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Review article

Adulteration of Herbal Medicine and its Detection Methods

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ABSTRACT

People are increasingly turning to the use of herbal medicines (HMs) due to the growing trend of embracing nature and concerns about the adverse effects of conventional treatments. HMs provide a sense of safety because they are natural and intended for long-term use. However, herbal medicines are also associated with adverse effects. Furthermore, the use of these medicines poses dangers associated with the deliberate inclusion of synthetic substances, the intentional or accidental substitution of plant species, or simply the risk of mislabeling. While reports of illegal synthetic or pharmaceutical substances being added often involve herbal weight-loss and weight gain preparations, aphrodisiacs, treatments for rheumatic and inflammatory diseases, antidiabetic medications, and antihypertensive preparations, it appears that the substitution of plant species occurs across various categories of herbal medicines. This narrative aims to review the types of adulteration in herbal medicine, the analytical techniques used for detecting adulteration. In conclusion, more studies on the adulteration of HMs are required to inform health authorities and limit the use of these substances. Therefore, it is necessary to coordinate and encourage regulatory policies on HMs on a worldwide scale. Relevant regulatory agencies all over the world must be proactive and keep enforcing the necessary safeguards to protect public health by ensuring that all herbal medications approved for sale are secure and of a high enough standard.

Keywords: Adulteration, herbal medicines, detection methods.

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INTRODUCTION

Herbal Medicines

Herbal medicines (HMs) are drugs derived from plants that naturally occur and contain phytochemical components. [1]. Ancient people relied on nature to treat their illnesses and diseases because they believed that nature provided them with plants and herbs that could effectively address any medical issue with minimal side effects. [2-4]

The trend of utilization of HMs is found to be increasing nowadays in Arabic countries and worldwide. Studies found that 80% of the citizens of Arabic countries depend on HMs for the treatment and prevention of common illnesses.[5,6] Albadr et al., (2018) found that about 73% of the population in Saudi Arabia have used HMs at least once during their lives.[7] A lower proportion of use was documented in Egypt and Jordan [8]. The reason for these high rates of use of these HMs was attributed to their affordable prices, availability, patient preferences, and belief in HMs rather than pharmaceutical medicines.[8,9] The market size of HMs in Middle East was estimated to exceed $8 billion in 2022 and is expected to rise in the next few years by 20%.[10]

The increasing demand for HMs and the lack of regulations have raised concerns about their purity and efficacy, which are readily available in the market. In developing countries, HMs are often mixed with medicinal (pharmaceutical) medicines such as steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and anxiolytics to enhance their potency.[11]

There have been numerous reports of dietary supplements and contaminated HMs being sold as "all-natural" when, in reality, they contained undisclosed synthetic substances that enhanced their therapeutic effects. Studies found that many HMs that are used for weight reduction, weight gain, sexual enhancements and analgesia are adulterated with known chemical and pharmaceutical agents.[12-15] Therefore, it is necessary to assess HMs and dietary supplements to determine their contents, efficacy, and safety profiles.[16,17]

Adulteration of Herbal Medicines

Adulteration of HMs is an increasingly challenging problem due to the high demand for these medicines. Adulteration is primarily the act of partially or completely substituting the original, raw herb with another substance that is either of lower quality or has no medicinal benefit to generate a profit by selling the herb cheaper.[18] The World Health Organization (WHO) defines counterfeit medication as "any product that contains a high concentration of impurities and contaminants, an incorrect number of active components, incorrect ingredients, or no active ingredients at all".[1,19] In the pharmaceutical industry, an adulterant is a substance that possesses pharmacological activity added to/ or substituted by the active labeled agent(s). However, a contaminant is an any by-product of the manufacturing process, and a 'diluent' is an inert substance that is added to the pharmacological agent.[20]

Adulteration of HMs is reported in developed and developing countries. In which 10% of HMs that are sold in community pharmacies and 50% of online products were found to be adulterated.[21-23] However, more than 80% of HMs that are sold in community pharmacies in African countries were found to be adulterated.[24]

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Direct or Intentional Adulteration

Intentional adulteration of HMs is made in two ways. Either by the addition of synthetic chemical drugs to increase efficacy or by using substances with morphological similarities to the original plant that could be of lower medicinal effectiveness and quality to gain more revenue. As a result, the therapeutic benefits that they claim to have are questionable. To maximize economic benefits, these procedures are applied to products that are more expensive and in high demand.[25] Panax ginseng is one of the commonly adulterated ingredients in HMs due to its tonic effects, increased demand, and high costs. Adulterated products were found to contain morphologically similar species such as *Platycodon grandiflorum, Codonopsis lanceolata, and Pueraria lobata* which have no medicinal effects (Figure 1).[26]

Indirect or Unintentional Adulteration

Unintentional adulteration typically occurs without the knowledge or consent of the producer. In which the proper herbal medicine may be partially or completely devoid of the active ingredients that could be present due to insufficient knowledge and/or carelessness of raw material collectors about the correct plant species and the specific part of the plant that contains a higher concentration of therapeutic ingredients.[27] Furthermore, the lack of appropriate evaluation procedures can render the identification of raw materials impossible. The location, climate, growth conditions, method of germination, and storage conditions can all have an impact on the quality of herbs. To achieve the highest therapeutic value, the herb should be collected at the proper time and season. Herb deterioration during storage causes the loss of therapeutic components, the transformation into inactive metabolites, and commonly, the production of harmful metabolites. Physical elements that contribute to deterioration include moisture, the amount and quality of light, air, and temperature. These physical characteristics may create an ideal habitat for the growth of germs, mites, and molds. Therefore, the reason for adulteration in HMs is not always solely driven by financial profit.[18]

Types of Intentional Adulteration

The most common types of intentional adulteration are listed in Table 1.

Methods of Adulteration

If a medication does not meet the recommended standard due to substitution, deterioration, mixing, sophistication, inferiority, or spoiling, it is considered adulterated.[28]

Adverse Effects of Adulteration

Adulteration is associated with a wide range of potential adverse effects, varying from mild to severe. Mild adverse effects might include allergic skin reactions, fatigue, gastrointestinal symptoms, mood disturbances, muscle weakness, pain, and respiratory tract symptoms. Moderate adverse effects might include confusion, convulsions, dermatitis, lethargy, seizures, leukopenia, and sensory disturbances. However, in severe cases, adulteration can lead to serious illness including carcinomas, cerebral edema, coma, intracerebral hemorrhage, renal and/or hepatic failure, and poisoning.[29] Lau et al., (2004) study reported that cases of fatal liver failure were recorded in Singapore due to the use of a herbal slimming product sold under the name of "Slim 10" that was advertised to be herbal, natural and safe. However, they found that it was adulterated with the hepatotoxic agent "N-nitrosofenfluramine".[30] Similarly, Zheng and Navarro (2015) study found that the same hepatotoxic agent was found in a slimming product and associated with more than 800 cases of liver injury in Japan between 2001 and 2002.[31]

Furthermore, due to the pharmacological activity of HMs, which can give rise to the development of adverse side effects and interactions with other HMs or with pharmaceutical medicines, similar to those between pharmaceutical drugs. Niggemann and Grüber (2003) study demonstrated that the coadministration of the Ayurvedic syrup Shankhapushpi, resulted in a decrease in phenytoin plasma levels and precipitated seizures in an already controlled epileptic patients.[36] Similarly, the St. John's wort (Hypericum perforatum) herb was found to interacts with fexofenadine,[37]and theophylline.[38] Interestingly, ginkgo biloba, a heavily used HMs for vertigo and cognitive disorders was found to interact with aspirin and warfarin.[39]

Herbal Medicines Classes Subjected to Adulterants

Herbal Medicines for Weight Loss

Herbal medicines are used for various reasons, and weight loss is one of the most popular ones. Some individuals start using these medicines because traditional diets without lifestyle modifications have been unsuccessful, while others hold the belief that a miraculous weight-loss HMs will allow them to sustain their current lifestyle. Furthermore, people buy these HMs because they are readily available online without a prescription.[40]

Formulations for herbal weight loss medicines may potentially contain illegally produced chemicals to enhance their effectiveness and maximize profits. These additives are often classified as anorectics,

Table 1. Types of intentional adulteration.[28]

Types	Definition	Examples
Morphologic adulteration	A type of adulteration in which the active ingredient is substituted with a substance that is morphologically similar herb but with lower or no therapeutic effects	Adraka *(Zingiber officinalis)* is adulterated with Japanese Ginger
Artificial adulteration	A type of adulteration in which artificially manufactured substances that are physically and/or biologically similar to the natural agents are used as an adulterant	Paraffin wax after yellow coloration substituted for beeswax.
Exhausted agent adulteration	A type of adulteration in which an unused or exhausted form of the medicine is sold as the original one after the chemical components have been removed, as a result, the plant material loses its therapeutic qualities.	Jiraka (*Cuminumcyminum)*
Pharmaceutical adulteration	A type of adulteration in which a pharmacologically active substance is added to the natural ones to improve natural characteristics of the natural herbal medicine.	Steroids are added to herbal medicines for the treatment of rheumatoid arthritis
Vegetative adulteration	A type of adulteration in which another vegetative part of the same plant or other plants are added to the original one together with the beneficial part.	The Stem portion of the plant *Bala (Sidacordifolia)* is added along with the leaf
Bulking adulteration	A type of adulteration in which an inert substance that devoid clinical effects are mixed with herbal medicines in powder form to increase weight and reduce cost	Brick powder mixed with Kampillaka powder Wheat flour mixed with Shunthi powder

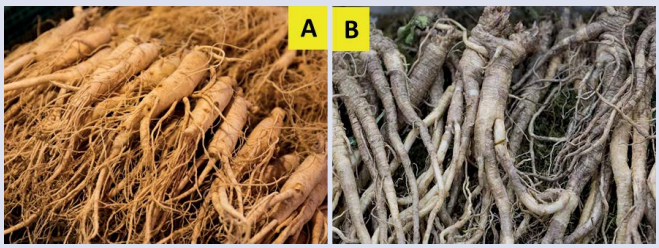

Figure 1. Similarity of the roots of Panax ginseng with Platycodon grandiflorum (A) Panax ginseng root (B) Platycodon grandiflorum.

laxatives, diuretics, anxiolytics, and antidepressants.[41] Anorectics, such as fenfluramine, sibutramine, fenproporex, diethylpropion, clobenzorex, rimonabant, phentermine, and mazindol, are the most common class of synthetic ingredients found in weight-loss HMs.[42] These anorectics in addition to lorcaserin (a selective agonist of serotonin receptors that helps control hunger and reduce caloric intake) were found to be the main ingredients of a herbal weight-loss medicine that was sold under the name of "Lose Quickly" in France. It has been demonstrated that large doses of lorcaserin can result in anxiety, hallucinations, agitations, and convulsions.[43] Benzodiazepines are often used as a masking agent with anorectics containing products to mask (alleviate) the adverse side effects of anorectics that include headaches, anxiety, irritability, and mood swings.[44-46]

Diuretics and laxatives can also be found in weight-loss HMs since they can precipitate weight loss and convince the users, even though the body is losing water instead of fat.[47] Studies from the Netherlands, the United Kingdom, the United States, and Iran, have reported the presence of various prescription medicines with anorectic effects or those causing weight loss as an adverse effect in weight-loss HMs, including caffeine, ephedrine, phenytoin, thyroxine, and topiramate.[25] Ernst and Pittler (2002) study found that the guarana extract, which was sold online as a weight loss HM, that it was a mixture of ephedra, ephedrine and pseudoephedrine and caffeine.[40,48,49] On the other hand, orlistat, an approved medication for weight reduction that act by reducing fat absorption, was also found to be an adulterant in weight loss HMs.[50]

Herbal Medicines for Weight Gain

Glucocorticoids, including dexamethasone, betamethasone, prednisolone, and triamcinolone, play critical roles in the treatment of wide range of autoimmune and inflammatory disorders.[51] However, glucocorticoids are a dual edge sword, in which they are associated with numerous deleterious effects, including increasing susceptibility to infections, osteoporosis, hyperglycemia, and hypertension.[52] Due to their availability, low cost, rapid onset of action and their high efficacy, dexamethasone, betamethasone, prednisolone, and triamcinolone are frequently utilized as adulterants in many HMs.[53]

Dexamethasone is the most commonly reported glucocorticoid to be found in herbal weight-gain medicines.[54] The use of HMs adulterated with dexamethasone was found to cause serious adverse effects, including nausea, fatigue, insomnia, anxiety, psychosis, exacerbation of schizophrenia, hypertension, and depression.[55,56] To enhance the action of weight gain products, cyproheptadine is also added to dexamethasone. [57]

Aphrodisiac Herbal Medicines

According to the United States Food and Drug Administration (FDA), aphrodisiac HMs, were found to be the most commonly adulterated products and containing undisclosed synthetic ingredients.[58] In which the majority of marketed herbal sexual enhancer were found to contain phosphodiesterase type 5 (PDE-5) inhibitors.[48] The main PDE-5 inhibitors found in HMs are sildenafil, vardenafil, and tadalafil. However, their counterparts, which are more difficult to identify in standard screening due to small structural variations in the molecular structure, can also occur. Because of their unknown safety, these analogs create a greater risk. HMs that aim to enhance women's libido may potentially contain adulterants such as flibanserin, which affects the serotonin system.[58]

Herbal Medicines for The Treatment of Rheumatic and Inflammatory Diseases

Rheumatic disease is another condition in which people often seek and use HMs. The adulteration of products with synthetic substances is often accompanied by adverse reactions, including gastrointestinal hemorrhages. These HMs were later found to be adulterated with pharmaceutical ingredients including; paracetamol, NSAIDs, and opioids, in addition to the herbal ingredients.[59] Due to their anti-inflammatory properties, glucocorticoids were also found in HMs that are claimed to cure rheumatic and/or inflammatory diseases. However, these adulterated HMs are associated with serious adverse reactions including immunosuppression, increased skin fragility, osteoporosis, and peptic ulcer.[60-62]

Herbal Medicines for Bodybuilding and Athletic Performance Enhancement

Athletes, including bodybuilders, are often fans of HMs. They seek substances that are not prohibited, which can enhance their performance and help them to increase their muscles' size. However, some HMs used by athletes contain a variety of active pharmacological ingredients, including glucocorticoids, cyproheptadine, and anabolic steroids.[63] Since these agents increase the deposition of visceral and truncal fat and stimulate of hunger, and weight gain.[64,65]

Athletes' formulas and tonics that are sold in gyms and sports centers were also found to be adulterated with anabolic-androgenic steroids, such as testosterone and its synthetic analogs, in addition to glucocorticoids, to enhance performance and improve physical appearance [66]. However, prolonged use of testosterone and /or its analogs can result in behavioral changes, hypertension, heart issues, abnormal blood coagulation, hepatic illnesses, loss of libido, gynecomastia (in male), and irregular menstruation (in female).[51,67]

Analytical Methods for the Detection of Adulteration in Herbal Medicines

The widespread availability of HMs and the potential for adulteration have become new threats that could impact global health and are a source of concern for everyone. On the other hand, analytical techniques have been developed to detect adulteration in HMs and counterfeit medicines to address this issue.[4,68] Once the adulterant class is selected, any other potential adulterants become potential interferents in the analytical measurement using the selected technique.[69,70] Furthermore, these interferents should be thoroughly investigated to ensure that the approach can be applied to real samples, where there is some unpredictability regarding the type and class of adulterant that will be identified.[71] Figure 2 Illustrate the most common analytical methods used for the detection of adulteration.

Chromatographic and Electrophoretic Methods

The majority of studies describing the adulteration of HMs utilize chromatographic techniques to detect and identify adulterants. Because these techniques have a high capacity for separation, they can be used with complex mixtures. High-performance liquid chromatography (HPLC) is an established technique that is widely used for routine analysis worldwide. Given the potential for confirming adulterants using structural data, the combination of mass spectrometry and

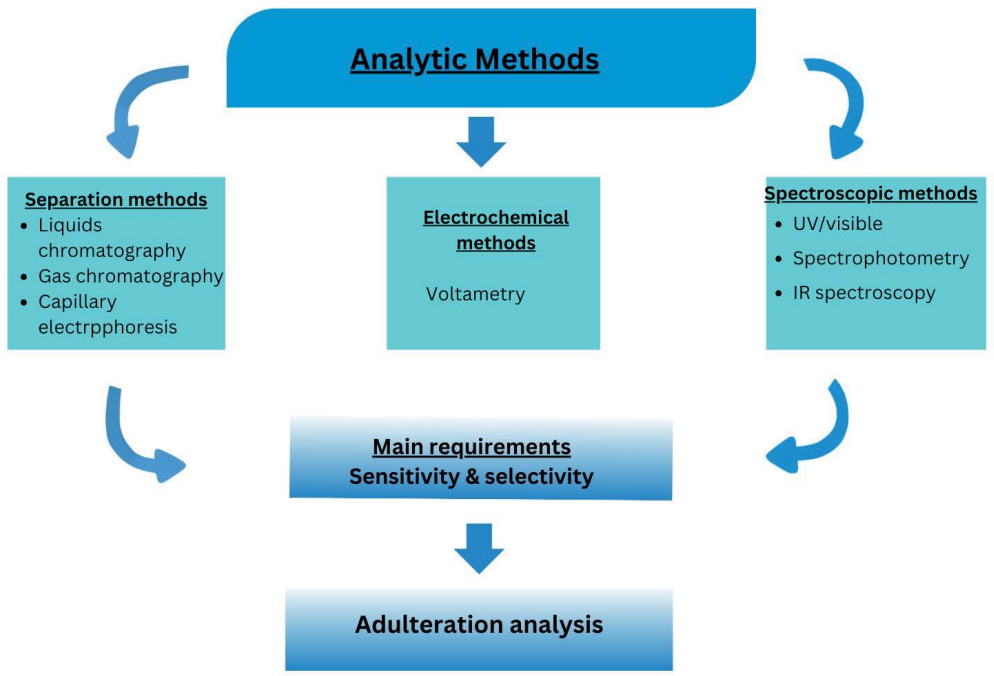

Figure 2. Most common analytical methods used for the detection of adulteration.[28]

nuclear magnetic resonance is highly favorable in this case.[72] Gas chromatography (GC), one of the chromatographic techniques, has also been extensively employed to identify adulterants in HMs.

The majority of the mentioned techniques were developed for screening and confirming adulterants by utilizing their specific retention times, along with additional spectral data.[73] Pharmaceutical ingredients are often measured and verified during the adulterant examination using high-purity reference standards.[74] Furthermore, the capillary electrophoresis (CE) separation technique also has been utilized to identify adulterants in HMs. The high-resolution power, quick analysis time, and minimal reagent and sample consumption of CE make it a popular choice for this type of investigation.[75]

CONCLUSIONS

Due to the widespread belief that HMs are safe, their use is popular. However, people are unaware of the potential risks associated with adulterated HMs containing undisclosed agents. The danger of using such medicines is the occurrence of adverse effects from unknown sources and potentially fatal drug-drug interactions. Fortunately, numerous analytical methods have been developed to detect adulteration in HMs. Therefore, more studies on the adulteration of HMs are required to inform health authorities and limit the use of these substances. In actuality, "safety" and "natural" are not interchangeable terms. Therefore, it is necessary to coordinate and encourage regulatory policies on HMs on a worldwide scale. Relevant regulatory agencies all over the world must be proactive and keep enforcing the necessary safeguards to protect public health by ensuring that all herbal medications approved for sale are secure and of a high enough standard.

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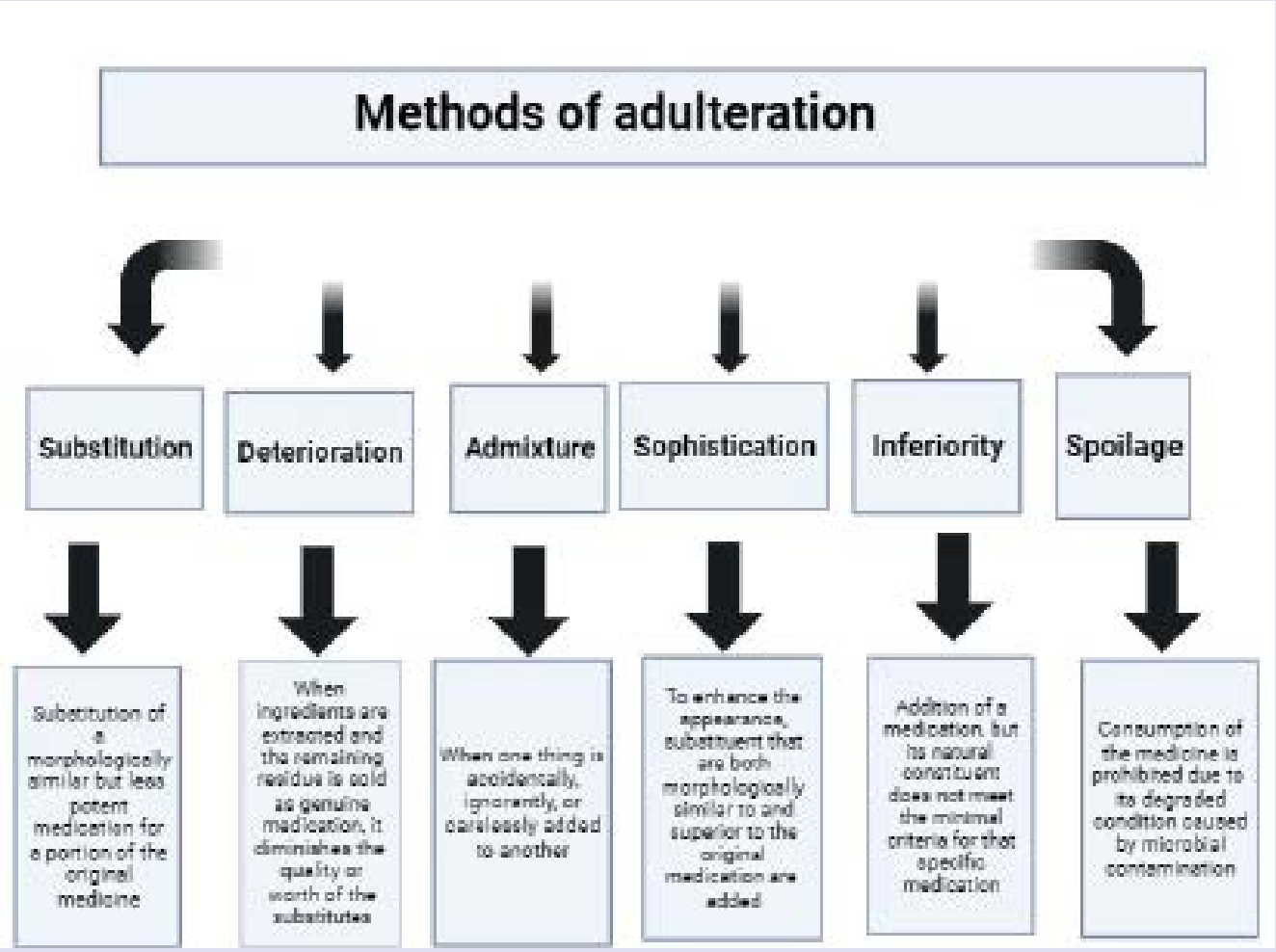
GRAPHICAL ABSTRACT



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