Abstract: The therapeutic properties of plants have been recognised since time immemorial. Many pathological conditions have been treated using plant-derived medicines. These medicines are used as concoctions or concentrated plant extracts without isolation of active compounds. Modern medicine however, requires the isolation and purification of one or two active compounds. There are however a lot of global health challenges with diseases such as cancer, degenerative diseases, HIV/AIDS and diabetes, of which modern medicine is struggling to provide cures. Many times the isolation of “active compound” has made the compound ineffective. Drug discovery is a multidimensional problem requiring several parameters of both natural and synthetic compounds such as safety, pharmacokinetics and efficacy to be evaluated during drug candidate selection. The advent of latest technologies that enhance drug design hypotheses such as Artificial Intelligence, the use of ‘organ-on chip’ and microfluidics technologies, means that automation has become part of drug discovery. This has resulted in increased speed in drug discovery and evaluation of the safety, pharmacokinetics and efficacy of candidate compounds whilst allowing novel ways of drug design and synthesis based on natural compounds. Recent advances in analytical and computational techniques have opened new avenues to process complex natural products and to use their structures to derive new and innovative drugs. Indeed, we are in the era of computational molecular design, as applied to natural products. Predictive computational softwares have contributed to the discovery of molecular targets of natural products and their derivatives. In future the use of quantum computing, computational softwares and databases in modelling molecular interactions and predicting features and parameters needed for drug development, such as pharmacokinetic and pharmacodynamics, will result in few false positive leads in drug development. This review discusses plant-based natural product drug discovery and how innovative technologies play a role in next-generation drug discovery.

Keywords: natural products; drug design and development; innovation; automation; computational softwares; bioinformatics; precision medicine; omics; global health
1. Introduction

The scourge of communicable and non-communicable diseases and the challenges of finding drug candidates that can treat these diseases with little or no side effects is a huge challenge. Despite the development of drugs for treating and managing diseases such as HIV/AIDS, malaria, hypertension, diabetes and cancer, these diseases continue to plague diverse populations worldwide with significant associated mortalities. There is need for innovative drug discovery strategies that skew from the current “blockbuster” Pharma R&D strategies. Currently, a viable approach will be to revert to “nature” for answers since it has worked for drug discovery in the past. Anticancer drugs such as Taxol (Taxus brevifolia), Vinblastine (Catharanthus roseus) and antimalarial drugs such as quinine (Cinchona spp.) and Artemisinin (Artemisia annua) were all discovered from natural products and are effective in treating these diseases. In the face of global public health challenges, natural products research and development (R&D) potentially plays a pivotal role in innovative drug discovery.

Plants are found in every habitable environment with most found on land. Faced with many stresses and challenges, coupled with being sedentary, plants have developed many molecules to ward off attacks from animals and environmental insults [1]. These same molecules give plants their ability to give off fragrances, colours and indeed toxicity. Many historical findings report on early use of plants for medicinal purposes [2]. The discovery of medicinal plants by early humans must have been a trial and error exercise necessitated by the need to ease disease manifestations. Before the advent of writing and recording of history, such knowledge was passed through generations through word of mouth. Many plants were recorded in the early years of having medicinal properties and were used to treat many pathological conditions [3–8]. Natural products from plants and animals have been the go-to source of drugs especially for anticancer and antimicrobial agents [9–13]. Traditional medicine has been overshadowed by modern medicine as the means of treatment for human diseases [14–16]. However, the past few decades have seen an increase in the use of medicinal plants for health promotion and treatment of diseases in many countries including developed countries [17–22]. Indeed, many medicinal plant extracts are now used as prescription drugs in numerous developed countries such as the UK, Germany, China and France [23,24].

About a quarter of all Food and Drug Administration (FDA) and/or the European Medical Agency (EMA) approved drugs are plant based, with well-known drugs such as Paclitaxel and Morphine having been isolated from plants (Figure 1) [25,26]. About a third of FDA-approved drugs over the past 20 years are based on natural products or their derivatives [27,28]. The discovery of penicillin from fungus led to the screening of many microorganisms for potential antibiotics [29]. Indeed, drug discovery from natural products revolutionised medicine. These include tetracycline from Streptomyces aureofaciens, artemisinin from Artemisia afra, doxorubicin from Streptomyces peucetius and cyclosporine from Tolypocladium inflatum [27,29,30]. Traditionally, plant extracts are used as concoctions made of combinations of different ingredients. Individually some of the ingredients do not have therapeutic activities, but require their synergistic activities [31].

Current challenges to the use of natural products and difficulty in accepting their therapeutic efficacy include: (1) lack of standardization procedures (2) lack of isolation of pure chemical products or compounds (3) lack of elucidation of biological mechanisms and rarely undergoing so-called controlled and (4) documented clinical trials according to “standards”. Historically, there is scientific evidence on the therapeutic efficacy of natural products and as previously mentioned this led to development of some blockbuster conventional medicines. Searching for new drug candidates from natural products is often made difficult by the complexity of the molecular mixtures. The therapeutic activity of plant extracts is usually because of the synergistic and simultaneous action of several chemicals [30,32]. Given the complex nature of many diseases including cancer and degenerative diseases, it is not surprising that the reliance on single compound-based drug discovery has failed to provide effective cures. Plant-based drug discovery therefore must start with a combinatorial approach when evaluating candidate compounds. The advent of novel technologies including quantum computing, profiling techniques, computational biology techniques, big data, microfluidics and artificial intelligence will
enable scientists to use a combinatorial approach to harness the therapeutic properties of plant-based natural products and simultaneously study their molecular effects in physiological conditions [33,34]. It is however possible that not all components of plant extracts have measurable effects. It has been suggested that one way to improve screening and simplify extracts is through the removal of possible interfering components such as polyphenolic tannins [35]. There are several reported innovative strategies which can be used to achieve this and these include pre-fractionation and extraction methods [36,37]. Indeed, these extraction strategies have resulted in higher hit leads during drug discovery [12,38–40]. Innovative extraction technologies including semi-bionic extraction [41], supercritical fluid extraction [42–44], microwave-assisted, ultrasonic-assisted and enzyme-assisted extraction [45], molecular distillation methods [46,47] and membrane separation technology [48,49] can be used to extract natural compounds efficiently from plants. These extractions strategies have been shown to have similar simulation to traditional methods allowing the extraction process to get most compounds from the natural product.

**Figure 1.** Two examples of successful stories of plant natural products that are being used in hospitals and clinics for disease treatment. (A) Morphine is isolated from *Papaver somniferum* also called opium poppy (B) Paclitaxel is isolated from *Taxus brevifolia* also called pacific yew. (Images credit: https://en.wikipedia.org/wiki).

Technologies such as high-performance liquid chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, microfluidics and computational algorithms have seen major
advances in the field of medicinal chemistry especially in the 20th century [50,51]. This has allowed the determination of chemical components of plants and their utilisation in drug discovery. High throughput assays using bioreactors and microfluidics systems has led to many drug discoveries using plant natural products. Some of these natural products include opium and morphine [52,53]. Several structural analogues of these compounds are used in clinics and hospitals today. Several new plant-based compounds are emerging as promising anti-cancer remedies. In one of our studies we investigated the anticancer activities of extracts from African lettuce (Launaea taraxacifolia), a plant cultivated extensively in Africa, especially West Africa. L. taraxacifolia extract caused WHCO1 cell cycle arrest at the G0/G1 phase by affecting differential expression of genes involved in cell cycle regulation, presenting its potential beneficial effects [22]. The medicinal plant Brucea javanica (L.) Merr. (Simaroubaceae) has been shown to have many properties and activities. Through both phytochemical and biological investigations, it was shown that Brucea javanica (L.) Merr. contains many compounds with medicinal properties. For example the seeds of Brucea javanica contain several compounds such as quassinoids that show many biological properties, such as antitumour and antimalarial effects [54].

A well-known malarial drug Artemisinin is a natural product from Artemisia annua also known as Sweet Wormwood [55,56]. Artemisinin and its structural derivatives are also used for diseases such as type I diabetes and cancer [57–59]. High throughput screening assays face many challenges. For example, the Rio Convention on Biodiversity is aimed at limiting the use of natural products and deals with intellectual property rights. This has the effect of limiting access to natural products as there are fears of extinction of natural species [29,60–65].

Current drug discovery strategies and modern medicine discard the use of whole plant extracts and are driven by single compound-based medicine. Taking the whole plant or extracts with no isolation of components as practised in traditional medicine, produces a better therapeutic effect than individual compounds. This is important as most of the plant metabolites likely work in a synergistic fashion or concurrently to give the plant extract its therapeutic effect. Research into the use of whole plant extracts must be done as this will allow scientists to determine the molecular basis of the therapeutic effect of the plant extracts. For example, anti-asthma herbal medicine made from extracts from Ganoderma lucidum, Glycyrrhiza uralensis and Sophora flavescens alleviates bronchoconstriction in an animal model whilst restoring cytokines balance, contributing to longer lasting anti-asthma benefit after treatment [66]. The therapeutic effect only emanates from the synergistic effect of chemical components of the three herbal ingredients [67,68]. The adoption of Good Manufacturing Practises has allowed the increased use of plant-based medicines and many are now undergoing clinical trial for FDA approval [69]. Skroza and colleagues showed that catechin and resveratrol have synergistic effects as confirmed by different antioxidant assays [70]. The same study also showed the synergistic effects of caffeic acid and resveratrol by the ferric reducing ability of plasma (FRAP) antioxidant assay [70]. Another study showed the synergistic effects of ethnomedicinal plants of the Apocynaceae family and antibiotics against clinical isolates of Acinetobacter baumannii [71]. Several other studies showed the synergistic effect of different plant extracts and conventional drugs including doxorubicin [72].

Innovative drug design from natural products is needed to combat global health challenges with the assistance of technological innovation. Most importantly is the need for new and innovative computational and analytical methods to identify chemical components of crude plant extracts in order to identify compounds causing the desired therapeutic effect and optimize extraction to exclude interfering components. Ultimately, more research should be focussing on combinatorial effects of chemicals from plant extracts and not just single compounds. How these combinations affect genes and proteins involved in many cellular processes must be investigated through available “-omics” platforms. Developments in the field of microfluidics and computational analysis have allowed for the designing and testing of plant extract chemicals in drug discovery. Technological advances, such as the development of new analytical and bio-informatic techniques, will aid the design of new structures, the synthesis of these new compounds and the biological testing of such compounds [73,74]. Natural products, offer an endless source of compounds to help in the design of pharmaceutically important
molecular products [75–77]. Below we discuss some of the major innovations currently taking place in these areas. We focus on the need for the use of “-omics” technologies, automation and big data during drug design and testing to allow for the rapid production of drugs and computer aided drug design from plant-based natural products.

2. Multidisciplinary Approach to Natural Products Drug Discovery Using Innovative Technologies

Innovative drug discovery from natural products requires a multidisciplinary approach utilising available and innovative technologies to package such natural product compounds for medical practice and drug development (Figure 2). The successful use of such an approach will allow the development of next-generation drugs to combat the ever-increasing health challenges of today and the future.

![Figure 2. Innovative technologies for natural product drug discovery. Application of these technologies can potentially lead to novel drug candidates from natural products.](image)

Most medicinal extract components often work in a synergistic manner to elicit their therapeutic effects so isolating individual components may be counter-productive. Innovative approaches are needed to study and to harness such compounds that can effectively lead to innovative drugs. In addition, a systems biology guided approach provides a different angle in natural products pharma-sciences [78]. This transcends looking for a specific molecule with a specific target and espousing the complete equilibrium of a physiological system undergoing synchronized mechanisms on multiple molecular targets. A systems biology approach coupled with application of available technologies such as genomics, transcriptomics, proteomics, metabolomics/metabonomics, automation and computational strategies will potentially pave the way for innovative drug design leading to better drug candidates. Molecular libraries of lead compounds from natural products R&D will serve as sources of lead compounds/herbal tinctures for innovative drugs. In the application of innovative technologies combined with systems biology, the focus should not be a reductionist approach of trying to source a single active compound but to consider the synergistic effects of compounds. It is important to emphasise that innovative drug discovery from natural products will require a non-reductionist strategy to understand their complex mechanisms of action at the molecular level.
3. Natural Products Drug Discovery Research and Development and Omics (Genomics Proteomics and Metabolomics/Metabonomics)

3.1. Genomics in Plant-Based Natural Products Identification and Biomarker Identification

The quality, precise identification and reliability in the plant species from which the natural product is obtained and to which the therapeutic properties are ascribed is very critical for successful innovative drug discovery. The use of a different or wrong plant species will likely affect the therapeutic properties due to different compounds and quantities that will be found in the species. Genomic methods are important in establishing an accurate identification method for plants and natural product species [78]. Genomic techniques such as DNA barcoding are established techniques that rely on sequence diversity in short, standard DNA regions (400–800 bp) for species-level identification [79]. DNA barcoding utilising genomics will provide a more robust and precise identification compared to traditional methods of morphological identification and local traditional (vernacular) names [80]. DNA barcoding of natural products has been applied in biodiversity inventories [81] and authentication of herbal products [82–84]. DNA barcoding was used in an integrative approach for identification of plant species such as *Amaranthus hybridus* L. and crude drugs recorded in the Japanese pharmacopoeia using ITS2 or *psbA-trnH* sequence amplification [80,85]. Genomic-based techniques represent an effective platform for natural product identification but different parts of the same plant with similar sequences may have different qualities, clinical utilities and indications due to the diverse conditions under which they grow.

To show consistency in the species and pharmacological molecules from natural products, bio-farming can be used to ensure consistency after the traditional species have been authenticated through DNA barcoding [86]. Markers developed from species through genomic techniques can be incorporated into DNA chips to provide an effective, high-throughput tool for genotyping and also plant species authentication [78,87]. Gene expression using microarray analysis is an innovative transcriptomic technology that allows a fast and effective analysis of many transcripts [78,88,89]. This transcriptomic analysis makes it possible to concurrently evaluate variations in multiple gene expressions [90]. This represents a robust tool for elucidating the molecular mechanisms of therapeutic natural products and biological networks underlying their pharmacological actions.

Besides its use in natural products identification, genomics can also be used in natural product or compound targeting. Whole genome sequencing combined with transcriptomic analyses has allowed the exploration of drug or compound targeting as never before. Transcription factor binding sites, protein modifications, alterations of the DNA structure as well as methylation patterns can now be analysed and measured at the genome level [91–96]. Several studies including our own have identified deletions, insertions, copy number variations, splicing variants and translocations associated with certain cancers, and in so doing identified new drug targets [97–102]. The development of novel and unrivalled technologies, allowing genome-wide analysis, has enabled the unbiased discovery of drug targets. These technologies together with the availability of huge databases of chemicals or compounds have enabled the shortening of the time required for the whole process of drug discovery from drug design all the way to clinical trials [103–109].

3.2. Proteomics in Natural Product Validation and Biomarker Identification

Complimentary to genomic and transcriptomic approaches to quality control and sample variation is the use of proteomic platforms in describing the mechanism of action of many natural products. Proteomic approaches to innovative drug discovery from natural products have the potential to elucidate the protein expression, protein function, metabolic and biosynthetic pathways based on therapeutic effects translating to consistency in quality and profile of the product [110,111]. Approaches such as mass-spectrometry utilising isotope tags and two-dimensional electrophoresis will give insight into quantitative protein profiling which generates quantitative data on a scale and sensitivity comparable to what is generated at the genomic level. Proteomics application has
been successfully used in identifying species of Chinese herbal medicine, *Panax ginseng* versus *Panax quinquefolium* [112,113]. The therapeutic effects of natural products can be elucidated using proteomics and imaging techniques to successfully study the metabolism of natural products and their compounds [114,115]. Proteomics is an effective way to elucidate multi-target effects of complex natural product preparations as well as the discovery of multiple compounds and fractions, characterisation of natural products and ultimately a molecular diagnostic platform [78,116].

For natural products to be used as drugs it is crucial that their target proteins be identified. Several methods including affinity chromatography have been in use to identify target proteins with relative success. The advent of technologies allowing for target protein identification without the modification of the natural product has resulted in natural products with increased activity. Such methods include cellular thermal shift assay which is based on the stabilisation of target protein when it binds to its ligand, thermal proteome profiling a method based on the stability of target proteins at high temperatures, bioinformatic-based analysis of connectivity and drug affinity responsive target stability. Due to their many structures and complexity, natural products do show a wide range of biological activities. This is probably due to their abilities to bind to several ligands. Every potential drug will have to be tested for side effects and this is due to its off-target effects. Complex natural compounds with potential target proteins will have to be evaluated properly to identify all its potential target proteins. One of the most utilised methods to identify target proteins and their biological activities is affinity chromatography [117–123]. This method is a pull-down method in which the natural product is immobilized on a physical solid support [124]. The identification of bound proteins is done using mass spectrometry. Modification of natural products however, can lead to reduced or loss of activity. The development of novel and innovative approaches, devoid of any modification, is paramount for the success of target identification [125,126]. Of late, several methods have been able to identify target proteins using label-free natural products. These new and improved methods measure the responses of natural product-target protein complex to proteomic and thermal treatment [127–129]. Using this new approach, it is possible to identify several target proteins for an individual natural product using proteomic analysis [13,130].

**Methods for Target Identification of Label-Free Natural Products**

Drug affinity responsive target stability (DARTS) is one of the direct methods used to identify target proteins using label free natural products [124]. This method takes advantage of the changes in stability of a natural product-bound protein versus an unbound protein when subjected to proteolytic treatment [130]. This method has been used to validate several target proteins for compounds such as resveratrol and rapamycin [129,131]. It is however difficult to use DARTS to identify low abundance protein targets in cell lysates [132]. Another method that takes advantage of ligand-induced changes to target proteins is stability of proteins from rates of oxidation (SPROX) [124,133,134]. This method measures the irreversible oxidation of methionine residues on target proteins [124]. A mixture of candidate drug compound and proteins is incubated with an oxidising agent and guanidinium hydrochloride in order to oxidise methionine. Generated peptides are then analysed through mass spectrometry to evaluate selective methionine oxidation. Analyses of oxidised and non-oxidised methionine-containing peptides versus the guanidinium hydrochloride concentration reveal that proteins bound to ligands show a larger transition midpoint shift than control samples [13,135–137]. Indeed, several target proteins of compounds such as resveratrol and cyclophilin A were verified using SPROX [133,137,138]. This method however requires highly concentrated proteins for analysis. Modifications of the SPROX method, named stable isotope labelling with amino acids in cell culture (SILAC)-based SPROX is an improvement of the original method and has the advantage of covering more target proteins [130,139–144]. This method is limited to only identifying of methionine containing proteins.

Cellular Thermal Shift Assay (CETSA) is a recently introduced method based on stabilisation of a target protein by binding to its ligand [145–147]. Cell lysates and intact cells are treated with
the candidate drug compound and heated to several temperatures and target protein is separated from destabilised protein and analysed by Western blot analysis. Shifts or changes in melting curves are detected when ligand–target interactions are plotted against temperature. This method has been useful in identifying target proteins of many anti-cancer therapeutic agents such as raltitrexed and methotrexate [145]. The advantage of this method is the obvious use of intact cells with no need for treatments or preparations. Due to the use of Western blot step it can be very selective. Some target proteins with unfolded binding sites, however, may not be detected. In addition, due to non-specificity of some antibodies used in Western blot step, off-target proteins may also be identified as false positives. Thermal Proteome Profiling (TPP) is an advanced modification of the CETSA method. This method identifies target proteins displaying thermal stability at high temperatures induced by ligand binding and the use of mass spectrometry to measure ligand–target protein interaction at cellular level [148–150]. This method uses isobaric mass tagging in for high resolution mass spectrometry. Most expressed soluble proteins will show melting curves resulting in the identification of both target and off-target proteins [13,127,148,151,152]. By identifying off-targets TPP can be used to study possible side effects of candidate drug compounds [150]. This method is very costly and is labour intensive.

Small interfering RNA and short hairpin RNA are obvious choices for target gene manipulation to functionally validate target protein and natural product interactions [153,154]. By knocking down target protein using interfering RNA it is possible to study off-target effects of candidate compounds. Recently clustered regularly interspaced short palindromic repeats-Cas9 (CRISPR-Cas9) genome editing approaches have been used to overcome off-target effects of candidate compounds and to delineate how many natural compounds work [155,156]. CRISPR-Cas9 based genome editing combined with high throughput sequencing and computer-based mutation analysis, referred to as DrugTargetSeqR, has been used to study drug resistance and for validation of several anti-cancer therapeutic agents [157–159].

3.3. Metabolomics and Metabonomics Approach to Natural Products Drug Discovery

Untargeted metabolomics and metabonomics approaches of discovering compounds of therapeutic interest from natural products have the potential to lead to innovative drugs for global health. Metabolomic profiling of natural products seeks to identify and quantify the complete set of its characteristic metabolites [160,161] while metabonomics broadly aims to evaluate the global and dynamic metabolic response of living systems to biological stimuli or genetic manipulation [162–165]. Drug discovery has traditionally focussed on metabolomics to identify metabolites but recently, the term metabonomics (although used interchangeably) has been reviewed to incorporate a systems biology guided approach to study the functions and perturbations of a biological system following a pharmacological effect. This elucidates a complete biological mechanism of both the natural product and its effect on a living system (Figure 3).
Figure 3. Exploiting the properties of plant extracts in the development of novel medicines inspired by compounds found in medicinal plant extracts.

Metabolomic profiling of natural products using technologies such as ultra-performance liquid chromatography–quadruple TOF MS (UPLC–MS) has enabled identification of compounds that confer therapeutic properties on herbs such as *Newbouldia laevis*, *Cassia abbreviata*, *Hyptis suaveolens* and *Panax* herbs [166–168]. As a quality control measure and to show consistency in species usage, metabolomics has been used in identification of processed *Panax* species (*Panax ginseng* and *Panax quinquefolius*) using Nuclear Magnetic Resonance (NMR) based metabolomics, UPLC–QTOF MS and multivariate statistical analysis [169]. Metabonomics approach to profiling natural products for drug discovery has been hailed as a critical phenotyping tool. The systems biology approach of this technique positions the profiling of natural products in an all-inclusive manner in terms of metabolite and biology systems effect (Figure 3). Metabolomic and metabonomics profiling using NMR, MS and UPLC can potentially elucidate the pharmacodynamic, pharmacokinetic and toxicological value of natural products.

3.4. Big Data in Drug Development for Natural Product Drug Development and Precision Medicine

Oomics analysis, like genomics, transcriptomics, proteomics, metabolomics and metabolomics, results in a generation of a complex multivariate dataset that requires computational and chemometric tools for interpretation. The use of computational platforms such as bioinformatics and multivariate statistical tools, will allow the application of oomics multidata to elucidate pathophysiological effects, target specificity and molecular effects, as well as elucidate the pharmacodynamic, pharmacokinetic and toxicological characterisation of natural products and their compounds. Applications used during the drug discovery process such as docking and virtual screening can make use of novel machine learning algorithms such as deep learning. Machine learning methods can be used for virtual screening of thousands of compounds allowing the utilisation of data from high throughput screening [170,171].

Computer-based screening of candidate compounds for drug discovery makes use of big databases especially to identify compounds of similar activity. Similarity in structure is equated to similarity in biological activity, with results not always supporting this idea. Knowledge of the chemical structure of candidate compounds together with knowledge about the target protein is utilised to study possible interactions between the two. Transcripntomic data, used as gene signature, can be used to compare differences and similarities in response to candidate compounds [172–176]. For example, the connectivity map allows scientists to associate disease-associated gene signatures
with drug signatures resulting in the identification of drugs that can potentially reverse the disease gene signature [177–181]. Generating a lot of data can have the consequence of losing the ability to understand its meaning. Big data must be useful and put into action. For big data to be useful during drug discovery it must be summarised into a little actionable information [182–184]. There are several data sources used for drug identification. These include ChemBank, PubChem, ChEMBL, DrugBank, UniProt, STITCH and the NIH Small Molecule Repository [185–188].

Connectivity Map (CMap) is a bioinformatic application that allows the study of diseases at the molecular level with the help of computers [189–191]. Established by the Broad Institute, the CMap is a collection of transcriptional data of many compounds-treated human cells [172–175,192]. The CMap associates gene expression signatures with compounds, genes and disease response allowing for its utilisation to show connections between compounds with the same modes of action and same physiological processes [172–174,192]. The CMap also allows associations to be made between diseases and drugs. The same pattern-matching analysis can be used for natural products, gene expression and diseases [173–176].

Using electronic databases of chemicals and protein targets and clinical data such as patient to patient variations in response to treatment, several strategies are being employed to reduce the cost of drug development and to increase the speed at which drugs are developed [193]. There are obvious challenges to the efficient development of drugs and these include the lack of models that can recapitulate the human body properly in terms of response to candidate compounds, the heterogeneity of individuals in terms of their response to candidate compounds and the inability to analyse biological processes properly during testing of candidate compounds [194–196]. Despite a heavy investment in research and development, most candidate compounds show weakened efficacy as the stages of drug development move towards clinical trials [197–201]. This strategy whereby information is collected without applying a hypothesis or any bias, analysed and then used to come up with new and innovative ideas is called Big Data [202–206]. Big data is now integrated with compound chemical structures, protein structures, compound toxicity and clinical trials and this has led to the development of complex algorithms needed for such analysis [207,208].

One major challenge with the use of big data-driven drug discovery is the relative low presence of similar somatic alterations in cancer patients enrolled in a study. This is caused by tumour heterogeneity, a chief cause of chemoresistance and drug treatment failure. A challenge to scientists using big data to inform drug development and testing is how to integrate a lot of information into a meaningful and manageable unit. For “omics” data to be meaningful and to revolutionise clinical medicine, clinical phenotype data has to be integrated with genomic, transcriptomic, proteomic and epigenomic data [33,193,209].

4. Automating Natural Product Drug Discovery

Automation is usually associated with negative feelings, with many people associating automation with loss of jobs and unfounded consequences such as robots taking over the world. In terms of drugs discovery automation, however, it has been used successfully to speed-up the process. Indeed many pharmaceutical companies already have high-throughput assays robustly used in the drug discovery process [210]. The design of most synthetic compounds is aided by computers using various softwares, as well as the synthesis of the compounds. Examples of softwares used during drug design include ADAM and EVE, used in target and hit finding [211,212]. New softwares and devices are being made to reduce problematic false positives an also to reduce material consumption during compound design, synthesis and biological testing [213]. For example, integrated microfluidics systems, with the ability to handle liquids and heat necessary for during-synthesis analyses and purification, are being designed by laboratories and pharmaceutical companies, for compound screening and synthesis of compounds [214,215]. This has allowed testing of several hypotheses within days. Even more advanced technologies through the use of artificial intelligence (AI) and ‘organ-on-chip’ technologies are now fully integrated in the drug discovery process, aiding scientists during drug design and optimisation of
the drug discovery process [213,216–219]. All these technologies have allowed the reduction of human mistakes and bias commonly made during drug design and optimisation, reduction in the amount of candidate compound needed for the testing, have reduced the time needed for testing of candidate compounds to days and allowed the recapitulation of disease biology more effectively than in vitro assays [220,221]. Many times, innovation and technological advances have raised false hopes and never lived up to expectations. Automation and innovation in drug discovery must be fast, but also sustainable in the long run [33,222].

Several factors are taken into consideration during compound or molecule design. These include absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and the final biological activity of the products. Thus, the optimisation of the drug discovery process is multidimensional. In the end, a balance has to be achieved in order to get the best in terms of compound activity and properties [213]. Automation will allow scientists to make the best decision regarding the best compound design with relevant biological activity whilst at the same time having desirable ADMET properties. Several concepts such as the diversity-oriented synthesis (DOS) and biology-oriented synthesis (BIOS) have been developed over the past few years to aid compound design and increasing compound collections with new chemical structures and constituents [223–228]. An even advanced concept is the function-oriented synthesis which seeks to mimic the function of a promising compound in order to get simple scaffolds and make their synthesis easier and simple [213,229,230]. Several automated compound generators that use deep learning techniques have been made and have allowed automated analysis of generated compounds to obtain even better designs of compounds with desired properties and biological activity [216,217,231,232]. Although deep learning models are used mainly to predict drug-target interactions and in the generation of new molecules, these models are also useful to predict ADMET properties of novel candidate drugs [233,234]. Several deep learning models have also been used to predict the binding affinity for candidate compounds during drug discovery [234]. Several compounds based on the imidazopyridine scaffold have been synthesised using automated computer-assisted de novo design resulting in the discovery of many ligands for G protein-coupled receptors antagonists [213,235,236]. It is also possible to use a virtual library enumeration parallel to target panel prediction to design a compound library and building block selection. Using integration of computational activity prediction and microfluidics-assisted synthesis enabled scientists to identify ligands with different binding profiles [236–239]. Thus, microfluidics synthesis and computer-aided target prediction can be used to generate bioactivity-focussed compound libraries rapidly and efficiently [235].

An important part of automation of compound synthesis is the availability and use of building blocks and chemical reactions that can result in diverse by-products. The use of small volumes of the starting compounds and compact synthesis coupled with in-line purification and analyses ultimately led to the development of novel machines to synthesise complex structures recapitulating the biosynthesis of most natural compounds [240–242]. Importantly, 3D printing can allow for the building of different microfluidic devices with several sophisticated and specialised algorithms to monitor product synthesis. 3D printing is very important for microfluidics platforms as most microfluidics systems are custom made for a specific function. Some of the latest approaches using automated robotic synthesis are remotely controlled making it even more efficient [243,244]. Some automated compound synthesis approaches are very versatile with only a small set of building blocks being needed to generate a diverse group of by-products [245]. Microfluidics based synthesis of compounds allows the continuous synthesis of compounds and not batch-wise. Cytochrome P450-catalysed drug oxidation can now be simulated meaning that in future on-chip chemotransformations of compounds can replace in vitro metabolite identification [246,247]. Microfluidics synthesis of compounds, coupled with in-process analysis and purification, is revolutionising drug discovery automation [248]. Besides the obvious avoidance of human exposure to chemicals and dangerous solutions, microfluidics also allows the use of minimum amounts of compounds and reagents [249–251]. Given that most animal models are very poor predictors of human response to drugs and biological testing, microfluidic systems
can aid in recapitulating human- and species-specific functions by incorporating organoid-based approaches. This allows for the generation of physiological relevant environments within the microfluidic devices and these can be stable over some time [252,253]. Several systems incorporating cancer cells or 3D cancer models have been developed and allow for the recapitulation of human tumours and their microenvironments [254–256]. Several constraints do exist for continuous flow systems such as microfluidics synthesis of compounds. The synthesis and eventual deposition of reactive reagents and by-products brings about the danger of fluidic surfaces instability as some of the reagents and solutions used in compound synthesis are incompatible with the microfluidic systems. In addition, clogging of channels of the microfluidic system is a major problem.

Several integrated microfluidics-assisted synthesise and test platforms are now available combining the reagent and compound selection and can adapt based on materials available for the subsequent steps during synthesis and testing of compounds. Several computational tools and networks (containing millions of reactions and pathways for compound synthesis) used for automated compound synthesis have been developed and aid in finding the optimal and innovative route to compound synthesis [257–260]. Drug design with the help of artificial intelligence is a requirement to have a sustainable drug discovery process [261–264]. Hypothesis generation if done by machines can result in the designing of compounds using several criteria at the same time. Such criteria can be biological activity, side-effects and synthesizability. Machine-guided hypothesis or generation of compound structures is also much faster and can generate different designs at the same time. Artificial intelligence is therefore an enabling technology, aiding the scientist in pattern recognition and can be optimised to do pattern recognition [265–267].

5. Computer-Aided Drug Design from Natural Products

Synthetic compounds with structures inspired by natural products can help solve many global health challenges while in many instances some of the new synthetic compounds would have been discarded as not suitable for drug designs. The so called “rule of three” and “rule of five” criteria often used for decision making with regard to drug leads is too strict and some of the new designs would have been failed [268–272]. In fact, many of the guidelines used during drug designing show human bias and therefore are limited in their scope and effectiveness, especially when applied to natural products [269–272]. Many therapeutic synthetic compounds have been developed using computer-aided designs and these include several anticancer agents [273–276]. The Scaffold Hunter software for example was used to simplify complex natural products to generate virtual fragments of small chemically attractive molecules [277]. The simple molecules visualised by such computational software must retain the same biological activity as the mother compound. Indeed, this method was already used to identify inhibitors and activators of pyruvate kinase [278]. However, it is also possible that natural-product derived simple molecules will exhibit weaker activities than the parent compound [275,276]. The PASS software has been used to predict the biological activities of simple structures or chemical structures obtained from the mother compound with considerable success [279,280]. The PASS software has predicted the anti-tumour activities of several marine alkaloids [278–280].

Indeed several individual compounds from St John’s wort were also predicted rightly to have cytochrome P450 modulating effects [278]. Several computational softwares, databases and web servers have been developed that can predict compound-target associations. Most if not all of these softwares use the similarity of new compound to known drugs to infer target and normal ligand–receptor docking. In the absence of any similarity between new compound and any known drug, the SPIDER software can compare computed features between natural products and new compound to predict the target of the new compound [281,282]. The identification of G-protein coupled receptor ligands was one of the success stories of the SPIDER software [282]. The use of computational drug design and target prediction is now tangible and will continue to influence drug development in the near future. However only previously studied targets or proteins can be predicted. Computer based quantitative structure activity approaches can be employed in natural product drug discovery to explain the molecular
basis of their therapeutic values and to predict possible derivatives that would improve activity [283].

The positive aspect of computer-based drug designs is that it guides optimization of lead compounds as to whether to increase their affinity or pharmacodynamic and pharmacokinetic properties.

New systems are being developed in order to detect candidate or lead compound toxicity at early stages of drug discovery [284–287]. Strategies employing in silico methods can be used to detect drug toxicity early on along the drug discovery process. Such approaches if combined with in vitro and in vivo biological testing can drastically decrease the time and cost of drug discovery and improve safety evaluation. Quantitative structure–activity relationship models aim to understand the relationship between the structure of a compound and its toxicity [288–291]. To understand the possible accumulation of the drug and its metabolism properties such as adsorption, distribution, metabolism and excretion must be evaluated [292–295]. To compound the issue of candidate compound toxicity, one has to consider environmental toxicity. So, during drug discovery the potential risk of having a drug in the environment must be addressed. These candidate compounds or lead compounds may have toxic effects on other animals.

The advent of advanced technologies has allowed scientists to discover the magnitude of tumour heterogeneity and the different patients’ responses to treatment [296–299]. Drug discovery however is based on the “one drug-one target” strategy. It is a fact that combination therapy is the gold standard nowadays. Thus, drug design must take a combinatorial approach, where two or more drugs either target the same pathway or act synergistically to achieve a cure. Conventional chemotherapeutic agents may be combined with targeted therapies such as kinase inhibitors [300–304]. Now, a few approaches for computer-based screening for combinatorial drug design and treatment are under development.

6. Natural Products and Precision Medicine

The past few years have seen genomics informing drug discovery but overall the clinical efficacy of the resultant drugs has been poor. This is largely due to the complex nature of diseases. Advances in technological and analytical tools used in genomics now allow for the rapid identification and interpretation of genetic differences driving patient specific features of disease (Figure 4) [33,222]. Precision medicine would then target these specific features to obtain a cure. At the heart of the Human Genome project lies the need to understand how genetics impacts disease and vice versa.

For oncologists and cancer scientists, how genetics can transform drug discovery has generated a lot of excitement. The rapid development of many new techniques now allows the analysis of patients’ and healthy individuals genomes (Figure 4). Importantly it is possible to link a patient’s genome and clinical presentation [305]. Investigations of whether specific proteins are drug targets culminated in many drugs in use today. Over time however, productivity in terms of drugs produced declined as there were no more definite new drug targets. The “gene to screen” approach was based on the realisation that genes expressed within a cell are the main contributor to the overall cellular phenotype [306,307]. Genome-wide association studies (GWAS) is a cost-effective and unbiased way of genotyping and comparison of genomic variations between patients with disease and healthy individuals. GWAS has led to the identification of genetic determinants of diseases and underlying mechanisms driving disease development.
Figure 4. Precision therapies in oncology can be designed to only affect cancer cells. Biomarkers can be identified through next generation sequencing, gene expression profiling and proteomics. Drivers and regulators of important pathways involved in cancer cell proliferation, survival and chemoresistance can be identified. Only with this knowledge can the development of novel drugs be achieved.

7. Conclusions

The low success rate of drug discovery requires a paradigm shift for innovative drug development strategies. Innovative drug discovery starts by deriving inspiration from natural products for effective treatment of disease conditions. The relevance of natural products in providing innovative drugs to find solutions to communicable and non-communicable diseases cannot be over-emphasized. Technological advances have made it possible to understand the profiles of these complex natural products with the potential to discover new drugs for use. An impressive number of blockbuster drugs have been isolated or synthesized from natural product lead compounds. This positions natural product drug discovery as a very successful strategy for the development of novel therapeutic drugs. In this era of advancing scientific technology, innovative drug discovery from natural products will potentially increase the success rate of new therapeutic moieties. Natural product drug discovery stands as a major contributor to solving global health challenges and achieving sustainable development goals on health.

Author Contributions: N.E.T. and K.D. wrote the main body of the Review manuscript. All authors reviewed and commented the manuscript.

Acknowledgments: The funding for this research was provided by the National Research Foundation (NRF) of South Africa (Grant Number: 91457: RCA13101656402), International Centre for Genetic Engineering and Biotechnology (ICGEB) (Grant Number: 2015/0001), Faculty of Health Sciences, UCT and the University of Cape Town.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Weng, J.K.; Philippe, R.N.; Noel, J.P. The rise of chemodiversity in plants. *Science* **2012**, *336*, 1667–1670. [CrossRef] [PubMed]
2. Lietava, J. Medicinal plants in a Middle Paleolithic grave Shanidar IV? *J. Ethnopharmacol.* **1992**, *35*, 263–266. [CrossRef]
3. Ernst, M.; Grace, O.M.; Saslis-Lagoudakis, C.H.; Nilsson, N.; Simonsen, H.T.; Ronsted, N. Global medicinal uses of Euphorbia L. (Euphorbiaceae). J. Ethnopharmacol. 2015, 176, 90–101. [CrossRef] [PubMed]
4. Gozubuyuk, G.S.; Aktas, E.; Yigit, N. An ancient plant Lawsonia inermis (henna): Determination of in vitro antifungal activity against dermatophytes species. J. Mycol. Med. 2014, 24, 313–318. [CrossRef] [PubMed]
5. Hotwani, K.; Baliga, S.; Sharma, K. Phytodentistry: Use of medicinal plants. J. Complement. Integr. Med. 2014, 11, 233–251. [CrossRef] [PubMed]
6. Liu, Q.; Lawrence, A.J.; Liang, J.H. Traditional Chinese medicine for treatment of alcoholism: From ancient to modern. Am. J. Chin. Med. 2011, 39, 1–13. [CrossRef] [PubMed]
7. Mannangatt, P.; Naidu, K.N. Indian herbs for the treatment of neurodegenerative disease. Adv. Neurobiol. 2016, 12, 323–336. [PubMed]
8. McGovern, P.E.; Mirzioian, A.; Hall, G.R. Ancient Egyptian herbal wines. Proc. Natl. Acad. Sci. USA 2009, 106, 7361–7366. [CrossRef] [PubMed]
9. Blunt, J.W.; Carroll, A.R.; Copp, B.R.; Davis, R.A.; Keyzers, R.A.; Prinsep, M.R. Marine natural products. Nat. Prod. Rep. 2018, 35, 8–53. [CrossRef] [PubMed]
10. Harvey, A.L. Natural products in drug discovery. Drug Discov. Today 2008, 13, 894–901. [CrossRef] [PubMed]
11. Harvey, A.L.; Clark, R.L.; Mackay, S.P.; Johnston, B.F. Current strategies for drug discovery through natural products. Expert Opin. Drug Discov. 2010, 5, 559–568. [CrossRef] [PubMed]
12. Harvey, A.L.; Edrada-Ebel, R.; Quinn, R.J. The re-emergence of natural products for drug discovery in the genomics era. Nat. Rev. Drug Discov. 2015, 14, 111–129. [CrossRef] [PubMed]
13. Chang, J.; Kim, Y.; Kwon, H.J. Advances in identification and validation of protein targets of natural products without chemical modification. Nat. Prod. Rep. 2016, 33, 719–730. [CrossRef] [PubMed]
14. Tansaz, M.; Tajadini, H. Comparison of leiomyoma of modern medicine and traditional Persian medicine. J. Evid.-Based Complement. Altern. Med. 2016, 21, 160–163. [CrossRef] [PubMed]
15. Xu, Q.; Bauer, R.; Hendry, B.M.; Fan, T.P.; Zhao, Z.; Duez, P.; Simmonds, M.S.; Witt, C.M.; Lu, A.; Robinson, N.; et al. The quest for modernisation of traditional Chinese medicine. BMC Complement. Altern. Med. 2013, 13, 132. [CrossRef] [PubMed]
16. Yuan, H.; Ma, Q.; Ye, L.; Piao, G. The traditional medical system and modern medicine from natural products. Molecules 2016, 21, 559. [CrossRef] [PubMed]
17. Banjari, I.; Misir, A.; Savikin, K.; Jokie, S.; Molnar, M.; De Zoysa, H.K.S.; Waisundara, V.Y. Antidiabetic effects of Aronia melanocarpa and its other therapeutic properties. Front. Nutr. 2017, 4, 53. [CrossRef] [PubMed]
18. Yatoo, M.I.; Dimri, U.; Gopalakrishnan, A.; Karthik, K.; Gopi, M.; Khandia, R.; Saminathan, M.; Saxena, A.; Alagawany, M.; Farag, M.R.; et al. Beneficial health applications and medicinal values of pedicularis plants: A review. Biomed. Pharmacother. 2017, 95, 1301–1313. [CrossRef] [PubMed]
19. Thomford, N.E.; Awortwe, C.; Dzobo, K.; Adu, F.; Chopera, D.; Wonkam, A.; Skelton, M.; Blackhurst, D.; Dandara, C. Inhibition of cyp2b6 by medicinal plant extracts: Implication for use of efavirenz and nevirapine-based highly active anti-retroviral therapy (HAART) in resource-limited settings. Molecules 2016, 21, 211. [CrossRef] [PubMed]
20. Thomford, N.E.; Dzobo, K.; Chopera, D.; Wonkam, A.; Maroyi, A.; Blackhurst, D.; Dandara, C. In vitro reversible and time-dependent cyp450 inhibition profiles of medicinal herbal plant extracts Newbouldia laevis and Cassia abbreviata: Implications for herb-drug interactions. Molecules 2016, 21, 891. [CrossRef] [PubMed]
21. Thomford, N.E.; Dzobo, K.; Chopera, D.; Wonkam, A.; Skelton, M.; Blackhurst, D.; Chirikure, S.; Dandara, C. Pharmacogenomic implications of using herbal medicinal plants on African populations in health transition. Pharmaceuticals 2015, 8, 637–663. [CrossRef] [PubMed]
22. Thomford, N.E.; Mkhize, B.; Dzobo, K.; Mphe, K.; Rowe, A.; Parker, M.I.; Wonkam, A.; Skelton, M.; September, A.V.; Dandara, C. African lettuce (Launaea taraxacifolia) displays possible anticancer effects and herb-drug interaction potential by CYP1A2, CYP2C9, and CYP2C19 inhibition. Omics 2016, 20, 528–537. [CrossRef] [PubMed]
23. Ji, S.; Fattahi, A.; Raffel, N.; Hoffmann, I.; Beckmann, M.W.; Dittrich, R.; Schrauder, M. Antioxidant effect of aqueous extract of four plants with therapeutic potential on gynecological diseases; semen persicae, Leonurus cardiaca, Hedyotis diffusa, and Curcuma zedoaria. Eur. J. Med. Res. 2017, 22, 50. [CrossRef] [PubMed]
24. Ruhsam, M.; Hollingsworth, P.M. Authentication of eleutherococcus and rhodiola herbal supplement products in the United Kingdom. J. Pharm. Biomed. Anal. 2017, 149, 403–409. [CrossRef] [PubMed]
25. Patridge, E.; Gareiss, P.; Kinch, M.S.; Hoyer, D. An analysis of FDA-approved drugs: Natural products and their derivatives. Drug Discov. Today 2016, 21, 204–207. [CrossRef] [PubMed]

26. Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggan, P.; McPhail, A.T. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J. Am. Chem. Soc. 1971, 93, 2325–2327. [CrossRef] [PubMed]

27. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod. 2012, 75, 311–335. [CrossRef] [PubMed]

28. Carter, G.T. Natural products and Pharma 2011: Strategic changes spur new opportunities. Nat. Prod. Rep. 2011, 28, 1783–1789. [CrossRef] [PubMed]

29. Li, J.W.; Vederas, J.C. Drug discovery and natural products: End of an era or an endless frontier? Science 2009, 325, 161–165. [CrossRef] [PubMed]

30. Li, F.S.; Weng, J.K. Demystifying traditional herbal medicine with modern approach. Nat. Plants 2017, 3, 17109. [CrossRef] [PubMed]

31. Kiyohara, H.; Matsumoto, T.; Yamada, H. Combination effects of herbs in a multi-herbal formula: Expression of juzen-taiho-to’s immuno-modulatory activity on the intestinal immune system. Evid.-Based Complement. Altern. Med. 2004, 1, 83–91. [CrossRef] [PubMed]

32. Leonti, M.; Verpoorte, R. Traditional Mediterranean and European herbal medicines. J. Ethnopharmacol. 2017, 199, 161–167. [CrossRef] [PubMed]

33. Özdemir, V.; Hekim, N. Birth of industry 5.0: Making sense of big data with artificial intelligence, “the internet of things” and next-generation technology policy. Omics 2018, 22, 65–76. [CrossRef] [PubMed]

34. Özdemir, V. Omics 2.0: An accelerator for global science, systems medicine and responsible innovation. Omics 2015, 19, 579–580. [CrossRef] [PubMed]

35. Wall, M.E.; Wani, M.C.; Brown, D.M.; Fullas, F.; Olwald, J.B.; Josephson, F.F.; Thornton, N.M.; Pezzuto, J.M.; Beecher, C.W.; Farnsworth, N.R.; et al. Effect of tannins on screening of plant extracts for enzyme inhibitory activity and techniques for their removal. Phytotherapy 1996, 3, 281–285. [CrossRef]

36. Eldridge, G.R.; Vervoort, H.C.; Lee, C.M.; Cremin, P.A.; Williams, C.T.; Hart, S.M.; Goering, M.G.; O’Neil-Johnson, M.; Zeng, L. High-throughput method for the production and analysis of large natural product libraries for drug discovery. Anal. Chem. 2002, 74, 3963–3971. [CrossRef] [PubMed]

37. Wu, S.; Liang, J. Counter-current chromatography for high throughput analysis of natural products. Comb. Chem. High Throughput Screen. 2010, 13, 932–942. [CrossRef] [PubMed]

38. Bugni, T.S.; Richards, B.; Bhoite, L.; Cimbora, D.; Harper, M.K.; Ireland, C.M. Marine natural product libraries for high-throughput screening and rapid drug discovery. J. Nat. Prod. 2008, 71, 1095–1098. [CrossRef] [PubMed]

39. Koehn, F.E. High impact technologies for natural products screening. In Natural Compounds as Drugs Volume I; Birkhäuser: Basel, Switzerland, 2008; Volume 65, pp. 175–210.

40. Wong, W.R.; Oliver, A.G.; Linington, R.G. Development of antibiotic activity profile screening for the classification and discovery of natural product antibiotics. Chem. Biol. 2012, 19, 1483–1495. [CrossRef] [PubMed]

41. He, G.; Yin, Y.; Yan, X.; Wang, Y. Semi-bionic extraction of effective ingredient from fishbone by high intensity pulsed electric fields. J. Food Process Eng. 2017, 40, e12392. [CrossRef]

42. Yoshioka, T.; Nagatomi, Y.; Harayama, K.; Bamba, T. Development of an analytical method for polycyclic aromatic hydrocarbons in coffee beverages and dark beer using novel high-sensitivity technique of supercritical fluid chromatography/mass spectrometry. J. Biosci. Bioeng. 2018. [CrossRef] [PubMed]

43. Hofstetter, R.; Fassauer, G.M.; Link, A. Supercritical fluid extraction (SFE) of ketamine metabolites from dried urine and on-line quantification by supercritical fluid chromatography and single mass detection (on-line SFE–SFC–MS). J. Chromatogr. B 2018, 1076, 77–83. [CrossRef] [PubMed]

44. Morales, D.; Piris, A.J.; Ruiz-Rodriguez, A.; Prodanov, M.; Soler-Rivas, C. Extraction of bioactive compounds against cardiovascular diseases from Lentinula edodes using a sequential extraction method. Biotechnol. Prog. 2018. [CrossRef] [PubMed]

45. Joana Gil-Chávez, G.; Villa, J.A.; Fernando Ayala-Zavala, J.; Basilio Heredia, J.; Sepulveda, D.; Yahia, E.M.; González-Aguilar, G.A. Technologies for extraction and production of bioactive compounds to be used as nutraceuticals and food ingredients: An overview. Compr. Rev. Food Sci. Food Saf. 2013, 12, 5–23. [CrossRef]
46. De Morais, S.R.; Oliveira, T.L.; de Oliveira, L.P.; Tresvenzol, L.M.; da Conceicao, E.C.; Rezende, M.H.; Fiuza, T.S.; Costa, E.A.; Ferri, P.H.; de Paula, J.R. Essential oil composition, antimicrobial and pharmacological activities of Lippia sidoides cham. (verbenaceae) from Sao Goncalo do Abaete, Minas Gerais, Brazil. Pharmacoén. Mag. 2016, 12, 262–270. [PubMed]

47. Gan, Z.; Liang, Z.; Chen, X.; Wen, X.; Wang, Y.; Li, M.; Ni, Y. Separation and preparation of 6-gingerol from molecular distillation residue of Yunnan ginger rhizomes by high-speed counter-current chromatography and the antioxidant activity of ginger oils in vitro. J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 2016, 1011, 99–107. [CrossRef] [PubMed]

48. Zhang, L.; Mei, J.; Xie, Y.; Li, M.; Liu, D.; He, C. Application of membrane separation technology in extraction process of Chuanxiong Chatiao granules. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China J. Chin. Mater. Med. 2012, 37, 934–936.

49. Williams, S.; Oatley, D.; Abdrahaman, A.; Butt, T.; Nash, R. Membrane technology for the improved separation of bioactive compounds. Procedia Eng. 2012, 44, 2112–2114. [CrossRef]

50. Wang, H.; Jiang, Y.; Ding, M.; Li, J.; Hao, J.; He, J.; Wang, H.; Gao, X.M.; Chang, Y.X. Simultaneous determination and qualitative analysis of six types of components in Naokintong capsule by miniaturized matrix solid-phase dispersion extraction coupled with ultra high-performance liquid chromatography with photodiode array detection and quadrupole time-of-flight mass spectrometry. J. Sep. Sci. 2018. [CrossRef]

51. Zhang, L.; Ge, Y.; Li, J.; Hao, J.; Wang, H.; He, J.; Gao, X.M.; Chang, Y.X. Simultaneous determination of cumbrianetin-beta-d-glucopyranoside and cumbrianetin in a biological sample by high-performance liquid chromatography with fluorescence detection and identification of other cumbrianetin-beta-d-glucopyranoside metabolites by ultra-high-performance liquid chromatography coupled with quadrupole-time of flight mass spectrometry. J. Pharm. Biomed. Anal. 2018, 153, 221–231. [PubMed]

52. Manglik, A.; Kruse, A.C.; Kobilka, T.S.; Thian, F.S.; Mathiesen, J.M.; Sunahara, R.K.; Pardo, L.; Weis, W.I.; Kobilka, B.K.; Granier, S. Crystal structure of the micro-opioid receptor bound to a morphinan antagonist. Nature 2012, 485, 321–326. [CrossRef] [PubMed]

53. Edwards, G. Forces of habit: Drugs and the making of the modern world. Addiction 2002, 97, 608–609. [CrossRef]

54. Zhao, L.; Li, C.; Zhang, Y.; Wen, Q.; Ren, D. Phytochemical and biological activities of an anticancer plant medicine: Brucia javanica. Anti-Cancer Agents Med. Chem. 2014, 14, 440–458. [CrossRef]

55. Tu, Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat. Med. 2011, 17, 1217–1220. [CrossRef] [PubMed]

56. Tu, Y. Artemisinin—A gift from traditional Chinese medicine to the world (Nobel lecture). Angew. Chem. Int. Ed. Engl. 2016, 55, 10210–10226. [CrossRef] [PubMed]

57. Li, J.; Casteels, T.; Frogne, T.; Ingvorsen, C.; Honoré, C.; Courtney, M.; Huber, K.V.M.; Schmittner, N.; Kimmel, R.A.; Romanov, R.A.; et al. Artemisinins target GABA_A receptor signaling and impair α cell identity. Cell 2017, 168, 86–100. [CrossRef] [PubMed]

58. Lai, H.; Singh, N.P. Oral artemisinin prevents and delays the development of 7,12-dimethylbenz[a]anthracene (dmab)-induced breast cancer in the rat. Cancer Lett. 2006, 231, 43–48. [CrossRef] [PubMed]

59. Lai, H.C.; Singh, N.P.; Sasaki, T. Development of artemisinin compounds for cancer treatment. Investg. New Drugs 2013, 31, 230–246. [CrossRef] [PubMed]

60. Return to Rio: Second chance for the planet. Nature 2012, 486, 19.

61. Barbault, R. 2010: A new beginning for biodiversity? C.R. Biol. 2011, 334, 483–488. [CrossRef] [PubMed]

62. Salazar, R.; Cabrera, J.A. Intellectual property rights in Costa Rica in the light of the biodiversity convention. J. Ethnopharmacol. 1996, 51, 177–193. [CrossRef]

63. Samper, C. Taxonomy and environmental policy. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2004, 359, 721–728. [CrossRef] [PubMed]

64. Seidl, P.R. Pharmaceuticals from natural products: Current trends. Anais da Academia Brasileira de Ciencias 2002, 74, 145–150. [CrossRef] [PubMed]

65. Tollefson, J.; Gilbert, N. Earth summit: Rio report card. Nature 2012, 486, 20–23. [CrossRef] [PubMed]

66. Wen, M.C.; Wei, C.H.; Hu, Z.Q.; Srivastava, K.; Ko, J.; Xi, S.T.; Mu, D.Z.; Du, J.B.; Li, G.H.; Wallenstein, S.; et al. Efficacy and tolerability of anti-asthma herbal medicine intervention in adult patients with moderate-severe allergic asthma. J. Allergy Clin. Immunol. 2005, 116, 517–524. [CrossRef] [PubMed]
67. Srivastava, K.; Sampson, H.A.; Charles, W.; Emala, S.; Li, X.-M. The anti-asthma herbal medicine ashmi acutely inhibits airway smooth muscle contraction via prostaglandin e2 activation of ep2/ep4 receptors. Am. J. Physiol.-Lung Cell. Mol. Physiol. 2013, 305, L1002–L1010. [CrossRef] [PubMed]
68. Yang, N.; Liang, B.; Srivastava, K.; Zeng, J.; Zhan, J.; Brown, L.; Sampson, H.; Goldfarb, J.; Emala, C.; Li, X.M. The Sphophora flavescens flavonoid compound trifolirhizin inhibits acetylcholine induced airway smooth muscle contraction. Phytochemistry 2013, 95, 259–267. [CrossRef] [PubMed]
69. Chan, K.; Shaw, D.; Simmonds, M.S.; Leon, C.J.; Xu, Q.; Lu, A.; Sutherland, I.; Ignatova, S.; Zhu, Y.P.; Verpoorte, R.; et al. Good practice in reviewing and publishing studies on herbal medicine, with special emphasis on traditional Chinese medicine and Chinese materia medica. J. Ethnopharmacol. 2012, 140, 469–475. [CrossRef] [PubMed]
70. Skroza, D.; Generalić Mekinić, I.; Svilović, S.; Šimat, V.; Katalinić, V. Investigation of the potential synergistic effect of resveratrol with other phenolic compounds: A case of binary phenolic mixtures. J. Food Compos. Anal. 2015, 38, 13–18. [CrossRef]
71. Chusri, S.; Siriyong, T.; Na-Phatthalung, P.; Voravuthikunchai, S.P. Synergistic effects of ethnomedicinal plants of Apocynaceae family and antibiotics against clinical isolates of Acinetobacter baumannii. Asian Pac. J. Trop. Med. 2014, 7, 456–461. [CrossRef]
72. Sharma, G.; Tyagi, A.K.; Singh, R.P.; Chan, D.C.; Agarwal, R. Synergistic anti-cancer effects of grape seed extract and conventional cytotoxic agent doxorubicin against human breast carcinoma cells. Breast Cancer Res. Treat. 2004, 85, 1–12. [CrossRef] [PubMed]
73. Medema, M.H.; Fischbach, M.A. Computational approaches to natural product discovery. Nat. Chem. Biol. 2015, 11, 639–648. [CrossRef] [PubMed]
74. Kim, E.; Moore, B.S.; Yoon, Y.J. Reinvigorating natural product combinatorial biosynthesis with synthetic biology. Nat. Chem. Biol. 2015, 11, 649–659. [CrossRef] [PubMed]
75. Akbulut, Y.; Gaunt, H.J.; Muraki, K.; Ludlow, M.J.; Amer, M.S.; Bruns, A.; Vasudev, N.S.; Radtke, L.; Willot, M.; Hahn, S.; et al. (-)-Englerin A is a potent and selective activator of TRPC4 and TRPC5 calcium channels. Angew. Chem. Int. Ed. Engl. 2015, 54, 3787–3791. [CrossRef] [PubMed]
76. Ludlow, M.J.; Gaunt, H.J.; Rubaï, H.N.; Musialowski, K.E.; Blythe, N.M.; Vasudev, N.S.; Muraki, K.; Beech, D.J. (-)-Englerin A-evoked cytotoxicity is mediated by Na\(^{+}\) influx and counteracted by Na\(^{+}\)/K\(^{-}\)-atpase. J. Biol. Chem. 2017, 292, 723–731. [CrossRef] [PubMed]
77. Muraki, K.; Ohnishi, K.; Takezawa, A.; Suzuki, H.; Hatano, N.; Muraki, Y.; Hamzah, N.; Foster, R.; Waldmann, H.; Nussbaumer, P.; et al. Na\(^{+}\) entry through heteromeric TRPC4/C1 channels mediates (-)-Englerin A-induced cytotoxicity in synovial sarcoma cells. Sci. Rep. 2017, 7, 16988. [CrossRef] [PubMed]
78. Buriani, A.; Garcia-Bermejo, M.L.; Bosiso, E.; Xu, Q.; Li, H.; Dong, X.; Simmonds, M.S.; Carrara, M.; Tejedor, N.; Lucio-Cazana, J.; et al. Ominic techniques in systems biology approaches to traditional Chinese medicine research: Present and future. J. Ethnopharmacol. 2012, 140, 535–544. [CrossRef] [PubMed]
79. Ganie, S.H.; Upadhyay, P.; Das, S.; Prasad Sharma, M. Authentication of medicinal plants by DNA markers. Plant Gene Res. Treat. 2013, 4, 1–12. [CrossRef] [PubMed]
80. Ghorbani, A.; Saeedi, Y.; de Boer, H.J. Unidentifiable by morphology: DNA barcoding of plant material in local markets in Iran. PLoS ONE 2017, 12, e0175722. [CrossRef] [PubMed]
81. Thompson, K.A.; Newmaster, S.G. Molecular taxonomic tools provide more accurate estimates of species richness at less cost than traditional morphology-based taxonomic practices in a vegetation survey. Biodivers. Conserv. 2014, 23, 1411–1424. [CrossRef]
82. Cao, M.; Wang, J.; Yao, L.; Xie, S.; Du, J.; Zhao, X. Authentication of animal signatures in traditional Chinese medicine of Lingyang Qingfei Wan using routine molecular diagnostic assays. Mol. Biol. Rep. 2014, 41, 2485–2491. [CrossRef] [PubMed]
83. Newmaster, S.G.; Grigruric, M.; Shanmughanandhan, D.; Ramalingam, S.; Ragupathy, S. DNA barcoding detects contamination and substitution in North American herbal products. BMC Med. 2013, 11, 222. [CrossRef] [PubMed]
84. Mishra, P.; Kumar, A.; Nagireddy, A.; Mani, D.N.; Shukla, A.K.; Tiwari, R.; Sundaresan, V. DNA barcoding: An efficient tool to overcome authentication challenges in the herbal market. Plant Biotechnol. J. 2016, 14, 8–21. [CrossRef] [PubMed]
85. Chen, X.; Xiang, L.; Shi, L.; Li, G.; Yao, H.; Han, J.; Lin, Y.; Song, J.; Chen, S. Identification of crude drugs in the Japanese pharmacopoeia using a DNA barcoding system. Sci. Rep. 2017, 7, 42325. [CrossRef] [PubMed]
86. Pulice, G.; Pelaz, S.; Matías-Hernández, L. Molecular farming in Artemisia annua, a promising approach to improve anti-malarial drug production. Front. Plant Sci. 2016, 7, 329. [CrossRef] [PubMed]

87. Gantait, S.; Debnath, S.; Nasim Ali, M. Genomic profile of the plants with pharmaceutical value. 3 Biotech 2014, 4, 563–578. [CrossRef] [PubMed]

88. Lv, C.; Wu, X.; Wang, X.; Su, J.; Zeng, H.; Zhao, J.; Lin, S.; Liu, R.; Li, H.; Li, X.; et al. The gene expression profiles in response to 102 traditional Chinese medicine (TCM) components: A general template for research on TCMs. Sci. Rep. 2017, 7, 352. [CrossRef] [PubMed]

89. Lee, K.-H.; Lo, H.-L.; Tang, W.-C.; Hsiao, H.H.-Y.; Yang, P.-M. A gene expression signature-based approach reveals the mechanisms of action of the Chinese herbal medicine Berberine. Sci. Rep. 2014, 4, 6394. [CrossRef] [PubMed]

90. Kiyama, R. DNA microarray-based screening and characterization of traditional Chinese medicine. Microarrays 2017, 6, 4. [CrossRef] [PubMed]

91. Jones, M.J.; Goodman, S.J.; Kobor, M.S. DNA methylation and healthy human aging. Aging Cell 2015, 14, 924–932. [CrossRef] [PubMed]

92. Kelly, T.K.; Liu, Y.; Lay, F.D.; Liang, G.; Berman, B.P.; Jones, P.A. Genome-wide mapping of nucleosome positioning and DNA methylation within individual DNA molecules. Genome Res. 2012, 22, 2497–2506. [CrossRef] [PubMed]

93. Nordlund, J.; Backlin, C.L.; Wahlberg, P.; Busche, S.; Berglund, M.L.; Flagstad, T.; Foretstier, E.; Frost, B.M.; Harila-Saari, A.; et al. Genome-wide signatures of differential DNA methylation in pediatric acute lymphoblastic leukemia. Genome Biol. 2013, 14, r105. [CrossRef] [PubMed]

94. Su, J.; Wang, Y.; Xing, X.; Liu, J.; Zhang, Y. Genome-wide analysis of DNA methylation in bovine placentas. BMC Genom. 2014, 15, 12. [CrossRef] [PubMed]

95. Zykovich, A.; Hubbard, A.; Flynn, J.M.; Tarnopolsky, M.; Fraga, M.F.; Kerkisick, C.; Ogborun, D.; MacNeil, L.; Mooney, S.D.; Melov, S. Genome-wide DNA methylation changes with age in disease-free human skeletal muscle. Aging Cell 2014, 13, 360–366. [CrossRef] [PubMed]

96. Barbosa, S.; Carreira, S.; Bailey, D.; Abaitua, F.; O’Hare, P. Phosphorylation and SCF-mediated degradation regulate CREB-H transcription of metabolic targets. Mol. Biol. Cell 2015, 26, 2939–2954. [CrossRef] [PubMed]

97. Bose, P.; Vachhani, P.; Cortes, J.E. Treatment of relapsed/refractory acute myeloid leukemia. Curr. Treat. Options Oncol. 2017, 18, 17. [CrossRef] [PubMed]

98. Ley, T.J.; Miller, C.; Ding, L.; Raphael, B.J.; Mungall, A.J.; Robertson, A.; Hoadley, K.; Triche, T.J., Jr.; Laird, P.W.; Baty, J.D.; et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N. Engl. J. Med. 2013, 368, 2059–2074. [PubMed]

99. Brat, D.J.; Verhaak, R.G.; Aldape, K.D.; Yung, W.K.; Salama, S.R.; Cooper, L.A.; Rheinbay, E.; Miller, C.R.; Vittucci, M.; Morozova, O.; et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N. Engl. J. Med. 2015, 372, 2481–2498. [PubMed]

100. Eckel-Passow, J.E.; Lachance, D.H.; Molinario, A.M.; Walsh, K.M.; Decker, P.A.; Sicotte, H.; Pekmezci, M.; Rice, T.; Kosel, M.L.; Smirnov, I.V.; et al. Glioma groups based on 1p/19q, and TERT promoter mutations in tumors. N. Engl. J. Med. 2015, 372, 2499–2508. [CrossRef] [PubMed]

101. Mwapagha, L.M.; Tiffon, N.; Parker, M.I. Delineation of the HPV11e6 and HPV18e6 pathways in initiating cellular transformation. Front. Oncol. 2017, 7, 258. [CrossRef] [PubMed]

102. Vogelsang, M.; Wang, Y.; Veber, N.; Mwapagha, L.M.; Parker, M.I. The cumulative effects of polymorphisms in the DNA mismatch repair genes and tobacco smoking in oesophageal cancer risk. PLoS ONE 2012, 7, e36962. [CrossRef] [PubMed]

103. Fishilevich, S.; Nudel, R.; Rappaport, N.; Hadar, R.; Plaschkes, I.; Iny Stein, T.; Rosen, N.; Kohn, A.; Twik, M.; Safran, M.; et al. Genehancer: Genome-wide integration of enhancers and target genes in genecards. Database 2017, 2017. [CrossRef] [PubMed]

104. Guo, X.; Long, J.; Zeng, C.; Michailidou, K.; Ghoussaini, M.; Bolla, M.K.; Wang, Q.; Milne, R.L.; Shu, X.O.; Cai, Q.; et al. Fine-scale mapping of the 4q24 locus identifies two independent loci associated with breast cancer risk. Cancer Epidemiol. Biomark. Prev. 2015, 24, 1680–1691. [CrossRef] [PubMed]

105. Ombrello, M.J.; Sikora, K.A.; Kastner, D.L. Genetics, genomics, and their relevance to pathology and therapy. Best Pract. Res. Clin. Rheumatol. 2014, 28, 175–189. [CrossRef] [PubMed]

106. Simmonds, P.; Loomis, E.; Curry, E. DNA methylation-based chromatin compartments and CHIP-seq profiles reveal transcriptional drivers of prostate carcinogenesis. Genome Med. 2017, 9, 54. [CrossRef] [PubMed]
128. Jafari, R.; Almqvist, H.; Axelsson, H.; Ignatoushchenko, M.; Lundback, T.; Nordlund, P.; Martinez Molina, D. The cellular thermal shift assay for evaluating drug target interactions in cells. *Nat. Protoc.* 2014, 9, 2100–2122. [CrossRef] [PubMed]

129. Lomenick, B.; Hao, R.; Jonai, N.; Chin, R.M.; Aghajan, M.; Warburton, S.; Wang, J.; Wu, R.P.; Gomez, F.; Loo, J.A.; et al. Target identification using drug affinity responsive target stability (darts). *Proc. Natl. Acad. Sci. USA* 2009, 106, 21984–21989. [CrossRef] [PubMed]

130. Schirle, M.; Bantscheff, M.; Kuster, B. Mass spectrometry-based proteomics in preclinical drug discovery. *Chem. Biol.* 2012, 19, 72–84. [CrossRef] [PubMed]

131. Dejonghe, W.; Olsen, R.W.; Huang, J. Identification of direct protein targets of small molecules. *ACS Chem. Biol.* 2011, 6, 34–46. [CrossRef] [PubMed]

132. Lomenick, B.; Olsen, R.W.; Huang, J. Identification of direct protein targets of small molecules. *ACS Chem. Biol.* 2011, 6, 34–46. [CrossRef] [PubMed]

133. West, G.M.; Tucker, C.L.; Xu, T.; Park, S.K.; Han, X.; Yates, J.R., 3rd; Fitzgerald, M.C. Quantitative proteomics approach for identifying protein-drug interactions in complex mixtures using protein stability measurements. *Proc. Natl. Acad. Sci. USA* 2010, 107, 9078–9082. [CrossRef] [PubMed]

134. Geiger, T.; Wisniewski, J.R.; Cox, J.; Zanivan, S.; Kruger, M.; Ishihama, Y.; Mann, M. Use of stable isotope labeling by amino acids in cell culture (SILAC) for protein-ligand binding analyses in complex biological mixtures using a shotgun proteomics approach. *Nat. Protoc.* 2014, 9, 132–140. [CrossRef] [PubMed]

135. Jin, L.; Wang, D.; Gooden, D.M.; Ball, C.H.; Fitzgerald, M.C. Targeted mass spectrometry-based approach for protein-ligand binding analyses in complex biological mixtures using a phenacyl bromide modification strategy. *Anal. Chem.* 2016, 88, 10987–10993. [CrossRef] [PubMed]

136. Saxena, C. Identification of protein binding partners of small molecules using label-free methods. *Expert Opin. Drug Discov.* 2016, 11, 1017–1025. [CrossRef] [PubMed]

137. Strickland, E.C.; Geer, M.A.; Hong, J.; Fitzgerald, M.C. False-positive rate determination of protein target discovery using a covalent modification- and mass spectrometry-based proteomics platform. *J. Am. Soc. Mass Spectrom.* 2014, 25, 132–140. [CrossRef] [PubMed]

138. Dearmond, P.D.; Xu, Y.; Strickland, E.C.; Daniels, K.G.; Fitzgerald, M.C. Thermodynamic analysis of protein-ligand interactions in complex biological mixtures using a shotgun proteomics approach. *J. Proteome Res.* 2011, 10, 4948–4958. [CrossRef] [PubMed]

139. Tran, D.T.; Adhikari, J.; Fitzgerald, M.C. Stableisotope labeling with amino acids in cell culture (SILAC)-based strategy for proteome-wide thermodynamic analysis of protein-ligand binding interactions. *Mol. Cell. Proteom.* 2014, 13, 1800–1813. [CrossRef] [PubMed]

140. Geiger, T.; Wisniewski, J.R.; Cox, J.; Zanivan, S.; Kruger, M.; Ishihama, Y.; Mann, M. Use of stable isotope labeling by amino acids in cell culture as a spike-in standard in quantitative proteomics. *Nat. Protoc.* 2011, 6, 147–157. [CrossRef] [PubMed]

141. Hoedt, E.; Zhang, G.; Neubert, T.A. Stable isotope labeling with amino acids in cell culture (SILAC) for quantitative proteomics. *Adv. Exp. Med. Biol.* 2014, 806, 93–106. [PubMed]

142. Laranche, M.; Bailly, A.P.; Pourkarimi, E.; Hay, R.T.; Buchanan, G.; Coulthurst, S.; Xirodimas, D.P.; Gartner, A.; Lamond, A.I. Stable-isotope labeling with amino acids in nematodes. *Nat. Methods* 2011, 8, 849–851. [CrossRef] [PubMed]

143. Ong, S.E.; Mann, M. A practical recipe for stable isotope labeling by amino acids in cell culture (SILAC). *Nat. Protoc.* 2006, 1, 2650–2660. [CrossRef] [PubMed]

144. Zhang, L.; Jin, J.; Zhang, L.; Hu, R.; Gao, L.; Huo, X.; Liu, D.; Ma, X.; Wang, C.; Han, J.; et al. Quantitative analysis of differential protein expression in cervical carcinoma cells after zeylenone treatment by stable isotope labeling with amino acids in cell culture. *J. Proteom.* 2015, 126, 279–287. [CrossRef] [PubMed]

145. Martinez Molina, D.; Jafari, R.; Ignatoushchenko, M.; Seki, T.; Larsson, E.A.; Dan, C.; Sreekumar, L.; Cao, Y.; Nordlund, P. Monitoring drug target engagement in cells and tissues using the cellular thermal shift assay. *Science* 2013, 341, 84–87. [CrossRef] [PubMed]

146. Schirle, M.; Jenkins, J.L. Identifying compound efficacy targets in phenotypic drug discovery. *Drug Discov. Today* 2016, 21, 82–89. [CrossRef] [PubMed]

147. Tang, H.; Duggan, S.; Richardson, P.L.; Marin, V.; Warder, S.E.; McLoughlin, S.M. Target identification of compounds from a cell viability phenotypic screen using a bead/lysate-based affinity capture platform. *J. Biomol. Screen.* 2016, 21, 201–211. [CrossRef] [PubMed]
169. Park, H.-W.; In, G.; Kim, J.-H.; Cho, B.-G.; Han, G.-H.; Chang, I.-M. Metabolomic approach for discrimination of processed ginseng genus (Panax ginseng and Panax quinquefolius) using UPLC-QTOF MS. *J. Ginseng Res.* 2014, 38, 59–65. [CrossRef] [PubMed]

170. Korotcov, A.; Tkachenko, V.; Russo, D.P.; Ekins, S. Comparison of deep learning with multiple machine learning methods and metrics using diverse drug discovery data sets. *Mol. Pharm.* 2017, 14, 4462–4475. [CrossRef] [PubMed]

171. Oprea, T.I.; Matter, H. Integrating virtual screening in lead discovery. *Curr. Opin. Chem. Biol.* 2004, 8, 349–358. [CrossRef] [PubMed]

172. Beck, A.; Eberherr, C.; Hagemann, M.; Cairo, S.; Haberle, B.; Vokuhl, C.; von Schweinitz, D.; Kappler, R. Connectivity map identifies HDAC inhibition as a treatment option of high-risk hepatoblastoma. *Cancer Biol. Ther.* 2016, 17, 1168–1176. [CrossRef] [PubMed]

173. Brum, A.M.; van de Peppel, J.; van der Leije, C.S.; Schreuders-Koedam, M.; Eijken, M.; van der Eerden, B.C.; van Leeuwen, J.P. Connectivity map-based discovery of parbendazole reveals targetable human osteogenic pathway. *Proc. Natl. Acad. Sci. USA* 2015, 112, 12711–12716. [CrossRef] [PubMed]

174. Cheng, J.; Yang, L.; Kumar, V.; Agarwal, P. Systematic evaluation of connectivity map for disease indications. *Genome Med.* 2014, 6, 95. [CrossRef] [PubMed]

175. Lamb, J. The connectivity map: A new tool for biomedical research. *Nat. Rev. Cancer* 2007, 7, 54–60. [CrossRef] [PubMed]

176. Lamb, J.; Crawford, E.D.; Peck, D.; Modell, J.W.; Blat, I.C.; Lerner, J.; Brunet, J.P.; Subramanian, A.; Ross, K.N.; et al. The connectivity map: Using gene-expression signatures to connect small molecules, genes, and disease. *Science* 2006, 313, 1929–1935. [CrossRef] [PubMed]

177. Hahn, C.K.; Berchuck, J.E.; Ross, K.N.; Kakoza, R.M.; Clauser, K.; Schinzel, A.C.; Ross, L.; Galinsky, I.; Davis, T.N.; Silver, S.J.; et al. Proteomic and genetic approaches identify Syk as an AML target. *Cancer Cell* 2009, 16, 281–294. [CrossRef] [PubMed]

178. Nair, M.; Sandhu, S.S.; Sharma, A.K. Prognostic and predictive biomarkers in cancer. *Curr. Cancer Drug Targets* 2014, 14, 477–504. [CrossRef] [PubMed]

179. Narayanan, R. Druggable cancer secretome: Neoplasm-associated traits. *Cancer Genom. Proteom.* 2015, 12, 119–131.

180. Roti, G.; Stegmaier, K. Genetic and proteomic approaches to identify cancer drug targets. *Br. J. Cancer* 2012, 106, 254–261. [CrossRef] [PubMed]

181. Verma, M.; Wright, G.L., Jr.; Hanash, S.M.; Gopal-Srivastava, R.; Srivastava, S. Proteomic approaches within the NCI early detection research network for the discovery and identification of cancer biomarkers. *Ann. N. Y. Acad. Sci.* 2001, 945, 103–115. [CrossRef] [PubMed]

182. Awale, M.; Visini, R.; Probst, D.; Arus-Pous, J.; Reymond, J.L. Chemical space: Big data challenge for molecular diversity. *Chimia* 2017, 71, 661–666. [CrossRef] [PubMed]

183. Denny, J.C.; Van Driest, S.L.; Wei, W.Q.; Roden, D.M. The influence of big (clinical) data and genomics on precision medicine and drug development. *Clin. Pharmacol. Ther.* 2018, 103, 409–418. [CrossRef] [PubMed]

184. Singh, G.; Schulthess, D.; Hughes, N.; Vannieuwenhuysen, B.; Kalra, D. Real world big data for clinical research and drug development. *Drug Discov. Today* 2018, 23, 650–660. [CrossRef] [PubMed]

185. Bento, A.P.; Gaulton, A.; Hersey, A.; Bellis, L.J.; Chambers, J.; Davies, M.; Kruger, F.A.; Light, Y.; Mak, L.; McGlinchey, S.; et al. The ChEMBL bioactivity database: An update. *Nucleic Acids Res.* 2014, 42, D1083–D1090. [CrossRef] [PubMed]

186. Bento, A.P.; Gaulton, A.; Hersey, A.; Bellis, L.J.; Chambers, J.; Davies, M.; Kruger, F.A.; Light, Y.; Mak, L.; McGlinchey, S.; et al. The ChEMBL bioactivity database: An update. *Nucleic Acids Res.* 2014, 42, D1083–D1090. [CrossRef] [PubMed]

187. Gaulton, A.; Hersey, A.; Nowotka, M.; Bento, A.P.; Chambers, J.; Davies, M.; Kruger, F.A.; Light, Y.; Mak, L.; McGlinchey, S.; et al. The ChEMBL bioactivity database: An update. *Nucleic Acids Res.* 2014, 42, D1083–D1090. [CrossRef] [PubMed]

188. Kruger, F.A.; Rostom, R.; Overington, J.P. Mapping small molecule binding data to structural domains. *BMC Bioinform.* 2012, 13, S11.

189. Roos, D.S. Computational biology. Bioinformatics—Trying to swim in a sea of data. *Science* 2001, 291, 1260–1261. [CrossRef] [PubMed]
190. Jennings, A.; Tennant, M. Discovery strategies in a pharmaceutical setting: The application of computational techniques. *Expert Opin. Drug Discov.* 2006, 1, 709–721. [CrossRef] [PubMed]

191. Chen, Y.P.; Chen, F. Identifying targets for drug discovery using bioinformatics. *Expert Opin. Ther. Targets* 2008, 12, 383–389. [CrossRef] [PubMed]

192. Segal, M.R.; Xiong, H.; Bengtsson, H.; Bourgon, R.; Gentleman, R. Querying genomic databases: Refining the connectivity map. *Stat. Appl. Genet. Mol. Biol.* 2012, 11. [CrossRef] [PubMed]

193. Kim, R.S.; Goossens, N.; Hoshida, Y. Use of big data in drug development for precision medicine. *Expert Rev. Precis. Med. Drug Dev.* 2016, 1, 245–253. [CrossRef] [PubMed]

194. Cappon, G.D. Nonclinical support of pediatric drug development in a global context: An industry perspective. *Birth Defects Res. Part B Dev. Reprod. Toxicol.* 2011, 92, 269–272. [CrossRef] [PubMed]

195. Kaneko, T.; Cooper, C.; Mdluli, K. Challenges and opportunities in developing novel drugs for TB. *Future Med. Chem.* 2011, 3, 1373–1400. [CrossRef] [PubMed]

196. Morford, L.L.; Bowman, C.J.; Blanset, D.L.; Bogh, I.B.; Chellman, G.J.; Weinbauer, G.F.; Coogan, T.P. Preclinical safety evaluations supporting pediatric drug development with biopharmaceuticals: Strategy, challenges, current practices. *Birth Defects Res. Part B Dev. Reprod. Toxicol.* 2011, 92, 359–380. [CrossRef] [PubMed]

197. Beggs, N.F.; Dobrovolny, H.M. Determining drug efficacy parameters for mathematical models of influenza. *J. Biol. Dyn.* 2015, 9, 332–346. [CrossRef] [PubMed]

198. Hwang, W.; Choi, J.; Kwon, M.; Lee, D. Context-specific functional module based drug efficacy prediction. *BMC Bioinform.* 2016, 17 (Suppl. 6). [CrossRef] [PubMed]

199. Jimenez-Diaz, M.B.; Viera, S.; Fernandez-Alvaro, E.; Angulo-Barturen, I. Animal models of efficacy to accelerate drug discovery in malaria. *Parasitology* 2014, 141, 93–103. [CrossRef] [PubMed]

200. Nelson, M.R.; Johnson, T.; Warren, L.; Hughes, A.R.; Chissoe, S.L.; Xu, C.F.; Watervorth, D.M. The genetics of drug efficacy: Opportunities and challenges. *Nat. Rev. Genet.* 2016, 17, 197–206. [CrossRef] [PubMed]

201. Tsugawa, J.; Onozawa, R.; Fukae, J.; Mishima, T.; Fujioka, S.; Tsuboi, Y. Impact of insufficient drug efficacy of antiparkinson agents on patient’s quality of life: A cross-sectional study. *BMC Neurol.* 2015, 15, 105. [CrossRef] [PubMed]

202. Gange, S.J.; Golub, E.T. From smallpox to big data: The next 100 years of epidemiologic methods. *Am. J. Epidemiol.* 2016, 183, 423–426. [CrossRef] [PubMed]

203. Docherty, A.B.; Lone, N.I. Exploiting big data for critical care research. *Curr. Opin. Crit. Care* 2015, 21, 467–472. [CrossRef] [PubMed]

204. Greene, C.S.; Tan, J.; Ung, M.; Moore, J.H.; Cheng, C. Big data bioinformatics. *J. Cell. Physiol.* 2014, 229, 1896–1900. [CrossRef] [PubMed]

205. Tan, S.S.; Gao, G.; Koch, S. Big data and analytics in healthcare. *Methods Inf. Med.* 2015, 54, 546–547. [CrossRef] [PubMed]

206. Wasser, T.; Haynes, K.; Barron, J.; Cziraky, M. Using ‘big data’ to validate claims made in the pharmaceutical approval process. *J. Med. Econ.* 2015, 18, 1013–1019. [CrossRef] [PubMed]

207. Reshef, D.N.; Reshef, Y.A.; Finucane, H.K.; Grossman, S.R.; McVean, G.; Turnbaugh, P.J.; Lander, E.S.; Mitzenmacher, M.; Sabeti, P.C. Detecting novel associations in large data sets. *Science* 2011, 334, 1518–1524. [CrossRef] [PubMed]

208. Omer, L.; Ellrott, K.; Yuan, Y.; Kandoth, C.; Wong, C.; Kellen, M.R.; Friend, S.H.; Stuart, J.; Liang, H.; Margolin, A.A. Enabling transparent and collaborative computational analysis of 12 tumor types within the cancer genome atlas. *Nat. Genet.* 2013, 45, 1121–1126. [CrossRef] [PubMed]

209. Chen, R.; Mias, G.I.; Li-Pook-Than, J.; Jiang, L.; Lam, H.Y.; Chen, R.; Miriami, E.; Karczewski, K.J.; Hariharan, M.; Dewey, F.E.; et al. Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell* 2012, 148, 1293–1307. [CrossRef] [PubMed]

210. Chapman, T. Lab automation and robotics: Automation on the move. *Nature* 2003, 421, 661–666. [CrossRef] [PubMed]

211. King, R.D.; Rowland, J.; Oliver, S.G.; Young, M.; Aubrey, W.; Byrne, E.; Liakata, M.; Markham, M.; Pir, P.; Soldatova, L.N.; et al. The automation of science. *Science* 2009, 324, 85–89. [CrossRef] [PubMed]

212. Sparkes, A.; Aubrey, W.; Byrne, E.; Clare, A.; Khan, M.N.; Liakata, M.; Markham, M.; Rowland, J.; Soldatova, L.N.; Whelan, K.E.; et al. Towards robot scientists for autonomous scientific discovery. *Autom. Exp.* 2010, 2, 1. [CrossRef] [PubMed]
213. Meanwell, N.A. Improving drug design: An update on recent applications of efficiency metrics, strategies for replacing problematic elements, and compounds in non-traditional drug space. Chem. Res. Toxicol. 2016, 29, 564–616. [CrossRef] [PubMed]

214. MacConnell, A.B.; Price, A.K.; Paegel, B.M. An integrated microfluidic processor for DNA-encoded combinatorial library functional screening. ACS Comb. Sci. 2017, 19, 181–192. [CrossRef] [PubMed]

215. Baranczak, A.; Tu, N.P.; Marjanovic, J.; Searle, P.A.; Vasudevan, A.; Djuric, S.W. Integrated platform for expedited synthesis-purification-testing of small molecule libraries. ACS Med. Chem. Lett. 2017, 8, 461–465. [CrossRef] [PubMed]

216. Gupta, A.; Muller, A.T.; Huisman, B.J.H.; Fuchs, J.A.; Schneider, P.; Schneider, G. Generative recurrent networks for de novo drug design. Mol. Inform. 2018. [CrossRef] [PubMed]

217. Merk, D.; Friedrich, L.; Grisoni, F.; Schneider, G. De novo design of bioactive small molecules by artificial intelligence. Mol. Inform. 2018. [CrossRef] [PubMed]

218. Zhang, L.; Tan, J.; Han, D.; Zhu, H. From machine learning to deep learning: Progress in machine intelligence for drug discovery in the big data era. Chin. J. Chem. 2018, 36, 462–470. [CrossRef] [PubMed]

219. Duch, W.; Swaminathan, K.; Meller, J. Artificial intelligence approaches for rational drug design and discovery. Curr. Pharm. Des. 2007, 13, 1497–1508. [CrossRef] [PubMed]

220. Esch, E.W.; Bahinski, A.; Huh, D. Organs-on-chips at the frontiers of drug discovery. Nat. Rev. Drug Discov. 2018, 14, 248–260. [CrossRef] [PubMed]

221. Eglen, R.M.; Randle, D.H. Drug discovery goes three-dimensional: Goodbye to flat high-throughput screening? Assay Drug Dev. Technol. 2015, 13, 262–265. [CrossRef] [PubMed]

222. Ozdemir, V.; Patrinos, G.P. David bowie and the art of slow innovation: A fast-second winner strategy for biotechnology and precision medicine global development. Omics 2017, 21, 633–637. [CrossRef] [PubMed]

223. Burke, M.D.; Lalic, G. Teaching target-oriented and diversity-oriented organic synthesis at Harvard University. Chem. Biol. 2002, 9, 535–541. [CrossRef]

224. Schreiber, S.L. Target-oriented and diversity-oriented organic synthesis in drug discovery. Curr. Opin. Chem. Biol. 2011, 15, 256. [CrossRef] [PubMed]

225. Maier, M.E. Design and synthesis of analogues of natural products. Org. Biomol. Chem. 2015, 13, 5302–5343. [CrossRef] [PubMed]

226. Basu, S.; Ellinger, B.; Rizzo, S.; Deraeve, C.; Schurmann, M.; Preut, H.; Arndt, H.D.; Waldmann, H. Biology-oriented synthesis of a natural-product inspired oxepane collection yields a small-molecule activator of the Wnt-pathway. Proc. Natl. Acad. Sci. USA 2011, 108, 6805–6810. [CrossRef] [PubMed]

227. Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. Biology-inspired synthesis of compound libraries. Cell. Mol. Life Sci. 2008, 65, 1186–1201. [CrossRef] [PubMed]

228. Wetzel, S.; Bon, R.S.; Kumar, K.; Waldmann, H. Biology-oriented synthesis. Angew. Chem. Int. Ed. Engl. 2011, 50, 10800–10826. [CrossRef] [PubMed]

229. Wender, P.A.; Quiroz, R.V.; Stevens, M.C. Function through synthesis-informed design. Acc. Chem. Res. 2015, 48, 752–760. [CrossRef] [PubMed]

230. Wender, P.A.; Verma, V.A.; Paxton, T.J.; Pillow, T.H. Function-oriented synthesis, step economy, and drug design. Acc. Chem. Res. 2008, 41, 40–49. [CrossRef] [PubMed]

231. Zhu, Q.; Sun, Y.; Challa, S.; Ding, Y.; Lajiness, M.S.; Wild, D.J. Semantic inference using chemogenomics data for drug discovery. BMC Bioinform. 2011, 12, 256. [CrossRef] [PubMed]

232. White, D.; Wilson, R.C. Generative models for chemical structures. J. Chem. Inf. Model. 2010, 50, 1257–1274. [CrossRef] [PubMed]

233. Rubio, D.M.; Schoenbaum, E.E.; Lee, L.S.; Schteingart, D.E.; Marantz, P.R.; Anderson, K.E.; Platt, L.D.; Baez, A.; Esposito, K. Defining translational research: Implications for training. Acad. Med. 2010, 85, 470–475. [CrossRef] [PubMed]

234. Jing, Y.; Bian, Y.; Hu, Z.; Wang, L.; Xie, X.S. Deep learning for drug design: An artificial intelligence paradigm for drug discovery in the big data era. AAPS J. 2018, 20, 58. [CrossRef] [PubMed]

235. Reutlinger, M.; Rodrigues, T.; Schneider, P.; Schneider, G. Combining on-chip synthesis of a focused combinatorial library with computational target prediction reveals imidazopyridine GPCR ligands. Angew. Chem. Int. Ed. Engl. 2014, 53, 582–585. [CrossRef] [PubMed]

236. Schneider, G. Automating drug discovery. Nat. Rev. Drug Discov. 2018, 17, 97–113. [CrossRef] [PubMed]
237. Reutlinger, M.; Rodrigues, T.; Schneider, P.; Schneider, G. Multi-objective molecular de novo design by adaptive fragment prioritization. *Angew. Chem. Int. Ed. Engl.* 2014, 53, 4244–4248. [CrossRef] [PubMed]

238. Schneider, P.; Rothlisberger, M.; Reker, D.; Schneider, G. Spotting and designing promiscuous ligands for drug discovery. *Chem. Commun.* 2016, 52, 1135–1138. [CrossRef] [PubMed]

239. Wang, L.; Wu, Y.; Deng, Y.; Kim, B.; Pierce, L.; Krilov, G.; Lupyan, D.; Robinson, S.; Dahlgren, M.K.; Greenwood, J.; et al. Accurate and reliable prediction of relative ligand binding potency in prospective drug discovery by way of a modern free-energy calculation protocol and force field. *J. Am. Chem. Soc.* 2015, 137, 2695–2703. [CrossRef] [PubMed]

240. Besnard, J.; Ruda, G.F.; Setola, V.; Abecasis, K.; Rodriguiz, R.M.; Huang, X.P.; Norval, S.; Sassano, M.F.; Shin, A.I.; Webster, L.A.; et al. Automated design of ligands to polypharmacological profiles. *Nature* 2012, 492, 215–220. [CrossRef] [PubMed]

241. Besnard, J.; Ruda, G.F.; Setola, V.; Abecassis, K.; Rodriguiz, R.M.; Huang, X.P.; Norval, S.; Sassano, M.F.; Shin, A.I.; Webster, L.A.; et al. Automated design of ligands to polypharmacological profiles. *Nature* 2012, 492, 215–220. [CrossRef] [PubMed]

242. Sutherland, J.D.; Tu, N.P.; Nemcek, T.A.; Searle, P.A.; Hochlowski, J.E.; Djuric, S.W.; Pan, J.Y. An automated synthesis-purification-sample-management platform for the accelerated generation of pharmaceutical candidates. *J. Lab. Autom.* 2014, 19, 176–182. [CrossRef] [PubMed]

243. Genovino, J.; Masquelin, T.; Hemmerle, H. A remote-controlled adaptive medchem lab: An innovative approach to enable drug discovery in the 21st century. *Drug Discov. Today* 2013, 18, 795–802. [CrossRef] [PubMed]

244. Nicolaou, C.A.; Watson, I.A.; Hu, H.; Wang, J. The proximal lilly collection: Mapping, exploring and exploiting feasible chemical space. *J. Chem. Inf. Model.* 2016, 56, 1253–1266. [CrossRef] [PubMed]

245. Li, J.; Ballmer, S.G.; Gillis, E.P.; Fujii, S.; Schmidt, M.J.; Palazzolo, A.M.; Lehmann, J.W.; Morehouse, G.F.; Burke, M.D. Synthesis of many different types of organic small molecules using one automated process. *Science* 2015, 347, 1221–1226. [CrossRef] [PubMed]

246. Stalder, R.; Roth, G.P. Preparative microfluidic electrosynthesis of drug metabolites. *ACS Med. Chem. Lett.* 2013, 4, 1119–1123. [CrossRef] [PubMed]

247. Genovino, J.; Sames, D.; Hamann, L.G.; Toure, B.B. Accessing drug metabolites via transition-metal catalyzed c-h oxidation: The liver as synthetic inspiration. *Angew. Chem. Int. Ed. Engl.* 2016, 55, 14218–14238. [CrossRef] [PubMed]

248. LaPorte, T.L.; Wang, C. Continuous processes for the production of pharmaceutical intermediates and active pharmaceutical ingredients. *Curr. Opin. Drug Discov. Dev.* 2007, 10, 738–745.

249. Chin, P.; Barney, W.S.; Pindzola, B.A. Microstructured reactors as tools for the intensification of pharmaceutical reactions and processes. *Curr. Opin. Drug Discov. Dev.* 2009, 12, 848–861.

250. Saaby, S.; Knudsen, K.R.; Ladaylow, M.; Ley, S.V. The use of a continuous flow-reactor employing a mixed hydrogen-liquid flow stream for the efficient reduction of imines to amines. *Chem. Commun.* 2005, 2909–2911. [CrossRef] [PubMed]

251. Brzozowski, M.; O’Brien, M.; Ley, S.V.; Polyzos, A. Flow chemistry: Intelligent processing of gas-liquid transformations using a tube-in-tube reactor. *Acc. Chem. Res.* 2015, 48, 349–362. [CrossRef] [PubMed]

252. Loskill, P.; Sezhan, T.; Tharp, K.M.; Lee-Montiel, F.T.; Jeeawoody, S.; Reese, W.M.; Zushin, P.H.; Stahl, A.; Healy, K.E. Wat-on-a-chip: A physiologically relevant microfluidic system incorporating white adipose tissue. *Lab Chip* 2017, 17, 1645–1654. [CrossRef] [PubMed]

253. Eyer, K.; Stratz, S.; Kuhn, P.; Kuster, S.K.; Dittrich, P.S. Implementing enzyme-linked immunosorbent assays on a microfluidic chip to quantify intracellular molecules in single cells. *Anal. Chem.* 2013, 85, 3280–3287. [CrossRef] [PubMed]

254. Ferrari, M. Frontiers in cancer nanomedicine: Directing mass transport through biological barriers. *Trends Biotechnol.* 2010, 28, 181–188. [CrossRef] [PubMed]

255. Zhang, Y.S.; Zhang, Y.N.; Zhang, W. Cancer-on-a-chip systems at the frontier of nanomedicine. *Drug Discov. Today* 2017, 22, 1392–1399. [CrossRef] [PubMed]

256. Galler, K.; Brautigam, K.; Grosse, C.; Popp, J.; Neugebauer, U. Making a big thing of a small cell–recent advances in single cell analysis. *Analyst* 2014, 139, 1237–1273. [CrossRef] [PubMed]

257. Kayala, M.A.; Azencott, C.A.; Chen, J.H.; Baldi, P. Learning to predict chemical reactions. *J. Chem. Inf. Model.* 2011, 51, 2209–2222. [CrossRef] [PubMed]
281. Reker, D.; Rodrigues, T.; Schneider, P.; Schneider, G. Identifying the macromolecular targets of de novo-designed chemical entities through self-organizing map consensus. *Proc. Natl. Acad. Sci. USA* 2014, 111, 4067–4072. [CrossRef] [PubMed]

282. Schneider, G.; Reker, D.; Rodrigues, T.; Schneider, P. Coping with polypharmacology by computational medicinal chemistry. *Chimia* 2014, 68, 648–653. [CrossRef] [PubMed]

283. Sliwoski, G.; Kothiwale, S.; Meiler, J.; Lowe, E.W. Computational methods in drug discovery. *Pharmacol. Rev.* 2014, 66, 334–395. [CrossRef] [PubMed]

284. DiMasi, J.A.; Feldman, L.; Seckler, A.; Wilson, A. Trends in risks associated with new drug development: Success rates for investigational drugs. *Clin. Pharmacol. Ther.* 2010, 87, 272–277. [CrossRef] [PubMed]

285. DiMasi, J.A.; Reichert, J.M.; Feldman, L.; Malins, A. Clinical approval success rates for investigational cancer drugs. *Clin. Pharmacol. Ther.* 2013, 94, 329–335. [CrossRef] [PubMed]

286. Hay, M.; Thomas, D.W.; Craighead, J.L.; Economides, C.; Rosenthal, J. Clinical development success rates for investigational drugs. *Nat. Biotechnol.* 2014, 32, 40–51. [CrossRef] [PubMed]

287. Loong, H.H.; Siu, L.L. Selecting the best drugs for phase I clinical development and beyond. In *American Society of Clinical Oncology Educational Book*. American Society of Clinical Oncology: Meeting; American Society of Clinical Oncology: Alexandria, VA, USA, 2013; pp. 469–473.

288. Chavan, S.; Nicholls, I.A.; Karlsson, B.C.; Rosengren, A.M.; Ballabio, D.; Consonni, V.; Todeschini, R. Towards global QSAR model building for acute toxicity: Munro database case study. *Int. J. Mol. Sci.* 2014, 15, 18162–18174. [CrossRef] [PubMed]

289. Cherkasov, A.; Muratov, E.N.; Fourches, D.; Varnek, A.; Baskin, I.I.; Dearden, J.; Gramatica, P.; Martin, Y.C.; Todeschini, R.; et al. QSAR modeling: Where have you been? Where are you going to? *J. Med. Chem.* 2014, 57, 4977–5010. [CrossRef] [PubMed]

290. Devillers, J. Methods for building QSARs. *Methods Mol. Biol.* 2013, 930, 3–27. [PubMed]

291. Sullivan, K.M.; Manuppello, J.R.; Willett, C.E. Building on a solid foundation: SAR and QSAR as a fundamental strategy to reduce animal testing. *SAR QSAR Environ. Res.* 2014, 25, 357–365. [CrossRef]

292. Kirchmair, J.; Goller, A.H.; Lang, D.; Kunze, J.; Testa, B.; Wilson, I.D.; Glen, R.C.; Schneider, G. Predicting drug metabolism: Experiment and/or computation? *Nat. Rev. Drug Discov.* 2015, 14, 387–404. [CrossRef] [PubMed]

293. Mukherjee, G.; Lal Gupta, P.; Jayaram, B. Predicting the binding modes and sites of metabolism of xenobiotics. *Mol. BioSyst.* 2015, 11, 1914–1924. [CrossRef] [PubMed]

294. Xiao, X.; Min, J.L.; Lin, W.Z.; Liu, Z.; Cheng, X.; Chou, K.C. Idrug-target: Predicting the interactions between drug compounds and target proteins in cellular networking via benchmark dataset optimization approach. *J. Biomol. Struct. Dyn.* 2015, 33, 2221–2233. [CrossRef] [PubMed]

295. Zhang, W.; Liu, F.; Luo, L.; Zhang, J. Predicting drug side effects by multi-label learning and ensemble learning. *BMC Bioinform.* 2015, 16, 365. [CrossRef] [PubMed]

296. Bastian, L.; Hof, J.; Pfau, M.; Fichtner, I.; Eckert, C.; Henze, G.; Prada, J.; von Stackelberg, A.; Seeger, K.; Shalapour, S. Synergistic activity of bortezomib and hdaci in preclinical models of b-cell precursor acute lymphoblastic leukemia via modulation of p53, pi3k/akt, and nf-kappab. *Clin. Cancer Res.* 2013, 19, 1445–1457. [CrossRef] [PubMed]

297. Stanciu-Herrera, C.; Morgan, C.; Herrera, L. Anti-cd19 and anti-cd22 monoclonal antibodies increase the effectiveness of chemotherapy in pre-b acute lymphoblastic leukemia cell lines. *Leukemia Res.* 2008, 32, 625–632. [CrossRef] [PubMed]

298. Dzobo, K.; Senthebane, D.A.; Rowe, A.; Thomford, N.E.; Mwapagha, L.M.; Al-Awwad, N.; Dandara, C.; Parker, M.I. Cancer stem cell hypothesis for therapeutic innovation in clinical oncology? Taking the root out, not chopping the leaf. *Omics* 2016, 20, 681–691. [CrossRef] [PubMed]

299. Dzobo, K.; Senthebane, D.A.; Thomford, N.E.; Rowe, A.; Dandara, C.; Parker, M.I. Not everyone fits the mold: Intratumor and intertumor heterogeneity and innovative cancer drug design and development. *Omics* 2018, 22, 17–34. [CrossRef] [PubMed]

300. Baselga, J.; Cortes, J.; Kim, S.B.; Im, S.A.; Hogg, R.; Im, Y.H.; Roman, L.; Pedrini, J.L.; Pienkowski, T.; Knott, A.; et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N. Engl. J. Med.* 2012, 366, 109–119. [CrossRef] [PubMed]
301. Kawajiri, H.; Takashima, T.; Kashiwagi, S.; Noda, S.; Onoda, N.; Hirakawa, K. Pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer. Expert Rev. Anticancer Ther. 2015, 15, 17–26. [CrossRef] [PubMed]

302. Swain, S.M.; Baselga, J.; Kim, S.B.; Ro, J.; Semiglazov, V.; Campone, M.; Ciruelos, E.; Ferrero, J.M.; Schneeweiss, A.; Heeson, S.; et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N. Engl. J. Med. 2015, 372, 724–734. [CrossRef] [PubMed]

303. Swain, S.M.; Baselga, J.; Miles, D.; Im, Y.H.; Quah, C.; Lee, L.F.; Cortes, J. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: Results from the randomized phase iii study cleopatra. Ann. Oncol. 2014, 25, 1116–1121. [CrossRef] [PubMed]

304. Swain, S.M.; Kim, S.B.; Cortes, J.; Ro, J.; Semiglazov, V.; Campone, M.; Ciruelos, E.; Ferrero, J.M.; Schneeweiss, A.; Knott, A.; et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (cleopatra study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013, 14, 461–471. [CrossRef]

305. National Academy of Sciences (US). The national academies collection: Reports funded by national institutes of health. In Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease; National Academies Press (US), National Academy of Sciences: Washington, DC, USA, 2011.

306. Debouck, C. Integrating genomics across drug discovery and development. Toxicol. Lett. 2009, 186, 9–12. [CrossRef] [PubMed]

307. Debouck, C.; Metcalf, B. The impact of genomics on drug discovery. Ann. Rev. Pharmacol. Toxicol. 2000, 40, 193–207. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).