Pharmacological Research 111 (2016) 546–555

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Advanced research technology for discovery of new effective compounds from Chinese herbal medicine and their molecular targets

Vincent Kam-Wai Wong [1], Betty Yuen-Kwan Law [1], Xiao-Jun Yao, Xi Chen, Su Wei Xu, Liang Liu *, Elaine Lai-Han Leung *

State Key Laboratory of Quality Research in Chinese Medicine/Macau Institute For Applied Research in Medicine and Health, Macau University of Science and Technology, Avenida Wai Long, Taipa, (SAR), China

ARTICLE INFO

Article history:
Received 3 June 2016
Received in revised form 19 July 2016
Accepted 19 July 2016
Available online 20 July 2016

Keywords:
Chinese herbal medicine
New phytochemicals
Mechanism
Omics
Biotechnology
Computational technology

ABSTRACT

Traditional biotechnology has been utilized by human civilization for long in wide aspects of our daily life, such as wine and vinegar production, which can generate new phytochemicals from natural products using micro-organism. Today, with advanced biotechnology, diverse applications and advantages have been exhibited not only in bringing benefits to increase the diversity and composition of herbal phytochemicals, but also helping to elucidate the treatment mechanism and accelerate new drug discovery from Chinese herbal medicine (CHM). Applications on phytochemical biotechnologies and microbial biotechnologies have been promoted to enhance phytochemical diversity. Cell labeling and imaging technology and −omics technology have been utilized to elucidate CHM treatment mechanism. Application of computational methods, such as chemoinformatics and bioinformatics provide new insights on direct target of CHM. Overall, these technologies provide efficient ways to overcome the bottleneck of CHM, such as helping to increase the phytochemical diversity, match their molecular targets and elucidate the treatment mechanism. Potentially, new oriented herbal phytochemicals and their corresponding drug targets can be identified. In perspective, tighter integration of multi-disciplinary biotechnology and computational technology will be the cornerstone to accelerate new arena formation, advancement and revolution in the fields of CHM and world pharmaceutical industry.

Contents

Abbreviations: CHM, Chinese herbal medicine; EGCG, epigallocatechin 3-gallate; TAIII, imosaponin A-III; DHRh-123, dihydrorhodamine-123; DARTS, drug affinity responsive target stability; TEMtfLC3, tandem fluorescent-tagged microtubule associated protein 1 light chain 3; mRFP, momomeric red fluorencent protein; GFP, green fluorescent protein; LC3, protein 1 light chain 3; AKT, protein kinase B; Atg 5, autophagy protein 5; mTOR, mechanistic target of rapamycin; TEM, transmission electron microscopy; LOX-1, 15-lipoxygenase-1; PPAR, proliferator-activated receptor; IDO, indoleamine 2,3-dioxygenase; BLI, bioluminescent imaging; Luc, luciferase; HIF-1, hypoxia-inducible factors 1; TKI, styrosine kinase inhibitors; PTM, post-translational modification; ROS, reactive oxygen species.

* Corresponding author.
E-mail addresses: lliu@must.edu.mo (L. Liu), lhleung@must.edu.mo (E.L.-H. Leung).
[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.phrs.2016.07.022
1043-6618/

1. Introduction

Chinese herbal medicine (CHM) has been used for thousands of years, and CHM is well-known of its holistic modulation effect on our body by combined usage of multiple herbs that contains a large variety of active compounds. To increase its diversity, and reduce the toxicity of crude drugs, there are multiple preparation methods, including cutting, soaking, boiling, stir-frying, steaming, calcining, etc, so as to increase the diversity of herbal compounds being extracted [1,2]. Beside physical and chemical methods (Fig. 1), traditional biotechnology also used living systems and organisms to develop or make useful products, or applied any technologies that involved biological systems, living organisms or derivatives to make products. One of the examples is the production of wine and vinegar by fermentation of wheat, which is the oldest application of microorganism to change and modify the chemical composition of a plant or crop materials both in China and other countries [3]. These old biotechnologies have also been applied in CHM preparation, in which fermentation has been used to generate new pharmaceutically active phytochemicals that do not exist naturally (e.g. Tempeh, [4]). However, old biotechnologies has its limitations due to the lack of power of gene and giant molecule manipulation, so limited new phytochemicals could be formed without desired genetic engineering [5]. CHM exhibits its medical advantages and strength by its special 3M's nature characteristics, 3 M stands for "multi-components", "multi-targets" and "multi-mode of action" [6], therefore, maintaining and even enlarging the pool and diversity of CHM effective compounds are the key to exhibit the strength of CHM. Owing to the natural biodiversity of herbs, it is in fact a natural existing chemical library which composes of multiple potential effective phytochemicals, however, new effective compound generation is random and slowly happens by natural evolution [7]. Also, the concentration and ratio of the effective components might vary greatly that is far beyond to satisfy the industrial production scale [8]. In addition, looking for new effective naturally-existing chemical components depending on new herbal species discovery from the nature, is a slow, random and difficult process [9].

Now modern biotechnology provides the breakthrough to solve these limitations, such as the "omics" technology can help to elucidating the complex treatment mechanism of CHM and human disease network [10,11]. The scope of modern biotechnology is no longer limited to application of microorganism, it has been expanded to include new and diverse sciences such as genomics, systems biology, recombinant gene technologies, cell imaging and labeling technologies etc. [12–16]. Furthermore, with advanced computational methods, more and more effective compounds can be identified in a high-throughput manner. Eventually, these technologies can enhance the chemical diversity of CHM; and help to elucidate the treatment mechanism of CHM, finally it can facilitate pharmaceutical industrial new drug discovery.

2. Enhancing the chemical diversity of CHM with new biotechnology

Chemical diversity is the fundamental base for supporting the new drug discovery. The increase of chemical varieties of CHM further facilitates the identifications of novel compounds, novel drug targets and novel biological activities of small-molecules. Nowadays, advanced research methodologies and modern biotechnologies are further adopted to enhance the chemical diversity of CHM by microorganisms-assisted phytochemicals production. In addition, the combined techniques of mutasynthesis, chemobiosynthesis, semi-synthesis, system biology, synthetic biology, omics technologies, computational system biology and evolutionary genetic engineering could massively diversify the natural products. As such, the increase of chemical diversity may help to expand the spectrum of new drug discovery on known targets as well as solving the problems of drug-resistant phenotype with more drug options.

2.1. Microorganisms-enhanced phytochemicals diversity

Traditional methods for the studies of phytochemicals by microorganism to discover microbial natural products particularly require the selection and incubation of strains, extraction, bioassay-guided purification and structure elucidation. Unfortunately, this approach is often tedious and time-consuming because of a high rediscovery rate. Along with the more understanding of microbial genomics, modern biotechnology has provided valuable insights into the principles of CHM product biosynthesis and therefore offers promising approaches for the discovery and engineering of new chemical entities from CHM [17].

In the recent decade, the rapid development of biotechnology techniques for deciphering microorganism's genomes transcriptomes, proteomes, metabolomes and fluxomes, together with recombinant DNA technology, system biology and computational modeling tools, have been advancing the genetically engineered bacterial, yeast, fungi and plant-fungus symbiotic co-culture system to yield tremendous diversity of chemicals, drugs, biorenewable fuels, foods, natural food colorants and other useful materials[18–20] (Fig. 1). For instance, the natural phytochemicals such as flavonoids, anthocyanins, isoprenoids, terpenoids, chalcone and novel carotenoid have been intensively produced by heterologous expression of methyl transferases and glycosyl transferases [21], chalcone synthase [22], stilbene synthase [23], carotenoid synthase [24] and terpene cyclase [25] using Saccharomyces cerevisiae and E. coli. system. The drugs and drug precursors for (i) anti-malarial agent: artemisinic acid [26]; (ii) anti-cancer agents: taxol [26], benzylisoquinoline alkaloids [27], doxorubicin [28] and mithramycin [28]; (iii) immunosuppressants: cyclosporine A [29], FK506 [29] and rapamycin [29]; (iv) antibiotics