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Quality Markers of Traditional Chinese Medicine: Concept, Progress, and Perspective

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ABSTRACT

As the most important complementary medication against a variety of diseases, traditional Chinese medicines (TCMs) have been extensively applied over thousands of years. Current quality control of herbal medicines, however, is in great dispute. Unlike chemical drugs, which have clear and validated quality standards, the content of only one (or a few) compounds of many herbs and preparations is currently assessed as an indicator of quality, even though the assessed compound(s) is neither closely associated with the efficacy nor representative of the medicine as a whole. Based on the clinical use, compatibility of multiple component prescriptions, and manufacturing process of TCM, the new concept of a TCM quality marker that was proposed in previous work is discussed further here. In addition, practical technological approaches are described for the qualitative analysis and quantification of TCMs including herbs, processed products, and preparations, which lead to the discovery and identification of specific chemicals as quality markers and new quality control patterns. The progress that has been made in TCM quality control is also addressed. This work provides useful information for the quality control of herbal medicines in the future.

1. Introduction

As a conventional therapy, traditional Chinese medicines (TCMs) have been extensively applied in the treatment of various kinds of acute and chronic diseases. There is no doubt that TCM is of particular importance in terms of efficacy and safety. TCM—which includes but is not limited to herbs, species, decoction, and preparations—provides alternative therapy that is complementary to chemical drugs and biological applications. Over the past decades, a great deal of progress has been made in clarifying the mechanisms and substantial basis of TCM [1–5], while the TCM pharmaceutical industry has rapidly developed. Most importantly, TCM has now been integrated into medical care along with other medications for patients who are already under treatment as well as for people who wish to maintain a better quality of life. TCM has gradually been recognized by developed countries including the United States and various European countries. Several TCM preparations that have been developed for various indications are currently in clinical trials in the United States [6–9]. Once marketing approval is granted by the authorities, these endeavors will assist in promoting global acceptance of TCM.

However, the quality control system for TCM is insufficient. Although monographs and standards for the quality control of herbs, processed products, and preparations have been established and recorded in official or private publications such as pharmacopoeia and directives (Table 1) [10,11]—which include definitions, characters, identification, tests, assays, storage information, and more—the information provided in these standards is insufficient to make a clear distinction between species with high similarity. For example, it is difficult to recognize which species *Flos Magnoliae* is derived from, since it can be obtained from *Magnolia biondii* Pamp., *Magnolia denudata* Desr., or *Magnolia sprengeri* Pamp., according to the *Pharmacopoeia of the People's Republic of China* (ChP) 2015 edition. Similar problems exist in the cases of Zicao and Mutong [12,13]; the former may be obtained from *Lithospermum erythrorhizon* (Zicao), *Arnebia euchroma* (Ruan Zicao), or *Onosma paniculatum* (Dian Zicao), while the latter can be obtained from both *Clematis armandii* Franch. (Chuan Mutong) and *Aristolochia manshuriensis* Kom. (Guan Mutong).

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Table 1
Pharmacopoeia and directives of TCMs in different countries or regions.

Pharmacopoeia and directives	Authority
The Pharmacopoeia of the People's Republic of China	China Food and Drug Administration, China[c]
European Pharmacopoeia	European Directorate for the Quality of Medicines & HealthCare, Council of Europe
Japanese Pharmacopoeia	Pharmaceuticals and Medical Devices Agency, Japan
British Pharmacopoeia	British Pharmacopoeia Commission, UK
Australian Regulatory Guidelines for Complementary Medicines	Therapeutic Goods Administration, Australia
WHO Monographs on Selected Medicinal Plants	World Health Organization, United Nations
Hong Kong Chinese Materia Medica Standards	Department of Health, Hong Kong, China
Thai Herbal Pharmacopoeia	Thai Food and Drug Administration, Thailand
Korean Pharmacopoeia	Ministry of Food and Drug Safety, Republic of Korea
American Herbal Pharmacopoeia[a]	American Herbal Pharmacopoeia[b], USA
British Herbal Pharmacopoeia[a]	British Herbal Medicine Association[b], UK
European Directive on Traditional Herbal Medicinal Products	European Parliament and Council, European Union

Adapted from Refs. [10,11].
[a] Unofficial pharmacopoeias.
[b] Private organizations.
[c] Rebranded and restructured as the National Medical Products Administration of the State Administration for Market Regulation of PRC since 2018.

In recent years, the need for a TCM quality control system has become a new hotspot attracting a great deal of research interest. A few years ago, the new concept of a TCM quality marker was proposed by Prof. Changxiao Liu et al. [14,15]. The present review discusses new methods and technologies to explore potential quality markers for TCM quality control, considering the complexity of TCM and the factors that affect TCM quality, and may provide insight into rational grounds for the establishment of an appropriate TCM quality control and assessment system. This paper also discusses progress that has been made in TCM quality control, with the aim of providing a valuable reference for future investigations.

2. A proposed quality marker for TCM

Unlike quality control for chemical drugs, which have clear quality standards for individual pharmaceutical products, investigations of TCM quality and the establishment of corresponding TCM quality standards are complicated. The question of how to formulate TCM quality standards and what methodology can be implemented for quality studies remains in dispute. Any pharmaceutical products—including but not limited to chemical entities, herbal medicines, and biological applications—must be demonstrated to have acceptable quality, efficacy, and safety before they are granted approval for marketing and become accessible to clinical practitioners and individual patients. The good news is that herbal medicines are currently being prescribed and applied in regions beyond Asian countries (and particularly beyond East Asia, where TCMs are common), and are gradually becoming accepted around the world. For example, TCMs are taken as complementary medicines and dietary supplements in European countries and are recognized within the European Union's regulatory framework. Monographs and standards for herbal medicines that are developed through modern technology to provide a modern standard for quality control may promote a more widespread acceptance of TCM.

However, the monographs and standards that have been formulated and are currently recorded in the ChP and other pharmacopoeia/directives—whether published officially or by private organizations—are unable to fulfill the requirements of quality control. The quality standards that are currently implemented are controversial. For example, the content of only one (or a few) compounds of many herbs and preparations is currently assessed as an indicator of quality, even though the assessed compound(s) is neither closely associated with the clinical efficacy of the TCM nor reflects its pharmacological actions, due to the limited number of chemicals tested. Thus far, the main focus of TCM quality assessment involves distinguishing authentic herbs from adulterants; however, the qualitative analysis and quantification of multiple specific components through modern analytical technologies are fundamental for the establishment of TCM quality standards with specificity and controllability.

Based on the conventional theory of TCM, the compatibility of multiple component prescriptions, the preparation of herbal medicines, and the clinical application of TCM, Liu et al. [14,15] proposed a new concept for a TCM quality marker called the Q-marker. Quality markers of TCM are believed to be intrinsic chemicals that exist in herbs and in products made from herbs—including processed products, extracts, and pharmaceutical preparations—or that are formed during processing and preparation. In order to be indicators of quality control, these compounds should be associated with the functions and properties of the TCM in question, such that they reflect its safety and efficacy. A TCM quality marker is a compound that may exist in the raw species, in the processed and final product, or even after the TCM has been absorbed into the bloodstream. Most importantly, the chemical structure of the compounds acting as quality markers should be verified, and the compounds should be specific ingredients that can be determined through qualitative and quantitative analysis. Consequently, the molecules that fulfill these requirements, as discussed in Refs. [14,15], are given special consideration before being chosen as quality markers. To be specific, a quality maker should be a compound that: ① is either intrinsic to the herb or formed during processing; ② is closely related to the functions and properties of the TCM and has a specific structure; ③ can be identified by qualitative analysis and quantification; and ④ preferably represents the "king" herb in terms of the theory of TCM compatibility, but may also represent the minister, guide, and assistant herbs.

3. An exploration of quality markers

The proposal of the new concept of a TCM quality marker triggered discussions on how to explore the chemical ingredients of TCMs as potential quality markers. Multidisciplinary strategies, including but not limited to conventional phytochemistry, analytical technology, bionics, system biology, computational approaches, and others have been utilized to identify compounds with characteristics that fulfill the requirements of a quality marker, based on TCM theory. Zhang et al. [16] elaborated the basic properties of *Corydalis Rhizoma* (Yanhusuo) and the mechanism of action, with a focus on multiple approaches to explore quality markers. Following these ideas, quality markers for *Leonurus japonicus* Houtt., *Penthorum chinense* Pursh., and *Polygonati Rhizoma* have been explored [17,18].

A particularly interesting and reasonable strategy for exploring TCM quality markers has recently been discussed; a diagram of the work flow is plotted in Fig. 1 [19]. To summarize this strategy, the substantial basis of a specific herb and its related preparations is first clarified. An analysis of as many of the chemical ingredients as possible is then performed by phytochemical investigation (liquid chromatography (LC), nuclear magnetic resonance (NMR) spectroscopy, and liquid chromatography–mass spectrometry (LC–MS)) to provide fundamental profiles of the chemical

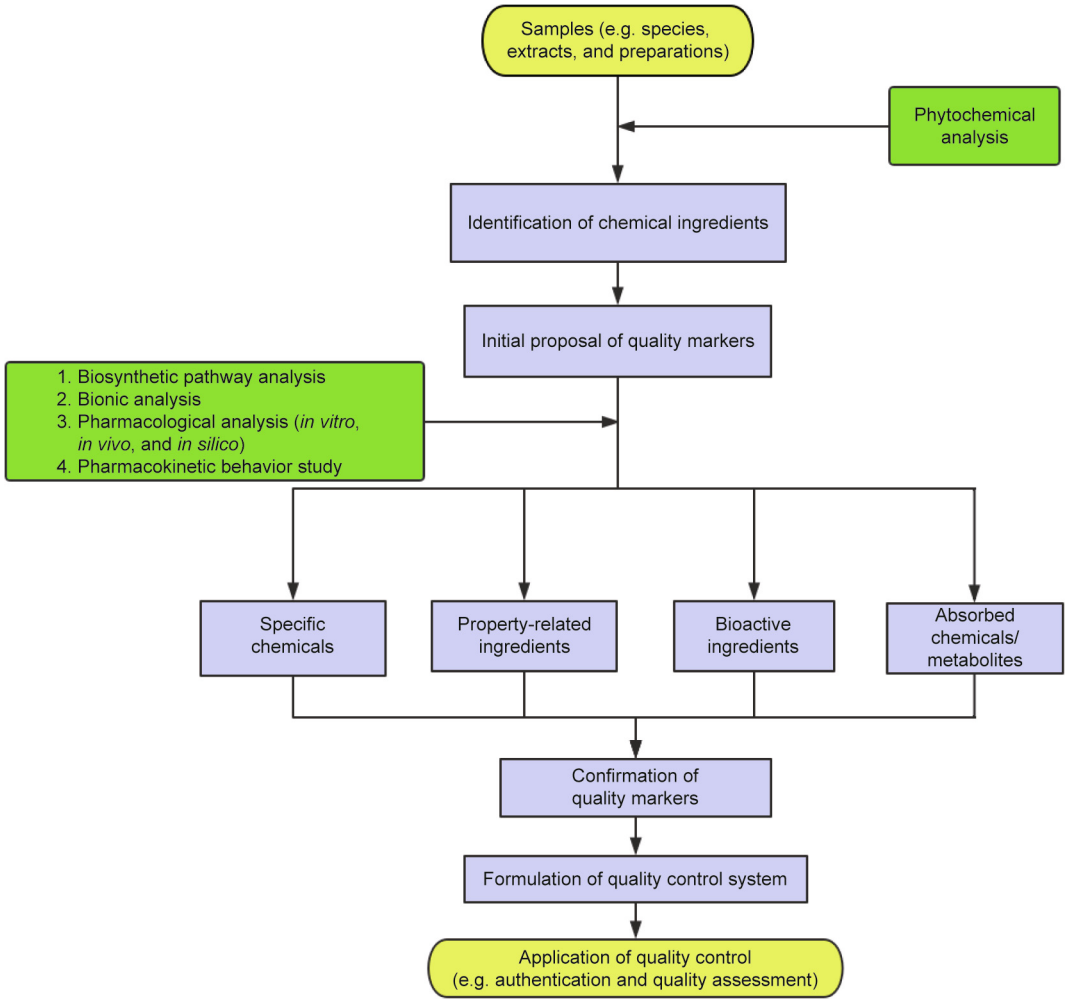

Fig. 1. A typical work flow diagram exploring potential quality markers. Reproduced from Ref. [19] with permission of Elsevier, © 2019.

ingredients. In addition to the structural characterization of chemical ingredients, biosynthetic pathway analysis can offer information on the chemicals attributed to specific components, since the majority of the chemicals in a TCM are secondary metabolites produced via various biosynthetic pathways. According to the theory of TCM, the chemical ingredients behind pungent, sweet, sour, bitter, and salty flavors can be identified as property-related ingredients by an integrated study using diverse methods such as bionic analysis (i.e., electronic nose and tongue) and computational calculations. The next step involves exploring the chemicals that are associated with the efficacy and therapeutic value of a specific herb. Single compounds and/or extracts are screened for their effects using either *in vitro* or *in vivo* models. In this procedure, a pharmacokinetic behavior study of the TCM may help to determine the representative compounds that reflect the compatibility of a multiple component prescription.

A pilot study on a quality marker for *Corydalis Rhizoma* was carried out based on the strategy of establishing a quality marker by integrating all the experimental results obtained from phytochemical analysis, pharmacological analysis, computational calculations of property-related ingredients, and biosynthetic pathway analysis [16]. A standard decoction of *Corydalis Rhizome* after vinegar processing was characterized by high-pressure liquid chromatography time-of-flight mass spectrometry (HPLC–TOF-MS). Of the 31 chemical ingredients, 28 were identified. All were alkaloids, and were classified into three groups: protoberberine, protopine, and aporphine alkaloids. These alkaloids shared *L*-tyrosine as the identical biogenic precursor. Based on an analysis of the biosynthetic pathway of the alkaloids and the specificity of *Corydalis Rhizoma*, tetrahydropalmatine, corydaline, coptisine, palmatine, dehydrocorydaline, *D*-tetrahydrojatrorrhizine, and protopine were initially proposed as potential quality markers. Protopine and aporphine alkaloids are downstream of biosynthesis and have better specificity, whereas protoberberine (e.g., tetrahydropalmatine and corydaline) are main ingredients in terms of content. Further pharmacological studies of extracts of tetrahydropalmatine, both *in vivo* and *in vitro*, confirmed its potent activity in pain relief via significantly prolonged latency in stretching experiments and regulation of the critical protein. For example, it caused endorphin to be up-regulated, while 5-hydroxytryptamine (5-HT) and norepinephrine were reduced. Network pharmacology analysis provided an additional prediction of tetrahydropalmatine, palmatine, protopine, and glaucine as representative ingredients for calculation. Most of the predicted targets and cell-signaling pathways were considered to be associated with analgesic effects in central nervous system at different stages. These chemicals were demonstrated to be bioactive ingredients that correlated with efficacy; glaucine was thus considered to be an additional quality marker. Supportive evidence of property-related ingredients was provided by homology modeling and docking of tetrahydropalmatine, optisine, palmatine, allocryptopine, *D*-glaucine, and protopine against the bitter taste receptor TAS2R10, and by a binding affinity

study with functional receptors related to pungent and bitter flavors, including 5-HT_{1A} receptor, μ-opioid receptor (OPRM1), β_2 adrenergic receptor (ADRB2), thromboxane-prostaglandin receptor (TP/TBXA2R), acetylcholine receptor (M2), and dopamine receptor (D2) [20]. Tetrahydropalmatine and protopine are believed to be able to function with these receptors. In addition, a pharmacokinetic study in rats after oral administration of the *Corydalis Rhizoma* extract indicated that tetrahydropalmatine, tetrahydrojatrorrhizine, protopine, corybulbine, α-allocryptopine, *N*-methyl tetrahydrobamarine, corydaline, tetrahydroberberine, dihydrochelerythrine, and dihydrosanguinarine were absorbed into circulation, and that seven of them were detected in brain tissues. The presence of tetrahydroberberine was attributed to coptisine, since the metabolism of coptisine may take place in the intestine, with the products then being absorbed in the form of tertiary alkaloids. Based on these extensive investigations, tetrahydropalmatine, corydaline, coptisine, palmatine, dehydrocorydaline, *D*-tetrahydrojatrorrhizine, and protopine were suggested as quality markers for *Corydalis Rhizoma*. Quantification approaches for these chemical ingredients and fingerprints of the vinegar process for *Corydalis Rhizoma* were established and extended for the quality control of its preparations, such as Yanhu Zhitong Dropping Pills [21].

4. Application of quality markers in quality assessment

The use of chemical markers as an indicator of the authenticity of herbs and the quality of related preparations is unclear or uncertain for most species, although efforts to explore the chemical ingredients of TCMs for the establishment of a quality evaluation and control system are unceasing. This section expands on the discussion of the progress that has been made in the application of a quality control and assessment system based on quality markers by providing examples of successful experiences with specific cases.

The dried root of *Salvia miltiorrhiza*, known as Danshen in Chinese, is widely used in treatment for cardiovascular and cerebrovascular diseases; it acts by improving blood flow and promoting circulation [22]. Its major bioactive ingredients have been investigated and classified into two groups: lipophilic tanshinones (tanshinone I, tanshinone IIA, cryptotanshinone) and hydrophilic phenolic acids (danshensu, salvianolic acid B, protocatechuic acid). Phenolic acids present bioactivities such as anti-atherosclerosis, anti-phlegmonosis, anti-oxidation, inhibition of platelet aggregation, improving microcirculation, and protecting against myocardial damage; while tanshinones are able to inhibit angiogenesis, dilate coronary arteries, enhance coronary flow, and protect against ischaemia [23–25]. Pharmaceutical preparations with Danshen as the main component are applied in clinical usage; for example, compound Danshen Dropping Pills (CDDP) and Compound Danshen Tablet (CDT) are listed in the ChP. The demand for Danshen is therefore increasing remarkably, and the market value of these products is in the millions or more US dollars. Adulterants of these species and raw materials of lower quality have become unavoidable, as they are driven by commercial interests. The establishment of a quality control and assessment system for this species, its extraction, and the final pharmaceutical products is critical for guaranteeing the safety and efficacy of Danshen.

A large-scale field investigation of Danshen and related medicinal plants in China was performed by Li et al. in the early 2000s and was published in 2008 [26]. Its goal was to distinguish *Salvia miltiorrhiza* from other species, in order to meet the official requirements of the ChP, which documents Danshen. A quantitative analysis of tanshinones and phenolic acids was performed, in addition to botanical authentication. Based on the survey, over 20 *Salvia* species were found to have been considered to be Danshen in local folk medicine, with the collecting locations, growing environment, and distribution of these species genus varying greatly. Samples from different plant species were collected and processed. The resulting data revealed that phenolic acids were detected in all tested samples; however, the contents were at trace levels, apart from rosmarinic acid and salvianolic acid B, which were the most abundant. For example, salvianolic acid B ranged from trace to 82.52 $mg \cdot g^{-1}$. Levels of tanshinones were demonstrated to be associated with the color of the root bark of the species. The different natural product profiles were attributed to either genetic or environmental changes; in particular, salvianolic acid B ranged from 30.95 to 55.77 $mg \cdot g^{-1}$ in various samples of *Salvia miltiorrhiza*. In addition, tanshinones and phenolic acids appeared to be less correlated, in terms of concentration, indicating that they might be two independent variables, and that both should be used as markers for quality control. According to the requirements for the quantification of Danshen recorded in the ChP (2005), the amounts of salvianolic acid B and tanshinone IIA should be no less than 30 and 2 $mg \cdot g^{-1}$, respectively. Several samples of *Salvia miltiorrhiza* achieved this requirement; these samples were distinguished from other species and concluded to be the official ones.

The quality of Danshen has been shown to be associated with the germplasma and harvest [27], When harvesting Danshen, it is essential to wait until the quantity of specific bioactive compounds reaches acceptable levels, rather than harvesting the plant at the root-swelling stage, although the latter is conventionally taken as the harvest time and is when the highest production of this herb occurs. Changes in the levels of cryptotanshinone, tanshinone IIA, danshensu, and salvianolic acid B were continuously examined in the roots of three germplasma, which were cultivated under identical conditions but collected at different harvest times. For example, the levels of cryptotanshinone and tanshinones IIA in Henan violet flower Danshen continued to decrease, while the levels of danshensu and salvianolic acid B accumulated in a very strange manner, by initially decreasing and subsequently increasing [27]. Changes in the levels of these chemical markers indicated the optimal harvest time, and provided key evidence in the selection of germplasma lines regarding the contents of the designated bioactive compounds.

Chemical markers were used as an indicator of the quality control of raw materials such as species and slices; these compounds were further applied as markers for the quality control of pharmaceutical preparations, with a particular focus on consistency. Based on the combined use of chromatographic separation and chemometric methods, quality investigations were performed on Danshen preparations [28–32]. Protocatechuic aldehyde, salvianolic acid B, cryptotanshinone, and tanshinone IIA were selected as markers for the quality control of CDT, in addition to ginsenoside Rg, ginsenoside Rb, and notoginsenoside R. The resulting data showed that salvianolic acid B was the most abundant compound in the samples manufactured by different companies, whereas the other three compounds were present in low concentrations in the tablets. Moreover, the content varied in the samples tested, with the variation being attributed to the quality of the raw materials that were used [29]. Similarly, the content of eight phenolic acids and tanshinones was examined in order to assess the quality of a granule of Danshen extract produced by different manufacturers [30]. Of the 15 batches of granules assessed, salvianolic acid B and rosmarinic acid were found to be the phenolic acids that were present in the greatest amounts, while tanshinone I, cryptotanshinone, and tanshinone IIA were found to be the hydrophobic components that were present in the greatest amounts. The content of salvianolic acid B, however, varied up to 30-fold by comparison. Most importantly, the contents that were identified did not align with the labeling of these granules, indicating a potential risk to

efficacy and safe use. HPLC fingerprints were combined with a similarity evaluation to investigate the quality of danshen and its preparations [33]. Danshen, CDT, CDDP, and Danshen injection (DSI) were analyzed by a similarity evaluation of their chromatographic fingerprints. The peaks of the chemical ingredients were identified by comparing with a reference. The correlation coefficients of the standard samples, including Danshen, CDT, and CDDP, were over 0.9, whereas those of the random samples and DSI had low correlation values and high variation, suggesting inconsistent quality.

A simple and rapid proton NMR (^{1}H NMR) technique for the qualitative and quantitative analysis of compound Danshen extract (CDE) and CDDP was established and was demonstrated to be a good supplement to the LC approach [31]. A total of 32 batches of CDE were studied by NMR; three phenolic acids (danshensu, salvianolic acid B, and protocatechuic aldehyde) were simultaneously determined and cross-tested by the LC approach. No significant differences were found in terms of the contents of three phenolic acids determined by both approaches. The established method was applied to 12 batches of CDDP. Again, the determined levels of the phenolic acids exhibited good consistency, indicating that this method provides an alternative method for the quality control of the final product.

With the development of sensitive analytical approaches and a more comprehensive understanding of the substantial basis/pharmacological action of TCM medicines, the criteria for quality control covering species, extracts, and preparations have been enhanced step by step. In the 2000 version of the ChP, danshensu and tanshinone IIA were selected as single markers for the quality control of CDDP and CDT, respectively. Today, multiple ingredients have emerged as quality markers of Danshen and its related preparations. Cryptotanshinone, tanshinone I, tanshinone IIA, and salvianolic acid B have been combined as integrative markers for Danshen. Although tanshinone IIA and salvianolic acid B have been chosen as markers for CDT, compound Danshen granule, and compound Danshen capsule, the specified contents are highly variable depending on the formulations and specifications in the 2015 version of the ChP, since different processing and manufacturing may lead to content change. Thus, the quality control system for Danshen may require further optimization. Other chemical ingredients in Danshen should not be ignored. For example, rosmarinic acid is an abundant chemical in the roots with a concentration ranging from 0.59 to 34.44 $mg \cdot g^{-1}$ and diverse bioactivities; it has been suggested as an optional marker [26]. A pair of atropisomeric trimeric caffeic acid derivatives, salvianolic acid T and U, were recently isolated from *Salvia miltiorrhiza* and provide an alternative and beneficial complement to the current quality control system of Danshen that can be considered in future [34]. An experimental approach to explore quality markers by utilizing salvianolic acids for injections has also been reported [35].

5. Optional approaches for quality control

In the identification of herbs, bioassays are an important complement to the use of chemical ingredients as indicators for the authentication of species and preparations. The potential of the DNA barcode in distinguishing authentic species from their adulterants has been explored. For example, ITS2 has been investigated as a potential DNA barcode in a large-scale study [36]. A total of 61 commonly used herbs and closely related species or adulterants were investigated, with over 4000 samples being collected in this experiment. The resulting data was positive with high rates of success. For the dataset containing 34 herbs and 111 adulterants, all the herbs were successfully distinguished from the adulterants; ITS2 was able to separate 48 herbs from closely related species in a dataset with 51 herbs and 2382 closely related species. DNA barcode technology is still in a very early stage of development today; however, it should be given special consideration for its potential for quality control.

Another alternative is bioactivity assay of herbal medicines. For example, Qin et al. [37] attempted to distinguish aconitum herbs by toxicity. The use of bioassays to evaluate toxicity by the determination of minimum lethal doses was established, and toxic exposure was calculated and compared. The experimental conditions were optimized in order to ensure reliability, although the study failed to explain the overall toxicity of the herbs, since the total toxicity of the extract was much higher than those of three toxic alkaloids measured by the LC approach in parallel. Even though it was not a successful application of bioassay, this approach is a promising tool for the safety assessment of herbs and requires further improvement.

6. Perspective

In summary, the efficacy and safety of TCMs are strongly associated with the chemical ingredients of many structurally diverse compounds. As TCMs are an important therapy against disease, their quality is of particular importance in guaranteeing their value in treatment and their safety for patients. Current quality control and standards for most herbs, processed herbal products, and TCM preparations are unsatisfactory, since either the quality assessment is insufficiently correlated with the efficacy, or the chemicals chosen for quality control are not representative of the medicine as a whole. Moreover, quality studies of herbs, processed products, and preparations are fragmented rather than integral.

There is a need to determine potential solutions to the issue of the quality of TCMs, which is a very serious problem for pharmaceutical industries. In past years, scientists have intensively discussed research strategies and technological approaches in detail by hosting high-end seminars, and the concept of quality markers and related studies has been given special consideration by central funding bodies such as the National Natural Science Foundation of China. Several major research projects in this new field are scheduled to receive financial support for investigating the scientific rationale of this concept. Recently, a special issue on quality markers was organized and published by the leading journal *Phytomedicine*. New methodologies, research patterns, and research efforts were reported. In addition to a discussion on the concept of quality markers [38], it was proposed that biological activity—and particularly biological response [39]—and intelligent quality management with near-infrared spectroscopy [40] be integrated into the evaluation of TCM quality. Pharmacokinetic studies of ingredients in herbs were also reviewed for the discovery and identification of quality markers [41,42]. Along with discussions of methods, investigational studies of quality markers using multiple approaches have been reported [43–48]. These studies cover a molecular connectivity index, an effect-constituent index, quality-marker-based chemical manufacturing and control, integrative pharmacology, and relevant data mining. Meanwhile, modern analytical technologies, including MS and chemometrics, have been applied to identify potential quality markers for coix seeds [49], ginseng [50,51], and pharmaceutical preparations [51–54]. All of these studies have greatly expanded the range of TCM quality control, guided by the concept of quality markers.

The concept of quality markers for TCMs was proposed on the basis of a combination of the biological properties, manufacturing processes, and compatibility principle of TCMs in order to integrate studies of TCM quality by emphasizing the relationship between the efficacy, substantial basis, and representative components of TCM. The proposed concept and—most importantly—the novel research pattern that resulted, with its focus on the traceability

and transitivity of quality throughout the entire quality control procedure, will eventually be beneficial to the establishment of a TCM quality control system.

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Compliance with ethics guidelines

Yazhuo Li, Ying Xie, Yufei He, Wenbin Hou, Maoliang Liao, and Changxiao Liu declare that they have no conflict of interest or financial conflicts to disclose.

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