 2014; Cherkasov et al., 2014; Devillers, 2013; Sullivan et al., 2014). Other softwares under development are able to predict and evaluate potential candidate drug metabolic pathway. Whilst virtual screening process have aided drug discovery, harmful effects of compounds can only be evaluated naturally. The potential harmful effects of compounds and drugs on animals and plants can only be studied in the natural environment.

The development of new drugs in indeed needed at this moment. Recent advances in analytical methods have revealed the magnitude of tumor heterogeneity and the varied patients' response to therapy (Bastian et al., 2013; Dzobo, 2019, 2020; Dzobo and Dandara, 2020; Dzobo et al., 2016, 2018; Stanciu-Herrera et al., 2008). Thus, new drugs that can cater for different patients are needed for therapy. Previously, drug discovery was based on a "wonder drug" that can cure all patients. However, recent reports indicate that not all patients respond in the same manner to the same drug. In addition, the "one drug-one target" strategy has been shown to be futile. It has been shown that combination therapy is the gold standard and must be applied during patients' treatment. Thus, drug design must be done with a view of using more than one drug for treatment. And in most cases more than one drug are needed to target the same pathway or act synergistically to achieve cure. Recent advances in immunotherapy mean that conventional chemotherapeutic agents can be used in combination with immunotherapy as well as stem cell therapy to achieve better cure for cancer patients for example (Baselga et al., 2012; Kawajiri et al., 2015; Swain et al., 2013, 2014, 2015). With this in mind, drug discovery has taken a new route with even computer-based screening going the combinatorial drug design way.

2.20.2.7 Natural products and precision medicine

Although genomics has been integrated into drug discovery, the resulting drugs haven't shown great efficacy. Part of the reason this is so is the complex nature of diseases and varied patients response to therapy. Lately, technological and analytical advances in genomics have allowed rapid diagnosis as well as interpretation of patient heterogeneity influencing therapy response (Ozdemir and Hekim, 2018; Ozdemir and Patrinos, 2017). Precision medicine via targeted therapy is able target specific disease features in order to have effective cure. Initiatives including the Human Genome and the Cancer Genome Atlas (TCGA) projects aim to understand the role of genetics and gene expression in disease progression and therapy response. With genetics informing drug discovery, many hoped that many drugs would be very effective at treating diseases. This hasn't materialized unfortunately. However, the rapid development of many technologies and softwares has allowed a deeper analysis of patients' genomes, creating a treasure trove of data that can be used during drug discovery. One of the major developments has been the ability to link a patient's genome and clinical features on presentation (National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease, 2011). Several studies on specific proteins and the possibility of drug interactions gave rise to many drugs currently in clinical use. The lack of new drug targets has led to a decline in drug productivity over time. One of the approach used in drug discovery is the "gene to screen" approach, which is based on genes being the main determinant of cell phenotype and thus can be used for drug screening (Debouck, 2009; Debouck and Metcalf, 2000). Furthermore, the use of genome-wide association studies (GWAS) to

compare variations in genomes between patients and healthy individuals provides an unbiased way of identifying genetic determinants of diseases. In addition, GWAS can allow scientists to delineate the underlying mechanisms driving disease development.

2.20.3 Conclusion

A paradigm shift in the way drug are designed and developed is needed to curb the rise in new infectious diseases and also drug resistance. Innovative ways to develop new drugs are needed. To achieve this, innovative strategies based on inspiration from natural products have helped in the designing and development of many compounds that are potential drugs. In this regard, technological advances have allowed profiles of complex compounds to be studied, resulting in many compounds being designed and synthesized. Indeed, many compounds and other blockbuster drugs have already been developed from natural products or from compounds derived from natural products. This makes natural products central to drug discovery and with recent trends in technological advances, will aid in increasing the success rate of new therapeutic moieties. Overall, natural products will remain a major contributor to drug development and in our effort to curbing global health challenges as well as achieving sustainable development goals on health.

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