REVIEW
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An appraisal of the regulatory policies governing the use of herbal traditional medicine

Keren Netzer[1*], Marissa Balmith[1], Brian Thabile Flepisi[1]

[1]Department of Pharmacology, University of Pretoria, Pretoria 0084, South Africa.

***Corresponding to:** Keren Netzer, Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, Dr Savage Road, Prinshof 349-Jr, Pretoria 0084, South Africa. E-mail: u21541818@tuks.co.za.

Author contributions

Keren Netzer drafted the article, carried out the literature research, collected the data, analysed the results and wrote the manuscript. Marissa Balmith and Brian Thabile Flepisi were responsible for conceptual contributions, providing critical input in research methodology and results, reviewing and editing the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

TM, traditional medicine; WHO, World Health Organization; HTM, herbal traditional medicine; CAM, complementary alternative medicine; CM, complementary medicine; THPs, traditional health practitioners; USA, United States of America; TCM, traditional Chinese medicine; ATM, African traditional medicine; GMP, good manufacturing practice; FDA, U.S. Food and Drug Administration; OTC, over the counter; EBP, evidence based practice.

Citation

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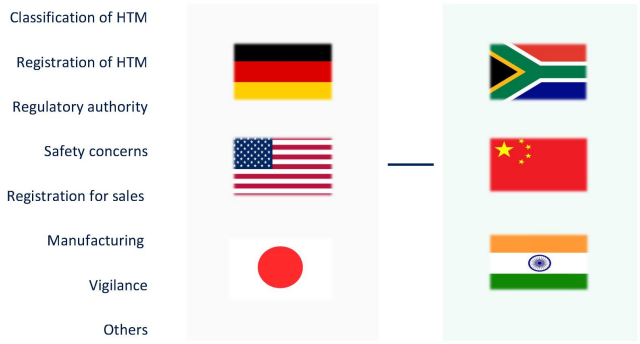
Abstract

The regulation of herbal traditional medicine (HTM) is of much importance as it ensures the safety, quality and efficacy thereof. However, there are variations in the regulation of HTM worldwide with some countries being more supportive of HTM than others. This literature review aimed to evaluate and compare the regulatory policies governing the use of HTM in developed and developing countries as well as to determine the regulatory challenges faced by regulatory authorities and governments across the world. The countries investigated in this study were Germany, the United States of America, Japan, South Africa, China and India. Variations were evident between countries, however, Germany and Japan were found to be more advanced with regards to the regulation of HTM. Germany and Japan had stricter regulatory policies and lesser safety concerns. South Africa and the United States of America appear to have inadequate or ineffective HTM regulatory systems which was seen by the countries' limited or lack of regulations and additional safety concerns. The findings showed the difference in HTM regulation between developed and developing countries were not as large as could be expected. The United States of America (developed country) was found to have poor HTM regulations, while China and India (developing countries) were found to have thorough regulations. The findings also show that both developed and developing countries continue to face challenges with regards to establishing regulations and registration procedures for HTM.

Keywords: herbal medicine; traditional medicine; regulatory policies; government guidelines; developed countries; developing countries



Background

Traditional medicine (TM), also known as indigenous or folk medicine, can be described as medicine that various cultures have developed over centuries on the basis of traditional knowledge passed down from previous generations [1]. The World Health Organization (WHO) defines TM as "the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" [2]. While TM has many facets such as yoga, aromatherapy, chiropractic care, massage, meditation, spiritual practices or prayer and exercise [3], the current study will focus on the herbal aspect of TM or herbal traditional medicine (HTM).

HTM has been used by many populations worldwide for the treatment of diseases long before conventional medicine and continues to contribute to the healthcare of the majority of the population [4]. HTM falls under the umbrella of complementary alternative medicine (CAM). CAM refers to a wide range of healthcare practices that are not part of a country's own tradition [5]. According to the WHO, trends in the use of HTM and CAM have been steadily increasing [6]. This trend has been reported in both developed and developing countries [7], where HTM is used as either a replacement (alternative) or add-on (complementary) to conventional medicine [8]. According to the WHO, 170 countries reported using HTM and CAM in 2018 [2], suggesting that these therapies are used by over 90% of WHO Member States.

The main reasons for HTM use in both developed and developing countries is due to its accessibility, perceived safety, fewer and less severe side effects [9] and relatively low cost [10]. Additionally, in cases where conventional treatment is ineffective, HTM has been prescribed for the symptomatic treatment of chronic diseases and degenerative disorders [8]. HTM can potentially be used to treat microbial resistance and novel diseases as well as aid in the development of conventional medicines against novel diseases [9]. This suggests that HTM could also potentially fill the void left by the inability of conventional medicine to combat an increase in cancer, heart disease, as well as other diseases [10].

As with any other medicine, there are risks associated with the use of HTM [11]. Most HTMs have not been evaluated in the laboratory and as such, there is a lack of clinical trials on HTM safety, quality and efficacy [12]. As a result, the mechanisms of action of HTMs are not well elucidated and adverse side effects, contraindications, and interactions with biomedical pharmaceuticals and foods are widely unknown [12]. Additionally, in some countries, HTM is prescribed by unlicensed traditional health practitioners (THPs) or CAM practitioners lacking basic training and qualifications, which may increase the risks associated with treatment errors [7]. This is expected as the individual providing treatments needs to have the proper qualifications and experience in order to provide safe treatments and be cognoscente of the medicines they are working with [7]. The lack of regulation or licensing of THPs may lead to misuse of the HTM by unqualified practitioners and loss of credibility of the system [13].

The risks associated with the use of HTM are exacerbated by its poor regulation seen in many countries [12]. In many cases, HTM is unregulated or the regulatory policies are not as effective as those of conventional medicine [14]. Drug regulations are a vital part of a healthcare system and provide clinicians and patients with reassurance that medicine is generally safe, of good quality and effective against a particular disease [15]. The regulations aim to ensure that the correct dosages are used and that indications, side effects and contraindications are known and listed. In addition, it ensures that product labelling is up to standard, and that drug prices are monitored [11]. HTM is no different from conventional medicine when it comes to the need for regulation as the misuse of HTM and lack of regulations have been associated with several risks [12, 16, 17]. An increase in the use of HTM has led to an increased demand to regulate the safety and efficacy of HTM [12]. The increased use of unregulated HTM worldwide may be associated with increased adverse effects [12]. The current study aimed to evaluate and compare the regulatory policies governing the use of HTM in developed and developing countries.

The review focused on the regulation of HTM in both developed and developing countries. Six countries were included, three of which were developed countries namely, Germany, the United States of America (USA) and Japan whereas the other three were developing countries namely, South Africa, China and India. These countries were selected to represent a large part of the global community using HTM as they have a high prevalence of HTM use [18], due to their geographical location as well as for country-specific reasons. Germany was selected as it is the largest and most advanced herbal industry in developed countries [19]. It is also the largest importer of herbal medicines in Europe and has a long history of herbal medicine use [20]. The USA was selected as it is regarded as the global standard with regards to drug development [21], and as such has been considered a useful country for comparative purposes. Despite this, not much emphasis has been placed on herbal medicine in comparison to other developed countries [20]. Japan was selected as it is a developed Asian country with a long history of HTM use [22]. Like Japan, South Africa was also selected for its long history of HTM use and to represent the African continent. China and India were selected as they are extensive users of HTM and are known to export HTM widely [23].

Terminology relating to TM

In many developed countries, HTM is conventionally known as CAM or herbal medicine [24]. As such, HTM in Germany and the USA will be referred to as CAM or herbal medicine in this review. In Japan however, the most common Japanese indigenous HTM is specifically referred to as Kampo, a medicine derived from traditional Chinese medicine (TCM) [22]. In most developing countries, different terms are used to describe indigenous HTM. In South Africa, indigenous TM is referred to as African traditional medicine (ATM), whereas TMs such as TCM or Ayurveda are referred to as CAM [25]. All indigenous TMs in China are referred to as TCM [26]. TM systems in India include Ayurveda, yoga, Unani, Siddha, homoeopathy and naturopathy [13]. While the term Ayurveda is not synonymous with Indian HTM, Ayurveda is the most widely used TM system in India and includes healing through herbal medicine. As such the name Ayurveda will be used in place of Indian HTM to be consistent with published literature.

Developed countries

Classification and registration of HTM in developed countries

The classification of HTM plays an important role in raising awareness of HTM and the various umbrella terms used to describe it [27]. The classification brings to light the various medicines available for the potential treatment of diseases and promotes research yielding evidence supporting its use [27]. On the other hand, the registration of HTM shows how much control a country has over the medicine. The classification of medicines determines the restrictions and regulations that will apply to the drug and may portray a country's attitude towards the medicines [28]. The classification, registration, regulation, prescription and safety concerns of HTMs are diverse across countries. The regulatory inconsistencies between countries and regions may be attributed to diverse cultures, histories and uses of HTM [24]. As such, the regulation and legislation of HTM differs between countries with some countries being more advanced than others [29].

When investigating developed countries it was found that TM has been classified as prescription or non-prescription medicine in both Germany and Japan [18]. In addition, Germany also classifies TM as herbal medicine [13], while Japan classifies TM as pharmaceuticals which sets the tone for their regulatory policies which are stringent and similar to those of conventional medicine [22]. The USA does not

classify TM as medicinal, but rather as dietary supplements [30]. With regards to the registration of HTM, Germany [20] and Japan [18] are known to register TM with their respective states while the USA had no formal registration of TM [18]. Since TM was not well classified in the USA with the registration processes being poorly well defined, the USA has received much criticism as it is believed that the regulation of TM as dietary supplements is not adequate [21].

TM in Germany is registered within the European Union [31]. Under the *Traditional Herbal Medicinal Products Directive* of the European Union, Germany has an established, simplified registration procedure for traditional herbal medicinal products through directive 2004/24/EC (the herbal directive) [31] (Table 1). Germany (and the European Union) have received praise in the literature due to the success of the herbal directive which has been recommended for other countries as well [32]. The aim of the directive is to protect public health while also allowing free movement of herbal medicinal products across the European Union [31]. The simplified registration procedure for herbal medicines targets those unable to meet the requirements for the classification of well-established medicinal use under directive 2001/83/EC [32]. The directive automatically registers herbal medicinal products in all member states if the medicine was registered by one member state and has been effective and beneficial [32]. Since the directive also requires premarketing quality and safety tests, the laws reduce the amount of unsafe herbal medicines on the market [32].

Regulation of HTM in developed countries

The authorities regulating HTM in Germany [20], the USA [20] and Japan [22] were found to be the same as those of conventional medicines. HTM in Germany is also regulated by the European Medicines Agency as Germany is part of the European Union [31]. As such, Germany's regulatory policies and laws are, for the most part, similar to those of the European Union (Table 1).

The regulatory policies governing the use of HTM are well defined in Germany. While the regulation of HTM in Germany is similar to the other countries in the European Union, in Germany, unlike other European countries, TM has a unique status due to the *Imperial Decree of 1901*, which at the time was unusual in allowing the sale of many plant-based medicines [20]. The decree was updated in 1961, allowing TM to be sold as medicinal agents [20].

Table 1 A summary comparison of HTM regulations in developed countries

Country	Germany	USA	Japan
Classification of HTM	Herbal medicine [13] Prescription medicines [18] Non-prescription medicines [18]	Dietary supplement [30] Botanical preparations [21]	Pharmaceuticals [22] Prescription medicines [18] Non-prescription medicines [18]
Registration of HTM	Registered [20] State-licensed [64] Traditional use – with directive 2004/24/EC [21] Conventional use – with directive 2001/83/EC [21]	Not registered [18] Dietary supplement – *Dietary Supplement Health and Education Act of 1994* (does not get registered) [21] Botanical drug – *Federal Food, Drug and Cosmetic Act* [21]	Conventional doctors [63] State-licensed [18]
Regulatory authority	BfArM [20] EMA [31]	FDA [20]	The Pharmaceuticals and Medical Devices Agency [22] The Subcommittee on Kampo Medicine and Products of Animal and Plant Origin of the Central Pharmaceutical Affairs Council [37]
Safety concerns	Self-medication [65] Limited knowledge on interactions and side-effects of herbal medicines [65] Poor communication with conventional physicians about HTM usage [65] Untested HTMs [12] Poor labelling [12] Lack of suitable quality controls [12] Poor patient information [12] Wrong species of plant used [12] Adulteration of products [12] Over dosage [12] Misuse by either healthcare providers or consumers [12] Concomitant use of HTM with conventional medicine [12]	Conventional practitioners knowledge [12] Supplements do not always contain herbal substances mentioned on the label [12] Supplements contain additional ingredients that are not provided on the label [21] Untested HTMs [12] Poor labelling [12] Lack of suitable quality controls [12] Poor patient information [12] Wrong species of plant used [12] Adulteration of products [12] Over dosage [12] Misuse by either healthcare providers or consumers [12] Concomitant use of HTM with conventional medicine [12]	Contamination of agricultural products [37] Untested HTMs [12] Poor labelling [12] Lack of suitable quality controls [12] Poor patient information [12] Wrong species of plant used [12] Adulteration of products [12] Over dosage [12] Misuse by either healthcare providers or consumers [12] Concomitant use of HTM with conventional medicine [12]

Data from various articles and regulatory authority webpages. USA, United States of America; BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte (the Federal Institute for Drugs and Medical Devices); EMA, European Medicines Agency; FDA, Food and Drug Administration; HTM, herbal traditional medicine.

As a result, for more than a century, Germany has sold plant-based medicines to be used for the prevention or treatment of various illnesses and conditions [20]. During this time, Germany has also studied herbal medicines and their indications by isolating the active ingredients of medicinal plants and evaluating their pharmacological effects [20]. This research was carried out under the directive of Commission E [20]. Commission E was established in 1987 and consists of physicians and scientists specialising in herbal medicine and related disciplines [20]. Commission E were tasked with evaluating the safety and efficacy of herbal medicines [20]. Until 1994, monographs on specific herbs were compiled and 380 monographs have been published on 360 plant species including single and combination products [20]. Currently, only herbal medicines with Commission E approved status are legally available and TM manufacturers must adhere to pharmacopoeias and monographs written by Commission E [20].

The thorough regulatory guidelines in Germany may be attributed to the decades that Germany has had to investigate herbal medicines. As a part of Germany's regulatory policies, HTMs are subject to quality assurance [20], and good manufacturing practice (GMP) guidelines are mandated [31]. The manufacturing sites are subject to sporadic inspections by the regulatory authorities [18]. Since herbal medicines in Germany are subject to the same manufacturing regulations as conventional medicines [18], periodic safety update reports need to be submitted [33]. Additionally, adverse reactions to the herbal remedies must be reported [13] (Table 2).

In the USA, the U.S. Food and Drug Administration (FDA) has limited jurisdiction as the FDA only monitors the toxicity of herbal medicines [24]. As such, manufacturers are permitted to market dietary supplements even if the product is found to be unsatisfactory by the FDA [21]. However, any new botanical preparations should be reported to the FDA prior to marketing, if not the label must clearly state that the FDA has not evaluated the medicine [20]. The manufacturer however, may still market the medicine (with a label stating that the FDA has not evaluated the medicine) if the FDA found the new drug ingredient unsatisfactory [21]. Products sold before 1994 are automatically considered safe and may remain on the market without filing a new drug ingredient notification [20].

Table 2 A comparison of HTM regulatory policies in developed countries

Regulatory measure	Germany	USA	Japan
Registration for sales	Provisions for registration [18] Simplified registration process [31] To be licensed, results from examinations on quality, efficacy and safety as well as appropriate expert opinions must be submitted [33] To sell the medicines, reports on the safety of medicinal products – periodic safety update reports must be submitted [33]	Does not have to be proven safe before marketing [35] Producers or marketers of herbal medicines containing new ingredients must notify the FDA prior to its sale [20]. If not, the label must state that the medicine has not been evaluated by the FDA [20] Dietary supplements sold before 1994 – safe. May remain on the market without filing a new drug ingredient notification [21]	Important adverse drug reactions must be listed [38] Information must be provided to healthcare professionals about the medicine [38] Kampo medicines that are not categorised as general OTC drugs must undergo new clinical trials [39] Safety requirements are also the same as those for conventional medicine [18] and thus must comply with the risk management plan document [38] Fifteen defined categories, kinds of active components, formulations, doses, modes of administration and regimens, effects and efficacies, and packaging units specified [39]
Manufacturing	Adherence to manufacturing information in the pharmacopoeias and monographs [18] Quality assurance [20] GMP required [31]	The manufacturer may market the dietary supplement if the FDA found the new drug ingredient notification unsatisfactory [21]. The label must state that the medicine has not been evaluated by the FDA [21] If the medicine has medical claims on the label, the product requires evidence of clinical studies [21] Dietary supplements – labelled with the term "dietary supplement" or with a similar term that describes the ingredient(s) [35]	Published list to satisfy approval criteria to be a general OTC drug [39] Requires GMP [13] The *Japanese Pharmacopoeia* is legally binding [18]
Vigilance	Formal mandatory system of reporting adverse reactions for herbal medicine [13] Sporadic inspections by authorities at production sites [18]	Dietary supplements may not be advertised as a treatment/cure/management for a disease [35] Manufacturers must report any serious adverse events reported to them [8] The FDA has safety monitoring responsibilities [35]	Sporadic inspections by authorities at the production sites or laboratories [18]
Others	The national policy for traditional and CM is integrated into *Social Code Five* and *Laws For Pharmaceuticals* [18]	No national plan for integrating traditional and CM into the mainstream healthcare system [18] No U.S. based indigenous health policy framework or national adopted policy on indigenous TM [66]	

Data from various articles and regulatory authority webpages. USA, United States of America; FDA, Food and Drug Administration; GMP, good manufacturing practice; HTM, herbal traditional medicine; CM, complementary medicine; OTC, over the counter; TM, traditional medicine.

Only herbal medicines with medicinal claims on the labels require clinical studies [21]. The FDA does not have the jurisdiction to assess the safety and efficacy of dietary supplements prior to marketing [34]. As such dietary supplements do not have to be proven safe or be satisfactory before they are marketed [35]. Once on the market, the FDA has safety monitoring responsibilities including monitoring the compulsory reporting of serious adverse effects by the manufacturers and voluntary adverse effects reporting by consumers and healthcare professionals [35]. The FDA also reviews labels and product information such as package inserts, literature, and online advertising [35]. Importantly, botanical dietary supplement products have yet to be subjected to mandatory GMP, quality assurance or quality management requirements [16] (Table 2).

While the TM regulatory policies in the USA were found to be poor, the FDA is working on new GMPs that will help ensure that supplements meet a higher level of GMP than food [16]. Additionally, to improve the status quo, the White House Commission on Complementary and Alternative Medicine Policy has proposed ten policy recommendations as well as policy measures for the incorporation of CAM [36]. The policies range from implementing "a wholeness orientation in healthcare delivery" to encouraging "partnerships as essential to integrated healthcare" to promoting the "dissemination of comprehensive and timely information" [36].

Japan differs from the other countries investigated in that Kampo medicine practitioners have self-imposed regulations from TM committees [37] (Table 1). Kampo medicine requires GMP [13] and since Kampo's safety requirements are the same as those for conventional medicine [18], Kampo must comply with the risk management plan document [38]. Kampo manufacturing sites and laboratories are subject to sporadic inspections [18] and by law, healthcare professionals must be well informed pertaining to the medicines [38]. Additionally, the important adverse effects of Kampo medicines must be listed [38] (Table 2). The Kampo medicines that satisfy approval criteria to be listed as general over the counter (OTC) drugs require the least documentation of all the OTC categories [39]. There are ten defined categories and types of active components, formulations, doses, modes of administration and regimens, effects and efficacies, and packaging units specified [39]. Kampo medicines that are not categorised as general OTC drugs may not rely on "historical" knowledge to be considered safe. Non-OTC Kampo medicines must therefore undergo new clinical trials [39].

In Japan, due to the rigorous regulatory policies, Kampo has been standardised and integrated into Japan's healthcare system [37] and as a result, unlike many other countries, a batch to batch inconsistency is uncommon [37]. The success in the regulations may be attributed both to the self-imposed regulations of the Kampo doctors but also the fact that Kampo medicine is exclusively be practised by trained western medicine practitioners [37]. The legal framework for this rose in 1948 when the *Medical Practitioners Law* restricted all types of medical practice to biomedical doctors but did not restrict the types of medical methods that they may use [37].

Safety concerns in developed countries

There was much overlap in the safety concerns of TM between all the countries investigated in this study. All countries showed concern about the consequences of untested medicines, labelling, contamination, unclear doses, misuse and drug interactions with conventional medicine [12]. Additionally, a general concern was that consumers sometimes treat themselves with HTM without consulting a doctor or are reluctant to admit using both treatments [24]. Untested medicines means that there is a lack of clinical trials on HTM safety, quality and efficacy [12]. Additionally, untested medicines have unknown mechanisms of action, adverse side effects, contraindications, and interactions with biomedical pharmaceuticals and foods are common for HTMs causing medicine misuse and increasing the adverse effects associated with the use of HTM [12]. Poor labelling results in medicines lacking ingredients listed or containing additional ingredients that may be dangerous [16], endangered [17] or illegal [16]. Poor good agricultural practice or GMP result in medicines containing varying concentrations of the active ingredient [24] leading to various efficacies and safety profiles of the medicines.

Identification of HTMs is also a problem experienced by all countries since almost all raw materials are harvested from the wild so misidentification or adulteration can easily occur [13]. Additionally, once in the marketplace, HTMs are frequently encountered in a form that makes correct identification practically impossible as they are commonly found in dried, powdered and comminute forms [13]. Misidentification of the plant can lead to deleterious effects as ingesting the wrong plant can be dangerous.

Furthermore, HTM users treating themselves with HTM without consulting a doctor or being reluctant to admit using both treatments [24] is potentially dangerous as drug-herb interactions are possible [13]. The interactions may lead to an enhanced activity from herbal or conventional medicine, or both, as well as intrinsic toxicity from the conventional ingredient which are potentially dangerous [13]. This is particularly a problem in the USA where health professionals are generally ignorant of herbal medicines' potential benefits and their interactions with pharmaceuticals [20]. There is seldom sufficient time in the year for professional curricula to include plant-based medicines causing practitioner bias and creating practitioners who are unable to have knowledgeable discussions about herbal medicines [20]. In Japan however, due to the rigorous regulations, few concerns were reported aside from the fact that raw produce needed for Kampo medicine is mostly imported [37]. As a result, the supply, quality, safety and cost of Kampo were not reliant on Japan alone [37]. Consequently, contamination of agricultural products with pesticides was considered common [37].

Developing countries

Classification and registration of HTM in developing countries

China and India classify TM as prescription or non-prescription medicines [18]. In addition, China subdivided TM into functional foods or drugs [20] with further subdivisions based on the class of HTM [40]. Classifications are listed under the *2001 Chinese Drugs Administration Law*, which divides TCM according to their method of preparation [40]. As mentioned, South Africa only classifies indigenous HTMs as TM, whereas TCM and Ayurveda are regarded as complementary medicine (CM). In South Africa, CM is registered with the Allied Health Professions Council of South Africa [18]. The legal framework governing the regulation of TM in South Africa is currently in progress and not yet well defined causing HTM risks to be exacerbated. However, the registration of ATM's is expected to be implemented in the near future [13]. In China and India, indigenous TMs are required to be registered with the respective states [18] (Table 3).

Regulation of HTM in developing countries

The authorities regulating TM in South Africa [41], China [40] and India [42] were found to be the same as those of conventional medicines. CM or non-indigenous TM in South Africa is regulated by the South African Health Products Regulatory Authority [41], however, there are plans to eventually include ATM as well [43] (Table 3). Only non-indigenous TMs are regulated in South Africa with these regulations being relatively new [25]. While South Africa recognised ATM, it was not integrated into the conventional healthcare system or education and regulatory systems within the country [24]. As such, the only ATM policies that have been passed in South Africa relate to licensing THPs [44] (Table 4).

The regulatory policies between South Africa, China, and India vary significantly. Unlike ATM in South Africa, TCM is well regulated in China. This is due to the integrated nature of the Chinese healthcare system [45] and *China's Medium and Long Term Planning for The Development of Traditional Chinese Medicine Standard 2011–2020*, which aims to perfect the TCM standard system [40]. The Peoples Republic of China has a fully integrated healthcare system where allopathic and TCM are equal so much so that their medical schools

have departments for both health systems and most hospitals have TM units [45]. In 2004, 97 TM research institutes in 30 universities and colleges were listed with 12,901 researchers and 234,558 TCM students [20]. Additionally, Chinese organisations overseeing TCM benefit from state support as the Chinese constitution supports the development and advancement of allopathic and TCM as well as their research, education, and training infrastructure [20]. China also aims to upgrade TCM to the preferred healthcare system in China and plans to do this through stricter monitoring and improved laboratory testing. The increased focus on TCM regulation and quality is intended to enhance the country's health and boost TCM exports [46].

In China, TCM is split into different classes with the safety, efficacy and quality requirements varying depending on the class under which the medicines fall [40]. According to Chinese law, TCM consists of three types of preparations namely Chinese crude drugs, TCM preparations, and prepared slices of Chinese crude drugs [40]. The pharmacological, toxicological and clinical studies required by the regulatory authorities depend on the class of TCM product being licensed [13]. TCM is also afforded supplement provisions [40] such as *Supplement Provision for Good Manufacturing Practice of Prepared Slices of Chinese Crude Drugs*, which allows special GMP requirements for manufacturing prepared slices [40]. Another example is the *Supplement Provision for Traditional Chinese Medicine Preparations Register* which grants different registration requirements for different TCM preparations [40]. For example, TCM preparations may be according to ancient tradition, for curing a syndrome or for curing a combination of diseases and syndromes [40]. Herbals classified as healthy foods have no comprehensive regulations except a few that are regulated under the *Provisional Law of the People's Republic of China on Food Hygiene* [20] (Table 4).

The *Pharmacopoeia of the People's Republic of China*, the *Chinese Materia Medica and Standards* for imported crude drugs are legally binding [18]. Specific labelling, efficacy and safety evaluations and a quality dossier are required to market TCM [9]. TCM is subject to mandatory post-marketing surveillance as reporting of adverse drug reactions are mandatory [13]. Since TCM has been standardised, all patent medicines with the same name must have the same proportion of ingredients [13]. Good agricultural practice and good laboratory practice are required [18] but GMP is currently voluntary for propriety Chinese medicines [46]. The mandatory enforcement of propriety Chinese medicines to GMP requirements is expected in the near future [46]. Propriety Chinese medicines are Chinese herbal medicines that have been processed into pills, powder, liquid, or other forms [46]. Medicines defined as propriety Chinese medicines are categorised into established, non-established and new medicines [46]. Before they can be legally sold, they must be licensed with the statutory Pharmacy and Poisons Board [46]. A secondary review is performed to ensure that all propriety Chinese medicines meet the board's registration standards for quality, safety and efficacy [46]. In China, post-registration monitoring of propriety Chinese medicines for the purpose of detecting any unfortunate adverse incidents has been in place since 2009 [46] (Table 4).

Table 3 A summary comparison of HTM regulations in developing countries

Country	South Africa	China	India
Classification of HTM	TM [24] CM [25] Recognised, not integrated [24]	Functional foods or drugs [20] Prescription medicines [18] Non-prescription medicines [18] Health foods and food products [18]	Prescription medicines [18] Non-prescription medicines [18]
Registration of HTM	Non-indigenous HTMs registered [41]	Registered State-licensed [18]	Registered [42] State-licensed [18]
Regulatory authority	South African Health Products Regulatory Authority [41]	NMPA [40]	DCC [42]
Safety concerns	Variable and unstudied dosages [67] Fake THPs take advantage of patients [13] Untested HTMs [12] Poor labelling [12] Lack of suitable quality controls [12] Poor patient information [12] Wrong species of plant used [12] Adulteration of products [12] Over dosage [12] Misuse by either healthcare providers or consumers [12] Concomitant use of HTM with conventional medicine [12]	Questionable research [13] Inconsistent drug evaluation standards [46] Governmental policies limiting free debate about TCM [49] Untested HTMs [12] Poor labelling [12] Lack of suitable quality controls [12] Poor patient information [12] Wrong species of plant used [12] Adulteration of products [12] Over dosage [12] Misuse by either healthcare providers or consumers [12] Concomitant use of HTM with conventional medicine [12]	Adulteration of market samples is a large problem due to poor good agricultural practice [9] Untested HTMs [12] Poor labelling [12] Lack of suitable quality controls [12] Poor patient information [12] Wrong species of plant used [12] Adulteration of products [12] Over dosage [12] Misuse by either healthcare providers or consumers [12] Concomitant use of HTM with conventional medicine [12]

Data from various articles and regulatory authority webpages. ATM, African traditional medicine; DCC, Drug Control Council; NMPA, National Medical Product Administration; HTM, herbal traditional medicine; TCM, traditional Chinese medicine; CM, complementary medicine; THP, traditional health practitioner; TM, traditional medicine.

Table 4 A comparison of HTM regulatory policies in developing countries

Regulatory measure	South Africa	China	India
Registration for sales	HTMs that are not indigenous to South Africa are to be regulated [41]. The registration considers quality, safety and efficacy [25] HTMs are to comply with labelling regulations and provide professional information for medicines for human use and patient information leaflet [25]	Supplement provisions [40] Good agricultural practice required for crude drugs [18] Good laboratory practice required for drug safety studies [18] The *Pharmacopoeia of the People's Republic of China* is legally binding [18] Specific labelling, efficacy and safety evaluations and a quality dossier are required to market HTM [9] The *Chinese Materia Medica* and *Standards For Imported Crude Drugs* are legally binding [18] New plant-based drugs need approval [9] All Chinese patent medicines of the same name must have the same proportions of ingredients [13] Propriety Chinese medicines are subcategorised and requires licensing prior to being sold [46]	Safety and efficacy data are compulsory for new herbal medicines, requirements depend on the nature of the herb and its market availability [9] Quality control tests [42]
Manufacturing	All unregistered HTM must state the disclaimer on all labelling stating that South African Health Products Regulatory Authority has not evaluated the product [25] Manufacturers, wholesalers and distributors of HTM are to be licensed [25]	GMP for manufactured licensed propriety Chinese medicines is currently voluntary [46]	Pharmacopoeia's contains monographs of quality standards for single-compound and for multi-ingredient drug formulations [42] HTM can only contain ingredients listed in specific recommended books [9] Standardised formulations published [42] In order for drugs to qualify to be in the pharmacopeia, the drugs must meet standards and assessment parameters [42] Manufacturing rules and specifications are listed in schedule T of the *Drugs and Cosmetics Rules* [47] The *Ayurveda Pharmacopoeia of India* is legally binding [18] The *Unani Pharmacopoeia of India* is legally binding [18] The *Siddha pharmacopoeia of India* is legally binding [18]
Vigilance		Post-marketing surveillance of adverse drug reactions are mandatory [13]	
Others	South Africa has an inclusive healthcare system [45] Legal structure and regulations for ATM in South Africa – still being established [13]	Fully integrated [45] Herbals classified as healthy are regulated under the *Provisional Law of the People's Republic of China on Food Hygiene* [20]	

Data from various articles and regulatory authority webpages. ATM, African traditional medicine; HTM, herbal traditional medicine.

Like China, the Indian government plans to update TM programmes as the favoured system of healthcare practise [42]. As such, India is believed to be making strides with regard to the regulation of HTM or Ayurveda. Like China, India benefits from a healthcare system comprising of 30 institutes involved with HTM as well as universities, hospitals and organisations [42]. In summary, the regulatory and educational needs of HTM practitioners are extensively covered in both China and India. Other countries would do well to follow suit and establish an integrated healthcare system as recommended by the WHO [17].

In India, good agricultural practice is required for Ayurveda which can only contain approved ingredients that are found in certain published literature [9]. The *Ayurveda Pharmacopoeia of India*, the *Unani Pharmacopoeia of India*, and the *Siddha Pharmacopoeia of India* are legally binding [18]. The pharmacopoeias contain monographs of quality standards for single-compound drugs for multi-ingredient drug formulations [42]. In order for HTM to qualify to be in the pharmacopoeia, the drugs must meet standards and assessment parameters [42] (Table 4).

Manufacturing rules and specifications are listed in schedule T of the *Drugs and Cosmetics Rules* [47]. The *1945 Drugs and Cosmetics Rules* contains rules for categorising drugs into schedules, as well as instructions for storage, distribution, show, and prescription for each schedule [47]. There are 25 schedules in the rule, ranging from schedule A to schedule Y [47]. Various rules and specifications for the production of Ayurvedic, Siddha, and Unani goods can be found in schedule T [47]. Schedule T calls for GMP hence testing drugs for heavy metals has become compulsory if they are to be exported [48]. Good clinical practice guidelines have been developed and adjusted to suit Ayurveda under the *Drugs and Cosmetics Rule* 158 B of 2010 [42]. Safety and efficacy data are compulsory for new herbal medicines however, requirements depend on the nature of the herb and its market availability [9] (Table 4).

Safety concerns in developing countries

The safety concerns in developing countries are similar to those of developed countries. However, additional concerns have been reported in the literature. Due to the lack of ATM regulations in South Africa, the risks associated with ATM were similar to those around the world, however, were more commonly seen on a larger scale.

Additionally, despite the fact that THPs are required to be registered in South Africa [45], a common concern was the issue of impostor THPs preying on patients many of whom are not licensed [13].

While there are legitimate regulations controlling HTM in China, Chinese research was deemed questionable as it presented with unclear evaluation standards [46]. Additionally, the government attempting to limit free debate about TCM raised questions about the safety and efficacy of TCMs [49]. Additionally, there are concerns about the inconsistent drug evaluation standards in China as seen in the definition/classification of products, market entry paths, GMP compliance, and requirements for evidence demonstrating drug safety and efficacy based on product history, non-clinical and clinical studies [46]. The prevalence of poor scientific studies on TCM and the lack of a systematic investigation caused concern among professionals with regard to the safety and efficacy of TCM [46]. The medical community's lack of trust in China's integrity is a safety concern as well [46].

In China, the medical community's lack of trust in China's integrity is considered a safety concern and is emphasized by the Beijing community's intent to introduce a law that illegalises TCM criticism [50]. This has raised questions especially now that the government is claiming that TCM is very efficient against COVID-19 [50 – 52]. According to reports, TCM has made significant contributions to the treatment of COVID-19 shown by a high efficacy rate in a multicentre, prospective, randomised control trials [53]. Some clinicians believe that the government's promotion of TCMs make it more difficult for scientists to question the safety, efficacy and quality of TCM because the issue would be elevated to a political level, limiting free debate [49]. As a result, clinicians are hesitant to openly condemn TCM [49].

In addition to a lack of trust in China, other TCM safety concerns include monitoring and enforcement [20]. Despite the fact that the Chinese government have introduced quality control schemes in the medical industry, there is still a need to enhance quality control in the production of herbal medicine [54] (Table 3). This is emphasised by the fact that several TCMs have been discovered to contain toxic substances that can interfere with cellular components like deoxyribose nucleic acid, causing cellular and/or genotoxicity [12]. In India, compliance is a major safety concern. While good agricultural practice is required, contamination of Ayurvedic medicines with heavy metals has been reported in India and abroad [9] (Table 3).

Regulatory challenges in developed and developing countries

While the selected countries may be more or less advanced with regards to regulating HTM, they face similar regulatory challenges. In 2002, the WHO identified challenges in the following areas concerning HTM national policy and regulation; regulatory/legal mechanisms, integration of traditional medical practice within the national healthcare system, equitable distribution of benefits with respect to indigenous knowledge and adequate resource allocation for TM development [13]. A decade later, the status quo has seen little change. In 2012, the WHO surveyed its Member States to assess the top regulatory challenges faced when regulating traditional and CM. In summary, WHO data from 2012 showed that 88% of its Member States thought a lack of research to be a challenge in regulating HTM [55]. Fifty two percent identified a lack of expertise in the national health authorities and regulatory agencies as a substantial challenge in regulations [55]. Other countries mentioned information sharing on regulatory issues as a priority [55].

Aside from the challenges mentioned in the WHO surveys the following regulatory aspects have also proven to be barriers in the regulation of HTM. The investigation of HTM is challenging as clinical trials for HTM safety and efficacy are more complex in comparison to conventional medicines [56], and as such so is HTM registration since registration necessitates investigation [24]. This is due to a variety of factors including (1) the complexity of a medicinal plant due to several possible natural constituents, (2) the complexity of a mixed herbal product, which may contain hundreds of natural constituents, (3) the time it would take to isolate every active ingredient in every medicinal herb, (4) the overall lack of herbal medicine knowledge in National Drug Authorities and (5) the lack of appropriate evaluation methods [56]. As a result, a common attitude is that if HTM is used within a local community with experience using the herb, there is no need to undergo any toxicity or efficacy tests unless it is sold outside the community [37].

Other challenges that arise when attempting to regulate HTM include the limited funding of research, research institutions and facilities involved in research and testing as well as the challenge to find suitably experienced and qualified researchers or THPs [17]. Another impediment is HTM's reputation in the modern medical system. One of the most important aspects of incorporating TM into primary healthcare is communication, cooperation and professional interrelationships between HTM and conventional medicine [10]. Unfortunately, conventional healthcare practitioners tend to disregard non-conventional practices if they fail to meet the standards acceptable to evidence-based medicine [13]. As a result, conventional practitioners tend to avoid discussion with patients on any 'unproven', 'alternative' or 'unscientific' practice by assertively dismissing it as being outside their scope of practice [13]. Conventional practitioners also tend to brush aside the topic by claiming that TM efficacy is only the placebo effect [13]. Conventional practitioners also dismiss TM because of the belief that the two health systems are incompatible in terms of the research involved and the source of information, and that the standard of healthcare would be jeopardised if THPs are permitted to function in public health facilities [5].

In some cases however, it is the attitudes of THPs that hinder HTM integration into the healthcare system. Many alternative healers reject the notion that HTM practitioners and medicines need to be regulated [43]. THPs often reject the notion that HTM is dangerous or feel that HTM has been used safely for hundreds of years and should not be regulated as stringently as conventional medicines [57]. Some THPs prefer to keep HTM secretive as they do not want regulatory bodies interfering in the culture's ancient traditions [58]. In African countries, information about ATM has always been passed down from healer to trainee by oral tradition during a long apprenticeship and no written record is maintained [13]. This secrecy has rendered ATM inaccessible to Western practitioners and delayed ATM's entry into formal healthcare [13]. The security of intellectual property and indigenous knowledge is one of the issues posed by THPs in collaboration with researchers [5]. Additional issues raised by THPs include claims that the registration processes are complex and expensive [43].

HTM testing methods are also in need of modification. Some researchers believe that randomised control trials should use locally relevant observational assessment methods such as the retrospective treatment, outcome and the dose-escalating prospective study [37]. It is believed that these methods are more cost-effective and more in line with the practical contexts of its usage [37]. Many believe that the development of new approaches to test HTM are needed [37] and critiques have focused on evidence based practice (EBP) as a method to test HTM [59]. EBP has been described as a dogmatic and reductionist methodology that devalues traditional knowledge as evidence, dismisses patient-centeredness and is incompatible with traditional and CM practices and theology [59]. Many traditional and CM disciplines have a low degree of EBP adoption due to a perceived lack of philosophical consistency, differing viewpoints on evidence hierarchies, and a lack of practitioner and industry support [59]. Additionally, since HTM is more often used for chronic illnesses than for acute ones, it is more difficult to assess the health results [54].

Finally, another concern about HTM regulations is Westernisation. It is believed that integrating HTM with modern medicine could potentially jeopardise the identity and integrity of HTM [60]. As such, many traditional healers are concerned that conventional medicine would modify and take ownership of traditional theories about medicinal plants and roots [61].

Prescribers of HTM in developed and developing countries

A final aspect of TM regulations is the regulation and licensing of TM

practitioners. As mentioned, the regulation of CAM practitioners or THPs is of great importance as it ensures the credibility TM systems by ensuring that TM is used by qualified and trained individuals only [13]. This ensures that those providing treatments are experienced enough to provide safe treatments and be cognoscente of the medicines they are working with which reduces medicine misuse and treatment errors [7].

HTM is prescribed by licenced conventional and CAM practitioners in Germany [62] but only licenced conventional practitioners are allowed to practise Kampo medicine in Japan [63]. As a result, Japan benefits from conventional practitioners' and the general public's awareness of the relevance of Kampo medicine [37]. In the USA, conventional practitioners do not prescribe HTM as they are generally uninformed of the potential benefits of herbal medicines' and their interactions with pharmaceuticals [20]. Importantly, in all the developed countries studied, prescribers of TM need to be licenced.

TM is prescribed by licensed conventional and CAM practitioners or THPs in China [18] and India [42]. Ayurveda training is conducted by colleges offering a basic biosciences curriculum followed by TM training [13]. However, this hybrid approach is not considered up to scientific or traditional standards [13]. As a result, the substandard quality of education in many colleges due to the hybrid curricula is a concern and upgrading training in Ayurveda is a priority [13].

In South Africa, conventional practitioners do not prescribe HTM, highlighting the rift between conventional and alternative medicine in the country [24]. Currently, the only major TM policies that have been passed relate to THPs namely the *Traditional Health Practitioners Act* of 2007 which officially recognises ATM and related practices as an integral portion of healthcare in South Africa [45]. The *Traditional Health Practitioners Act* also governs the establishment and operation of training institutions [5]. In South Africa, even though practising THPs must be registered in accordance with the *Traditional Health Practitioners Act*, very few THPs are registered with the Traditional Health Practitioners' Association [45].

Conclusion

The use of HTM is unlikely to decline and as such, unless thorough regulatory policies are implemented, neither are the adverse effects caused by the use of HTM. The results have shown that various strategies to regulate HTM have been implemented. This review has shown that developed/developing countries like Germany, Japan, India and China have more structured guidelines to ensure the safety, efficacy and quality of TM. While it may be thought that developed countries have better control over medicines and HTM than developing countries, the findings showed that this was not the case. The USA (developed country) was found to have poor regulations to control the use and prescription of HTM whereas China and India (developing countries) were found to have thorough regulations. However, this finding does not imply that the state of a country's control over medicine is not impacted by its stage of development as the countries selected do not represent the entire developed and developing world. In fact, it is known that both developed and developing countries continue to struggle to establish regulation and registration procedures for HTM and both experience the effects of unregulated, or in some cases, under-regulated HTM.

Prospective

Since HTM is affected by geographical and environmental factors, it would be beneficial to evaluate regulatory policies of HTM in countries with rich HTM resources and a long history of application. For comparison and analysis purposes, these countries ought to be selected from countries where HTM is widely used and regulations or policies are well established. Additionally, for an in depth comparison, the main laws and regulations on HTM issued by various major countries should be studied and compared.

It is imperative to recognise the need for regulating HTM and obtain government support to provide many people with the necessary safe, quality, and accessible healthcare. However, due to the uniqueness of each country's HTM, the incorporation of international regulations and recommendations to govern all countries may not be appropriate for HTM regulation. This study proposes that it would be more beneficial for regulations to be standardised as the basis of HTM regulation, with each country incorporating additional regulations to provide flexibility based on the differences in each country. This will allow for easier integration of HTM into the global healthcare system. However, in order to set standards for a common regulatory system, it is important to improve communication and cooperation among national regulators and establish an internationally shared research database.

For this to be successful, governments must play a role in improving HTM's status. With regards to government, HTM should be given independence hence, a separate sub-regulatory body working under the main regulatory body would be beneficial. This will provide HTM practitioners and users the independence they feel is important. Countries also need TM or THP councils and self-imposed regulations and restrictions from TM councils (as seen in Japan) are recommended. If the council contains qualified and experienced members, the council's self-imposed regulations will be appropriate for HTM. Additionally, the council may have a better understanding of HTM than the average committee member from a Department of Health as the councils contain THPs and TM experts.

Additionally, government funding should be allocated to TM institutions. Research is expensive but important in ensuring that HTMs are safe. Since government funding is seldom sufficient, states should harmonise and work together to cut the costs and the workload regarding HTM research. Quality, safety and efficacy tests should be attuned to the countries' budget. As such, cheaper scientific testing should be established. The tests should be affordable but not compromise the safety and efficacy profile of HTM. For countries without established assays, quantitative assays of major constituents can serve as a preliminary guide to potency, pending identification of active ingredients or compounds. Other quantitative procedures, e.g. alcohol- and/or water-soluble extractive values and volatile oil content are useful low-cost indicators of quality. Additionally, to cut costs, countries can rely on the research and monographs written by recognised and reliable sources such as Commission E in Germany when researching plants for HTM.

To decrease the amount of plants that need to be tested, acknowledging that certain herbs are inherently safe (supported by scientific studies and literature) will be beneficial. This will allow for more focus to be placed on herbs that are more complex in nature. These plants should be organised into a hierarchy of priorities and grouped into plants that need testing (which would be tested first) and plants that are widely used (which would be tested at a later stage to seal and authenticate their safety). As such, a list of herbs and practices that do not require registration and testing should be drawn up in order for more attention to be given to the medicines and practices that require thorough assessment. In order to further simplify HTM registration, differentiating between HTM sold within and outside of communities with a history of using the medicine may be beneficial. The registration of HTM's sold outside of communities before those sold within communities may make the task of registration easier and more organised. Countries may benefit also from manufacturers having to demonstrate safety and quality, but not efficacy as seen in the United Kingdom. This could reduce costs and time associated with testing for efficacy. Efficacy should be studied at a later stage once regulations are already in place.

Additionally, it has been proposed that in order to facilitate HTM integration or acceptance into society, inter-system cooperation must be encouraged. Whether the integration of HTM into the healthcare system will support implementing regulations or vice versa, the reputation of TM in the conventional medicine system and of conventional medicine must be addressed. THPs and clinicians must acknowledge the strengths and weaknesses in conventional and HTM and move forward out of our era of distrust and paranoia. As recommended by the WHO in 2000, THPs should be trained in a short

course in conventional medicine if they do not already have a degree or official training required for safe practice. All practitioners who dispense HTMs need official thorough training and continuous education. THPs need to be more aware of the issue of toxicity relating to HTM and must understand that infrequent adverse drug reactions will not be recognised without a formal reporting system. Basic training and qualifications of CAM practitioners and THPs need to be regulated to ensure that the practitioner is qualified and experienced enough to be cognoscente of the materials they are working with and provide safe treatment. Additionally, THPs must be made aware that post manufacturing monitoring is extremely important. The Yellow Card adverse drug reaction reporting scheme (as seen and implemented in the UK [13]) should be an international standard to ensure that the uncommon side effects associated with the use of HTM can be recognised and monitored.

Attitudes towards HTM in conventional communities also need to be addressed. THPs should be respected within the medical community. It should be recognised that THPs contribute to promoting health as they may serve as a referral point to conventional medical doctors. This can be seen in certain places in South Africa where THPs have been trained to refer patients to clinics when necessary. It is also important to train conventional doctors in HTM and as such, HTM should be included in medical curriculum. Conventional healthcare providers must understand the belief systems, social circumstances and attitudes relating to the practice and use of HTM. Conventional practitioners must also be trained to question patients about non-conventional treatments patients are using. This can be achieved by ensuring that a culturally sensitive case history is conducted.

With the implementation of appropriate regulations, HTM can become a respected, trusted, legitimate and integral part of the global healthcare system. By implementing the appropriate regulation HTM will benefit the global population by increasing access to healthcare, providing new and improved cures to a multitude of diseases and by providing patients with the care that they choose.

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