Received: 26 July 2022 | Revised: 2 September 2022 | Accepted: 24 September 2022

DOI: 10.5185/amlett.2023.011712

OPEN ACCESS

REVIEW

Multi-omics Technology for Demystifying Herbal Medicine

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ABSTRACT

Herbal medicine (HM) is a fruitful source of chemical substances that has contributed greatly to the pharmaceutical industry and novel therapeutics. Natural products derived from HM continue to be a rich source of lead compounds because of their high structural diversity and potent bioactivities. However, despite the success of active ingredients derived from HM in drug discovery, compatibility issues that make huge challenging for extended timelines of effective evaluation, chemical composition identification, active ingredient screening and target confirmation. However, some approaches solely cannot effectively elucidate the overall effect and action mechanism due to complexity muti-components of HM. Thus, integration strategies combining modern analytical techniques with HM are increasingly being developed in the era of big data and omics. The updated mass spectrometry has been used to identify natural product structure and their mode of action on biological processes. Their molecular properties are validated through the use of recent high-throughput multi-omics including transcriptomic, proteomic and metabolomic tools and bio-informatics, molecular docking, network pharmacology techniques that enable to accelerate natural product discovery. We summarized several important omics technical platforms and multi-omics-based integration approach as powerful strategies to demystify HM and discover new bioactive molecules.

KEYWORDS

Herbal medicine; multi-omics; natural product; lead compound; effect.

INTRODUCTION

Herbal medicine (HM) represents the richest source of chemical diversity and bioactive molecules for early-stage drug discovery [**1**]. The contributions of natural products derived from HM have been documented [**2-4**]. Rapid identification of lead compounds and isolation of active molecules from HM would benefit to facilitate the development of new drugs. As a key part of complementary medicine, HM has increasingly drawn attention as an important source for drug discovery [**5,6**]. Although, it remains an essential source of drugs and drug candidates, great difficulties for HM research are efficiently to discover novel natural products, due to traditional isolation approach, low discovery rates of compounds, low detection rate of trace components. Fortunately, multi-omics-based technology as a powerful strategy, such as transcriptomics, proteomics, metabolomics, etc, has been recognized as effective approaches to reveal the effect and discover targets of HM components and natural products [**7-10**]. Compared with traditional methods, multi-omics can provide a more detailed molecular mechanism map of the biological systems.

Chemical compounds discovery and drug development from natural product has entered a new era that driven by multi-omics [**11-14**]. With the rapid development of modern analytical technology, advanced multi-omics strategies can provide enormous possibilities for discovery of new natural products [**15-17**]. Despite the progress has been made, successful elucidation of effect mechanism and target exploration of HM remains a great challenge of time-consuming process that rely on the of multi-omics integration strategies. Advances in mass spectrometry, network pharmacology, bioinformatics, molecular docking, etc. are driving new applications of multi-omics in natural product discovery and development [**16-20**]. This review summarizes a series of successful application using high-

throughput omics (e.g., transcriptomics, proteomics, and metabolomics) for HM, emerging integrative multi-omics methods and techniques are also introduced; specific examples were provided to overcome these practical problems and decipher pharmacological action and identify new ingredients as well as their action target pathways for bioactive molecules.

Transcriptomics

Transcriptomics has become a translational platform for HM study due to its high throughput, accuracy, sensitivity, and specificity. Transcriptomics approaches showed that the inhibitory effect on hepatic glucose production of a classic traditional herb medicine *Huanglian-Renshen-Decoction* were associated with the activation of PI3K/Akt/FoxO1 signaling [**21**]. An herbal *Chaiqin chengqi decoction* has been applied to the treatment of acute pancreatitis. Transcriptomics analysis has showed it decreased Akt phosphorylation and induced response of antioxidant protein Nrf2/HO-1 in pancreatic and adipose tissues, ameliorated the severity of obesity-related alcohol-induced AP by down-regulating PI3K/Akt signaling and activating of antioxidant protein response [**22**]. The protective mechanisms of helenalin on hepatic fibrosis were investigated using transcriptomics analysis. Interestingly, it indicated that helenalin regulated the PI3K/Akt-NF-κB signaling, and inhibited the glycerophospholipid metabolism by down-regulating the target genes, ultimately ameliorating hepatocyte damage [**23**]. The modulatory mechanism of *ELeng* capsule for endometriosis treatment was explored by transcriptomics. The potential mechanism was related with functional molecules including the regulating angiogenesis and inducing apoptosis [**24**]. The therapeutic mechanism of a traditional formula *Qingfei Xiaoyan Wan* in the suppression of allergic asthma was evaluated by ranscriptomics analysis and screened out six genes with the highest values and the differentially expressed genes were mainly enriched in cytokine signaling pathway and inflammatory response [**25**]. The potential function and underlying mechanism of celastrol on osteoarthritis (OA) were determined. A total of 96 genes involved in mTOR signaling pathway were recognized as the therapeutic target [**26**]. The effects and mechanisms of *Phlomis umbrosa Turczaninow* root extract on OA were investigated using transcriptomic analysis. The findings insight into the effect mechanisms of down-regulating cartilage damage factors and up-regulating chondrogenesis via influencing transcription factors [**27**].

Proteomics

Poteomics as an effective strategy in advancing knowledge of molecular processes and identifying new therapeutic targets has become a constitutional part of multi-omics. High-throughput proteomics approach was utilized to identify the underlying targets for Sodium tanshinone IIA sulfonate treating stroke, and total 285 proteins were changed, and Alb, mTOR, Cltc, Dync1h1, Stxbp1 and Sptan1 were found as the key proteins and enriched in PI3K/AKT and HIF-1 signaling pathway [**28**]. The root and rhizome of *Valeriana jatamansi Jones* can treat various mood disorders. Its anti-anxiety effect was disclosed and total 80 differentially expressed proteins were discovered by proteomics and involved in protein digestion and absorption, and cholesterol metabolism [**29**]. Pharmacological effect and mechanism of *Huanglian Jiedu Decoction* against cerebral ischemia were explored by proteomics analysis. Enrichment analysis showed 8 targets were identified as targets; Rap1 signaling pathway was a key pathway to the therapeutic effects that mediates regulation of oxygen balance and the basic cell functions [**30**]. The possible mechanisms of herbal prescription *Xuefu Zhuyu decoction* for treating acute traumatic brain injury were revealed through proteomics. Of note, 17 differentially expressed proteins were regulated and related to PI3K-Akt signaling [**31**]. The protective effect of *Guri Gumu-13* pill on acetaminophen-induced liver injury was investigated based on proteomics. Total 237 proteins were identified and 58 differentially expressed proteins were regulated and therapeutic effects were related to linoleic acid and retinol metabolism regulation [**32**]. The effects and underlying mechanism of *Tuomin-Zhiti-Decoction* treating allergic rhinitis were explored by integrative analysis of proteomics and network pharmacology. IL-6 and CD40 were discovered as potential protein targets; wogonin and quercetin could play key roles in treatment [**33**]. A natural compound celastrol (Cel), can exerts anti-cancer properties. Quantitative chemical proteomics was used to identify the protein targets and elucidate its anti-cancer activity. Total 100 proteins were identified as targets and related with suppression of protein synthesis [**34**].

Metabolomics

Metabolomics could establish a direct relationship between the content changes of effective components and phenotypes of phytochemical components in medicinal plant. It is further used to identify quality markers (Q-marker) for distinguishing the function related bioactivity and discovering active components. Mass spectrometry-based metabolomics was used to discover potential biomarkers and effect mechanisms after agarwood treating smoke (AIS). A total of 138 components were identified, such as sesquiterpenes and flidersia type 2-(2-phenylethyl) chromones that exerted high docking abilities with potential biomarkers, involved in arginine and proline metabolism and tryptophan metabolism, etc [35]. A plant metabolomics strategy was developed to research the potential Q-marker of *Periplocae Cortex*. It showed that nine ingredients can be regarded as Q-marker of Periplocae Cortex [**36**]. The molecular mechanism and pharmacological properties of *Salacca zalacca* fruit extract on obese-diabetic rats were evaluated using metabolomics approach, and improve amino acid metabolism and energy metabolism, involving 2-oxoglutarate, citrate, acetate, lactate, glucose, succinate and 2-hydroxybutyrate [**37**].

Metabolomics coupled with chemometrics strategy was established for screening of bioactive-chemical quality marker from HM. Citric acid, linolenic acid, isorhamnetin-3-O-neohesperidoside, typhaneoside were discovered as Q-markers for pollen of *T. orientalis* [**38**]. Cell metabolomics provided an effective approach to reveal the anti-proliferation mechanisms of petroleum extracts of *Farfarae Flos*, and found targets were related to aurora-A, glutathione S-transferase Mu 1, glutathione S-transferase P 1, heme oxygenase-1, and progesterone receptor, which were associated with PI3K/Akt pathway [**39**]. Untargeted metabolomics was used to analyze the components and metabolic mechanism of traditional prescription *Wutou* decoction. Importantly, 18 components in vitro were identified in rheumatoid arthritis rat, and showed L-ephedrine, aconitine, L-methylephedrine, albiflorin, quercetin and paeoniflorigenone as Q-markers are the key components [**40**]. The effective mechanism of a classic prescription *Si-Miao-Yong-An-Tang* for thromboangiitis obliterans treatment were revealed based on urine metabolomics, a total of 22 biomarkers were regulated, which were closely related to the cysteine and tyrosine metabolism [**41**]. The pharmacological effects, effective constituents, and targets of *Keluoxin* against diabetic retinopathy were investigated, 64 biomarkers in blood were discovered by nontargeted metabolomics, involved steroid hormone biosynthesis and sphingolipid metabolism, etc; astragaloside IV, chrysophanol, emodin and rhein were screen as effective constituents and related to the mammalian target of mTOR and AMPK signaling pathways [**42**].

Multi-omics strategies

Recently, the omics detection tools have been widely used in various medicinal herbs. The multi-omics integration approach has been a potent tool in contributing to our understanding of natural product-driverd from HM and to decipher regulatory biological processes and target discovery. Multi-omics was analyzed the anti-tumor mechanism of *Marsdenia tenacissima (Roxb.) Moon* and explored active components and identified anti-tumor targets. Tenacissosides I, H, and G were active ingredients for hepatocellular carcinoma treatment, and could inhibit angiogenesis, promote apoptosis, and improve immune function, respectively, which exerts beneficial effects of multi-components and multi-targets [**43**]. Therapeutic mechanism of a traditional patent drug *Tripterygium Wilfordii Hook F* pills for immunological non-responders treatment was investigated using multi-omics, and found it regulated great majority of down-regulated genes, and triptolide as bioactivity compound, inhibited IFN-γ production and immune cell activation as well as expression of downstream genes [**44**]. Multi-omics analysis of metabolome and proteome was applied to reveal the protective effect and potential therapeutic mechanism of gross saponins of *Tribulus terrestris L. Fruit* against ischemic stroke. A total of 359 differential proteins and 110 metabolites were screened and mainly associated with sphingolipid metabolism, complement and coagulation cascades, glycerophospholipid metabolism, etc. [**45**]. The effective mechanism of total flavonoids extracted from *Astragali Radix* against cyclophosphamide-induced leucopenia were demonstrated by systems biology. Using metabolomics methods, PI3K-Akt and Jak-STAT signaling pathway were regulated by total flavonoids. Total flavonoids exhibited protective effects via promoting cell proliferation, modulating immunologic functions at the system level [**46**].

Multi-omics disclosed the antidepressant-like effect mechanisms of the low polarity fraction of *Bupleuri Radix*. Total 16 biomarkers were screened and associated with antidepressant effect, and involved taurine and hypotaurine metabolism, glyoxylate and dicarboxylate metabolism, primary bile acid biosynthesis, and correlated with gut microbiota [**47**]. Metabolomic, proteomic and transcriptomic profiles of lung tissues from *Bufei Yishen* formula (BYF)-treated chronic obstructive pulmonary disease (COPD) rats have been characterized to determine the underlying the effects and therapeutic mechanisms of BYF at the system level. Numerous metabolites proteins and genes were discovered and regulated by BYF; potential targets were associated with inflammatory response, lipid metabolism and oxidative stress [**48**]. Integrating transcriptomics, proteomics, and metabolomics were applied to reveal the effect and mechanism of *Bufei Jianpi* formula (BJF). Long-term anti-COPD effect targets of BJF were detected and related to focal adhesion, antioxidant activity and lipid metabolism [**49**]. An integrated analysis of miRNAome, metabolome and proteome were performed to reveal the underlying efficacy mechanism of geniposide on the hepatoprotection. The significantly differentially expressed 28 miRNAs, 7 metabolites and 20 proteins were identified, respectively. Geniposide could regulate citrate cycle metabolism pathways via targeting dehydrogenase and promoting functional recovery [**50**]. Multi-omics was utilized to explore the pharmacological actions and therapeutic mechanisms of *Zhen-Wu-Bu-Qi Decoction* that exhibited anti-inflammatory properties and protected against colon injury through manipulating PI3K-MAPK/NF-κB signaling pathway [**51**]. A multi-omics analysis is used to explore anti-osteoporosis mechanism of the root of *Achyranthes bidentata Blume* [**52**]. A total of 22 biomarkers were identified and indicated that glycine and threonine metabolism, glyoxylate and dicarboxylate metabolism were major intervened pathways. The abundance of *Oscillospira* was negatively correlated with anti-osteoporosis effect, whereas *Turicibacter*, *Anaerofilum* and *Rothia* bacteria was positively correlated with effect. System pharmacology analysis could reveal the effective mechanism of effective ingredients from herbs against rheumatoid arthritis [**53**]. It provided a systematic method to screen active components and optimize their proportion, reveal the overall effects for medicinal herbs via multi-omics integration.

Future outlook

Phytochemicals of HM are major sources of lead compounds for medical and pharmaceutical industry. However, the research on the effect and targets of HM has many challenges due to multi- component characteristics. Recently, researchers have successfully identified novel compounds, revealed the effects and screened the target proteins of HM with chemical multi-omics approaches that provide a more comprehensive picture of the bioactive components from HM, which use modern scientific language to clarify the and detailed action mechanism of HM. In this context, this review highlights recent advances in multi-omics technology focuses on transcriptomics, proteomics metabolomics and integrative multi-omics and efforts to demystifying HM and uncover active natural products, describe multi-omics approaches to characterize active compounds, discuss potential functional mechanism. Multi-omics techniques have become key tools for interpretation of HM, insighting into the effect mechanisms of action, predicting the biological activity of HM, assisting bioactive leads discovery, and serving as a tool for quality control and evaluation, could accelerate discoveries of novel drugs from HM.

ACKNOWLEDGEMENTS

The authors are grateful for the generous support from the Program of Natural Science Foundation of State (Grant No. 81973745, 82104733, 81302905), Talent Lift Engineering Project of China Association of Traditional Chinese Medicine (QNRC2-B06), Natural Science Foundation of Heilongjiang Province (YQ2019H030), and Project Supporting Fund.

CONFLICTS OF INTEREST

There are no conflicts to declare.

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GRAPHICAL ABSTRACT

High-throughput multi-omics including transcriptomics, proteomics and metabolomics and bio-informatics, molecular docking, network pharmacology techniques enable to advance effective evaluation, chemical composition identification, active ingredient screening and target confirmation for herbal medicine.