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Research Article

Drug Discoveries from Natural Resources

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Abstract

Chemical drugs from natural resource consist of half number of all drug categories. Growing attentions have been emphasized on this special type of chemical drug development. Medicinal chemistry/pharmacological efforts call for high-quality systems for drug inventions and clinical evaluations. Integrating and cutting-edge technical utility for natural chemical drug developments is inevitable for pharmaceutical sciences. This article addresses the landscape of natural chemical drug development and clinical utility in the future.

Keywords: Natural Plant, Phytochemistry, Traditional Chinese Medicine, Herbal Medicine, Cancer Pharmacology, Drug Development, Antineoplastic Drug, Antiviral Drug, Anti-Diabetic Drug, Animal Model

Introduction

Pharmacologic characters

Difference between synthetic drugs and natural chemical drugs, natural chemical drugs is of stronger medical armaments—high therapeutic index as well as low-rate of acquired drug-induced resistance in clinical trials. This character shows a potentially higher capability for pharmacotherapy and greater medical significance.

Medical significance

Natural components and drugs, as we can imagine, play huge role in large-population of infectious patients. To strengthen this argument, several well-known modern drugs are exemplified herein. For example, the most effective antibiotics (penicillin, streptomycin or cephalosporin) are all natural chemical products. They are more useful than a series of synthetic agents (sulphonamide) before utility of antibiotics. Without modern antibiotics, people with cold or surgery may suffer unexpected losses globally. More popularly, many natural products and drugs are widely utilized as anti-diabetic agents and different types of cancer worldwide. In addition, digitoxin (a natural chemical drug) was found against fatal heart symptoms. It is not difficult to see that these kinds of drugs play key roles in the treatment of many diseases and face new challenge for the generations to come [1,2].

Major challenge

Medicinal chemistry/pharmacological effort for drug developments likes finding a needle from a hay-stake owing to the complicated processes of drug screening conventions [1,2]. As a result, new initiatives must be explored to overcome these kinds of obstacles. This perspective systematically analyzes on this matter in detail and highlights it with modern touches.

Historic overview

General scenario of herbal medicine

Herbal medicine has a long history of evolution in styles and practice worldwide. In its early stage, herbal or animal medicines are widely utilized over many different countries, including Greece, Allopathic medicine, Ayurveda medicine in India and traditional Chinese medicine [3-7]. Yet, most of such countries lost this tradition. As a well-known country with this legend, China still maintains herbal medicine in modern day because China preserves many ancient medical books by leading publication systems in the early world [5,7].

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China has a long reputation of treating a wide variety of diseases by herbal medicine. This type of medical practice dates back at least 2000 years. Several earliest medical books were published between 100BC to 1900AD. It has been successfully managed for large endemics since the era of Zhong-Jin Zhang (AD150-219) in China [5]. According to theory of TCM, human diseases can be categorized with patient's imbalance between Yin and yang disorders. TCM doctors try to combat these patterns of symptoms (like fever, cough and immune deficiency) by strengthening, modulating and offsetting these damaged "Yin-Yang" in human bodies by formulated herbals [8-11]. The formulated herbal medicines contain large component of chemical admixtures and somewhat like modern drug combinations in western styles of therapeutic philosophy.

TCM routines for various diseases

TCM has its advantageous and disadvantageous areas for managing diseases. The advantageous areas for TCM can be both acute disease (like microbial or viral infection) [8-11], and chronic diseases (like cancer, diabetes, obesity, bone diseases and metabolic symptoms) [12-24].

Apart from different disease types, some disease symptoms are also within the range of TCM. For example, Ma-Xing-Shi-Gan-Tang is prescribed to remove toxic heat obstruction in the lungs of infected patients. These items of herbal formula are historically used as the preventive measures attacked by widespread epidemics similar as avian flu or Ebola epidemics in modern days [24-31].

In viral epidemics, a series of disease risk-factor is somewhat like "Helium--liqi" in ancient Chinese nomination in medical literatures. "Helium" is a high contagious disease that belong to outside invaders. The character of "Helium" is a process somewhat like microbial/viral infection in symptoms of high infectivity, sudden, climate-related. Hygiene and isolation are workable options for disease managements in the same times.

Diabetes (Xiaoke diabetes, a Chinese definition of diabetes) characterized with symptoms of thirsty, hungry and urination has been noticed over two thousand years in China [32-34]. In the second half of last century, type 2 diabetes mellitus (T2DM) were gradually recognized as a major public healthcare problem worldwide [32-34]. The incidence of T2DM in China and other developing/developed countries have been all growing due to incomplete knowledge towards causality, pathogenesis, antidiabetic therapeutics [32-42]. Despite some therapeutic advances, T2DM treatments are not widely successful in clinical trials. Currently, a lot of herbs and natural products, even natural chemical drugs are first-line anti-diabetic drugs for patients with T2DM.

Past Experience

From herbal medicine to natural chemical drug

There are many differences between herbal medicine and natural chemical drugs. However, a deeper understanding of herbal medicine may help us discovery more effective natural chemical drugs. As we can see, different movements may promote natural chemotherapeutic drug developments. To clarify our vision on this matter, the major characters of TCM must be introduced first.

TCM treats patients according to their abnormal symptoms and disease categorizations (majorly outside invaders and body-organ dysfunction) [7]. (Figure 1) Many pathogenic symptoms of serious diseases such as pulmonary obstructions, fever and coma can take longer times by different formulae of herbal medicines.

Modern medical practice calls for new drug developments and clinical applications. Although few herbal medicines have been published for specific viruses such as Ebola, avian flu, Zika therapeutics in ancient Chinese books, a great number of new chemical ingredients from microbial or plants in western countries have been available for modern diseases [7]. Previously, ingredients from microbial or plants in western society were very expensive for practical utility. Now, these ingredients are much cheaper due to technical advancements, especially extraction methodology [1-2]. Next generations of cutting-edge technology will enable us quick development of natural chemical drugs. (Figure 1) depicts general routine of TCM in the clinic that may help western doctors understand Chinese medicine with a closer look (Figure 1).

In TCM, formulae of herbal medicine may be represented in different forms and dosage—different formulae (Fangji, prescription). Different herbal formulae can be utilized to treat one disease or symptom. However, one herbal formula can be utilized for different diseases or symptoms in a similar clinical situation. It may be regarded as tricky in western philosophy. But it is usual strategies in TCM practice. Next-generations of cutting-edge technology will enable us quick development of modern pharmaceuticals. All of these medical explorations and drug development must go through robust experimental verifications.

Economic considerations

Currently, many different types of modern drug developments need huge funds to support. Drug producer is a pillar industry for a small number of world-leading countries, which is a highly competitive and adventurous job worldwide [43-48]. Nevertheless drug discovery, development and manufacture have been entering into a bottleneck stage over the past two decades—declining of drug productivity and successful rates

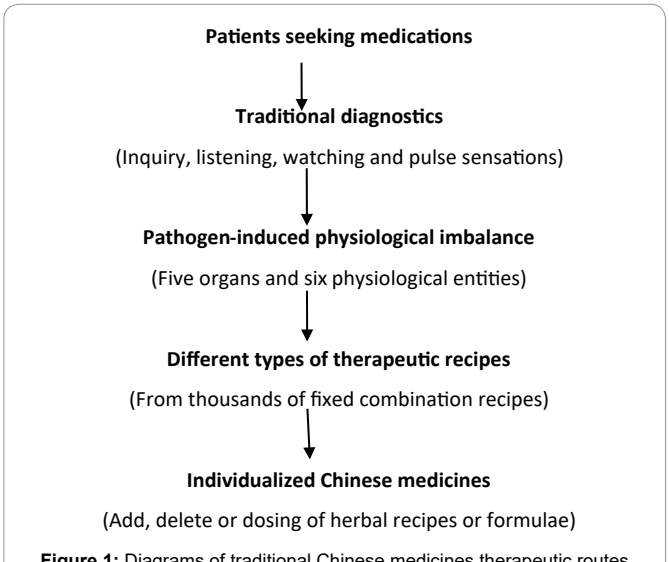

Figure 1: Diagrams of traditional Chinese medicines therapeutic routes

(phase II and phase III study) year-by-year [43]. These constantly declining of drug successful rates in clinical evaluation have multiple causalities, such as higher therapeutic demanding for new drugs as well as rising cost for cutting-edge equipment utility. As a consequence, a great amount of money needs to be paid off for drug screening, experimental mechanistic studies and systematic clinical evaluations. It therefore results in skyrocket economic burden for social/medical insurance for patients. Despite greater fortune of each licensing(1-2 billion USD) in US and other developed countries [43-48], cancer therapies only improve slightly, especially for cancer metastasis treatments. Thus, it needs to learn from TCM to promote drug developments [1-2].

The most used herbs in India and China are cheaper and low toxicity [3-4]. However, some rare Chinese herbs or animals, Such as ginseng are very expensive. Some herbal drugs, such as aconite "fuzi", are very toxic and even lethal for overdosing. These drug utilities need to be carefully manufactured (detoxication processes—heat treating) and prescribed by experienced TCM doctors.

Likely, Fuzi is a very useful herb for the treatment of cold-driven solid tumor growth in clinical trials. As usual, Fuzi must be low doses (<15-20 g). Yet in patients with cold-driven solid tumor treatment, the dosage of Fuzi can be utilized as high as 50 g, or even 100 g in some urgent clinical situations.

Present Landscape Of Tcm In World Arena

Scenarios

Overall, TCM must be translated into modern drug developments and clinical evaluations. In the past, a great amount of work for natural chemical drugs has been undergone. However, most of these efforts and processes are based on western medical philosophy. Generally speaking, almost half chemical drugs in western markets are coming from natural microbial, plant and animals. Despite a lot of successes in this respect, many obstacles still need to overcome. Yet, currently no specific drug developmental system has been widely utilized and wholly dependent upon. Updating drug development routine is an inevitable avenue.

Glory and hardship

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 influenced globally. The hidden rule behind this scenario is unclear.

TCM has its own advantages and medical significance even though we do not fully understand why?. This article emphasizes this matter by giving new vision without intending to promote them into the center stage of all international arenas. We only wish that TCM can be an important science discipline, especially in natural chemical drug study and clinical validity. Certainly, TCM is not always omnipotence and positive. Their disadvantages and negative sides are also easy to note.

Drug development transformation

Facing the situations of high risks, cost surge and low productivity in modern drug developments [43-47], creative study for science and technology can provide such opportunity and unprecedented insights into powerful therapeutics against many new diseases, highly mortality and new pathogens in TCM.

The advantages of natural chemical drugs comparing with synthetic chemotherapeutic agents as usual are low toxicities and drug cocktail (mixture ingredients). Of course, the drug combinational rules widely used in China may play pivotal roles for a variety of new lethal virus infections and late-staged cancer managements, which desperately needs good paradigm propagations worldwide [49-59].

To ensure a smooth progress of natural chemical drug developments, new ideas and perspective must be explored. Drug developers who have dual insights into both western and eastern medicine may be indispensable. Some medical articles and books in this respect can also attract the attentions of broad-ranges and get quick feedbacks in the clinic.

Natural chemical drug development is smoothly progressing. Presently, many first-line drugs against common diseases, such as microbial-infections, malaria, diabetes and cancer are more popular by natural chemical drugs in clinical trials. Marked advantages of disease managements have been achieved by natural chemotherapeutic agents, such as penicillin, artemisinin, metformin, doxorubicin, camptothecin and so on.

Current Insights

Paradigm introductions for viral-infection, diabetes and cancer

Since virus-induced human mortality acts differently(Ebola or avian flu with quick human mortality and HIV or Zika with slow pathogenesis processes), drug evaluative routines, disease pathologic discovery and drug mechanisms must be carried out by alternative ways [24-30]. For Ebola or avian flu treatment, quick disease management or viral proliferative inhibition is the key and emphasized. Yet for HIV or Zika infections, managing damaged human organs or physiological entities (immune rebuilding or cerebral damage protections) is more important to understanding [60-73].

Similarly, tumors are categorized with different historic subtypes and pathologic stages. This pathologic variation is very suitable for individualized therapeutics such as TCM, drug sensitivity testing and pharmacogenetic approaches [74-82] (Table 1).

The key quality of different chemotherapeutic agents is the balance between therapeutic responses and toxicities/risks, displaying as a therapeutic index gain. Many currently incurable diseases, such as HIV-infections in human bodies may come from shortage of effective natural chemotherapeutic drugs and fundamental knowledge of patho-therapeutic relationship. The only limitation of natural chemotherapeutic agents was the costs of drug purifications and natural product cultivation/collections. However, with the modern purification and cultivation technology, natural chemical agents will be much cheaper in the future. Owing to this advancement, a growing number of natural chemical drugs may get into the markets. There will be a plenty of herbal products in future pharmaceutical markets.

Table 1: Patho-therapeutic relations for outside invaders in TCM

Disease causality	Main symptoms	Therapeutics
风邪 **(wind evil)**	**Sudden & movable** Different types of colds Movable headache Urticaria/nettle-rash	**Prevent wind/expel wind** Fang-fen Jin-jie Leaf of bamboo and so on
寒邪 **(cold evil)**	**Pain & stasis** Whole-body pains and ache Immovable Solid cancers Circulation stasis	**Warm & circulation promotion** Si-ni-tang Huang-qi Fu-zi And so on
湿邪 **(wet evil/damp evil)**	**Phlegm & Damp** Gastro-intestinal symptoms Xiaoke (diabetes) Phlegm-damp syndrome (cough and so on)	**Clearance & anti-inflammation** Yi-yi-ren Di-huang
热邪 **(heat evil)**	**Heat-related symptoms** Fever Sweat Coma Unconsciousness	**Expel heat & stay cold** Yin-qiao Jing-yin-hua Water melon Shi-gao and so on
厉气 **(li-qi)**	**Fever, infection & Deaths** Fever Diarrhea Bleeding And so on	**Isolation and treatments** Qing-Hao Ma-hua-san

Educations and publications

Herbal medicines were generated from rules of thousand years. Though a great number of first-line and second-line pure therapeutic chemical drugs such as campthothecine, harringtonine and so on were discovered from herbal resources by western scientists, some of them were long reported in TCM books and literatures [50]. Medicinal chemists and pharmacologists worldwide are paying growing attentions from surveying TCM books and past/new literatures [53]. Although these past literatures/book are valuable for modern medicine, these TCM books and literatures are unpopular in normal medical universities worldwide, even in China. Limited courses of herbal medicine decrease the quality clinical practices and drug developments until now. As a result, medical educations and publications should be emphasized in both developed and developing countries.

Comparisons between western medicine and TCM in clinical cancer treatments

Cancer treatment by TCM is one of hotspots in modern China. Many TCM hospitals in China have a special department of cancer therapeutics. TCM for cancer treatments has been positively reported in China [50-56]. According to the current principles of TCM, human bodies are balanced by the fighting between inner upright strength(Righteousness) and outside damaging air(Evil). Generally speaking, current principle of TCM therapies seeks therapy by strengthening upright air rather than expelling outside evils. Additionally, expelling exogenous wind-heat recipes are also utilized for cancer therapies by TCM.

There are two pathways of therapeutics—malignant targets and symptom relieving in TCM. Solid cancer is regarded as syndrome of blood/qi stasis and phlegm-damp syndrome. To achieve phlegm-damp syndrome controls, cancer patient symptoms and syndromes may be clinically treated. It is also manifested as survival benefits in cancer patients. Besides symptom ameliorating, TCM can sometimes play decisive roles in cancer treatments [72-73].

Cancer assistant therapy

Apart from first-line anticancer drug, herbal or natural compounds can be used as assistant therapeutic agents to treat cancer growth, invasive and remote metastasis [57]. These structures of compounds are less cytotoxic in western medical encyclopedia, such as curcumin, anthocyanins and so on [68]. In western countries, cancer assistant therapies are presence with nutrient supportive, pain relieving, cardiovascular detoxication, antioxidants and many others. Though promising, cancer assistant therapies are not mainstreams of clinical cancer treatments in most western countries. At this stage of medical knowledge, the core of cancer assistant therapeutics is to combine cytotoxic anticancer drugs and assistant therapeutic agents (mostly natural chemical or biological compounds) [68]. Generally, drug combination for cancer is as good as therapeutic combination paradigm for HIV [65-67] (Figure 2,3), (Table 2).

Future Direction

Ideology promotion

The qualities of natural drug developments can be improved

Table 2: A comparison between western therapy and TCM practice

Categories	*Western therapy*	*Chinese therapy*
Diagnostics	Instruments	Inquiry, listening, 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 until now
Relative costs	High (especially new drugs)	Generally low and easy accessed

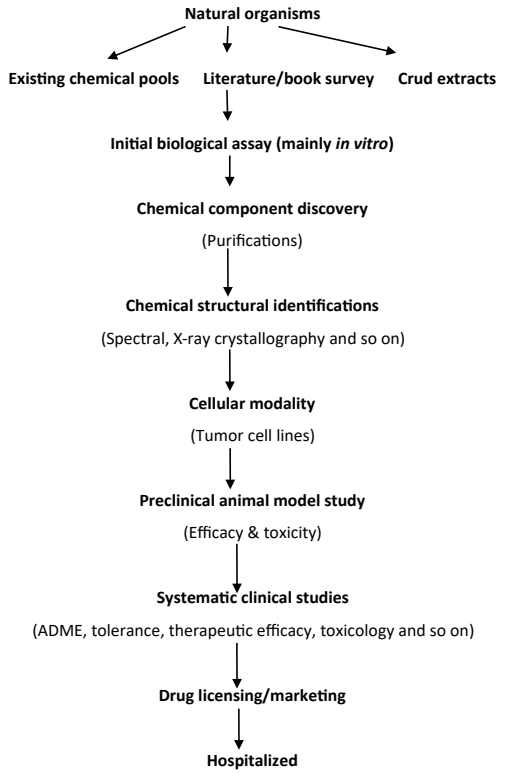

Figure 2: Western models of natural chemical drug discoveries

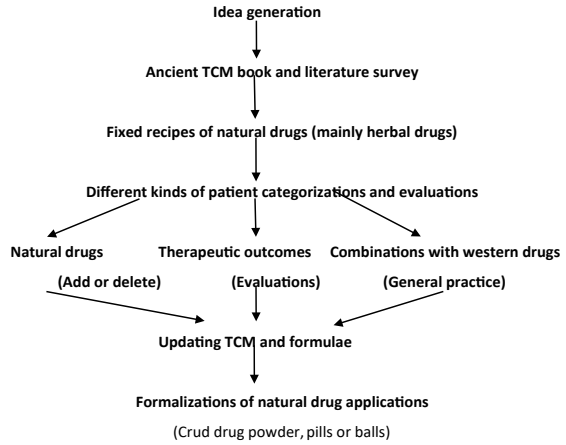

Figure 3: Chinese versions of drug developments

by a deeper understanding of herbal medicine practice and theories. But it is easier said than done because of a great deal of variability between western and eastern medicine.

The investigation of herbal medicine looks like to translate eastern therapeutic legend into western medical paradigms. Currently, most people in China believe that natural herbs have no toxicity. This stereotypic view has no scientific basis. But many natural chemotherapeutic agents generally show less toxicities comparing with synthetic chemical agents at same therapeutic ranges [1,2]. Until now, we commonly do not know why. Natural chemical drugs are somewhat like gifts from god and we shall pass these gifts down to our future generations. It appears that nature is the greatest medicinal chemist in this very planet.

Therapeutic study for new diseases

Zika virus epidemic in America continent is an emerging medical crisis that is receiving growing body of global attention. Good Zika knowledge must be established as early as possible. Like aforementioned theory and paradigms, innovation of Zika therapy by TCM [31], or natural chemotherapeutic agents may be useful in the future [68]. We suggest that TCM study may create workable solution on Zika pathogenesis and therapeutics in the future.

Genomic study

Apart from general pathway for pathogenesis and therapeutics, new generations of techniques may be borrowed for TCM and natural chemical drug developments, such as cancer genomic study [70,71], and HIV-integration into human genomes [72,73]. But these issues face ethical debates and regulatory challenges [74].

Teamwork

Besides pharmacologists and medicinal chemists, many specialists and experts can also participate in natural chemical drug developments. Excellent teamwork from other disciplinary experts is very important for improving the quality of natural drug development. Breaking barriers between existent mindset and drug development rules may be new efforts.

Treatment of neoplasm metastasis by TCM

Neoplasm metastasis is a multi-step and multi-level phenotype that is responsible 90% cancer mortality in the clinic [83-88]. More seriously, it has been found that many different states of metastatic cells/cluster (ever-changing character) in

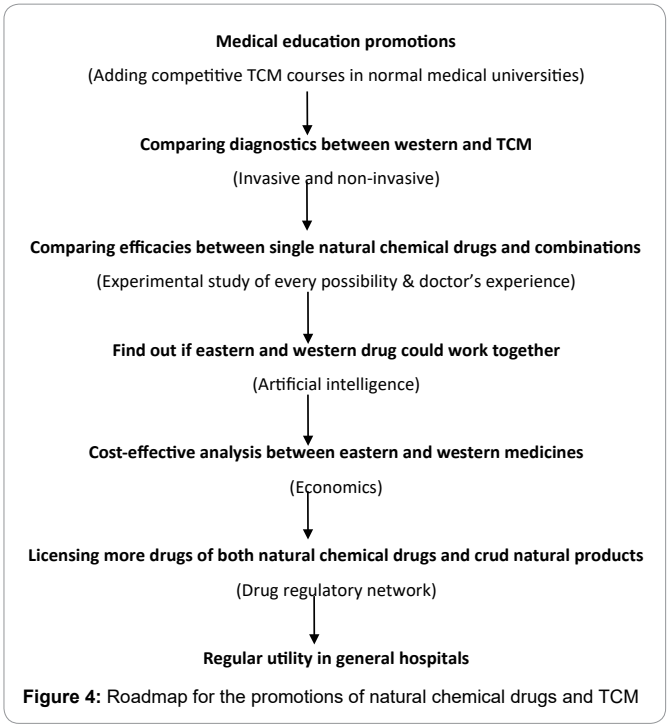

Figure 4: Roadmap for the promotions of natural chemical drugs and TCM

wide-ranges of human organs/tissues—now widely known as neoplasm plasticity [86-88]. A lot of currently-licensed drugs only target narrow-range of these various metastatic states. Nevertheless, TCM is famous for solving whole-body disease and body/organ imbalance. The question of whether TCM can be an alternative solution for neoplasm metastasis is open to us now.

Quick adjust of therapeutic strategy

In TCM practice, doctors commonly change their therapeutic strategy according to past medication. This phenomenon is not common in western treatments. In western treatment, there is a less possibility of changing therapeutics in most clinical trials. Oppositely, many therapeutic drugs are required to treat patients lifelong. Balanced therapeutics of these two systems may be promoted in disease treatments (Figure 4).

Conclusion

Herbal medicine and natural chemical drugs are interrelated in for both basic and practical values [1,2]. A lot of creative ideas and scientific approaches can promote medical armaments against dangerous diseases. As a result, new natural chemical drug discovery and developmental system must be established for high-quality and wider-range drug development and clinical applications [89-92]. To achieve this goal, integration of western and eastern medical practices is a top priority and a future fashion.

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Conflicts Of Interests

None

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