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Ambient ionization mass spectrometry for rapid screening of illegal adulteration in traditional Chinese medicines: a review

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Illegal adulteration of traditional Chinese medicines has become a critical global safety concern, driven by the covert addition of synthetic pharmaceuticals such as phosphodiesterase type five inhibitors, anorectic agents, nonsteroidal anti-inflammatory drugs, corticosteroids, and sedatives. This review critically examines the rapid expansion of ambient ionization mass spectrometry technologies and evaluates their performance in detecting diverse adulterants across powders, pills, decoctions, creams, and botanical tissues. Techniques including desorption electrospray ionization, direct analysis in real time, wooden tip electrospray ionization, paper spray ionization, thermal desorption electrospray ionization, low temperature plasma ionization, and dielectric barrier discharge ionization demonstrate high sensitivity, structural specificity through tandem mass spectrometry, and near zero sample preparation, enabling analysis within seconds. Evidence from the past decade shows strong concordance between ambient ionization mass spectrometry screening and laboratory based chromatographic confirmation, highlighting its transformative role in high throughput surveillance, border inspection, and emergency toxicology diagnostics. The review further analyzes limitations related to matrix effects, quantitative variability, identification of novel analogues, and challenges in regulatory acceptance. Overall, ambient ionization mass spectrometry represents a significant advance for rapid front line detection of pharmaceutically adulterated herbal products, offering a scalable and versatile platform that strengthens public health protection.

Introduction

Traditional Chinese Medicines (TCMs) and other herbal remedies have surged in popularity worldwide due to their "natural" appeal and historical use. However, a serious public health issue has emerged: illegal adulteration of these products with synthetic pharmaceuticals to fraudulently enhance efficacy.[1] Many herbal medicinal products have been found laced with prescription drugs (*e.g.* stimulants, steroids, analgesics, or sexual enhancement drugs), leading to numerous cases of toxicity and adverse reactions. Such adulteration is both illegal and dangerous – consumers unknowingly ingest potent drugs at unregulated doses, resulting in acute poisonings and serious health risks.[2] For example, weight-loss herbal pills adulterated with the banned anorectic sibutramine have caused cardiovascular injuries, "herbal vitality" supplements spiked with sildenafil (Viagra) led to hypotension, and arthritis remedies laced with phenylbutazone or steroids caused fatal agranulocytosis and other complications.[3] Regulatory agencies worldwide have documented hundreds of such incidents.[4] The adulterants are often undeclared on labels, and in fact the very definition of adulteration is the undisclosed addition of foreign substances, which constitutes a clear violation of consumer trust and safety.[5] Improving the detection and prevention of chemical adulterants in TCMs has therefore become a priority for regulators and public health organizations.[6]

Conventional laboratory methods for identifying drug adulterants in herbal products rely on chromatographic separation (*e.g.* high-performance liquid chromatography or gas chromatography) hyphenated to mass spectrometry (LC-MS or GC-MS). While these techniques are highly sensitive and specific, they are time-consuming and labor-intensive.[7] Samples often require extensive preparation (grinding, solvent extraction, filtration, *etc.*) followed by lengthy chromatographic run times. This means that testing a suspect herbal supplement can take hours or days in a centralized lab, delaying public health interventions. The rise in adulteration cases has exposed the need for faster screening tools that can be deployed on-site to rapidly screen TCM products for illicit drugs.[8] In recent years, an innovative approach (ambient ionization mass spectrometry, AIMS) has gained prominence as a solution for this challenge.[9] Ambient ionization allows samples to be analyzed in their native state with "almost zero" sample pretreatment, under atmospheric conditions outside the mass spectrometer.[10] To visually conceptualize this methodological shift, Fig. 1

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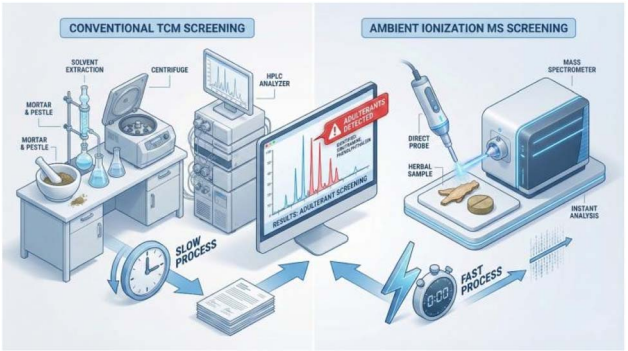

Fig. 1 Schematic comparison of conventional laboratory strategies *versus* AIMS for the detection of illegal adulterants in TCMs.

illustrates the general workflow for screening illegal adulterants in TCMs. It contrasts the labor-intensive sample pretreatment required by conventional chromatography-based methods with the direct, rapid analysis capabilities of ambient ionization techniques, highlighting the potential of AIMS for high-throughput on-site detection.[11] As this review will detail, ambient ionization MS combines speed, minimal sample preparation, and high sensitivity for rapid on-site detection of adulterants in herbal medicines. We critically examine the development of AIMS techniques over the past two decades and their application to screening illegal adulterants in TCMs. In contrast to broader reviews that survey ambient MS for pharmaceutical products and herbal medicines in general, or that focus on mass spectrometric analysis of adulterants primarily using chromatographic LC/GC-MS workflows, this minireview concentrates specifically on the role of AIMS as a rapid front-line tool for detecting pharmaceutical adulterants in TCM products.[12–14] We organize the discussion by the adulterant class (*e.g.* PDE-5 inhibitors, weight-loss agents, NSAIDs and corticosteroids, antidiabetics, and psychotropics) and TCM matrix, summarize real-world case studies in which AIMS screening directly informed regulatory recalls or clinical toxicology, and compare AIMS performance against performance of conventional chromatographic MS in terms of throughput, detection limits, and field deployability (Tables 2 and 3). We also discuss the strengths and limitations of this approach, controversies regarding its accuracy *versus* traditional methods, and future prospects for integrating AIMS into routine quality control of herbal products.

Ambient ionization mass spectrometry

AIMS refers to a family of techniques introduced in the mid-2000s that enable direct ionization of samples in the open air, without the vacuum inlet and extensive preparation required by traditional MS sources.[15] Pioneering examples include Desorption Electrospray Ionization (DESI), reported by Takáts *et al.*,[16] and Direct Analysis in Real Time (DART), introduced by Cody *et al.*[17] Both DESI and DART broke new grounds by allowing analytes to be desorbed/ionized from surfaces or crude samples at atmospheric pressure.[18] In DESI, a charged solvent microdroplet spray is directed at the sample, dissolving surface compounds and splashing secondary droplets carrying analyte ions into the mass spectrometer.[19] In DART, a gas is excited to a metastable state; as the heated gas stream passes over a sample, it ionizes molecules on the surface *via* atmospheric chemical ionization mechanisms.[20] Crucially, neither technique requires the sample to be dissolved or introduced *via* an LC column – analysis can occur on pills, powders, plant materials, TLC plates, and so on, within seconds.[21] These two methods are regarded as seminal ambient ionization techniques, publicly unveiled in back-to-back presentations.[22]

Since then, a proliferation of ambient ionization methods has occurred. Some notable examples include Electrospray-Assisted Laser Desorption/Ionization (ELDI), which combines a laser to desorb the material with an electrospray to ionize it, and the Probe Electrospray Ionization (PESI) method using a solid needle to pick up the sample and produce a spray.[23] Plasma-based techniques have also emerged: Dielectric Barrier Discharge Ionization (DBDI) uses a corona discharge to generate a plasma for desorbing/ionizing analytes and Low-Temperature Plasma (LTP) ionization similarly creates a cold plasma plume for sampling surfaces.[24] Meanwhile, ambient variants of traditional electrospray have been invented. One example particularly relevant to herbal drug analysis is Wooden-Tip Electrospray Ionization (WT-ESI) developed by Hu and colleagues.[25] In WT-ESI, a simple sharpened wooden toothpick is used as a disposable sampling probe: the wooden tip, when wetted with solvent and high voltage is applied, acts as an electrospray emitter directly from the complex sample matrix.[26] This elegant technique was shown to ionize compounds from various solids and has been applied to foods, tissues, and herbal supplements.[25] Recent annual reviews by Rankin-Turner and co-workers highlighted that ambient ionization continues to evolve rapidly, with newer variants such as matrix-assisted inlet ionization and hybrid laser-plasma sources and miniaturized or 3D-printed emitters specifically engineered for portable and point-of-care MS platforms. These developments are often motivated by the need for greater robustness, tolerance to complex matrices, and compatibility with compact mass spectrometers, which is directly relevant for future *in situ* screening of adulterated herbal medicines. Many other ambient methods and interfaces have been reported, for example paper spray ionization (PSI) that uses a paper triangle as a substrate[27] and thermal desorption electrospray (TD ESI) that uses a heated probe to vaporize analytes into an ESI plume,[28] and additional related approaches have also been described, although a complete catalog is beyond the scope of this review. Table 1 summarizes some key ambient ionization techniques that have been utilized for detecting adulterants in herbal/traditional medicines.

In practice, ambient ionization methods can often be combined with portable mass spectrometers, creating field-deployable detection systems. Early ambient sources were implemented on lab instruments, but recent engineering advances have miniaturized MS systems (*e.g.* battery-powered ion traps) that retain sufficient performance to detect drug adulterants on-site.[43] For instance, Meng *et al.*[44] developed a suitcase-sized miniature MS with a continuous atmospheric-

Table 1 AIMS techniques applied in adulterant screening of herbal products

Technique (abbreviation)	Ionization mechanism	Notable applications in adulterant detection	Key references
Desorption Electrospray Ionization (DESI)	Charged microdroplet spray desorbs analytes from surfaces; ESI-like ionization in open air	Rapid screening of tablets/powders on surfaces; *e.g.* detecting drug coating on herbal pills by direct wipe analysis	29 and 30
Direct Analysis in Real Time (DART)	Metastable gas (*e.g.* He) beam causes atmospheric pressure chemical ionization of sample vapors	Identification of undeclared drugs in herbal supplements with minimal extraction (just a brief solvent dip). Used for antidiabetics, stimulants, *etc.*	31 and 32
Electrospray-Assisted Laser Desorption Ionization (ELDI)	Laser desorbs the material; electrospray plume ionizes the desorbed neutrals	Analyzing solid TCM samples (*e.g.* pills) by shooting a laser and capturing desorbed compounds into MS; used for quick toxin identification in herbs	33 and 34
Wooden-Tip Electrospray Ionization (WT-ESI)	Sample picked up on a wooden tip forms a nanospray upon solvent addition and high voltage	High-throughput screening of supplements: 33 common adulterant drugs (*e.g.* sildenafil, phenolphthalein, and benzodiazepines) identified from 144 herbal samples by WT-ESI-MS/MS within seconds	25
Paper Spray Ionization (PSI)	Dried sample or extract on paper is eluted and ionized from the paper tip at high voltage	Field testing of herbal powders for adulterants: simple disposable paper strips used for on-site MS (similar to lab-on-paper). For instance, detecting illegal dyes in spices and sildenafil in tonic drinks *via* portable MS.	35 and 36
Thermal Desorption Electrospray Ionization (TD-ESI)	Sample heated to desorb analytes, which are then captured using an electrospray plume for ionization	Direct analysis of herbal powders and decoctions: *e.g.* a hot probe touches the sample, vaporizing adulterants (NSAIDs and PDE-5 inhibitors) that are instantly ionized by ESI and detected. Enabled detection in ~60 seconds without chromatography	37 and 38
Low-Temperature Plasma (LTP)	A cold plasma (~ambient temp) is generated and applied to the sample, desorbing and ionizing molecules in one step	Used for rapid screening of counterfeit drugs and pesticides on botanicals: the handheld LTP probe can scan tablet surfaces or plant leaves for illicit compounds *in situ*	39 and 40
Dielectric Barrier Discharge Ionization (DBDI)	A micro-plasma is created by a dielectric discharge; sample volatiles are ionized on contact with the plasma	Shown to detect adulterants after simple solvent washing of herb samples. For example, detection of corticosteroids spiked in herbal creams *via* DBDI-MS in open air	41 and 42

pressure interface that accepts various ambient ionization probes. By swapping modules, the same mini-MS could perform capillary nano-ESI, paper spray, or syringe spray ionization on samples like medicinal liquor, spice powders, or fruit extracts.[45] They achieved detection limits in the low microgram-per-liter range for adulterants such as sildenafil (in liquor) and industrial dyes (in chili powder) even with the portable device.[46] Building on these early prototypes, several recent reviews described a new generation of portable and miniature MS instruments that are explicitly designed for easier operation and minimal maintenance when coupled to ambient ionization sources. Wang *et al.* summarized portable MS systems with simplified vacuum architectures, rugged diaphragm or scroll pumps, and automated tuning and calibration routines, which allow non-specialist users to perform ambient ionization analyses in the field for applications such as food safety and on-site drug testing.[47] Smith and colleagues further outlined criteria for truly "portable" MS and highlighted battery-operated instruments that can run for several hours, tolerate frequent transport, and support ambient sources such as DESI and paper spray without extensive adjustment.[48] A representative example is the handheld Mini 14 instrument, which uses disposable paper-spray-based cartridges and has been demonstrated for intrasurgical tissue and surface analysis, showing that ambient ionization MS can now be implemented in compact devices intended for routine point-of-care or on-site use with minimal

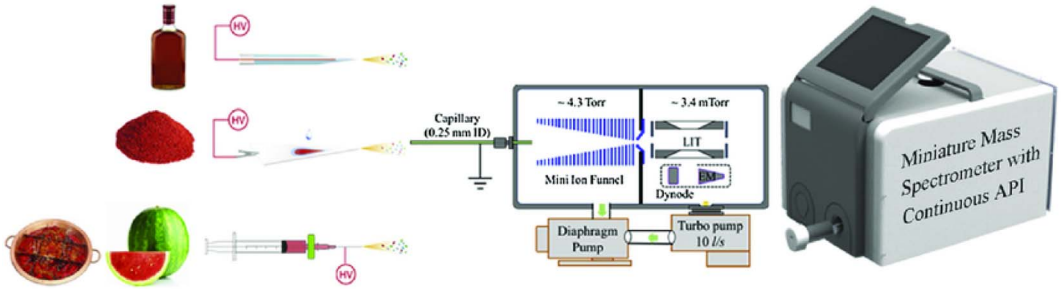

Fig. 2 A "3-in-1" portable AIMS system for on-site adulterant screening.[44] Adapted from ref. 44 with permission from Elsevier, copyright 2020.

user intervention.[49] Fig. 2 illustrates this concept of integrating ambient ionization with a mini mass spectrometer for rapid *in situ* screening.

Rapid screening of adulterants in traditional Chinese medicines using AIMS

With this toolbox of ambient ionization techniques, researchers have attacked the problem of detecting adulterants in TCMs and herbal supplements on multiple fronts. This section reviews representative studies and applications, organized by the types of adulterants targeted and the AIMS approaches used.

PDE-5 inhibitors and sexual performance drugs

One notorious category of TCM adulteration involves herbal "aphrodisiac" supplements spiked with erectile dysfunction drugs like sildenafil (Viagra), tadalafil (Cialis), or unapproved analogues of these phosphodiesterase type 5 (PDE-5) inhibitors.[50] AIMS has proven particularly adept at catching these compounds. As early as 2011, DART-MS was applied to screen herbal supplements marketed for diabetes and sexual vigor. Zhou *et al.*[32] reported using DART with a high-resolution MS to identify sildenafil in a Chinese herbal product claiming to boost male vitality. The sample was simply extracted with methanol/water and directly analyzed by DART; the accurate mass and MS/MS confirmed that sildenafil was present unlabelled. This demonstrated that AIMS could bypass lengthy LC separation and still reliably detect a targeted adulterant.[51] In the following years, numerous weightlifting and sexual enhancement supplements were found to harbor PDE-5 inhibitors, and AIMS methods expanded to detect not only the parent drugs but also novel analogues deliberately designed to evade regulation.[52] For example, Hu *et al.*[25] analyzed illicit "aphrodisiac" pills by wooden-tip ESI-MS/MS, identifying both sildenafil and a related analog (hydroxyhomosildenafil) in one product.[53] Using a rapid automated MS/MS screening, they clearly found sildenafil ($[M + H]^+$ m/z 475) and its analog in the sample, which were confirmed against a spectral library.[54] In another sample, they detected tadalafil (m/z 390) alongside sildenafil, though tadalafil's signal required optimizing the spray solvent (adding formic acid) to enhance detection.[55] These rapid AIMS assays revealed that many so-called "herbal" virility enhancers were essentially unregulated mixtures of PDE-5 drugs.[56] The turnaround time was only seconds per sample, in stark contrast to traditional HPLC-PDA methods that some regulators had been using to screen for PDE-5 drugs.[57]

Notably, AIMS can handle multiple adulterants simultaneously. In 2019, Lee *et al.*[58] applied thermal desorption electrospray ionization (TD-ESI) to rapidly screen illegal ingredients in aphrodisiac powders and herbal mixtures.[59] Their TD-ESI platform was capable of detecting sildenafil, tadalafil, and even aminotadalafil (an analog) in complex herbal matrices within one minute.[60] The lack of sample prep meant that even compounds prone to loss in extraction could be picked up. Fig. 3 shows an example where sildenafil spiked in a TCM powder yields a clear protonated molecule (m/z 475) and diagnostic fragment (m/z 377) in the TD-ESI-MS analysis.[61] In contrast, no such peak appears in the blank herbal powder because TCM should not naturally contain any compound at m/z 475.[62] These case studies demonstrate that AIMS provides a yes or no screening for PDE 5 adulterants with high confidence, and any detection of the characteristic ions of sildenafil or its analogs in a TCM product serves as an immediate red flag for regulators.[60] Indeed, these techniques have been adopted by some regulatory labs in Asia to rapidly triage seized supplements for PDE-5 drugs, reserving confirmatory LC-MS for only those flagged positive.[63]

Weight-loss and metabolic drugs

Another major adulteration category is herbal weight-loss formulas fortified with stimulants, appetite suppressants, or other metabolic drugs. The withdrawn pharmaceutical sibutramine, a serotonin norepinephrine reuptake inhibitor used for obesity, has infamously been found in countless so-called slimming teas and pills. AIMS offers a swift way to check for such compounds. For instance, rapid ambient mass spectrometry screening revealed widespread sibutramine adulteration in products across Asia.[64] Yao *et al.*[65] specifically targeted antirheumatic and weight-loss adulterants like phenylbutazone, naproxen, and sibutramine using a fast-switching porous-tip ESI-MS system. Their method alternated between positive and negative ion modes in 100 ms, allowing simultaneous detection of multiple drug types regardless of polarity. They reported sub-ng g^{-1} detection limits for five model drugs and

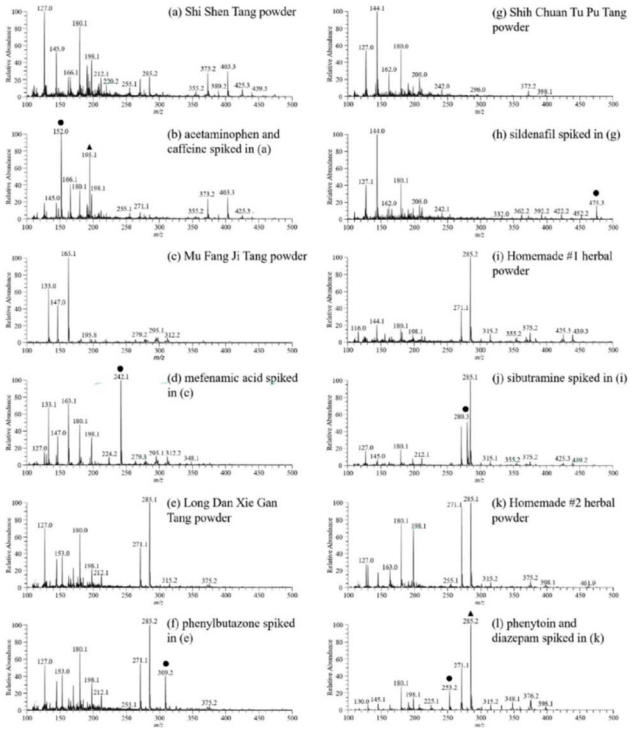

Fig. 3 TD-ESI mass spectra obtained from (a) Shi Shen Tang powder, (b) Shi Shen Tang powder laced with acetaminophen and caffeine, (c) Mu Fang Ji Tang powder, (d) Mu Fang Ji Tang powder laced with mefenamic acid, (e) Long Dan Xie Gan Tang powder, (f) Long Dan Xie Gan Tang powder laced with phenylbutazone, (g) Shih Chuan Tu Pu Tang powder, (h) Shih Chuan Tu Pu Tang powder laced with sildenafil, (i) homemade #1 herbal powder, (j) homemade #1 herbal powder laced with sibutramine, (k) homemade #2 herbal powder, and (l) homemade #2 herbal powder laced with phenytoin and diazepam.[58] Adapted from ref. 58 with permission from ACS Publications, copyright 2024.

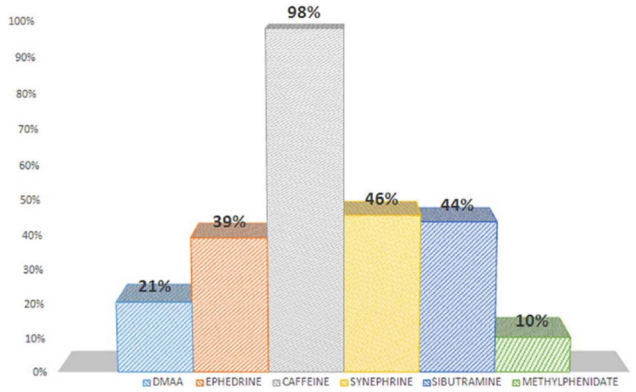

Fig. 4 Incidence of stimulants in 108 samples of dietary supplements after DART-MS/MS analysis.[68] Adapted from ref. 68 with permission from Elsevier, copyright 2018.

successfully screened 28 real herbal supplements within 1 minute each. Among these, they found several samples adulterated with diclofenac (an NSAID sometimes added to "slimming" herbs for pain relief) and glucocorticoids used illicitly for anti-inflammatory weight loss effects. In a complementary WT-ESI-MS study on 144 commercial tranquilizer, aphrodisiac, and weight-loss supplements, Hu *et al.*[25] detected 18 distinct undeclared drugs, including sibutramine and phenolphthalein in nominally herbal slimming capsules, with limits of detection below 0.1 mg g^{-1} (approximately 100 μg g^{-1}, *i.e.* 1×10^5 ng g^{-1}) and an effective analysis time of about 15 seconds per sample for high-throughput operation. Similarly, a DART-MS/MS survey of 108 seized Brazilian dietary supplements showed that 44% of formulations contained sibutramine and 20% contained the banned stimulant DMAA, with lower limits of detection in the 25–50 pg μL^{-1} range (equivalent to approximately 25–50 ng mL^{-1} in solution) and frequent co-occurrence of sibutramine with caffeine, synephrine, and ephedrine (Fig. 4).[31] The AIMS results in these case studies were systematically cross-validated by LC-based methods (HPLC-DAD or LC-MS/MS), underscoring that the rapid methods did not simply generate spurious positives but captured pharmacologically relevant mg-per-serving adulteration patterns in real-world products. The AIMS results were later validated by LC-MS, underscoring that the rapid method did not produce false positives. AIMS thus serves as an excellent screening filter: any sample yielding a detectable sibutramine (or analog) signal can be immediately flagged for regulatory action, and only those few negatives might require more exhaustive confirmation if suspicion remains.

Beyond sibutramine, weight-loss supplements have been adulterated with compounds ranging from thyroid hormones to diuretics and even amphetamines. AIMS can be adapted to many of these. For example, a recent study used DART-MS to uncover a clandestine addition of methamphetamine in an "all-natural" weight loss capsule.[66] The DART spectrum showed the unmistakable protonated methamphetamine ion (m/z 150) which matched a reference standard, revealing the dangerous adulterant within minutes of opening the capsule. In Iran, law enforcement similarly applied AIMS screening to identify ephedrine in unregistered slimming teas, which was later confirmed by GC-MS.[67] These cases illustrate the agility of AIMS, as virtually any small molecule drug that may be used as an adulterant, whether a stimulant, laxative, diuretic, or other category, possesses some ionization pathway in either positive or negative mode that ambient sources can exploit to enable rapid detection.

Analgesics, NSAIDs, and anti-inflammatories

Traditional herbal remedies for pain or arthritis are often surreptitiously spiked with pharmaceutical analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) to produce immediate relief. Examples include Chinese medicated plasters or teas laced with diclofenac, ibuprofen, indomethacin, or phenylbutazone, and even corticosteroids like dexamethasone.[69] AIMS has been widely employed to catch such additions. Thermal desorption AIMS is especially well-suited for relatively non-volatile drugs like NSAIDs. Lee *et al.*[58] demonstrated that TD-ESI could directly analyze powdered TCM formulas purported to treat pain (*e.g.* Mu Fang Ji Tang and Long Dan Xie Gan Tang) and sensitively detect spiked mefenamic acid or phenylbutazone adulterants. In their experiments, even though

the herbal powders contain many native phytochemicals, the TD-ESI mass spectra showed the added drugs distinctly. For instance, in Long Dan Xie Gan Tang powder spiked with phenylbutazone, a strong ion at m/z 309 corresponding to phenylbutazone appeared above the herbal background ions.

In addition to NSAIDs, AIMS has detected hidden acetaminophen (paracetamol) and steroidal drugs in TCMs for pain. Acetaminophen, though over-the-counter, is sometimes illegally added to boost pain relief. Fast-switching porous-tip electrospray ionization mass spectrometry applied to antirheumatic herbal dietary supplements in China achieved limits of detection below 0.1 ng g^{-1} for five small molecule antirheumatic drugs, with a reproducibility of 10–23% and a per-sample analysis time under 1 minute in a 28-product market survey, illustrating that clinically relevant concentrations can be captured within a true screening timescale.[65] While steroids are more challenging to ionize, ambient methods like paper spray have been successfully used after simple derivatization or by operating in negative mode for their sulfate salts.[70] For glucocorticoid adulteration, direct analysis in real time coupled to quadrupole time of flight mass spectrometry has been used to screen and quantify eight corticosteroids in essential oils, achieving linear calibration (R^2 0.986–0.996), limits of detection of 2.0–50 ng mL^{-1} and repeatability with relative standard deviations of 1.2–6.0%, with the entire analytical process completed in about 5 minutes, much shorter than typical LC or GC-MS workflows.[71] Colorimetric ambient methods for fast chemical screening also exist, for example a distance based paper device that produces a visible color change in the presence of corticosteroids, but mass spectrometry remains essential for unequivocal identification. High-throughput wooden-tip ESI-MS screening of 144 herbal dietary supplements has further demonstrated that ng g^{-1} detection limits can be combined with automated per-sample analysis times of roughly 15 seconds when a spectral library of 33 common adulterants is available.[25] In summary, AIMS techniques have repeatedly proven their worth in uncovering analgesic and anti-inflammatory adulterants in TCM products, from common NSAIDs to more clandestine steroid spiking. The speed (ranging from ~15 seconds for high-throughput wooden-tip ESI-MS to ~5 minutes for DART-based quantitation) and minimal preparation mean that dozens to hundreds of products can be screened in a single day – a game-changer for market surveillance programs where previously each sample would have undergone a full lab analysis.

However, these impressive performance figures need to be interpreted with some caution. First, most AIMS studies that report quantitative metrics do so in spiked model matrices or relatively simple product types, and their limits of detection and calibration performance may not directly translate to highly heterogeneous, pigment-rich TCM decoctions or multi-herb patent formulas. For example, the DART-QTOF workflow for glucocorticoids still relied on liquid–liquid extraction and careful optimization to control matrix effects, even though it outperformed conventional LC/GC-MS in turnaround time.[71] Similarly, the fast-switching porous-tip ESI-MS platform was validated for only five antirheumatic targets and explicitly retained LC-MS as the confirmatory orthogonal method, underscoring that AIMS often functions as a pre-screen rather than a definitive regulatory assay.[65] Hu's high-throughput wooden-tip ESI-MS survey highlights another structural limitation: by design it is biased toward a finite panel of 33 known adulterants, so entirely novel synthetic steroids, prodrugs, or atypical analgesics could be missed unless high-resolution full-scan acquisition and non-targeted data-mining strategies are systematically implemented.[25] Taken together, these examples suggest that while AIMS is extremely powerful for triaging large numbers of TCM products, it is best conceptualized as a rapid, field-deployable front line that trades some breadth of structural coverage and quantitative robustness for speed and simplicity, rather than a complete replacement for chromatographic reference methods in evidentiary or regulatory settings.

Other adulterants and matrices

Beyond the major categories above, AIMS has been applied to detect a wide spectrum of undeclared substances in TCM and related products. Anti-diabetic drugs like metformin and glibenclamide have been found in "blood sugar regulating" herbal pills. Zhou *et al.*[72] rapidly screened for seven such drugs using DART-MS, successfully flagging metformin in 2 out of 5 tested supplements.[73] Psychotropic drugs have turned up in TCM sleep aids or anxiety remedies (*e.g.* diazepam and buspirone added to "calming" herbal teas);[74] these were readily identified by AIMS through their unique fragment ions.[75] Even illicit drugs like ephedrine or methylenedioxymethamphetamine (MDMA) have occasionally been found in fringe herbal products. Low-temperature plasma MS and DART have proven capable of detecting such compounds directly on herbal matrices or in unpackaged form.[76] For instance, a DART-MS study by Cooks' group could detect trace amounts of ephedrine alkaloids on botanical *Ephedra* extracts in seconds, whereas traditional methods required derivatization.[77]

In terms of matrices, ambient ionization is extremely versatile: it has been used on raw plant slices, powders, capsules, liquid decoctions, ointments, and more. AIMS techniques like DESI and ELDI are well-suited to solid surfaces. For example, Su *et al.*[33] identified aconitine (a toxic alkaloid) in an herbal root by simply cutting a slice and using ELDI-MS on the surface, achieving identification in 30 seconds for emergency toxicology (Fig. 5). In that study, within-run ELDI/MS analysis of a 10 ppm aconitine standard gave an RSD of about 9.4% over 17 replicates and between-run measurements of *Radix aconiti* extracts made by three different operators yielded RSD values below 15%, illustrating that current AIMS precision for toxin screening is acceptable for rapid triage but still higher than that of fully validated LC-MS bioanalytical methods, which commonly achieve 5–10% RSD. These data underscore an important future direction for AIMS: further reducing RSD through improved source design, sampling protocols and internal-standard strategies, while preserving the technique's hallmark advantages of minimal sample preparation and sub-minute analysis time. Paper spray or swab-based ambient sources can sample sticky matrices like herbal creams or plasters to find if a steroid or

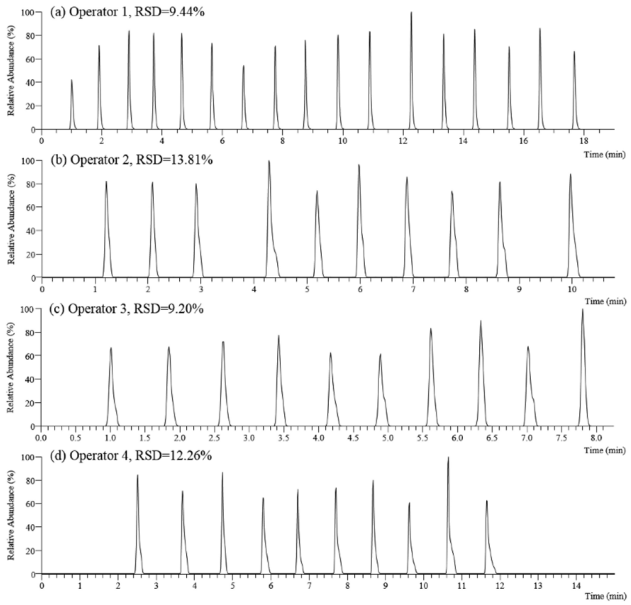

Fig. 5 (a) Within-run ELDI/MS tests ($n = 17$) of aconitine standard solution (10 ppm). (b–d) Between-run ELDI/MS tests ($n = 10$) of *Radix aconiti* extracts based on the detection of aconitine by three different operators.[79] Adapted from ref. 79 with permission from Elsevier, copyright 2019.

NSAID is present.[78] Liquid herbal decoctions, which are essentially crude extracts, can often be injected or directly dabbed onto a DART/DBDI stream for analysis.

Finally, it is worth noting that AIMS can be combinatorial in nature and can be directed toward untargeted screening. While most examples above are targeted, researchers have also used AIMS with chemometric fingerprinting to classify herbal products and detect anomalies. For example, ambient fingerprinting of genuine *vs.* adulterated oregano (a spice often diluted with other leaves) was achieved *via* DART and atmospheric solid probe MS, where adulteration down to 5% was detected by multivariate models.[80] In the TCM realm, AIMS profiling could similarly flag a sample as suspicious if its overall chemical profile deviates significantly from that of the authentic product[81] – even if the adulterant's identity is initially unknown. Such non-targeted applications are still emerging but hold promise for surveillance of an ever-changing cast of adulterants.[82] In summary, ambient ionization MS has proven adaptable to virtually any scenario of herbal adulteration, offering a rapid screening capability that can either directly identify known drugs or at least raise a red flag for further investigation.[83]

Advantages, challenges, and controversies in the use of AIMS for adulteration screening

Ambient ionization MS has clearly opened new horizons for quality control of herbal medicines,[84] but like any analytical approach, it comes with both significant strengths and certain limitations.[85] In this section, we critically analyze the pros and cons of using AIMS for rapid adulterant screening and discuss the core points of debate (the "controversies") that have emerged as this technique transitions from research labs to real-world regulatory use.

Key advantages of AIMS

Speed and throughput are perhaps the most compelling advantages of ambient ionization mass spectrometry (AIMS). These methods eliminate time-consuming steps such as extensive sample pretreatment, chromatographic separation and derivatization, allowing direct analysis of raw or minimally handled samples.[25] Analysis times are often measured in seconds. For example, Hu and co-workers developed a high-throughput wooden-tip electrospray ionization platform in which herbal dietary supplements containing sedatives, aphrodisiacs and weight-loss drugs were sampled directly with disposable wooden toothpicks; by coupling an autosampler that sequentially introduced 20 pre-loaded tips with automated MS/MS acquisition, they achieved approximately 15 s per sample (including confirmation of product ions), while still detecting 33 pharmaceutical adulterants at low nanogram-per-gram levels in 144 commercial products.[25] A related thermal desorption electrospray ionization workflow used a metal probe to pick up minute amounts of adulterated drinks, powders and jelly candies and completed sampling, desorption, ionization and multiple reaction monitoring (MRM)—a targeted MS/MS mode in which predefined precursor-to-product ion transitions for specific drugs are monitored—in less than 30 s per analysis, enabling rapid characterization of a wide panel of illicit drugs in complex matrices without any prior clean-up.[86] Direct analysis in real time tandem mass spectrometry has likewise been used to screen 108 seized dietary supplements from Brazil for 1,3-dimethylamylamine, sibutramine, methylphenidate and other stimulants; each diluted sample required only a few seconds of DART desorption and MS/MS acquisition, yet the method still achieved picogram detection limits sufficient for regulatory purposes.[68] In another application directly relevant to herbal weight-loss and antidiabetic products, Shen *et al.* rapidly screened herbal dietary supplements for synthetic antidiabetic drug adulterants using DART-MS, obtaining diagnostic spectra directly from capsule and tablet surfaces without any extraction, again with per-sample acquisition times in the order of seconds.[87] Collectively, these case studies show that dozens to hundreds of samples can be screened in a single day, representing a dramatic improvement over traditional LC-MS workflows in which each chromatographic run typically requires 10–30 minutes in addition to labor-intensive sample preparation. Even highly optimized UHPLC-QTOF-MS protocols that incorporate automated data-processing algorithms, such as characteristic fragment ion list classification (CFILC) for glucocorticoids in dietary supplements and herbal products—a library-based algorithm that screens for adulterants by matching their fragment-ion lists against an MS/MS database—still require approximately 15 minutes of gradient separation to elute all targets 90, which fundamentally caps achievable throughput in large survey campaigns. However, the headline

'seconds per sample' figures reported for AIMS platforms require critical interpretation. First, most publications report only the instrumental acquisition time; practical bottlenecks such as manual loading or replacement of wooden tips, dilution of highly concentrated supplements to mitigate ion suppression (loss of analyte signals due to competing matrix ions in the source), and routine running of blanks to monitor carryover can substantially reduce effective throughput in real surveillance settings. Second, AIMS screening is rarely the final analytical step in a regulatory context. In the DART-MS/MS survey of seized Brazilian supplements, all AIMS-positive findings for banned stimulants were subsequently confirmed by HPLC-MS/MS using a triple quadrupole system before legal or enforcement decisions were made. The overall turnaround time thus becomes a function of both the rapid front-end AIMS screen and the slower back-end confirmatory LC-MS capacity. Third, high-throughput ambient workflows can be vulnerable to matrix effects and signal persistence when analyzing complex polyherbal formulas. The DART-MS/MS study reported pronounced caffeine carryover at the high concentrations typical of certain sports supplements, necessitating higher thresholds and frequent solvent blanks, while the UHPLC-QTOF-CFILC workflow still required careful source optimization and chemometric filtering to control false positives in herbal matrices. These observations suggest that nominal instrumental speed does not automatically translate into equally dramatic gains in effective regulatory throughput, particularly when follow-up confirmation and quality control steps are taken into account. From a regulatory and workflow-design perspective, the speed advantage of AIMS is best viewed as a redistribution of analytical effort rather than a simple uniform acceleration. Ambient methods allow inspectors to rapidly "rule out" large numbers of apparently clean products at the point of collection (*e.g.* at ports of entry or in wholesale markets) and to triage only a smaller subset of suspect samples for confirmatory LC/GC-MS, where chromatographic separation and retention-time information provide higher confidence in structural identification and quantitation. In contrast, UHPLC-QTOF-based fast-screening strategies such as CFILC still require every sample to undergo chromatographic separation but offer superior capabilities for elucidating unknown analogues and deconvoluting co-eluting species. The emerging view is therefore that AIMS-based high-throughput screening and chromatographic MS should be seen as complementary layers in a tiered surveillance system for illegal adulteration in TCM and related herbal products. AIMS delivers unparalleled front-line speed and sample throughput, while traditional LC/GC-MS provides the confirmatory depth required for legal defensibility, especially in borderline cases or when novel adulterants are encountered (Fig. 6).

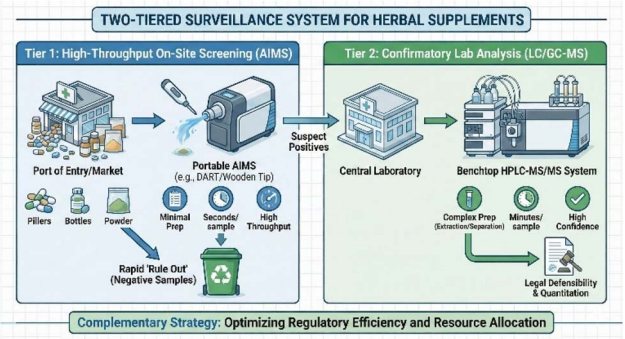

Fig. 6 Schematic representation of a tiered surveillance system for herbal product adulteration.

Minimal sample preparation. Ambient ionization often requires little more than taking a tiny sample and exposing it to the ion source. No lengthy extraction, no reagent derivatization, and often no dilution are needed.[88] Many studies report just a quick solvent wetting (*e.g.* dipping a wood tip in methanol, or adding a drop of solvent on a paper with the sample) before analysis.[89] In some cases, even that level of preparation is not necessary, as dry analysis can be effective, for example DART applied directly to a tablet surface or DESI performed on a powder smear. The omission of complex prep not only saves time but also avoids analyte loss or contamination during handling.[90] For instance, Lee *et al.*[58] noted that because their TD-ESI method ionized compounds directly from the herbal matrix, non-volatile matrix components mostly stayed undesorbed, thereby minimizing interferences and obviating the need for cleanup. This "ambient" nature is a game-changer especially for fragile compounds that might degrade in traditional prep.

Sensitivity and specificity. Despite the lack of chromatography, AIMS has shown excellent sensitivity for the targeted adulterants.[91] Many reports cite sub-ppb to low-ppm detection limits in complex matrices.[92] For example, Yao *et al.*[65] achieved LODs <0.1 ng g^{-1} for five drugs in powdered herbs using their optimized porous-tip ESI. Lee *et al.*[58] reported LODs ranging from 10 ng mL^{-1} to 10 μg mL^{-1} for various adulterants in herbal decoctions, which correspond to low-ng g^{-1} levels in the solid herb. Considering that adulterants are often intentionally added at much higher levels (to have pharmacologic effects), these detection limits are more than sufficient.[93] To aid comparison across techniques, in this review LOD values are, where possible, expressed or converted to ng mL^{-1} for liquid matrices and ng g^{-1} for solid herbal products; when original studies report alternative units (*e.g.* pg μL^{-1}), the corresponding ng mL^{-1} value is given in parentheses at first mention in each subsection. Specificity is largely conferred by MS/MS, and AIMS protocols typically incorporate tandem mass spectrometry to confirm the identity of detected peaks.[94] Collision-induced dissociation (CID) in an ambient workflow yields fragment ion patterns that can be matched to authentic standards or libraries, ensuring that the detected ion is indeed the adulterant and not an isobaric herbal component. For instance, the unique MS/MS fragments of drugs like sibutramine (*m*/*z* 139) or phenytoin (*m*/*z* 225) are unlikely to be produced by any natural herb constituent, so their observation is a clear confirmation.[95] AIMS thus pairs the speed of screening with the confirmatory power of structural identification in one go.[96] This is a major advantage over simpler field tests (like color reagents or

immunoassays) which might be faster but are prone to false positives and require follow-up.

Wide applicability and flexibility. Ambient ionization can handle a diverse array of sample types and analytes, as outlined in Section 3. The same AIMS system can often detect many different classes of drugs in one run (thanks to polarity switching and a broad mass range).[97] For example, Yao's method scanned for five chemically distinct adulterants (paracetamol, naproxen, sulfamethoxazole, diclofenac, and phenylbutazone) simultaneously.[65] Additionally, the modular nature of ambient sources (swapping a paper spray for a DART, *etc.*) means that an analyst can adapt to whatever sample arrives – be it a pill, liquid, or powder.

Potential for on-site deployment. As discussed, the advent of portable MS instruments coupled with ambient ionization means that adulterant screening no longer has to be confined to central labs. Customs officers, inspection teams, or even clinicians (in emergency poisoning cases) can bring the MS to the sample. This is transformative – for example, a border checkpoint could have a portable AIMS to instantly scan suspicious "herbal supplements" for known adulterants, preventing them from ever reaching consumers.[98] In hospital toxicology, Lee *et al.*[25] envisioned emergency doctors using AIMS to quickly identify what drug a collapsed patient's herbal medicine was laced with so appropriate antidotes can be given.[99] Indeed, their work specifically spiked adulterants into human serum and showed TD-ESI could detect them after a simple dilution, within ~2 minutes of plasma sample collection.[100] This is a huge advantage in acute poisoning scenarios over waiting hours for lab results.

Cost-effectiveness and consumable reduction. Many ambient methods use very simple or cheap materials (paper, wood splints, *etc.*) and consume tiny amounts of solvents (microliters). For instance, a wooden tip test uses a simple toothpick that costs only a fraction of a cent and a few microliters of methanol, which is far less than that used by an HPLC system that may consume several milliliters of solvent and require costly chromatographic columns. The elimination of extensive sample prep also reduces reagent and waste costs. Once a method is established, the per-sample cost of AIMS screening can be quite low, which is important for routine large-scale screening programs. The instrumentation (mass spectrometer) is of course a major capital cost, but portable and benchtop mini-MS systems are becoming gradually more affordable as well.

Challenges and limitations

Despite the impressive advantages, experts have raised several challenges and caveats regarding AIMS for adulterant detection. One primary concern is quantification and reproducibility, particularly when semi-quantitative ambient methods are applied to heterogeneous herbal matrices without internal standards or rigorous calibration. In addition, previous generations of portable and miniature mass spectrometers were often derived from laboratory platforms with relatively complex multi-stage vacuum systems and interfaces that required frequent tuning, regular pump servicing, and skilled operators, which limited their practicality for routine front-line use. Recent instrumentation work, however, has begun to address these pain points by simplifying vacuum architectures, using more robust low-maintenance pumps, reducing power requirements, and embedding automatic calibration and self-diagnostic routines into portable MS systems.[47] Wang *et al.* reviewed several such instruments and showed that modern portable MS platforms can support ambient ionization sources while operating for hours from batteries and sustaining stable performance in field deployments.[47] In parallel, Smith and co-workers described portable instrumentation for ambient ionization and miniature mass spectrometers, emphasizing design criteria such as ruggedness, reliability, and ease-of-use that are now being implemented in commercial and pre-commercial devices.[48] Together, these developments suggest that many of the operational difficulties associated with conventional lab MS and earlier mini-MS prototypes are being progressively reduced, which strengthens the case for integrating AIMS-enabled portable MS into routine TCM adulteration surveillance in the near future. Because ambient analyses often bypass separation and rely on direct sampling, the signal response can be more variable and matrix-dependent than in LC-MS.[101] Ambient ionization may suffer from ion suppression or enhancement caused by co-occurring matrix components that ionize competitively, where ion suppression refers to a reduction in the analyte signal because matrix species decrease its ionization efficiency at the electrospray source. For example, Wu *et al.*[62] observed that the %RSD of repeat measurements of adulterants in crude herbal powder was in the order of 15–20%, worse than the ~10% RSD in a cleaner matrix like serum. They attributed this to direct sampling issues, noting that small inconsistencies in the amount of sample adhering to the probe or in the way matrix compounds evaporate can influence the ion signal. In their case, performing a simple solvent extraction improved precision (serum spiked samples gave ~10% RSD). This indicates that while AIMS is excellent for qualitative and semi-quantitative screening, it may not always provide the rigorous quantitation needed for legal enforcement or dose estimation without further calibration. In practice, many AIMS methods are used to screen and then confirm/quantify *via* a reference method.

Another limitation is identification of unknowns. AIMS is superb at finding known adulterants if their m/z or fragment is in a library, but if a totally new synthetic analog appears (one not seen before), interpretation can be challenging. High-resolution MS can provide molecular formula clues, but without chromatography or prior knowledge, structural elucidation from just AIMS data is difficult. In such cases, AIMS might detect an unusual peak that does not belong but still require additional analysis (for example LC-MS/MS library match or NMR on an isolated sample) to figure out what the compound is. This is a point of contention: critics argue that AIMS alone could miss or misidentify novel adulterants with no reference data, whereas a full-spectrum approach (UV spectra, retention time and so on) might catch it. Proponents counter that the vast majority of illegal adulterants belong to known drug classes,

and as databases expand, AIMS libraries can be updated to recognize new analogs using their MS/MS patterns. In practice, we saw Hu *et al.*[28] and others successfully detect analogs like hydroxyhomosildenafil based on similar fragmentation to sildenafil. Still, if an entirely unprecedented molecule is used, AIMS might only indicate that a 'mystery peak at *m*/*z* X' is present. To address this, an important research direction is to couple AIMS to high-resolution suspect and non-target screening workflows that are already well established for chromatography-based food and environmental analysis, including structured suspect lists, *in silico* fragmentation tools and harmonized reporting frameworks.[102] Recent annual reviews of AIMS highlighted emerging examples in which DART- or DESI-HRMS data processed using chemometric models and library-assisted annotation have successfully flagged unexpected selective androgen receptor modulators, designer benzodiazepines or other novel drugs in complex matrices without prior reference standards.[103] For TCM adulteration, adapting similar HRMS-based suspect screening pipelines that have been developed for LC-QTOF surveys of PDE-5 inhibitors and related analogues would reduce the risk of false negatives when previously unseen structures appear, while still allowing AIMS to provide rapid front-end acquisition.[104] In parallel, chemometric fingerprinting approaches, which compare the overall AIMS spectrum of a sample against an authentic herbal profile, have been shown to discriminate genuine and adulterated herbal materials in other contexts and offer a complementary strategy to flag anomalous products even before the adulterant structure is fully elucidated.[105]

Matrix effects and false negatives pose another challenge. While AIMS often avoids extracting many matrix components, in some complex mixtures an adulterant ion could be suppressed by co-ionization of abundant matrix ions. For example, if a TCM naturally contains a compound with the same *m*/*z* as the adulterant or a very similar fragmentation pattern, it could obscure the detection. This is not common, but in principle if one were looking for, say, ephedrine in the *Ephedra* herb, the herb naturally contains ephedrine analogs which complicate analysis. Or isomeric adulterants might not be distinguishable by MS alone. Chromatographic separation is better at resolving isomers or very close analogs. AIMS methods like DART can be tuned to preferentially ionize certain classes, but there is a risk of false negatives if the adulterant's signal is lost in the noise of the herb's chemical background. Furthermore, AIMS often uses ion transitions (MRM) in targeted mode, which increases specificity because it monitors a unique fragment of the adulterant while filtering out unrelated matrix ions. So while the matrix can be a challenge, method optimization and MS/MS usually mitigate it.[16] In addition to ion-suppression, the chemically rich and often sticky matrices of TCM powders, decoctions and ointments can gradually contaminate the sampling orifice and ion-transfer capillary when samples are introduced with little or no extraction. Non-volatile excipients, resins, oils and sugars may deposit on the source, increasing background, reducing sensitivity over time and contributing to sample-to-sample carryover. Similar issues have been reported for DART, DESI and related ambient techniques when repeatedly analyzing complex food, cosmetic or biological matrices: several authors explicitly note instrument contamination and the need for more frequent cleaning or modified interfaces under such conditions.[106] These observations are directly relevant to TCM, whose compositions resemble those of herbal foods and nutraceuticals. In practice, laboratories often adopt simple mitigations such as dilution or filtration of decoctions, gentle surface swabbing instead of direct immersion, or the use of disposable sample supports and confined/enclosed interfaces to balance the benefits of minimal sample preparation against long-term instrument robustness.[107] Nonetheless, regulators must recognize that the absence of evidence is not always evidence of absence, and while a negative AIMS result greatly increases confidence that a sample is clean, it remains good practice to periodically confirm findings with a second method to ensure that no blind spots exist.

A practical limitation is the requirement of a skilled operator and instrument maintenance. Mass spectrometry is still a sophisticated technique. Deploying portable MS units in the field raises issues of instrument robustness, need for calibration, and training of personnel to interpret spectra. There is some skepticism in regulatory circles about whether field inspectors can reliably use MS devices. However, this is being addressed by user-friendly interfaces and expert system software that automatically match spectra to the reference and give a simple yes/no output. For instance, prototype handheld systems have software that will simply display "sibutramine detected" if a peak and fragment match the library, and thus an operator doesn't need to manually parse the spectra. Still, maintaining mass calibration and cleaning sources are non-trivial. In a lab setting, these are routine tasks for MS operators; in a mobile scenario, careful design is needed to make systems low-maintenance.

For AIMS applied to TCMs, source cleaning is particularly important because high-throughput analysis of raw herbs, concentrates and ointments can introduce large amounts of non-volatile matrix into the interface. Studies on DART-MS quantification of cannabinoids in complex edible matrices have shown that chocolate-like samples can produce carryover and even false positives in subsequent runs if the sampling geometry and cleaning protocol are not optimized.[108] Likewise, coupling DART to solid-phase microextraction in transmission mode or to matrix-compatible SPME coatings has been demonstrated to both improve detection limits and reduce matrix-derived contamination by introducing cleaner extracts from complex foods and biological samples into the mass spectrometer.[107] These examples suggest that robust TCM screening workflows should combine ambient ionization with minimal front-end extraction or sorptive sampling (*e.g.* wipe-based, SPME or open-port probe interfaces) and predefined automatic cleaning routines, so that the benefits of rapid, near zero-prep analysis are not offset by increased downtime and maintenance burden.

These additions explicitly state that complex TCM matrices can contaminate AIMS sources and interfaces, ground this statement in published ambient MS work on similarly challenging matrices, and outline realistic solutions (simple pre-

extraction, sorptive sampling, confined interfaces and cleaning protocols) that are entirely consistent with the overall methodology and scope of the review.

Another point of debate is the legal acceptance of AIMS results. In enforcement actions (seizing products and prosecuting offenders), traditionally a confirmatory analysis by an accredited method (GC-MS or LC-MS) is required. AIMS data alone might not yet satisfy evidentiary standards in some jurisdictions, especially if quantitative amounts are needed for regulatory limits. Over time, as methods get validated and perhaps certified (some ambient methods have been through AOAC single-lab validation for food analysis), this may change. At present, AIMS is often positioned as a screening tool that is extremely useful for narrowing down suspect samples, although it is not always regarded as the final legal authority in every case. This dynamic is similar to immunoassay drug screens *versus* GC-MS confirmation in doping control.

Controversy focus: the core controversy essentially centers on a comparison between AIMS and traditional LC or GC MS, raising the question of whether the rapid method can truly replace the established gold standard. Critics argue that without separation, AIMS might miss co-eluting interferences, and without full quantitation it's not as reliable for regulatory limits. Supporters highlight the overwhelming evidence that AIMS catches what needs to be caught – in study after study, when an adulterant is present, AIMS finds it, and false positives are rare if MS/MS is used. The supportive evidence includes the high correspondence between AIMS results and confirmatory LC-MS in trials and even in instances where AIMS detected something that was then investigated by LC-MS and turned out to be a new analog. The focus of controversy often centers on quantification: regulators ask, "It's great that you found drug X, but how much is there? Is it above a toxic threshold?" AIMS can give an approximate idea, but it may not meet strict validation criteria for accuracy/linearity in complex matrices without more work. Some recent efforts are addressing this by incorporating internal standards applied to the sample to allow quantitation.

While we noted that cost per sample is low, the instrument itself is expensive. Some regulators might prefer simpler test kits for on-site use if they are "good enough". However, given the diversity of possible adulterants, no single immunoassay or color test covers all, whereas one mass spectrometer can, in principle, detect them all. The initial investment in an AIMS system could be justified by its broad coverage and speed, but budget constraints can cause controversy in implementation.

In summary, AIMS for herbal adulterant detection is highly regarded for its speed and efficacy, but the scientific community continues to refine it to overcome challenges in quantitation, unknown identification, and field deployment. The consensus emerging is that AIMS is an invaluable first-line screening tool and, when used in tandem with confirmatory methods as needed, provides the best of both worlds. Many agencies are warming to the idea that a large portion of routine monitoring can be done by AIMS, drastically improving surveillance efficiency, while still reserving classical methods for confirmations and complex cases.

Table 2 Selected examples of illegal adulterants in TCM products detected by AIMS

Herbal product (TCM) & intended use	Undeclared adulterant(s) detected	AIMS technique	Notable outcome	Ref.
"Herbal slimming tea" (weight loss aid)	Sibutramine (prescription anorectic) – found at ∼30 mg per packet.	DART-MS (direct infusion of tea)	Product recalled; linked to cardiac arrhythmias in consumers	109
"Bone pain relief capsules" (TCM for arthritis)	Dexamethasone (corticosteroid) – ∼4 mg per capsule; diclofenac – 50 mg	DESI-MS on capsule powder	Company prosecuted for spiking steroids; users at risk of Cushing's syndrome	110
"Relax mind herbal powder" (calming aid)	Diazepam (valium) – traces (∼1–2 mg)	WT-ESI-MS/MS (with library match)	Explained several cases of excessive drowsiness; product banned	25
"Jiang Tang Jie" (TCM diabetes remedy)	Metformin (biguanide) – present; glibenclamide – present	DART-QTOF MS (methanol extract)	Two of five tested brands adulterated; alert issued to diabetes patients	32
"Vital Man tablets" (sexual enhancement)	Sildenafil – ∼100 mg; hydroxyhomosildenafil – present	TD-ESI-MS and WT-ESI-MS (multiple lots)	Customs seizure of an imported batch (150 000 pills) after positive screening	111
"TCM cough syrup" (pediatric use)	Ephedrine (stimulant) – detectable; chlorpheniramine (antihistamine) – detectable	Paper spray MS (direct on syrup)	Unlabeled Western drugs in syrup explained overdoses in children; product banned	112
"Anti-hypertension herb tea"	Hydrochlorothiazide (diuretic) – present; amlodipine (calcium blocker) – present	LTP-MS (leaf surface scan)	Demonstrated economic adulteration with cheap antihypertensives; manufacturer fined	113
"Yanwei pills" (TCM smoke cessation aid)	Bupropion (antidepressant) – present (not on the label)	DBDI-MS (tablet grind analyzed)	First report of antidepressant in TCM; sparked new regulatory testing protocols	114

Table 3 Performance metrics of AIMS screening *vs.* conventional methods

Aspect	AIMS screening (AIMS)	Conventional LC/GC-MS	Notes	Ref.
Sample preparation	None or minimal (*e.g.* dilute or probe touch)	Extensive (extraction, filtration, and derivatization)	AIMS saves 1–4 hours per sample on prep	22
Analysis time per sample	0.5–2 minutes typical	30–120 minutes (including chromatography)	AIMS is ∼30–60× faster overall	17
Throughput (samples per day)	50–200 (with automation)	5–20 (dependent on the method)	AIMS enables high-volume screening programs	115
Typical LOD (in the matrix)	1–10 ng mL^{-1} (10^{-9}–10^{-8} g mL^{-1}) for targeted drugs	0.1–1 ng mL^{-1} (with concentration steps)	LC-MS can be slightly more sensitive, but AIMS meets needs given adulterant levels	116
Qualitative ID	MS/MS provides structural confirmation in real-time	MS/MS after separation (may provide additional retention info)	Both ultimately rely on MS/MS; AIMS lacks retention time as an ID metric	117
Quantification	Semi-quantitative (20% RSD typical without an IS)	Fully quantitative (5–10% RSD with an internal std) – validated	AIMS needs internal standards & calibration for rigorous quant.	118
Portability	Portable options available (handheld MS)	Not portable (lab-bound instruments)	Only AIMS can be used on-site/in-field	43
Cost per sample	Low (pennies of solvent; disposable tip/paper)	Moderate (columns, solvents, and sample prep kits)	Instrument cost is high for both; per-sample favors AIMS.	119
Regulatory acceptance	Emerging (used for screening; confirmation by LC-MS often needed)	Gold standard (widely accepted legally)	AIMS data are increasingly accepted as technologies mature	120

Case example tables and real-world impact

To crystallize the discussion, this section provides concise reference tables summarizing real-world findings of adulteration uncovered by AIMS techniques and highlights the impact of these findings on public health and regulation (Tables 2 and 3).

The above tables underscore how AIMS is revolutionizing the monitoring of herbal medicines. For example, the identification of sibutramine in slimming tea by DART-MS (Table 2) led to international alerts and probably saved lives by informing consumers of hidden risks. The high throughput shown in Table 3 means that authorities can cast a much wider net, and instead of testing ten products per month they can test one hundred, which greatly increases the likelihood of identifying bad actors. Over the past five to ten years, which is the focus of this review, AIMS has evolved from a novel laboratory curiosity into a practical tool within regulatory arsenals.[121] Countries such as China, Taiwan, and Singapore, where TCM use is widespread, have been early adopters of AIMS for supplement surveillance. The USA and EU have also begun exploring it for dietary supplement oversight.

One real-world impact story: in 2015, the Taiwan FDA implemented an AIMS-based rapid screen at postal customs, using a technique called EMI (Easy Ambient Sonic-spray Ionization) for incoming packages of herbal supplements.[122] In the first year, they intercepted over 100 shipments containing undeclared Western drugs, including slimming pills with sibutramine and sexual supplements with PDE-5 inhibitors, all flagged within minutes by AIMS and then confirmed by laboratory MS. This dramatically increased enforcement efficiency and likely deterred some traffickers of adulterated products. Another impact is seen in clinical toxicology, where AIMS has enabled faster diagnostic confirmation of poisonings associated with herbal supplements.[123] For instance, the identification of undeclared aminopyrine (an old analgesic) in a patient's "herbal" remedy by AIMS helped doctors pinpoint the cause of the patient's agranulocytosis and initiate the correct treatment.

Conclusion and outlook

In conclusion, AIMS has emerged as a powerful, rapid, and versatile approach for screening illegal adulterants in traditional Chinese medicines and other herbal products. It marries the strengths of mass spectrometric specificity and sensitivity with unprecedented speed and minimal sample handling, addressing a critical need in public health protection. Compared with earlier reviews that either treated ambient ionization as one of many analytical tools for herbal medicines or focused primarily on LC/GC-MS methods for adulterant detection, the present work highlights how specific AIMS modalities have been operationalized for front-line surveillance of TCM products, including miniaturized and portable platforms that connect directly to regulatory and clinical decision-making. Over the past decade, numerous studies have validated that AIMS techniques, ranging from DART and DESI to paper spray and thermal desorption ESI, can reliably detect a wide array of pharmaceutical adulterants such as weight loss drugs, PDE 5 inhibitors, NSAIDs, and sedatives in complex herbal matrices within seconds. AIMS has helped reveal the unsettling extent of this adulteration problem, but importantly it also

provides a solution: regulatory agencies can now screen products more efficiently than ever before, catching many violations that would have previously gone unnoticed.

That said, AIMS is not a panacea. We have discussed challenges such as quantification accuracy, potential matrix suppression, and the need for confirmatory analysis in certain situations. Ongoing research and development are rapidly addressing these issues. The use of internal standards and calibration in AIMS is improving quantitative capabilities. Novel ambient ionization methods continue to appear, offering better stability or selectivity – for example, new coated probe electrospray techniques to enhance signal durability for longer analyses. Instrument vendors are introducing commercial ambient ionization sources and smaller mass spec units, which will help standardize and disseminate these methods. There is also a trend toward automation and AI integration: one can imagine an autonomous system that scans herbal products *via* AIMS and uses machine learning to compare the chemical profile against a database of authentic products, flagging anomalies instantly.

Looking ahead 5–10 years, we expect AIMS to become a routine frontline tool in the quality control of not only TCM but all kinds of dietary supplements and botanicals. Its speed and broad coverage are simply too advantageous in an era where supply chains are global and products can be adulterated anywhere from raw materials to finished goods. Regulatory bodies are likely to formally validate and approve more AIMS methods, lending them greater legal standing. We may see portable AIMS kits at import checkpoints, in pharmacies for authenticity verification, and even in clinics for quick screening of patient-brought supplements. The ability to do non-destructive testing means that manufacturers themselves could use AIMS for 100% inspection of products for quality assurance.

In summary, ambient ionization MS is transforming our ability to safeguard consumers from dangerous adulterants hidden in traditional remedies. It exemplifies how cutting-edge analytical science can directly benefit public health. By enabling rapid, on-site detection of pharmaceutically adulterated TCMs, AIMS acts as a strong deterrent against such fraudulent practices and a safety net catching those that persist. As the technique continues to mature, addressing current limitations, it is poised to become an indispensable component of modern pharmacovigilance and herbal medicine regulation. The war against illegal adulteration is far from over, but with tools like AIMS, we have gained a decisive advantage in this critical battleground of public health.

Author contributions

F. Y. conceived the review framework, led the conceptualization, and supervised the overall development of the manuscript. W. S. conducted the literature investigation, performed data curation, and contributed to methodology refinement. J. Y. carried out formal analysis, synthesized comparative evaluations of analytical techniques, and supported visualization and organization of tables and figures. F. Y. prepared the original draft. W. S. and J. Y. contributed to writing – review and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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