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Review

Discovery of quality control markers from traditional Chinese medicines by fingerprint-efficacy modeling: Current status and future perspectives

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ABSTRACT

Quality control (QC) is crucial for ensuring the safety and effectiveness of traditional Chinese medicines (TCMs). Due to extremely complicated phytochemical matrices and characteristic mode of "multi-component, multi-target, integrated adjustment", discovering of QC markers from TCMs is a big challenge. Fingerprint-efficacy (FE) modeling method is currently proposed as an effective and reasonable attempt. This review summarizes the methodologies of FE modeling and applications in screening QC markers, meanwhile the future perspectives are also briefly discussed so as to provide inspiration and reference for follow-up study of FE relationship for TCMs.

Contents

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1. Introduction

Traditional Chinese medicines (TCMs) are gaining increasing attention worldwide due to their long-standing clinical practice and well-performed therapeutic efficacy [1]. As the safety and effectiveness of TCMs are strongly correlated to their quality, quality control (QC) of TCMs has been a key issue drawing extensive research interest [2,3]. With the advancement of analytical techniques, continuous improvement has been made in qualitative and quantitative analyses of TCMs [4,5]. However, due to extremely complicated phytochemical matrices and characteristic mode of "multi-component, multi-target, integrated adjustment", quality evaluation by the characterization of single or several chemical constituents in TCMs is incomplete, because in many cases the analytes are selected merely owing to their abundance rather than efficacy [6]. Thereby, a meaningful TCMs QC system should be established to simultaneously consider the chemical and pharmacological properties. The concept of quality markers or Q-markers towards this endeavor has been proposed and elucidated for settling the issues in research field of quality standards and effective substances [7–11]. In this review, the term of QC markers is defined as specific bioactivity-related ingredients that reflect the inherent quality of TCMs and can be used to elaborate the authenticity, efficacy and safety-based quality standards for TCMs.

Up to date, several strategies have been applied for the discovery and identification of QC markers successfully. Initially, conventional phytochemical method forward to extract, separate, purify and verify QC markers [12] is simple but low-efficiency, time- and labor-consuming. It is also insufficient to reflect the holism of TCMs owing to ignorance of the possible synergism of multiple constituents and missing of the minor components. Meanwhile, bioactivity-guided separation method [13], established on the desired pharmacological screening model, tracks QC markers based on activity evaluations, overcoming the defects of blind separation and high consumption. But some limitations, such as heavy workload, misleading of the false positives or false negatives and missing of desired ingredients, indicate that the discovery cycle of bioactive substances remains prolonged [14]. Besides the separation-based methods, on-line screening technology, including pre-column affinity-based screening and post-column bioassay, simultaneously conducts separation, screening and identification of QC markers in TCMs [15,16]. Nevertheless, this approach neglects the combinatorial roles and integrative effects of multi-components, and is often limited by the complicated design of experimental equipment. In addition, the emerging pharmacophore-guided knockout/knockin chromatography, is established to rapidly filter ineffective compounds and automatically target QC markers [17], whereas the knowledge of quantitative structure-activity relationship (QSAR) is the necessary prerequisite and pharmacophore modeling is difficult for the majority of natural products.

Therefore, it is imperative to develop a rational approach to find QC markers of TCMs and the research of fingerprint-efficacy (FE) relationship came into being. In order to discover QC markers and clarify the material basis of efficacy, the FE relationship method combines characteristic chromatographic peaks with pharmacological effects by multiple chemometric methods to investigate the correlations between components and efficacy, and to find the QC markers reflecting the therapeutic effects of TCMs. After years of exploration and development, the study of FE relationship modeling has formed a general workflow, including the following procedures: (i) optimizing appropriate methods to establish chromatographic fingerprints; (ii) selecting proper pharmacological models and indicators to acquire pharmacodynamic information; (iii) utilizing suitable statistical toolboxes to model FE relationship and find candidate components; (iv) verifying the pharmacological activities of candidates. The schematic flow is shown in Fig. 1.

Recently, several overviews about the research of FE relationship approaches have been published on the quality evaluation of TCMs [18,19], but they focus on evolution of conception. In this review, we mainly summarize the methodologies of FE modeling and the latest applications in screening QC markers, from a more specific and practical angle. In particular, challenges and future perspectives of some cutting-edge strategies including bioactive equivalent constituents, multivariate data fusion, network pharmacology are discussed.

2. Chemical profiling and pharmacological characterization of TCMs

2.1. Chemical profiling of TCMs

The inherent quality of TCMs may vary significantly from different plant species, geographic sources, harvesting seasons, and processing processes, etc. In this context, chromatographic fingerprint is well recognized as a powerful means for comprehensive characterization of chemicals in TCMs [20]. In general, fingerprint constructs a relative complete picture of chemical components in TCMs to determine not only the absence or presence of active ingredients but also the complete set of ratios of all detectable analytes [21]. Thus, the chemical profiling and the fingerprint analysis represent a rational approach for the quality evaluation of TCMs.

Various techniques including HPTLC, HPLC, GC, CE, etc. have been proposed to construct specific fingerprints for recognition of multiple compounds of TCMs [5]. Among which, HPLC is most popular for its high sensitivity and accessibility. With the development of analytical instruments, especially the hyphenated techniques, such as HPLC-DAD, HPLC-MS, HPLC-NMR, GC–MS, CE-DAD, and CE-MS, etc. [4], separation and detection of the main compounds in fingerprint become more sensitive and accurate. Furthermore, these instruments combined with advanced means recently being developed in chemometrics, database searching, and structural elucidation techniques have enhanced the qualitative and quantitative ability of fingerprint significantly [22,23]. Two/multi-dimensional chromatography, as an emerging analytical technique, has shown powerful separation ability, high peak capacity, and excellent detectability in the analysis of complex samples compared with single-dimension HPLC. After selecting an appropriate technique for analyzing herbal samples, proper pretreatments of the original data are prerequisite to standardize the data for further analysis, such as peak-alignment, similarity analysis and transforming the data, etc. [24,25]. The combination of off-line comprehensive two-dimensional liquid chromatography, hydrophilic interaction chromatography (HILIC) and reversed phase liquid chromatography (RP-LC), was develop for the analysis of anthocyanins. The off-line HILIC × RP-LC was used to separate and identify diverse anthocyanins in blueberries, red radish, black beans, etc. and improved the resolution [26].

Overall, chromatography is a powerful technique for separating the individual compound and constructing the fingerprints to reflect characteristics of TCMs. The comprehensive fingerprints can