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ADULTERATION OF HERBAL MEDICINES: DETECTION METHODS AND REGULATORY RESPONSES

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Abstract

Herbal medicines are used by a large share of the world's population, yet the products on sale are frequently not what their labels claim. This review summarises published work on how herbal materials are adulterated, from substitution and filler plants to undeclared synthetic drugs and toxic metals, and on the methods used to detect them. It covers morphological, microscopic and chromatographic tests, DNA barcoding and sequencing, and spectroscopic and metabolomic approaches, then compares regulatory responses in the World Health Organization, the European Union, the United States and India. A synthesis table collects representative findings. The review reports no new data. Evidence shows that no single method suffices, reference libraries are incomplete, and enforcement lags behind supply chains.

1. INTRODUCTION

Herbal medicines are used in every region of the world, as traditional remedies, as over-the-counter products and, increasingly, as dietary supplements. The World Health Organization has reported that a large majority of its member states acknowledge some form of traditional or complementary medicine, with herbal products making up a large part of it [1]. Many consumers regard these products as natural and therefore safe, an assumption that reviews of the clinical literature have repeatedly challenged [2]. Safety problems arise not only from the plants themselves, which can be toxic or can interact with prescribed drugs, but also from what is

in the bottle. A product may contain a different species from the one named on the label, may be diluted with cheap filler, or may carry a conventional drug that is not declared at all [3, 4].

The word adulteration is used loosely, and it helps to separate its meanings. In pharmacognosy it covers the deliberate or negligent addition of foreign material, the substitution of a genuine drug by an inferior or different one, and the addition of an active compound to make a weak product appear potent. Contamination with metals, microbes, pesticides or mycotoxins is a related but distinct problem, since it is usually unintentional, although reviews of quality problems tend to treat the two together [3, 5]. The consequences are practical. Patients can be harmed by an undeclared steroid or a toxic substitute, can be denied the benefit of the intended plant, and can be misled about what they are paying for. Rare or protected species may also be driven further towards extinction when they are traded illicitly [6].

This review brings together published evidence on how adulteration occurs, how it is found, and how regulators have responded. It does not report any new analyses. It begins with the forms and extent of the problem, then looks at classical morphological and chromatographic methods, DNA-based identification, and spectroscopic and metabolomic techniques, before comparing regulatory frameworks and discussing limitations. Throughout, the aim is to distinguish what the literature has established from what has been claimed, because prevalence figures for adulteration vary widely with sampling, method and definitions, and strong statements on both sides of the debate are common. Where the evidence is thin or contested, the text says so. The emphasis is on methods that a quality-control or regulatory laboratory could realistically adopt.

2. FORMS AND EXTENT OF ADULTERATION

Several distinct patterns recur in the literature. Substitution replaces the labelled plant with a related or look-alike species that is cheaper or easier to obtain, sometimes because the two share a vernacular name. Admixture dilutes the genuine material with fillers such as rice, wheat, soybean or other plant matter, and extenders, colourants and flavourings may be added to disguise it. Spiking adds a pure synthetic drug or a purified natural compound to boost apparent activity. Mislabelling covers products that declare the wrong plant part, grade or origin [3, 7]. A single product can show more than one pattern at once, and the older distinction between accidental and intentional adulteration is often impossible to draw from the analytical result alone.

Adulteration with synthetic drugs is the most dangerous form, and the evidence for it is substantial. A systematic review of Chinese herbal products found numerous reports of undeclared conventional drugs, including corticosteroids, non-steroidal anti-inflammatory agents and hypoglycaemic agents [4], and further surveys described the same pattern in Asian remedies more widely [5]. A study of patent medicines bought in New York found Western pharmaceuticals in a number of samples [8]. In the United States, analysis of regulatory warnings issued over about a decade identified hundreds of supplements containing unapproved ingredients, mostly in the categories of sexual enhancement, weight loss and muscle building [9]. Laboratory work has documented a continuing stream of new analogues of phosphodiesterase inhibitors added to such products, designed to evade routine screens [10].

Botanical substitution has been harder to measure, and the numbers are contested. A study applying high-throughput DNA sequencing to herbal supplements sold in North America reported products containing plant species not named on the label, together with fillers and contaminants [7]. A later review of authentication studies across many countries found that adulteration was reported in a large fraction of commercial products tested [11], and deep sequencing of traditional Chinese medicines turned up plant and animal DNA from protected and potentially toxic species [6]. Industry groups have criticised some of these studies, arguing that DNA tests may fail in extracts and that detection of a species does not prove deliberate fraud. Both

sides have a point, and a cautious reading accepts that substitution is common without placing much weight on any single percentage.

The causes are mainly economic and structural. Herbal raw materials pass through long chains of collectors, traders, processors and manufacturers, and wild harvesting, seasonal scarcity and price volatility create incentives to substitute cheaper material [12]. Identity is hard to verify once a plant has been dried, cut, powdered or extracted, so that fraud at an early stage may go unnoticed by later handlers. Vernacular names are inconsistent, and the same common name can refer to different species in different regions. Comparisons of Rhodiola material by NMR metabolomics and HPTLC, from traditional resource to commodity, showed marked differences in chemical profile between samples, and analysts working on value chains have argued that quality assurance has to start at the point of collection and cannot rely on end-product testing alone, an argument that has influenced regulatory guidance on good practice [12, 13].

Adverse events have often been the route by which adulteration was first noticed. Case reports of Cushingoid features after a herbal arthritis remedy, of hypoglycaemia after a so-called natural diabetes product, or of severe hypertension after a slimming capsule have led clinicians to ask for chemical analysis and found conventional drugs in the pill [2, 4, 5]. Such discoveries depend on alert prescribers and on spontaneous reporting systems that accept reports about herbal products, which many do not. Pharmacovigilance for herbal medicines is hampered by incomplete labelling, by the habit of patients not mentioning supplements to their doctors, and by the difficulty of linking an event to a specific batch. The true burden of harm from adulterated products is therefore probably underestimated [3, 9].

Contamination with toxic metals is a neighbouring problem that deserves mention because of its clinical weight. Reports of lead poisoning linked to Ayurvedic medicines in several US states, and a clinical review of lead encephalopathy from traditional medicines, identified toxic metals, chiefly lead, as a recurrent finding, sometimes at levels that would exceed accepted daily intake limits if the product were taken as directed [14, 15]. In some traditional systems metals are added deliberately after specific processing, which makes it a matter of formulation as much as of adulteration, and critics note that the processing claims are seldom supported by modern toxicological data. Whether such products are classed as adulterated depends on the legal framework, which is one reason why definitions differ among countries and publications.

3. MORPHOLOGICAL AND CHROMATOGRAPHIC METHODS

The classical approach starts with the senses and the microscope. Trained pharmacognosists examine the shape, colour, odour and texture of whole or cut material, and the microscopic features of powders, such as trichomes, crystals, stomata and starch grains, can identify a species and reveal foreign matter. Pharmacopoeial monographs set out these identification tests for hundreds of drugs, along with limits for foreign matter, ash and extractive values [16, 17, 18]. The methods are cheap, need little equipment and remain the first line of defence at the point of purchase. Their weakness is that they depend on expertise that is becoming scarcer, and they lose power when the material has been ground, extracted or processed into capsules, at which point the diagnostic features are gone.

Thin-layer chromatography, especially in its high-performance form (HPTLC), is the workhorse of chemical identification. The sample extract and a reference extract are developed side by side, and the pattern of bands under visible and ultraviolet light is compared. The technique is simple, can analyse many samples on one plate, and gives a visual fingerprint that can be documented and shared [19, 20]. Atlases of reference chromatograms exist for many common drugs. HPTLC can spot gross substitution when the fingerprint of a related species differs, but it cannot always distinguish closely related species with similar chemistry, and a band-matching test can be passed by a product spiked with the marker compound. For this reason, it is best used as a screen with

confirmation by another method.

High-performance liquid chromatography gives higher resolution and quantitative data. Two approaches dominate. Assay of one or a few chemical markers sets a minimum content of an active or characteristic compound, and works well when the marker is specific to the correct species [21]. Chromatographic fingerprinting records the whole profile and compares it with that of an authentic reference by similarity indices or multivariate statistics, an approach widely adopted in the quality assessment of traditional Chinese medicines [22]. Fingerprints are less easily defeated than single-marker assays, since adding one pure compound does not reproduce the whole pattern, but they depend on consistent extraction and on the natural variability of the plant being captured in the reference set.

Any analytical method used for authentication needs validation. The usual principles of analytical method validation, covering specificity, accuracy, precision, detection and quantification limits, linearity and range, apply equally to herbal testing and to chromatographic fingerprints of herbal medicines, though the complexity of botanical matrices makes some of them difficult to demonstrate [23]. Specificity is the central concern, since the method must discriminate the genuine material from every plausible adulterant, and that requires authentic reference materials and a defined list of likely substitutes. In practice, laboratories often lack either. Comparative studies of plant material from different sources show that chemical variability within a species can be as large as the difference between species, which complicates any threshold-based test [24].

4. DNA-BASED AUTHENTICATION

DNA barcoding identifies a species from a short, standardised stretch of DNA, compared against a reference library. The idea came from work on animals with the mitochondrial cytochrome c oxidase subunit I gene [25]. For land plants, no single region performed as well, and a working group of botanists recommended the combination of the chloroplast genes rbcL and matK as a core barcode [26]. Subsequent evaluations found that the internal transcribed spacer 2 (ITS2) of nuclear ribosomal DNA discriminated a large proportion of medicinal species and was easier to amplify from processed material [27]. In practice, authentication laboratories often use several loci together, because the resolving power of each differs between plant families.

The method has clear strengths for authentication. It does not depend on the plant's chemistry, which varies with growing conditions and harvest time, and the DNA sequence is the same in every tissue and at every season. It can identify fragments too small for microscopy and can detect a species that should not be present, which makes it well suited to substitution and admixture. Several reviews describe how barcoding has been applied to medicinal plant raw materials and to finished products [28, 29], and routine use in a testing laboratory for natural health products has been demonstrated [30]. For a regulator trying to check a label against a product, a sequence match to a vouchered reference is persuasive evidence.

The method also has well-documented limits, which are the source of much of the dispute about prevalence figures. DNA is damaged by heat, drying, extraction with solvents and long storage, and highly processed products such as extracts, tablets and capsules may contain little amplifiable DNA, so that a failed test cannot be interpreted as proof of substitution or of authenticity [28, 31]. Short mini-barcodes can partly overcome degradation. Reference libraries are incomplete, especially for the many closely related or poorly studied species used in traditional medicine, and a sequence with no good match can be misassigned. Finally, closely related species may share barcode sequences, and hybridisation can confuse the picture further [27, 31].

High-throughput sequencing has extended barcoding from single samples to mixtures. In metabarcoding, DNA from a multi-ingredient product is amplified with general primers and the pool of amplicons is sequenced, giving a list of all species present. Applied to traditional Chinese medicines, it detected plant and animal species that were not

declared, including some that are legally protected [6]. The approach is powerful but only semi-quantitative, since amplification biases make read counts unreliable measures of proportions, and it is sensitive to cross-contamination in the laboratory. A positive result for a minor species could reflect trace carry-over in a shared factory, and the possibility of lawful use as an excipient cannot be ignored [6, 11].

A further point is that DNA identifies the plant, not the pharmacology. A product may contain the correct species, with a perfectly matching barcode, and still be spiked with a synthetic drug, extracted with an unsuitable solvent or contaminated with heavy metals. DNA tests are blind to all of these. The corollary is that authentication programmes should combine DNA identification with chemical profiling, and that a clean DNA result should not be presented as a certificate of quality [11, 31]. Practitioners increasingly describe the two approaches as complementary, one answering the question of what plant is present and the other what is in the extract, and neither replaces the other.

5. SPECTROSCOPIC AND METABOLOMIC APPROACHES

Nuclear magnetic resonance spectroscopy takes an untargeted view of a sample, recording signals from all the abundant constituents in a single reproducible measurement. The resulting profile can be compared with reference spectra or analysed by multivariate statistics, and the technique is quantitative without compound-specific standards [32]. In a comparison of NMR, ultra-high-performance liquid chromatography and HPTLC applied to turmeric along its value chain, the methods gave complementary information on chemical variability and on adulteration [24]. Diffusion-ordered NMR has been used to detect undeclared synthetic compounds in herbal slimming products without chromatographic separation [33]. The main drawbacks are cost, the need for specialist instruments and lower sensitivity than mass spectrometry for trace adulterants.

Vibrational spectroscopy offers speed. Near-infrared, mid-infrared and Raman measurements need little or no sample preparation and take seconds, which suits screening at ports, markets or manufacturing sites. The spectra are broad and overlapping, so interpretation relies on chemometric models trained on authentic and adulterated samples, an approach that has been reviewed extensively in the food-fraud literature and is transferable to herbal materials [34]. The models are only as good as their training sets. A model built on one supplier's authentic material may flag a legitimate sample from another origin as adulterated, and an adulterant not represented in the training data will be missed. Portable instruments are attractive but need local calibration.

Mass spectrometry coupled to liquid chromatography is the standard way to find synthetic drugs in herbal products. Targeted methods search for a defined list of compounds, such as sildenafil and its relatives, corticosteroids or sibutramine, at very low levels. The difficulty is that illicit manufacturers modify the structure of these drugs slightly to produce analogues that do not appear on the target list, and the number of such analogues recorded in food supplements has grown steadily [10]. High-resolution instruments allow non-targeted screening, where unexpected compounds are identified by accurate mass and fragmentation patterns, and this has become the preferred strategy for regulatory laboratories dealing with hidden analogues [9, 10].

Toxic elements are measured by atomic absorption or inductively coupled plasma techniques, and the International Council for Harmonisation guideline on elemental impurities sets permitted daily exposures against which results can be judged [35]. Heavy metal testing is not a means of detecting adulteration in the strict sense, but it forms part of any quality programme, because the same low-cost practices that lead to substitution also lead to contamination. The reports on Ayurvedic medicines show how serious the problem can be when testing is omitted [14, 15]. Together with testing for pesticide residues, mycotoxins and microbial counts, element analysis rounds out the minimum set of tests that regulators expect on

herbal raw materials and finished products [35, 36].

6. REGULATORY RESPONSES

Regulatory responses and detection findings are collected together in table 1. At the international level, regulators and standard-setting bodies have issued guidance that treats quality as a property of the whole supply chain. These include the European Medicines Agency guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin, the United States Pharmacopeia chapter on articles of botanical origin, the International Council for Harmonisation guideline on elemental impurities, and the European guideline on specifications for herbal substances and preparations [16, 35, 36, 37]. They are advisory, but many national systems have borrowed from them. The more recent global report on traditional and complementary medicine documents national policies and regulations, and shows that regulation of herbal products remains uneven, with many countries lacking even a definition of the product category [1].

Standards written into pharmacopoeias are the formal expression of what authentication should look like. A monograph for a herbal drug typically defines the botanical source and plant part, gives macroscopic and microscopic descriptions, sets a thin-layer chromatographic identity test, specifies limits for foreign matter, loss on drying, ash and sometimes marker content, and lists tests for contaminants [16, 17, 18]. The strength of this system is that the tests are public, repeatable and legally referenced. Its weakness is that monographs take years to revise, cover only a fraction of the species in trade, and are generally written to detect natural adulteration or poor quality rather than the deliberate spiking with synthetic drugs that causes most serious harm [10, 17].

The European Union chose a registration route. Directive 2004/24/EC introduced a simplified procedure for traditional herbal medicinal products, under which a manufacturer can rely on evidence of long use instead of clinical trials, provided that quality and safety documentation is supplied [38]. Quality is judged against the European Pharmacopoeia, whose monographs require identification by macroscopic and microscopic examination, thin-layer chromatography and assay for many herbal drugs [17]. The approach makes authentication a legal condition of marketing in principle. Its reach is nevertheless limited to products that choose to register as medicines, and many herbal items are sold as food supplements under looser rules, which in effect leaves a parallel market with fewer controls.

The United States follows a different philosophy. The Dietary Supplement Health and Education Act of 1994 classed herbal supplements as a category of food, so that manufacturers do not need premarket approval of safety or efficacy, and the regulator has to prove that a product is unsafe or misbranded after it reaches the market [39]. A final rule on current good manufacturing practice, published in 2007, did add duties, including identity testing of each dietary ingredient, specifications and complaint handling [40]. Enforcement still relies largely on inspection and on warnings after problems are detected, and analysis of those warnings shows how many products with undeclared drugs were sold before action was taken [9].

Table 1: Selected findings on herbal adulteration, detection methods and regulatory instruments

Topic	Reported finding or provision	Ref.
Metals in Ayurvedic products poisoning reports and review	Toxic metals, chiefly lead, repeatedly found, with clinical poisoning linked to some products	[14, 15]
Chinese herbal medicines systematic review	Numerous reports of undeclared corticosteroids, anti-inflammatory and hypoglycaemic drugs	[4]
Supplements with FDA warnings decade of notices	Hundreds of products with unapproved ingredients, chiefly sexual enhancement and weight loss	[9]
Herbal products in North America DNA sequencing	Unlisted species, fillers and contaminants reported in tested products	[7]

Topic	Reported finding or provision	Ref.
Traditional Chinese medicines deep sequencing	Plant and animal DNA from protected and toxic species detected	[6]
ITS2 region plant barcode	Validated as a barcode for identifying many medicinal plant species	[27]
HPTLC fingerprints visual comparison	Band patterns against reference extracts identify species and flag gross substitution	[19, 20]
Turmeric value chain NMR, UHPLC, HPTLC	Methods gave complementary data on chemical variability and adulteration	[24]
Weight-loss herbal products DOSY NMR	Undeclared synthetic compounds detected without chromatographic separation	[33]
European and ICH quality guidance collection and specifications	Quality treated as a property of the whole chain, from collection practice to finished-product specifications	[36, 37]
EU Directive 2004/24/EC traditional use	Simplified registration for traditional herbal medicines with quality documentation	[38]

India regulates Ayurvedic, Siddha and Unani medicines under a dedicated chapter of the Drugs and Cosmetics Act of 1940 and the rules made under it, which require manufacturing licences, adherence to good manufacturing practice and compliance with the standards of official texts [41]. The Ayurvedic Pharmacopoeia of India includes monographs and test methods for many herbal drugs, including identification, foreign matter and ash values [18]. The challenge here is the same as elsewhere: a large and fragmented industry, with many small manufacturers, a big informal market and limited testing capacity. Reports of metal-containing remedies and of drug-adulterated products sold online suggest that the formal framework does not reach everything that is sold [5, 14, 15].

The entries in table 1 are divided among prevalence studies, DNA methods, chemical methods and regulatory instruments, as shown in fig. 1. The spread is fairly even, which hides a mismatch in effect. Detection research has produced more methods than regulators have adopted, and the regulatory documents say less about which methods should be used than about the general principle that identity must be verified [16, 37, 38, 40]. Pharmacopoeial standards, which should connect the two, are still mostly based on morphology and chromatography, with DNA methods only gradually entering official texts. The gap between what laboratories can do and what the law requires them to do is, in the opinion of many authors, the practical heart of the problem [12, 31].

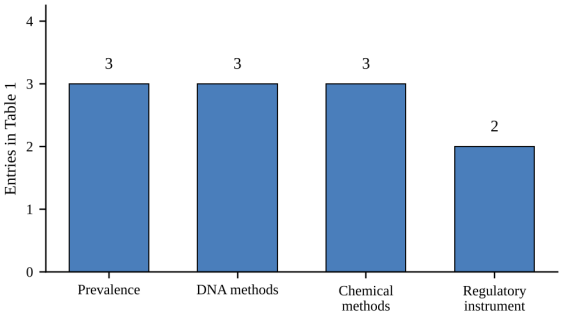


Fig. 1: Number of entries in table 1 by topic group

7. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations of the literature should be kept in view. Most prevalence studies use convenience samples bought from shops and websites, with differing definitions of adulteration and methods of varying sensitivity, so that percentages cannot be compared across studies or extrapolated to the market as a whole [3, 11]. Reference libraries and reference materials are incomplete, which means that negative results are as uncertain as positive ones. Publication bias is likely, because laboratories that find nothing may not publish. Finally, few studies link an analytical finding to harm in patients, and the clinical importance of substitution with a related species is often unknown, even though the regulatory importance is clear.

A tiered strategy that combines methods is the most defensible response. Botanical examination and HPTLC screen the raw material, DNA barcoding confirms the species, chemical profiling by HPLC or NMR checks the extract, and mass spectrometry screens finished products for synthetic drugs and metals [12, 13, 31]. Results are most reliable when they are interpreted together and when each method has been validated

against known adulterated samples. Open databases of sequences, spectra and chromatograms linked to vouchered specimens would make such strategies cheaper, and funding for them is a reasonable use of public money, since the same infrastructure serves industry, regulators and researchers. Where a single method must be chosen because of cost, it is better to pick one that answers the most probable question for the product in hand than one that is merely the most sophisticated.

Prevention is likely to deliver more than detection. Traceability from collector to consumer, contracts that specify identity testing at each transfer of ownership, and cultivation of high-value species instead of wild collection reduce the opportunity and incentive to substitute [12]. Training of inspectors and of laboratory staff in pharmacognosy, which has been declining in many countries, would help preserve the skills on which authentication ultimately depends. Regulators could also adopt risk-based sampling, directing testing at product categories with a record of problems, and publish results so that manufacturers have an incentive to comply. None of these measures is new, but evidence of their effect on adulteration rates is almost absent and would be worth gathering.

Economic analysis of the problem is surprisingly thin. If testing costs more than the margin on a cheap herb, small producers will either skip it or pass the cost to buyers, and if penalties are rare and mild, deliberate adulteration remains profitable. Studies that estimate the cost of authentication per batch, compare it with the price of the material and model the effect of penalties would help policy makers choose between stricter rules and more support for testing [12]. Some of the more successful schemes, in which buyers pay a premium for verified material, suggest that market incentives can complement regulation where the product has recognised value.

8. CONCLUSION

Adulteration of herbal medicines is well documented, though its true extent is uncertain. Synthetic drugs concealed in remedies, toxic metals, filler plants and botanical substitution have each been reported repeatedly in different regions and by different methods [4, 7, 9, 14]. The causes lie in long and opaque supply chains, in the economics of scarce raw materials and in regulatory systems that, in several large markets, treat many herbal products as foods [12, 39]. The range of detection tools is now broad, from microscopy and HPTLC through DNA barcoding to NMR and high-resolution mass spectrometry, and each reveals something the others miss [19, 27, 32].

Progress will depend on using these tools together, on open reference libraries and validated methods, and on regulations that name the tests expected rather than only the principle of identity [23, 31]. Prevention through traceability and agreement on specifications at each transfer along the chain is likely to be more effective than inspection of finished goods [12, 37]. Patients and prescribers should treat unregistered herbal products with caution, particularly those advertised for weight loss, sexual function or glucose control, where undeclared drugs are most often found [9, 10]. Better evidence on the real prevalence and clinical harm of adulteration would sharpen priorities and is a reasonable goal for future work [3, 11].

9. ABBREVIATIONS

DNA-Deoxyribonucleic acid, DOSY-Diffusion-ordered spectroscopy, EU-European Union, FDA-Food and Drug Administration, GACP-Good agricultural and collection practices, GMP-Good manufacturing practice, HPLC-High-performance liquid chromatography, HPTLC-High-performance thin-layer chromatography, ITS2-Internal transcribed spacer 2, NMR-Nuclear magnetic resonance, UHPLC-Ultra-high-performance liquid chromatography, WHO-World Health Organization

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Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. World Health Organization. WHO global report on traditional and complementary medicine 2019. Geneva: WHO; 2019.
2. Ernst E. Harmless herbs? A review of the recent literature. Am J Med 1998;104:170–8.
3. Shaw D. Toxicological risks of Chinese herbs. Planta Med 2010;76:2012–8.
4. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med 2002;252:107–13.
5. Ernst E. Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends Pharmacol Sci 2002;23:136–9.
6. Coghlan ML, Haile J, Houston J, *et al.* Deep sequencing of plant and animal DNA contained within traditional Chinese medicines reveals legality issues and health safety concerns. PLoS Genet 2012;8:e1002657.
7. Ivanova NV, Kuzmina ML, Braukmann TWA, Borisenko AV, Zakharov EV. Authentication of herbal supplements using next-generation sequencing. PLoS One 2016;11:e0156426.
8. Miller GM, Stripp R. A study of Western pharmaceuticals contained within samples of Chinese herbal/patent medicines collected from New York City's Chinatown. Leg Med 2007;9:258–64.
9. Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Administration warnings. JAMA Netw Open 2018;1:e183337.
10. Venhuis BJ, de Kaste D. Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements: a history, analytical aspects and health risks. J Pharm Biomed Anal 2012;69:196–208.
11. Ichim MC. The DNA-based authentication of commercial herbal products reveals their globally widespread adulteration. Front Pharmacol 2019;10:1227.
12. Heinrich M. Quality and safety of herbal medical products: regulation and the need for quality assurance along the value chains. Br J Clin Pharmacol 2015;80:62–6.
13. Booker A, Zhai L, Gkouva C, Li S, Heinrich M. From traditional resource to global commodities: a comparison of Rhodiola species using NMR spectroscopy–metabolomics and HPTLC. Front Pharmacol 2016;7:254.
14. Centers for Disease Control and Prevention. Lead poisoning associated with Ayurvedic medications, five states, 2000–2003. MMWR 2004;53:582–4.
15. Karri SK, Saper RB, Kales SN. Lead encephalopathy due to traditional medicines. Curr Drug Saf 2008;3:54–9.
16. United States Pharmacopeial Convention. Articles of botanical origin, general chapter 561. In: United States Pharmacopeia 42–National Formulary 37. Rockville: USP; 2019.
17. Council of Europe. European Pharmacopoeia. 10th ed. Strasbourg: European Directorate for the Quality of Medicines and HealthCare; 2019.
18. Ayurvedic Pharmacopoeia of India. Part I, volume I. New Delhi: Ministry of Health and Family Welfare, Government of India; 1990.
19. Sherma J, Fried B, editors. Handbook of thin-layer chromatography. 3rd ed. New York: Marcel Dekker; 2003.
20. Spangenberg B, Poole CF, Weins C. Quantitative thin-layer chromatography: a practical survey. Berlin: Springer; 2011.
21. Li S, Han Q, Qiao C, *et al.* Chemical markers for the quality control of herbal medicines: an overview. Chin Med 2008;3:7.
22. Xie P, Chen S, Liang YZ, *et al.* Chromatographic fingerprint analysis: a rational approach for quality assessment of traditional Chinese herbal medicine. J Chromatogr A 2006;1112:171–80.
23. Gong F, Liang YZ, Xie PS, Chau FT. Information theory applied to chromatographic fingerprint of herbal medicine for quality control. J Chromatogr A 2003;1002:25–40.
24. Booker A, Frommenwiler D, Johnston D, *et al.* Chemical variability along the value chains of turmeric (Curcuma longa): a comparison of nuclear magnetic resonance, ultra high performance liquid chromatography and high performance thin layer chromatography. J Ethnopharmacol 2014;152:292–301.
25. Hebert PDN, Cywinska A, Ball SL, deWaard JR. Biological identifications through DNA barcodes. Proc R Soc Lond B 2003;270:313–21.
26. CBOL Plant Working Group. A DNA barcode for land plants. Proc Natl Acad Sci USA 2009;106:12794–7.

27. Chen S, Yao H, Han J, *et al.* Validation of the ITS2 region as a novel DNA barcode for identifying medicinal plant species. PLoS One 2010;5:e8613.
28. Techen N, Parveen I, Pan Z, Khan IA. DNA barcoding of medicinal plant material for identification. Curr Opin Biotechnol 2014;25:103–10.
29. Sucher NJ, Carles MC. Genome-based approaches to the authentication of medicinal plants. Planta Med 2008;74:603–23.
30. Wallace LJ, Boilard SMAL, Eagle SHC, *et al.* DNA barcodes for everyday life: routine authentication of natural health products. Food Res Int 2012;49:446–52.
31. Parveen I, Gafner S, Techen N, Murch SJ, Khan IA. DNA barcoding for the identification of botanicals in herbal medicine and dietary supplements: strengths and limitations. Planta Med 2016;82:1225–35.
32. Holmes E, Tang H, Wang Y, Seger C. The assessment of plant metabolite profiles by NMR-based methodologies. Planta Med 2006;72:771–85.
33. Vaysse J, Balayssac S, Gilard V, *et al.* Analysis of adulterated herbal medicines and dietary supplements marketed for weight loss by DOSY 1H-NMR. Food Addit Contam Part A 2010;27:903–16.
34. Bansal S, Singh A, Mangal M, Mangal AK, Kumar S. Food adulteration: sources, health risks, and detection methods. Crit Rev Food Sci Nutr 2017;57:1174–89.
35. ICH Harmonised Tripartite Guideline. Guideline for elemental impurities Q3D. Geneva: ICH; 2014.
36. European Medicines Agency. Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products. London: EMEA; 2008.
37. European Medicines Agency. Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin. London: EMEA; 2006.
38. European Parliament and Council. Directive 2004/24/EC amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union 2004;L136:85–90.
39. US Congress. Dietary Supplement Health and Education Act of 1994, Public Law 103-417. Washington, DC: US Congress; 1994.
40. US Food and Drug Administration. Current good manufacturing practice in manufacturing, packaging, labeling, or holding operations for dietary supplements; final rule. Fed Regist 2007;72:34752–958.
41. Government of India. The Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945. New Delhi: Ministry of Health and Family Welfare; 1945.