STRATEGIES IN DRUG DISCOVERY

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ABSTRACT

When there are diseases or conditions without appropriate remedial product, a drug discovery is desired. Current research involves various approaches in drug discovery strategies: Economy based, source based, traditional medicine, target based, disease based, data based, network based, technique based and me-too strategy. Economy-based approach is initiated and planned according to disease distribution and treatment requirement. Source based approach includes natural, recombinant and synthetic sources. Traditional medicine comes from traditional research and people experience. Target based is the approach in which a modulation of nominated biochemical process is theorized to be potentially useful in treatment of a particular clinical condition. In disease based strategy, researchers use statistical information about diseases distribution to select an applicable goal for their studies. Data based strategy links databases for chemical structures, ligands, organization of data, and structure activity data based on literature. Network based approach helps researchers to develop drugs for changing the cellular network or resolving malfunction in cellular network. In some countries because of equipment deficiency, the scientists endeavor to focus the research on some of the instrument related experiments due to the imposed deficiency. A drug that is structurally very similar to already known drugs, with only minor differences, is called me-too drug. The approach discovered me-too drugs, is me-too drug strategy. This paper evaluates the main drug discovery approaches.

KEY WORDS: Drug discovery, Drug design, Strategies.

INTRODUCTION

Because of a disease or medical condition without appropriate and available medical supply, a drug discovery program commences. This unmet clinical need is the underlying cause of motivation for the project. The research, as in academia, generates information to develop a premise that the alteration of a protein inhibition or activation pathway may result in a therapeutic effect in a disease state. The result of this activity is the choice of a goal and usually is followed by further justification former to develop into the lead discovery phase which would validate a drug discovery endeavor (Fig. 1). During lead discovery, a search can cause finding a drug-like small molecule or biological therapeutic, which is commonly named a candidate. The candidate molecule will progress to preclinical level, and if ending well, to clinical level and finally appear in the marketed as a medicine.

Previously, trial and error approach was an approach to find new drugs. Potentially, if whatever supposed to have a medicinal value in a particular disease, its efficacy could be tested on patients (Hughes *et al*., 2011). In this study a brief review of the types and difference of drug discovery strategies is provided.
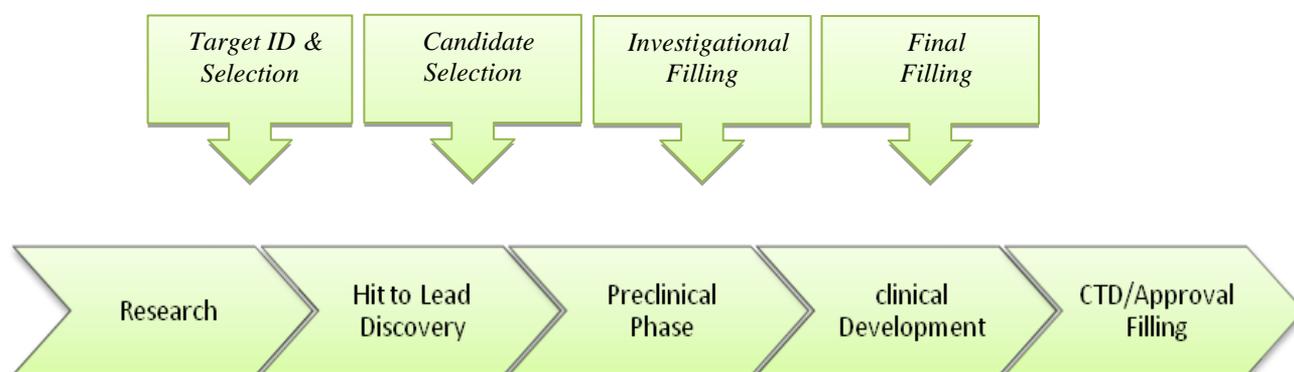

Fig. 1. The approximate timescale for drug discovery development from target and validation to CTD and approval filling of a compound. FDA, Food and Drug Administration; IND, Investigational New Drug; NDA, New Drug Application.

1. Economy based: Scientists in all over the world, try to find drugs with good marketing potential. Therefore, they choose diseases which draws patient attention. According to statistical information about disease broadcast and their treatment request, scientists select dugs with well future prediction. For example, Agency for Healthcare Research and Quality (AHRQ) reported top therapeutic classes by total purchases in 2013and the Top Prescribed Drugs by Total Expenditures in 2013 in below tables (Anon., 2013a, b).

By citing the information, like above data, make good decision criteria for there searchers and companies to initiate or plan a study. For instance in Table 1 cardiovascular diseases are in the first ranking thus it can be a good choice. In Table 2 adalimumab had most purchases between drugs thus it can be a good selection too. This strategy to choose a drug or disease for research is called economy based (Anon., 2013b).

2. Source based: Among the drugs from natural sources have been many of alkaloids, glycosides, vitamins, hormones and antibiotics. Many of drugs from natural sources may be prepared synthetically. Examples of the latter include several vitamins and hormones. Whereas others like alkaloids morphines, reserpine and quinine, cardiac glycosides, most of antibiotics, and hormones ones like insulin, in many countries, continue to be obtained more economically direct from natural sources. Many drugs also are prepared by semi-synthetic means as semi-synthetic penicillins (Singh, 2002).

Table 1. Top therapeutic classes by total purchases, (Anon., 2013a).

Total purchase ranking	Therapeutic class	Total purchases	Total number of persons with purchase
1	Cardiovascular Agents	713,733,758	70,167,729
2	Central Nervous System Agents	613,475,569	85,639,504
3	Metabolic Agents	511,451,988	55,674,450
4	Hormones/Hormone Modifiers	243,720,246	46,744,669
5	Psychotherapeutic Agents	240,027,988	32,115,881
6	Respiratory Agents	186,089,210	36,758,166
7	Gastrointestinal Agents	171,261,059	31,813,213
8	Anti-Infective	153,985,554	74,668,023
9	Topical Agents	142,099,960	45,039,364
10	Nutritional Products	107,530,332	21,327,289

Table 2. Top prescribed drugs by total expenditures, (Anon., 2013b).

Total expenditures ranking	Prescribed drug (generic name)	Trade name(s) sold under	Total expenditures	Total number of persons with expenditures
1	Adalimumab	Humira	9, 557, 761, 504*	##
2	Fluticasone-Salmeterol	Advair	6, 866, 584, 951	3, 871, 807
3	Rosuvastatin	Crestor	6, 670, 796, 641	4, 397, 156
4	Insulin Glargine	Lantus, Toujeo	6, 100, 490, 080	3, 099, 784
5	Esomeprazole	Nexium	6, 015, 865, 533	3, 420, 016
6	Aripiprazole	Abilify	5, 755, 711, 559	993, 185
7	Duloxetine	Cymbalta, Irenka	5, 520, 899, 163	2, 713, 243
8	Atorvastatin	Lipitor	4, 644, 575, 604	13, 077, 835
9	Tiotropium	Spiriva	4, 434, 165, 082	2, 042, 727
10	Insulin Isophane (Nph)	Humulin N, Novolin N	3, 731, 168, 776	3, 806, 497
11	Etanercept	Enbrel	3, 612, 147, 381*	##
12	Clopidogrel	Plavix	3, 317, 346, 070	4, 332, 687
13	Omeprazole	Prilosec	3, 098, 606, 800	13, 175, 164
14	Simvastatin	Zocor	3, 003, 263, 500	16, 543, 080
15	Sitagliptin	Januvia	2, 939, 842, 846	1, 446, 355
16	Quetiapine	Seroquel	2, 911, 057, 895	1, 307, 036
17	Budesonide-Formoterol	Symbicort	2, 780, 413, 690	1, 855, 563
18	Gabapentin	Fanatrex, Gralise, Horizant, Neurontin	2, 658, 071, 478	6, 966, 595
19	Pregabalin	Lyrica	2, 641, 188, 522	1, 513, 081
20	Valsartan	Diovan	2, 579, 964, 873	1, 891, 768
21	Bupropion	Aplenzin, Budeprion, Buproban, Forfivo, Wellbutrin, Zyban	2, 391, 146, 133	4, 283, 550
22	Albuterol	Accuneb, Proair, Proventil, Ventolin, Vospire	2, 328, 406, 320	14, 674, 248
23	Metformin	Fortamet, Glucophage, Glumetza, Riomet	2, 238, 570, 072	13, 588, 848
24	Ezetimibe	Zetia	2, 182, 595, 721	1, 575, 646
25	Oxycodone	Oxecta, Oxyado, Oxycontin, Roxicodone	2, 156, 869, 296	4, 254, 843

Less than 100 sample persons.
* Relative standard error equal to or greater than 30%.

2.1. Natural based: From thousands years ago plants have been used as remedies (Samuelsson, 2004). Primarily, various form of raw drugs such as tinctures, teas, aqueous extracts, powders, and other herbal formulations were taken as treatment (Balick and Cox, 1996).The application methods for special diseases and the particular type of plant used in each case were passed through word of mouth, during mankind history. Ultimately, data about remedial plants were recorded in herbals. In recent studies, the medicinal plants have involved the separation and detection of active compounds, start with morphine which was isolated from opium in 19th (Samuelsson, 2004; Kinghorn, 2001). The isolation of early drugs such as cocaine, codeine, digitoxin, and quinine are based on the medicinal plants approach in drug discovery. Some of these drugs, in addition to morphine, are still used (Butler, 2004; Newman et al., 2000). Isolation of bioactive compounds from plants continues to be performed in the modern health care system. Drug development techniques have been applied to the herbal medicines standardization, elucidate analytical marker substances. Anticancer and chemopreventive drug discovery using medicinal plants, and finally natural based drug discovery has progressed to include a lot of inquiry fields and various analysis methods. The drug discovery process commonly starts with someone who gathered and identifies the plant(s) of interest such as a botanist, ethnobotanist, ethnopharmacologist, or plant ecologist. Collection maycontaintaxa with different aspects such as antibacterial activity for which compound(s) have not been elicited (e.g., traditionally used medicinal plants) or may be randomly collected for screening program. The intellectual property rights of a given country where plant(s) are gathered, should be regarded (Baker et al., 1995). Plant extracts are provided by Phytochemists, biological screening are carried out for these extracts by pharmacological assays, and then the active compound(s) are isolated and characterized with bioassay-guided fractionation. In addition, molecular biology has been necessary to natural based drug discovery through the designation and implementation of suitable screening tests achieved physiological molecular targets. All of these fields are in Pharmacognosy acknowledgment.

Since about 200 years ago, the pharmacognosy have been theoretically and practically evolving (Samuelsson, 2004; Kinghorn, 2001) as drug use from remedial plants has improved from the unfeasible drugs formulation to the isolation of active compounds in drug development. The American Society of Pharmacognosy mentions to pharmacognosy as ''the study of the physical, chemical, biochemical and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources''. As practiced today, the wide study of natural products from various sources containing plants, bacteria, fungi, and marine organisms are accomplished by pharmacognosy scientists. Pharmacognosy involves the study of herbal and botanical remedies, with a modern perspective in mind, which includes the search for single compound leads that may be continued through further development into Food and Drug Administration (FDA)-approved medicines (Cardellina, 2002; Tyler, 1999). Swedish scientists have recommended a revised explanation for pharmacognosy because of these types of activities, namely as ''a molecular science that explores naturally occurring structure–activity relationships with a drug potential''(Bruhn and Bohlin, 1997). Plentiful methods have been used to detect compounds for drug discovery consist of isolation from natural sources such as plants, synthetic chemistry, combinatory of synthetic chemistry and natural sources, and molecular modeling (Geysen et al., 2003; Ley and Baxendale, 2002; Lombardino and Lowe, 2004). Despite pharmaceutical companies recently has an interest in molecular modeling, semi-synthetic, and other synthetic chemistry techniques and investing organizations, natural products, exclusively medicinal plants, stay a necessary source of new drugs, new drug leads, and new chemical entities (NCEs) (Butler, 2004; Newman et al., 2000; 2003). Natural products or natural product derivates were almost one quarter of the best marketing drugs in all over the world, in both 2001 and 2002 (Butler, 2004).

Recombinant: Nowadays, about one-third of drugs in development are biopharmaceuticals which refer to "derived from biological sources". These drugs generate with biotechnology methods particularly genetic engineering or hybridoma technology or via biopharmaceutical techniques such as recombinant human technology, gene transfer and antibody production methods. Nearly all bio-therapeutic agents in medical usage are biopharmaceuticals. Otherwise, any medically utilizable drug whose manufacture consists of microorganisms or genetically modified organism (GMO) or compounds that are produced by living organisms (e.g. proteins), or bioprocessing is labeled a biopharmaceutical (Rader, 2007; 2008). Biopharmaceutical drugs generally are huge, complicated protein molecules taken from alive cells. However, there is no accurate scientific description of a biopharmaceutical. Manufacturing of biopharmaceutical proteins including antibodies has been prevalent. Mammalian cells, yeast, insect cells and bacteria are the available production systems nowadays. For example, the production processes of large molecules used as vaccine against viral infection are given in Fig. 2. The production systems selection depends on the nature of the protein being produced.

Biopharmaceuticals are produced as the outcome of utilizing genetic information of the living organisms and the science deals with it has already been developed into an independent discipline. The biopharmaceutical manufacturing is in development way and is impressively shifting the drugs production process from the use of chemical synthesis (traditional pharmaceuticals) to bio-manufacturing (biologics) (Rathore and Winkle, 2009). The aims of development of a biopharmaceutical include clinical efficiency, approval by regulatory authorities and commercial viability.

Production of new drugs and vaccines progression via biopharmaceutical research requires focused efforts on several stages, as well as multiple talents and expertise.

In the last years, several technologies such as production of monoclonal antibodies in protein free media; designing chemically defined cells, genome based technologies, refining vaccine industrial processes, a potential cancer treatment and non-ribosomal peptide synthesis (Dutton and Scharer, 2007) are progressed similar function to unit operations for manufacturing advanced biopharmaceuticals (Locatelli and Roger, 2006). The biopharmaceutical manufacturing is the most essential part in industrial biotechnology, and is one of the most fast developing high-tech industries (Rader, 2007; Lowe and Jones, 2007).
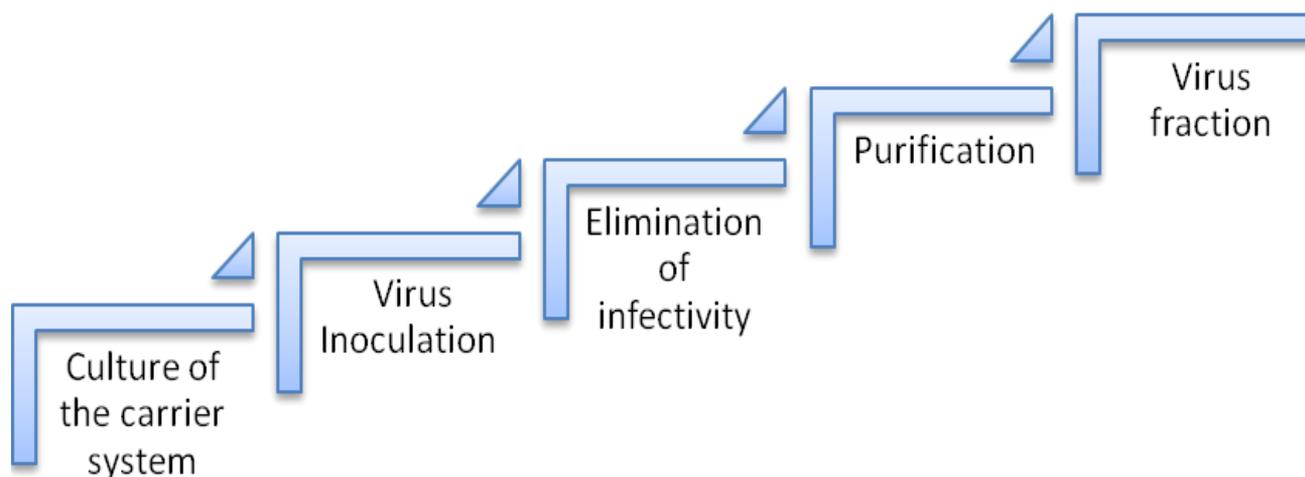
Fig. 2. Vaccine against viral infection (Lowe and Jones, 2007).

2.2. Synthetic: Synthetic drugs are made chemically to produce molecules that are not found in nature, present in minute amounts in nature or to try making other derivate of the molecule. Twenty five percent of synthetic drugs used in the U.S. are derived from plants (i.e., opiates, digitalis, taxol). First the active compounds are isolated from a plant, then the molecule synthesized in the lab and mass-produced in industry.

Whether artificial or natural, the most required criteria for usage of a medicine are proof of concept, e.g., effectiveness. Further, approved identity, purity, potency, safety, quality, stability are among the basic criteria monitoring factors.In 1994, a law due to cut costs for the corporate dietary supplement industry was passed. According to this law, herbal drugs are not required to demonstrate strict presence of the above criteria (Singh, 2002).

Comparison of these three source based strategy:
- In terms of diversity, synthetic drugs are more diverse than other ones
- From the aspect of selectivity, recombinant drugs are more selective than others
- In terms of potency, synthetic drugs are more than natural drugs and natural drugs are much more than recombinant

3. Traditional medicine: Medicinal Plants are an essential source to public health care system in the traditional societies. About 70–80% of the rural populations in Asian nations, for primary health care, depend on traditional medicine, today (Pei, 1998) even though allopathic medicine might be accessible in these societies. In rural areas, food, health care and wood-derived energy are the basic desires, but any alternative choices to ensure the survival of these traditional medicines do not exist in rural societies, and an essential source of income in these societies is also medicinal plants. The economic development of rural communities are contributed by their sale and barter and it helps modern industrial growth (Pei, 1998). These plants have a main role in the region biodiversity and have substantial protection value for global biodiversity.

Ethnobotanists as branch of scientist has been widely tried to record the native knowledge on the use of plants and to makethe inventory of useful plants from local flora in various countries. Also, ethnopharmacology is defined as, "a research field to study the usage of medicinal plants by native cultures and to accredit scientifically their effects and adverse effects" (Farnsworth, 1993). Since they are culturally allow developing nations to enhance health, ethnopharmacological techniques can be suggested for use in such countries (Farnsworth, 1993).

4. Target based: The strategy in modulation of a biochemical mechanism which is hypothesized potentially useful to treat a specific disease is called target-based or hypothesis-based strategy. The biochemical factor (enzyme, receptor, channel, etc.) may then be used directly in lead discovery using a screening approach or rational design. Active molecules that may be chosen as 'leads' for optimization are compounds that adjust the selected biochemical mechanism (Brown, 2007).

A single gene, gene yield or molecular mechanism that has been known on the basis of genetic study or biological observations can be a target (Brown and Superti-Furga, 2003; Erickson, 2003; Kerns and Di, 2003; Knowles and Gromo, 2003; Lindsay, 2003). The literature does not classify target based approach in various classes, but in current studies, they are generally categorized into two classes: genetic or mechanistic targets. Genes or gene products that have mutations (e.g. the familial forms of Alzheimer's disease) in a particular disease or that are participate in a higher disease risk (e.g. predisposing the individual for developing schizophrenia or depression) are used in genetic target strategy. By contrast, receptors, genes, enzymes, and so on that typically do not genetically differ from the normal population are used in mechanistic target strategy (Sams-Dodd, 2005).

5. Disease based: Researchers use statistical information to select an applicable goal for their studies. In disease-based strategy, scientists use statistical data about disease distribution and drugs market. The ranking of statistical organizations helps researchers to choose the disease with more demands in all over the world or a particular region. This strategy helps to choose a good topic with a good future in marketing and demands.

For instance, according to WHO statistical information, the top 10 diseases which is caused death in the world, were ranked in 2000 and 2012 (Anon., 2012).The highest incidence of mortality rate during 2000 to 2012 are attributed to cardiovascular conditions (ischemic heart disease), stroke, pulmonary conditions (lower respiratory infections and chronic obstructive lung disease). HIV deaths in 2012 became less than 2000. This can be a basis for drug discovery program planning in the academia or pharmaceutical industry.

The number of deaths increases because of chronic diseases worldwide. 2.9% mortality in 2012, up from 2.2% mortality in 2000 are caused by lung cancers (trachea and bronchus cancers). Likewise, 2.7% mortality in 2012, up from 2.0% mortality in 2000 are caused by diabetes (Anon., 2012).

For example in 2012, heart disease had the most number of mortality and increased in comparison with 10 years before (Ghosh *et al*., 2006). Therefore, study on heart disease in drug development could be more beneficial.

6. Data based: Data based strategy links databases for chemical structures, ligands, organization of data, and structure activity data based on literature or screens out comes to provide access to wide reference sets of ligands related to a general target family.

One of the popular approaches to be utilized in lead accommodation step is structure based virtual screening (Fig. 3). It is realized as a complementary strategy to investigational high throughput screening (HTS) to enhance the rapidity and effectiveness of the drug discovery and development process (Ghosh *et al*., 2006). This includes obvious molecular docking, to forecast binding site between each ligand and target and the mode of each binding, to evaluate binding affinity. The screened compounds from the databases are categorized according to pick out and experimentally assay a small subset for biological activity considered to be suitable for a do nor receptor (Kroemer, 2007; Lyne, 2002; Shoichet, 2004). Several successful applications have been declared according to virtual screening in the field of molecular docking (Finn, 2012; Jenwitheesuk and Samudrala, 2005; Kuck *et al*., 2010; Pierri *et al*., 2010; Taylor *et al*., 2002; Wang *et al*., 2012; Waszkowycz, 2002). While the energy evaluations involved are crude, the library compounds are accessible, making experimental testing affordable and in case of the false positives during the docking process can be assessed by experimental means (Shoichet, 2004).
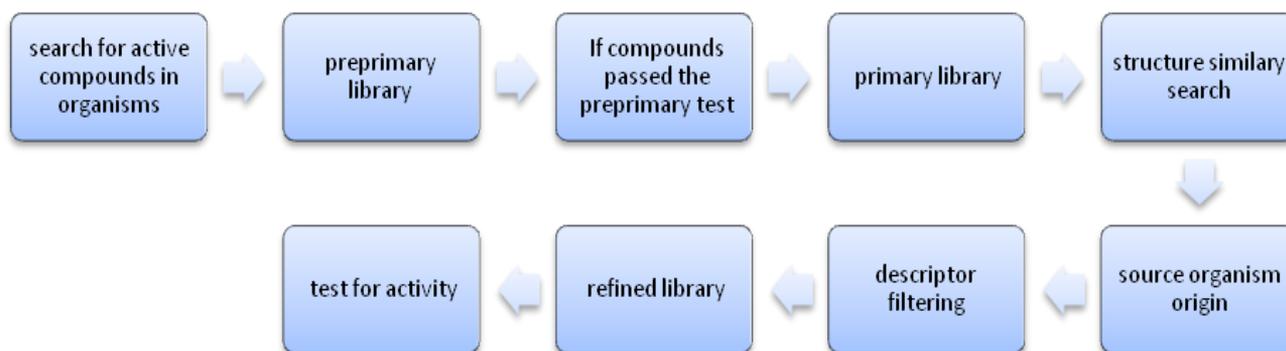

Fig. 3. Virtual screening process (Saadat *et al*., 2013).

In the lack of the receptor 3D data, ligand-based drug design is utilized and this strategy depends on information about molecular binding with the biological target of interest. In ligand based strategy, the most essential and widely used tools are 3D quantitative structure activity relationships (3D QSAR) and pharmacophore modeling. They can predict appropriate models for lead identification, isolation and optimization (Acharya *et al*., 2011).

7. Network based: The cellular network and its environment manage the cell and organism behavior and is essential to the comprehension of function, malfunction and drug discovery. Early drug discovery searched "magic bullets"; i.e., maximally selective molecules for specific targets related to particular diseases. For example, below picture, from KEGG database, shows a part of the biosynthesis net work of the secondary metabolites (Figs. 4 and 5). In case of improper implementation of one or more components of this network, the pathway could not work well. Thus scientists try to change one or more elements in the particular pathway with several methods (Kanehisa, 2016).

8. Technique based: Many modern scientists may not have enough instruments for design and examining their inovations, therefore in some laboratories the scientists endeavor to implement some of the experiments due to drug development. This kind of drug discovery is almost only performed in the developing countries. For instance in one laboratory, NMR and chemical hood are available, thus scientist would use these instrument for drug development and they use the instrument to complete or modify other studies due to their available instruments and techniques, too.
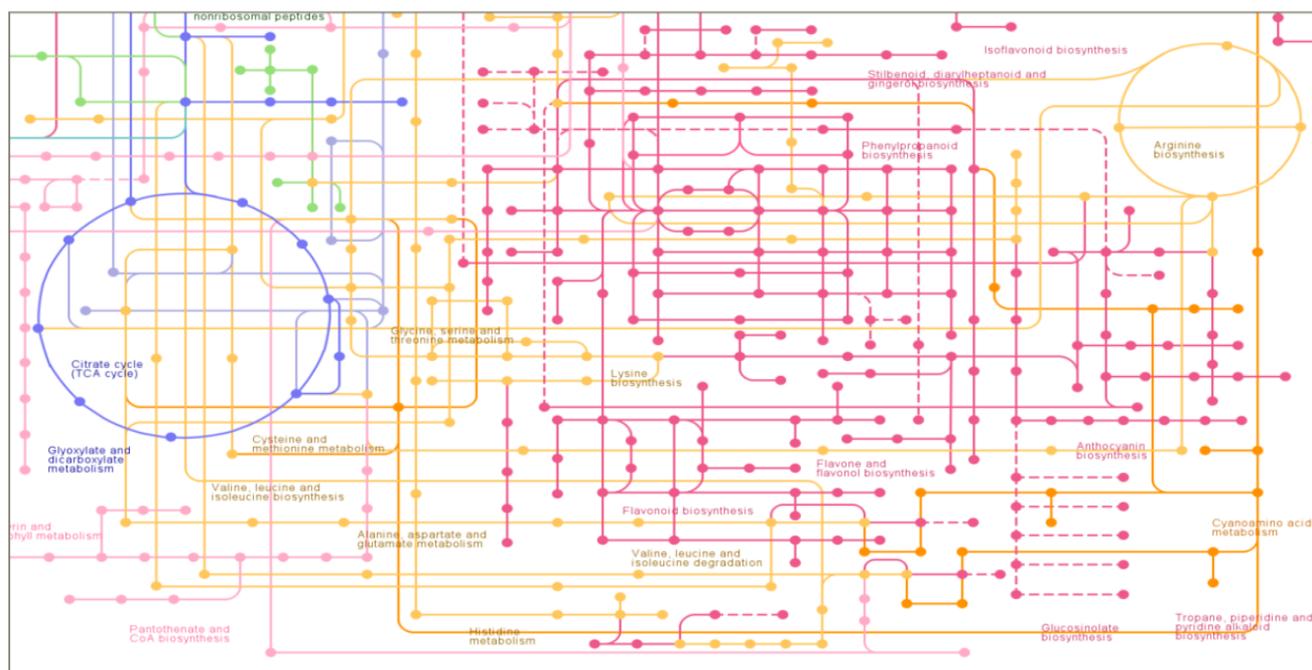
Fig. 4. A sample of network involved in the biosynthesis of secondary metabolites (Kanehisa, 2016).
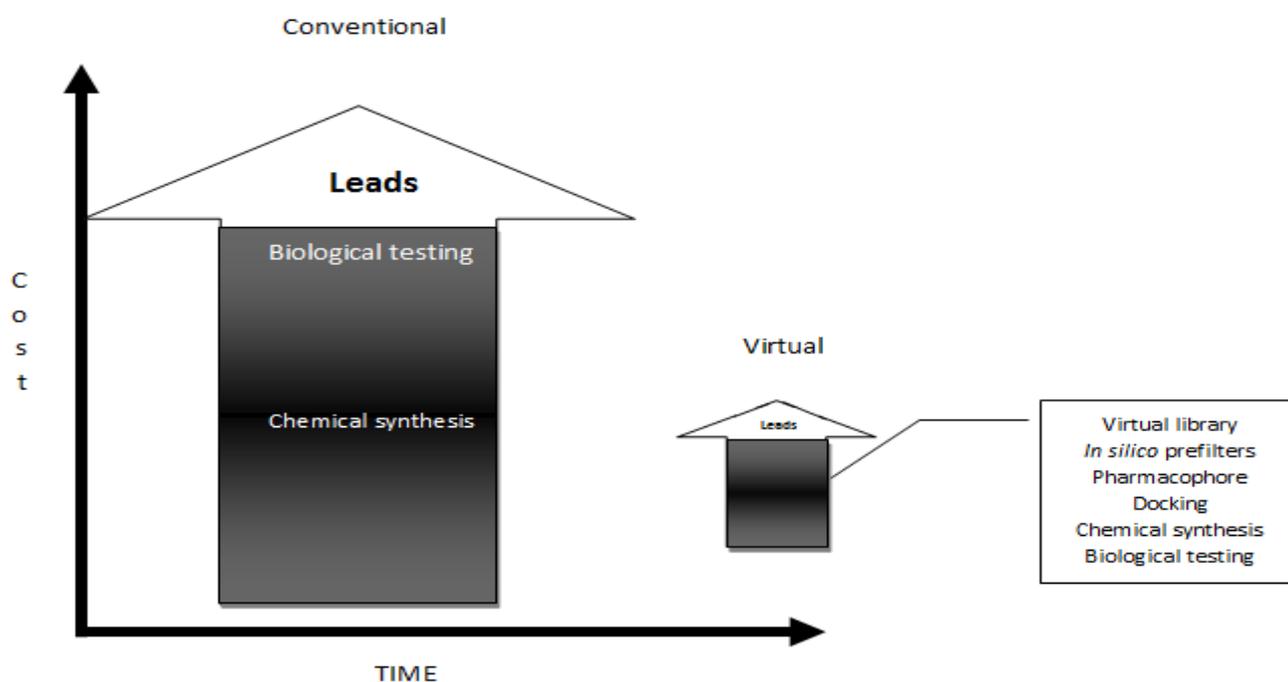

Fig. 5. The expected cost and time requirements as compared between conventional and virtual screening (Kapetanovic, 2008).

9. Me- too strategy: In this strategy, the scientists try to improve or reproduce a drug which has already been discovered. For example, try to improve their absorbance and elimination with modifying structures with adding some functional groups or making new formulation of drugs like nanoliposomes. The products which largely increase existing drugs action are called me-too drugs. A lot of recent books (such as Angell (2004), Avorn (2004) and Goozner (2004) have heaped criticism on the drug industry for the increased amount of investment that is focused on new drugs which have the same mechanism of action to pre-existing drugs. Other books, such as Calfee (2000) and DiMasi and Paquette (2004) have favored me-too drugs, because this strategy provides more therapeutic choices and improves competition in drug industry. DiMasi and Paquette have also reported that Regardless of imitation, in many cases because of parallel development, me-too drugs are approved after other drugs in its class.

Conclusion

A drug discovery program starts up because of diseases or clinical conditions without appropriate medical treatment. Discovery of a new drug from an early idea to product is a complicated process. Several approaches are utilized for drug

development. In this review, we tried to compile and explain different strategies in drug discovery: Economy based, source based, traditional medicine, target based, disease based, data based, net work based, technique based and me-too strategy. Economy based approach involves disease prevalence and therapeutic needs. Source based is divided to three sections according to the origin of molecules: natural, recombinant and synthetic sources. Traditional medicine comes from experience of ordinary people, traditional approaches and books written by traditional practitioners. Another approach to drug discovery is target based. In this strategy, modulation of a specific molecular mechanism is studied for treatment of a particular disease by researchers. In other cases, scientists may use statistical data about diseases distribution to choose an applicable goal for their studies, this kind of approaches is called disease based strategy. Chemical substance structures, ligand formulas, classification systems, and structure activity relationship data are gathered from literature databases to select an appropriate aim in drug discovery studies; this kind of hypothesis selection is called data based strategy. Enhancing of cellular network or malfunction resolving the cellular network can be another idea. Researchers use this approach for drug development which is named Network based strategy. In some countries, the lack of instrumentations may cause the scientists to focus their studies on some aspects of the available equipment o the related experiments. A drug that is structurally very similar to the already known drugs, with only minor differences, is called me-too drug. The approach discovered me-too drugs, is me-too drug strategy. In this paper, the above-mentioned approaches were discussed and exemplified in detail.

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