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Field-induced wooden-tip electrospray ionization mass spectrometry for high-throughput analysis of herbal medicines

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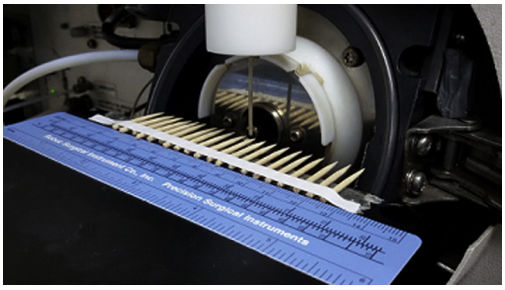
HIGHLIGHTS

- A high-throughput field-induced wooden-tip ESI-MS method was developed.
- An analysis speed of 6 s per sample was achieved.
- The method was applied for high-throughput analysis of herbal medicines.
- Rapidly tracing origin and assessing quality consistency and stability were achieved.
- We provide an effective method for high-throughput analysis of herbal medicines.

GRAPHICAL ABSTRACT



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ABSTRACT

This study demonstrates the first application of field-induced wooden-tip electrospray ionization (ESI) mass spectrometry (MS) for high-throughput analysis of herbal medicines. By application of an opposite and sample-contactless high voltage on the MS inlet rather than wooden tips, a high-throughput analysis device is easily set up, and a relatively fast analysis speed of 6 s per sample was successfully achieved. In addition, fast polarity switching between positive and negative ion detection mode is readily accomplished, which provides more complete chemical information for quality assessment and control of herbal medicines. By using the proposed method, various active ingredients present in different herbal medicines were rapidly detected, and the obtained mass spectra were served as the samples' fingerprints for tracing the origins, establishing the authenticity, and assessing the quality consistency and stability of herbal medicines. Our experimental results demonstrated that field-induced wooden-tip ESI-MS is a desirable method for high-throughput analysis of herbal medicines, with promising prospects for rapidly differentiating the origin, determining the authenticity, and assessing the overall quality of pharmaceuticals.

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1. Introduction

Herbal medicines are playing an important role in diseases treatment and health care due to their desirable therapeutic efficacy, inexpensive, easy access, and few adverse effects [1]. According to the definitions of World Health Organization (WHO), herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations [2]. It has been reported that 1.5 billion people used herbal medicines worldwide [2,3] and over US$ 100 billion of global sales of herbal medicines were attained in 2008 [1,4], and these were expected to increase in the future. With the tremendous expansion in the use of traditional medicine worldwide, the therapeutic efficacy, safety, and quality of herbal medicines have become important concerns for both health authorities and the public [2]. In general, the contents of active ingredients present in herbal medicines may vary significantly due to a series of factors such as variations in raw materials from different cultivation areas and climatic conditions as well as differences in production procedures by different manufacturers, which may lead to their quality and therapeutic efficacy fluctuation. Thus, development of systematical and comprehensive quality standards for herbal medicines is imperative. Moreover, seeking adequate and acceptable methodologies for quality assessment and control of herbal medicines is necessary, and rapid and high-throughput analytical methods are primarily desirable.

Mass spectrometry (MS) is a powerful tool for the analysis of complicated samples due to its desirable sensitivity and unparalleled specificity. The atmospheric pressure ionization (API), i.e., electrospray ionization (ESI) [5,6] and atmospheric pressure chemical ionization (APCI) [5], together with various types of ion collision dissociation techniques [7–10] have significantly extended the applications of MS in biological, environmental, and pharmaceutical analysis. Recently, the development of ambient ionization technique [11–15] allows MS for direct analysis of complex samples under ambient and open-air condition with minimal or no sample pretreatment and no chromatographic separation, and thus becomes an excellent choice for rapid and high-throughput analysis of pharmaceuticals and herbal medicines. During the past two decades, a series of ambient ionization methods such as desorption electrospray ionization (DESI) [16–20], direct analysis in real time (DART) [21–24], desorption atmospheric pressure chemical ionization (DAPCI) [25,26], electrospray laser desorption/ionization (ELDI) [27,28], extractive electrospray ionization (EESI) [29–31], direct electrospray probe (DEP) [32,33], probe electrospray ionization (PESI) [34–39], laser ablation electrospray ionization (LAESI) [40–43], dielectric discharge barrier ionization (DBDI) [44], low-temperature plasma (LTP) [45,46], desorption corona beam ionization (DCBI) [47], paper spray [48–52], wooden-tip ESI [53–59], direct ionization [60], tissue spray [61], leaf spray [62], needle biopsy spray [63], pipette-tip ESI [64,65], aluminum foil ESI [66], extraction spray [67,68], and touch spray [69], etc., have been developed and implemented into analytical practices. These ambient ionization methods have been applied for a large number of applications including pharmaceutical and herbal medicine analysis [17,23,24,26,52,55–59], biological analysis and imaging [18–20,36–38,40,42,48,50], *in vivo* analysis [15,30,31,40], *in situ* analysis [41,42], and even single-cell analysis [39–43], etc. Several ambient ionization methods, such as DESI, DART, and paper spray, have been applied for high-throughput analysis. For example, pharmaceutical samples have been high-throughput analyzed by DESI-MS using a moving belt with a speed of 3 samples/s [17]. High-throughput process of DART-MS is easily achieved at a speed of 3 samples/min by using an autosampler [22]. A high-throughput paper spray-MS method has been developed for fast analysis of complex samples with an analytical speed of 7 s/sample [51].

Among ambient ionization methods, wooden-tip ESI is a recently developed one which applied wooden tips as solid substrates for loading samples and ionizing analytes for direct mass spectrometric analysis. By application of a high voltage and some spray solvent on a sample-preloaded wooden tip, analytes are desorbed from sample matrix into solvent, moving to the pointed end by the electric field and leading to formation of Taylor cone, which are then produced charged droplets and ions for mass spectrometric analysis. Wooden tip is hard, slim, hydrophilic, and porous, which is easy to load different forms of samples in many cases. In addition, the narrow-stick shape of wooden tip avoids rapid diffusion and vaporization of spray solvents, enabling longer signal duration time. Moreover, the disposable use of wooden tip greatly reduces memory effects and cross-contamination of analysis. Till now, wooden-tip ESI has been applied for analysis of a wide variety of samples including illicit drugs in raw urine [55], raw plant materials [56], pharmaceuticals [57], and herbal products [58,59], etc. However, there is still no report for the application of wooden-tip ESI-MS for high-throughput analysis. Because a high voltage must be applied on each wooden tip when it passes through the MS inlet for analysis, such a device for high-throughput analysis is relatively difficult to design. If the high voltage is unnecessary to apply on the wooden tips, the device of high-throughput wooden-tip ESI-MS analysis will be much easier to design.

Field-induced ESI gives such an opportunity. It is well known that ESI is performed by application of a high voltage on a capillary emitter (in front of MS inlet) where the sample solution sprays out to form a Taylor cone and produce charged droplets and ions for mass spectrometric analysis. Alternatively, an opposite high voltage can also be applied on the MS inlet, allowing the creation of a strong electric field between the capillary emitter and MS inlet to induce ESI from the sample solution. The latter ESI mode is named field-induced ESI, and it possesses the characteristic that high voltage is contactless to sample. The idea of field-induced ESI has been applied to make commercial ESI sources since its invention [70]. There are also a few ambient ionization methods operated with field-induced mode have been reported recently. For example, field-induced direct ionization was reported for *in vivo* and real-time monitoring of secondary metabolites of living organisms [71]; and polarization induced ESI-MS was reported for direct analysis of liquid, viscous, and solids samples under ambient condition [72].

Wooden-tip ESI can also be operated under field-induced mode with the application of an opposite high voltage on MS inlet. Under this condition, high-throughput analysis is easily achieved because the high voltage is unnecessary to apply on the sample-preloaded wooden tips one by one. In addition, fast polarity switching of the high voltage between positive and negative ion detection mode can be readily accomplished, which provides more complete chemical information for quality assessment and control of herbal medicines. In this study, we demonstrated the first time application of field-induced wooden-tip ESI-MS for high-throughput analysis of herbal medicines. The raw herbal materials were cut and sharpened to produce wooden tips and serve themselves as solid substrates for analysis. The herbal preparations and products were loaded by wooden toothpicks to achieve analysis. Various active ingredients present in different herbal medicines were detected and identified, and the obtained mass spectra were served as the samples' fingerprints for rapidly tracing the origins, establishing the authenticity, and assessing the quality consistency and stability of herbal medicines.