

Discover Natural Chemical Drugs in Modern Medicines

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Abstract

More recently, it has been gradually recognized that natural chemical drugs often exhibit higher therapeutic efficacy and lower toxicities than synthetic drugs in most disease managements and therapeutics. After this discovery, growing attentions have been focused on this type of drug development chain updating worldwide. Yet, these kinds of pharmacological efforts still like finding a needle from hay-stakes owing to drug screening system limitations globally. As a result, higher efficient drug screening routines must be established-including new generations of experimental models, quick plant chemical discovery processes structurally and extractive quality, revisit from ancient wisdoms, especially from traditional Chinese medicine. This article addresses this matter in detail and future perspectives.

Keywords: Natural plant; Phytochemistry; Traditional chinese medicine; Medicinal chemistry; Drug development; Anticancer drug; Viral treatment; Antineoplastic drug develop; Ebola; Avian flu; Zika; Cancer treatment

Backgrounds

Differences between synthetic drugs and natural chemical drugs, natural-borne drugs are of great medical significances-higher therapeutic index than synthetic chemical drugs. This character shows higher capability to overcome drug-resistance. For example, the most effective antibiotics (penicillin, streptomycin or cephalosporin) are natural chemical products. They are much better than a series of synthetic agents (sulphonamide) and so on. Yet, these kinds of pharmacological efforts still like finding a needle from hay-stakes owing to the complicated processes of diversity drug screening models. As a result, new initiatives must be established to overcome these kinds of drawbacks. This perspective addresses and systematically analyzes on this matter and highlights it with modern touches.

Historic Review

Traditional Chinese Medicine (TCM) as a major therapeutic option in China

China has a long history and reputations of treating a wide variety of diseases of both human origins and lethal pathogen from outside natural sources. These medical practices came back from 2000-5000 year ago. Several medical books of this kind were published afterwards. For example, cold symptoms of large human population in ancient times (similar to viral infections like seasonal flu, avian flu and Ebola infections) were treated by TCM over two thousand years [1], which probably makes China the most populated country in the world. It has been repeated for viral epidemic control and managements since the era of Zhong-Jin Zhang (AD150-219) in China [1-3]. According to norm or theory of TCM, virus-induced fever can be caused by patient's deficiency in "Yang" inner energy. TCM doctors try to combat these virus-induced patterns of symptoms (like fever, cough etc.) by strengthening, modulating and offsetting these damaged "Yang" in human bodies by formulated herbal medicines [2-3]. The formulated herbal medicines contain large component chemical admixtures and somewhat like modern drug combinations in western ways of therapeutics.

TCM routines for infected patients

Several formulated soups treat for cold symptoms (like viral acute infective stages) and high fever for almost every lethal virus infections by "Gui-Zhi Soup", "Ma-Huang Soup", "Da-Qing-Long Soup" and "Ge-Geng Soup" [1]. These cheap medical herbal formulations can be available all the times without any specific preparations and storages. Historically, this custom has been successively managing a great numbers of virus-infected endemics and save the life of millions over the long history of China (over 2,000 years). We suggest that this type of treatment should be considered in Ebola, HIV, avian flu, Zika epidemic control and eliminations [2-4].

Theoretically, viral disease treatments could be used against exogenous wind-heat symptoms by "Yin-Qiao-San" for viral-induced fever, diarrhea and others. In addition, TCM treats against exogenous wind-cold symptoms by "Jing-Fang-Bai-Du-San". The utilities of Ma-Xing-Shi-Gan-Tang were to remove toxic heat obstruction in the lungs of infected patients with 100% effectiveness in clinical occasions [4-11]. These items of treatment of herbal formula can also be used historically as the preventive measures attacked by lethal viruses in endangered areas similar to avian flu or Ebola epidemics nowadays. Generally speaking, the TCM treatments for every patient are better under the surveillance of an experience TCM doctor or by modern types of disease diagnostics. After this therapeutics, patient's conditions can be commonly improved in clinics.

Methodology

From TCM to drug developments

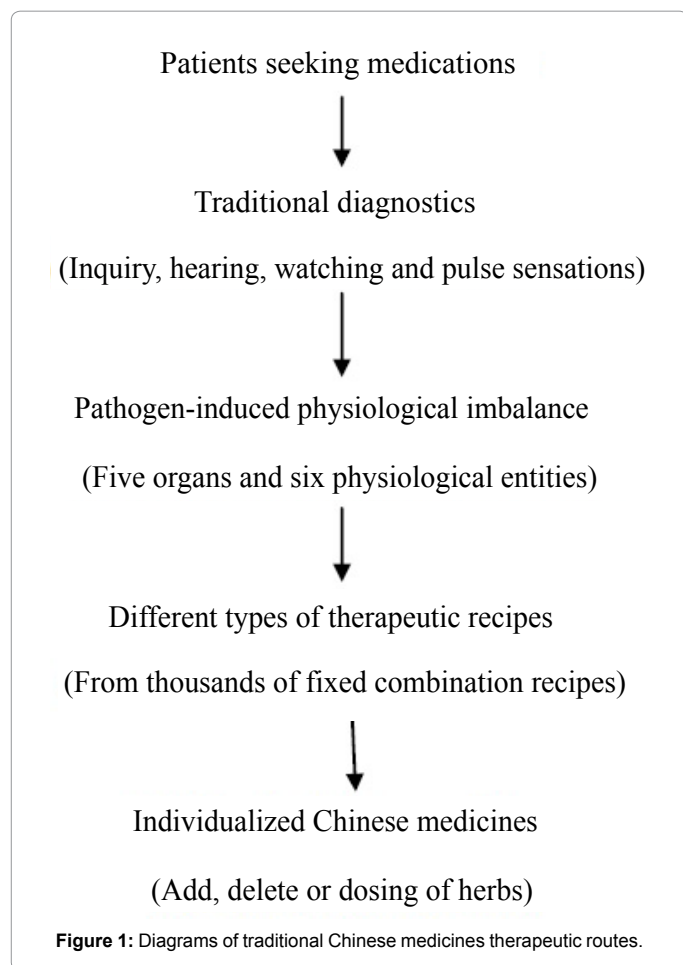
TCM treats patients according to their abnormal symptoms (Figure 1) [12]. Many pathogenic symptoms of serious diseases such as pulmonary obstructions, fever and so on can be remedied by different

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forms of herbal medicines. This property of medical practice calls for new drug developments. Although few chemical compounds have been systematically studied for Ebola, avian flu, Zika therapeutics in ancient TCM books, a great number of new chemical ingredients from microbial or plants in western countries have been available than synthetic chemical agents to treat modern diseases [5]. Previously, ingredients from microbial or plants in western society were very expensive. Now, these ingredients are much cheaper due to technical advancements [5].

Cost-effective considerations in clinical treatments and drug developments

Currently, different types of active drug developments are entering into bottleneck stages. Drug manufactory is a pillar industry for small number of world-leading countries, which is a highly competitive and risky job worldwide [13-16]. Nevertheless drug discovery, development and manufacture have been entering into bottleneck stages since two decade ago-productivity and successful rates of clinical drug evaluation was declining year-by-year [13]. As a consequence, greater amount of money must be paid for drug screening, mechanistic studies and clinical assessments. It therefore results in skyrocket economic burden for social and medical insurance. Despite greater fortune of each licensing (1-2 billion USD) in US and other developed countries [13-16], cancer therapies only improve slightly, especially for cancer metastasis treatments. Thus, it needs to streamline all processes from TCM to modern drug developments [13-16].

In herbal medicine treatments from Chinese side, most widely used herbs are cheaper and low toxicity. However, some rare Chinese herbs or animals, such as “Ginseng”, are very expensive. Some herbal drugs, such as “fuzi”, are very toxic and even lethal for overdosing. These drug utilities need to be carefully manufactured (detoxication processes) and prescribed by experienced doctors.

Results

Overall, TCM must be translated into modern drug developments and discoveries. In the past, a great amount of work for natural chemical drugs has been undergone. Generally, almost half chemical drugs are coming from natural microbial, plant and animals. Despite these successes, many obstacles still need to be overcome. Yet, currently no specific drug developmental system has been widely utilized.

Transient glory

TCM in the past is an underdog comparing with Western medicine. In the previous two centuries, TCM commonly shows negative impression among western countries. Yet, TCM never lost its territory in China no matter how strongly the western medicine has been developed. The hidden rules behind scenario are unclear. TCM has its own advantages and medical importance even though we do not fully understand yet. This article aims and focuses on this matter by given our own vision. We do not intend to promote them into the center stage of all medical arenas. We only wish that TCM can be an important science discipline, especially in natural chemical drug developments. Certainly, TCM is not always omnipotence. Their disadvantages are also multiples from western medical points of view.

In future, if we still maintain present course, no big breakthroughs will be made. As a result, a big promotion against lethal virus, such as avian flu or Ebola in China is necessary. Accordingly, new therapeutic paradigms and long-term Chinese medical policy countrywide can be established. Nobel laureate for physiology and medicine (You-Yu Tu, China) of 2015 is the best example of new paradigm from TCM. She and other young Chinese scientists discovered (Qing-Hao-Su or *artemisinin*) from a series of ancient Chinese medical literatures, such as *Compendium of Materia Medica* [11] and finally saved the lives of millions of Africa malaria people where the Ebola was originated at same locations nowadays. This may be not a coincidence. Potential relationships need to be found.

Drug developers in new era

Facing the situations of high risks, growing costs and low productivity in modern drug developments [13-16], future efforts for scientific or technologic updating are necessary such as options against Ebola-epidemics, Zika virus [10], mortalities and others.

The advantages of natural chemical drug therapies comparing with synthetic chemotherapeutic agents as usual are low toxicities and drug cocktail (mixture ingredients). Of course, the drug combinational rules widely used in TCM [16-17] may play pivotal roles for a variety of lethal virus infections and late-staged cancer managements, which desperately needs good paradigm propagations worldwide.

Natural chemical compound developments are smoothly progressing. Presently, many first-line drugs against common diseases, such as microbial-infections, malaria and cancer are more popular by natural chemical compounds. Marked advantages of disease managements have been achieved by natural chemotherapeutic agents, such as penicillin, *artemisinin*, *doxorubicin*, *camptothecin* and so on.

Discussion

Since virus-induced human mortalities are different (Ebola or avian flu for quick human mortality and HIV or Zika for slow pathogenesis and human mortality), drug discovery or developmental routines must be established in alternative ways. For Ebola or avian flu treatment, quick disease management or viral proliferative inhibition is key. Yet HIV or Zika infections, modulating damaged human organs or physiological entities (immune or cerebral) is more important.

The key of different chemotherapeutic agents is the balance between therapeutic responses and toxicities/risks, displaying as therapeutic index gain. Many currently incurable diseases, such as HIV-infections in human bodies [2] might come from shortage of natural chemotherapeutic drugs. The only limitation of natural chemotherapeutic agents was the expensive costs of drug purifications and natural product collections. However, with the modern purification technology advancements, natural chemical agents are much cheaper now [5]. Owing to this advancement, growing number of natural chemical drugs can be getting into the markets.

Literature and Educations

Herbal medicines were generated five thousand years ago. They are still very popular in China. Though a great number of first-line and second-line pure therapeutic chemical drugs such as *camptothecine*, *harringtonine* and so on were discovered from herbal resources by western scientists, some of them were long reported in TCM books and literatures. Medicinal chemists and pharmacologists worldwide are paying serious attentions on new agent discovery from surveying TCM books and literatures [5,18-20]. Although these literatures are valuable for modern medicine and drug developments, these TCM books and literatures are unpopular in normal medical universities, even in China. As graduates from Chinese leading medical universities, we only took parts 3 TCM courses. These TCM educational courses were very limited for high quality clinical practices and drug developments. As a result, these types medical educations and drug developments should be major topics in China.

Combinations of Western Medicine with TCM in Cancer Treatments

Cancer treatment by TCM is one of hotspots in modern China and even earns growing popularity worldwide. Many TCM hospitals in China have the special departments of cancer therapeutics. TCM for cancer treatments has been positively reported in China [19-25]. According to the very rules of TCM, human bodies are balanced by the fighting between inner upright strength and outside damaging air. Generally speaking, TCM therapies are mainly based on either strengthening inner upright air or expelling the outsider damaging air. In most cases of cancer treatments, seeking strengthening upright air therapy rather than expelling outside damaging air therapies is proved to be higher utilities and therapeutic outcome improvements. Most TCM doctors in China hold such a view in cancer assistant therapies now [18]. Additionally, expelling exogenous wind-heat recipes are also utilized for cancer therapies by TCM.

Apart from first-line anticancer drug developments, herbal or natural compounds can be used as assistant therapeutic agents to treat cancer growth, invasive and remote metastasis [19-25]. These sides of cancer therapies are of great medical significance but shortages in western medical backgrounds. In western countries, cancer assistant therapies are represented with nutrient, cardiovascular complication agents, antioxidants and so on [26]. Though promising, cancer assistant

therapies are not mainstreams of clinical cancer medical care in western countries. At this stage of medical knowledge, the central dogma of cancer assistant therapeutics is to combine cytotoxic anticancer drugs and assistant therapeutic agents (mostly natural chemical or biological compounds, such as heparin, warfarin and so on) [26]. Generally, drug combinations can be a good therapeutic paradigm for HIV and late-staged cancer patients (Table 1) [26-32].

Future Direction

The qualities of natural chemotherapeutic agent developments might be improved by deeper understanding of TCM theories and general treatment routines (ancient Chinese wisdoms). But it is easier said than done because of a great difference between western and eastern medical systems. The discoveries of natural chemotherapeutic agents look like to translate eastern therapeutic legend into western medical paradigms. Currently, most people in China believe that natural herbs have no toxicities at all. This is a misleading point of view. But many natural chemotherapeutic agents generally show much less toxicities than those of synthetic chemical agents at same therapeutic ranges. But we do not know why? Natural chemical drugs are somewhat like gifts from god and we shall pass these gifts down to our future generations.

Zika therapy by TCM or natural chemotherapeutic agents

Zika virus epidemic in America is an emerging medical crisis that is receiving growing bodies of world attentions [33]. Good Zika managements must be established as early as possible. Like aforementioned theory and paradigms, testing water of Zika therapy by TCM [10] or natural chemotherapeutic agents might be a good avenue owing to shortage of proper therapeutic options worldwide nowadays [10]. We herein suggest that TCM or natural chemical drug developments might be workable avenues for future scientific investigations on Zika pathogenesis [33] and therapeutics [10].

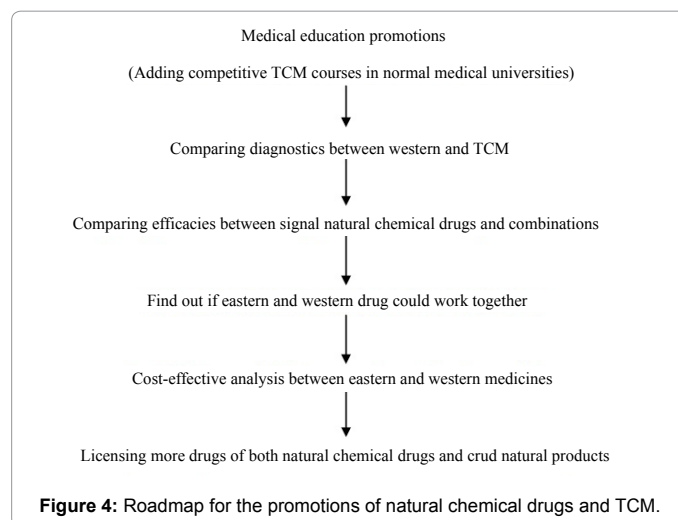
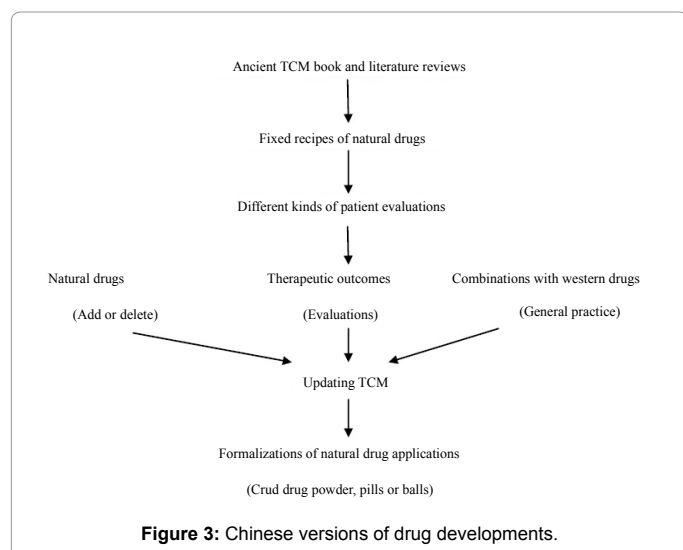
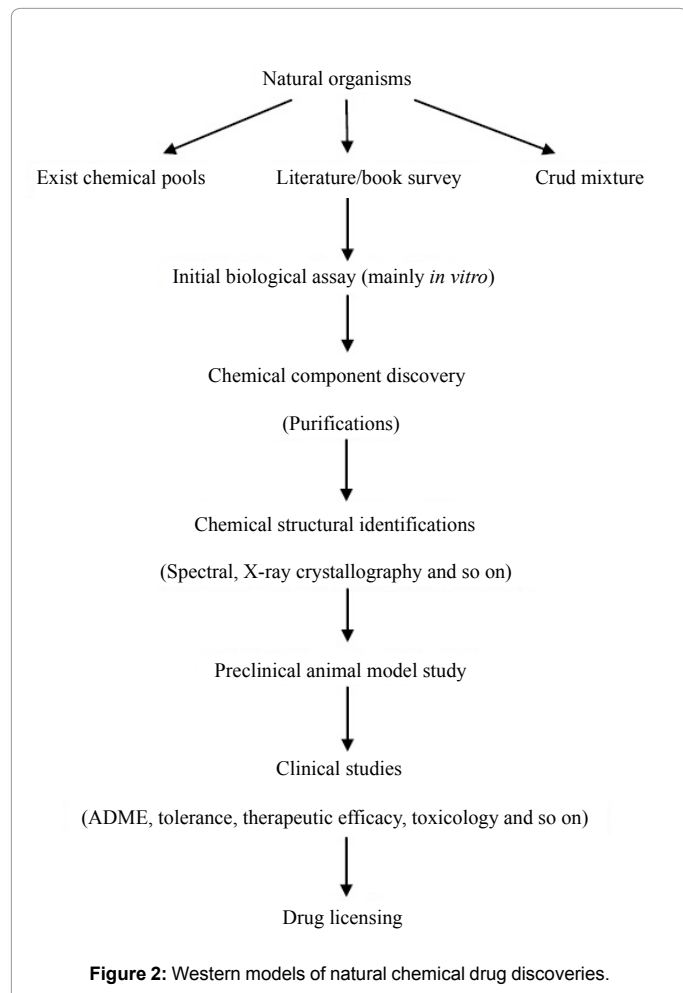
Joint-efforts among pharmaceutical companies of different countries

Although seas of literatures are addressing natural drug developments and clinical applications, few pharmaceutical companies pay serious attentions and show special interests for taking TCM as a foundation. The ideas for both world-leading pharmaceutical companies and traditional Chinese medical doctors are commonly single-minded and one-way ideology. They speak different styles of scientific languages and carry different patterns of research-print in natural chemical drug developments-see from Figures 2 and 3. The different ways of drug developments previously never converge (Figures 1 and 2). As a result, in our impressions, these types of drug developments and clinical therapeutics are not in high-quality. The only way for high-qualified investigations is to integrate experts and specialists of multi-disciplinary (Figure 4). Like the discovery of *artemisinin* (2015 Nobel physiology and medicine laureate work), it is an amalgamation

Categories	Western therapy	Chinese therapy
Diagnostics	Instruments	Inquiry, hearing, watching and pulsing
Drug numbers	1-3 drugs commonly	3-8 herbs
Suitability	Acute disease	Chronic disease processes
Toxicity	Various	Only some toxic drugs
ADME (such as P450)	Commonly available	Difficult to undergo
Relative costs	High (especially new drugs)	Generally low

Table 1: A comparison between western therapy and TCM.

of approximately 600 excellent young Chinese scientists or experts of that times-including medicinal chemists, pharmacologists, chemical analysts, traditional Chinese medicine graduates, conventional doctors and so on. Although it was the hardest time of People's Republic China (1970s), the scientific achievements and qualities were much higher



than those types of work in China nowadays. It is a good lesson for us. In our points of view, this model can be duplicated now and in future.

Conclusion

Natural chemical agents or drugs are important armaments for the managements of a great number of refractory, inherited and outsider invasion/infections-induced diseases [5,34]. New natural chemical natural chemical compound discovery pipelines and drug developmental chain must be established for favorably wider clinical applications. In future, we must focus on the discovery and developments of highly effective chemotherapeutic drugs on this basis. In order to achieve this goal, integration of western and eastern medical practices is a top priority.

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