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Thin Layer Chromatographic Method for Detection of Conventional Drug Adulterants in Herbal Products

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Abstract: Commercially available conventional drugs have been used to adulterate herbal products. Considering the rapid growth of herbal products' market, it is essential to screen herbal products for the presence of conventional drugs. Simple analytical methods are needed for the rapid screening of conventional drugs that are likely to be adulterated in herbal products. Thin layer chromatography (TLC) methods for screening twelve conventional drugs in herbal products have been developed and applied. The analytes were extracted from herbal products using acetonitrile:methanol:acetic acid:water (4:4:1:1, *v*/*v*). Solvent mixture of dichloromethane:ethyl acetate:methanol (75:15:10, *v*/*v*) separated well trimethoprim, sildenafil, paracetamol, and sulfamethoxazole while pyrimethamine, metronidazole, and sulfadoxine were well separated by dichloromethane:ethyl acetate:methanol (77.5:12.5:10, *v*/*v*). In addition, acetyl salicylic acid, ibuprofen, diclofenac, quinine, and lumefantrine were well separated by ethyl acetate:methanol:30% ammonia (75:22.5:2.5, *v*/*v*). Chromatographic separations were found to be highly reproducible, and more than 10 samples can be analysed in one run. The method was applied in the screening of 229 herbal products. Consequently, 24.0% of the samples contained one adulterant, while 21.4% contained at least two adulterants. All conventional drugs detected in herbal products were not mentioned on the labels and therefore the consumers are kept unaware of their side effects and health problems. Further studies for confirming and quantitatively determining the adulterants in a wide range of products as well as a systematic toxicological analysis of the adulterants in herbal products are recommended.

Keywords: adulteration; herbal drugs; synthetic drugs; herbal medicines

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1. Introduction

The use and demand for herbal products in both developed and developing countries is increasing [1]. The adulteration of herbal products is a growing menace in sub-Saharan African countries [2–4]. Adulteration in the context of herbal products is the intentional addition of undeclared drugs/chemical substances or substitution with non-drug components, or the addition of foreign non-drug materials into a product [5,6]. In Tanzania, traditional health practitioners have reported that some of their colleagues add conventional drugs to their herbal preparations to compel the users that herbal preparations are potent [7]. Cheating on the efficacy of some herbal products has been reported where adulteration with conventional drugs is performed by some practitioners to position the herbal product brand in the market [8]. The adulteration of herbal products with conventional drugs has been reported in Asia, Europe, Africa, USA, and Brazil [4,9–11]. Nevertheless, the extent and levels of the adulteration of herbal products remain poorly documented.

The adulteration of herbal products with conventional drugs pose health risks. The use of adulterated herbal products may result into herbal–drug interactions that can lead to adverse health problems [12–15]. Moreover, the use of herbal products containing variable amounts of conventional drugs may contribute to antimicrobial resistance. However, the impacts of such adulterants on the quality of herbal products remain poorly understood.

The ever-increasing popularity of herbal-based medications dictates that the national and international regulatory bodies assess the quality of herbal products. The screening of herbal products for the presence of conventional drugs is an integral part in assessing the quality of herbal products. However, the methods/techniques for screening the quality of herbal products are limited. Consequently, most herbal products remain unscreened for adulteration. This calls for the development of an easy and rapid method/technique for screening the quality of herbal products in the market. Different methods are reported for the detection of conventional drugs in herbal products. Capillary electrophoresis has been used for the analysis of adulteration in herbal medicines and dietary supplements for weight control [16]. Thin layer chromatography (TLC), high-performance thin layer chromatography (HPTLC), and high-performance liquid chromatographic (HPLC) have been used for the determination of erectile dysfunction drugs and steroids in herbal preparations [17,18]. High-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) has been used for the screening and determination of erectile dysfunction drugs and antibiotics in herbal products [19–21]. Thin layer chromatography (TLC) is simple, less expensive, and easy to execute, and its components have low electrical power requirements [22]. For instance, the separation step does not require power, and, when indicator chemicals are used for visualization, it can be applied using a hand-operated sprayer. However, when an ultraviolet (UV) lamp, which is a common visualization light system, is used, power is required. TLC is also fast and can analyse several samples at a time and, with appropriate modifications, can be taken to the field [23–27]. Other chromatographic techniques such as gas chromatography (GC) and high-performance liquid chromatographic (HPLC) can be used for the detection of conventional drugs, although the costs for their continuous operation are higher than those for TLC. Mass spectrometric (MS) detection is a most convenient tool for confirmation; however, it is not available in many laboratories, or the laboratory infrastructure does not make their continuous use possible. TLC can be used for screening the conventional drugs in laboratories where there is an irregular supply of electricity or a limited budget for using GC and HPLC techniques and where the application of mass spectrometric detection is not feasible. Therefore, TLC is widely used for the screening of samples before using confirmatory techniques and in resource-limited settings. In addition, the simultaneous analysis of samples and standards statistically increases its analytical precision and accuracy [28]. In this study, simple and rapid TLC methods that can be used for screening purposes prior to more demanding techniques were developed and used to detect conventional drugs mentioned in Table 1. The selection of conventional drugs was based on their common usage in Tanzania. During the optimization of the mobile phase's composition, an emphasis was placed on achieving the best possible overall separation of the selected conventional drugs.

Table 1. Structures of the selected conventional drugs for the developed method.

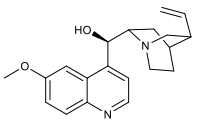
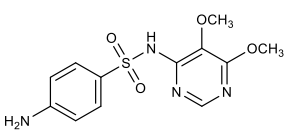
Compound Name	Chemical Structure
Quinine	
Sulfadoxine	

Table 1. *Cont.*

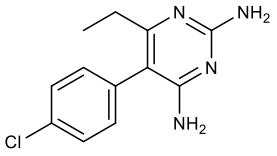
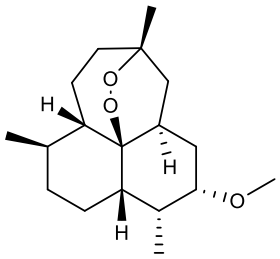
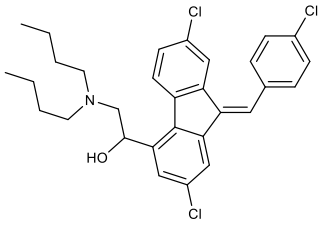
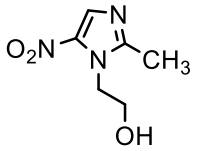
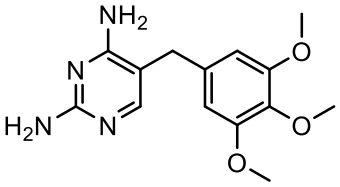
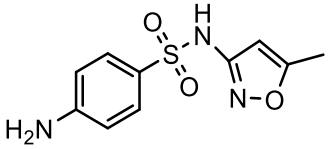
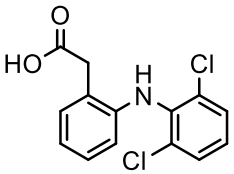
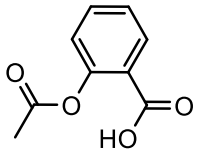
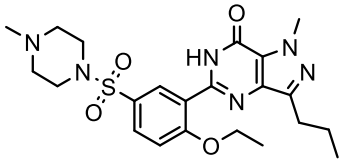
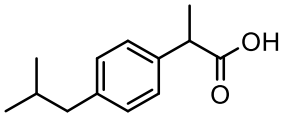
Compound Name	Chemical Structure
Pyrimethamine	
Artemether	
Lumefantrine	
Metronidazole	
Trimethoprim	
Sulfamethoxazole	
Diclofenac	
Acetyl salicylic acid	
Sildenafil	

Table 1. *Cont.*

Compound Name	Chemical Structure
Ibuprofen	

2. Materials and Methods

2.1. Materials, Reagents and Chemicals

Reagents used included HPLC grade methanol (Finar, India, 99.8%), HPLC grade acetonitrile (Finar, India, 99.9%), water for HPLC (Carlo Erba, France), HPLC grade ethyl acetate (Loba Chemie, India, 99.5%), dichloromethane (Finar, India, 99.9%), and analytical grade 30% ammonia solution (Loba Chemie, India). Precoated TLC sheets (ALUGRAM Xtra SIL G/UV_{254}, Macherey-Nagel, Germany) were used as the chromatographic plates. Chromatographic developments were carried out in a rectangular glass and chromatographic spots were visualized using ultraviolet lamps emitting 254 and 366 nm radiation. Analytical standards of metronidazole, trimethoprim, sulfamethoxazole, sildenafil, paracetamol, pyrimethamine, sulfadoxine, acetyl salicylic acid, ibuprofen, diclofenac, quinine, and lumefantrine were from Sigma Aldrich. All analytical standards had purity above 99%.

2.2. Preparation of Standards and Samples

Individual reference standard solutions were prepared by dissolving each analytical standard in methanol, producing 1.0 mg mL^{-1}, and they were stored at −20 °C. Mixture of standards were prepared at 0.2 mg mL^{-1} using methanol as diluent.

Next, 5 g of the sample in a 100 mL Erlenmeyer flask 20 mL of the extraction solvent mixture (acetonitrile:methanol:acetic acid:water, 4:4:1:1, v/v) was added. The mixture was sonicated for 20 min. It was then passed through Whatman filter paper (No. 1) before analysis.

2.3. Optimization of Mobile Phase Composition for TLC Method

The optimal mobile phase compositions for the separation of the selected conventional drugs were achieved by testing solvents of various compositions of ethyl acetate and methanol; dichloromethane, ethyl acetate, and methanol; dichloromethane, ethyl acetate, and acetone. Individual standard solutions were spotted on the 20 cm × 10 cm TLC plates, which had been divided into 20 strips with width of 1.0 cm. Aliquots of 5 µL of each of the standards were spotted on TLC plates at a distance of 1 cm using a micropipette. The plates were developed in a closed glass chamber containing developing solvents having prior saturation at 25–30 °C. Chromatograms were observed on UV light at 254 nm and retention factors (R_f) were established for each analyte using Equation (1). In addition, the peak shape and the separation were visually assessed.

$$R_f = \frac{\text{Distance moved by the analyte}}{\text{Distance covered by the mobile phase}} \quad (1)$$

2.4. Application of the Optimized Method

2.4.1. Sample Collection

Herbal products described for various ailments were randomly obtained from shops, street vendors, open markets, clinics, and home-based practitioners using the covert method of sampling from July 2018 to April 2019. The address of the centres were gathered from district coordinators for traditional and alternative medicine. Large business cities of Dar es Salaam and Arusha as well as the urban areas of Njombe and Manyara regions in Tanzania were included in the study. Of the 229 collected samples, 34 were from Arusha, 45 were from Dar es Salaam, 64 were from Manyara, and 86 were from Njombe. Samples were

bought from shops (30%), street vendors (29%), clinics (22%), home-based practitioners (17%), and open markets (2%). The major health problems indicated on the labels were bacterial infections (24%), painkiller (31.9%), malaria (17.5%), erectile dysfunction (10.9%), diabetes (8.3%), and others (7.4). Most of the samples were packed in well-designed plastic bottles (75.4%). Others were packed in paper bags (17.2%), used water bottles (5.3%), and some were wrapped in pieces of newspaper (2.1%). All samples were in powder form and, after purchase, were stored in a freezer to maintain their integrity.

2.4.2. Analysis of Collected Samples

Aliquots of 5 µL of each of the sample extracts were spotted on the TLC plates using a micropipette and two spots of a mixture of standards were also applied. The plates were developed in a closed glass chamber containing developing solvents. Similarities between the retention factors of detected spots from samples with standards led to the identity of analytes in the samples. Figure 1 shows a photograph of the chromatogram for the separation of the samples and a mixture of standards.

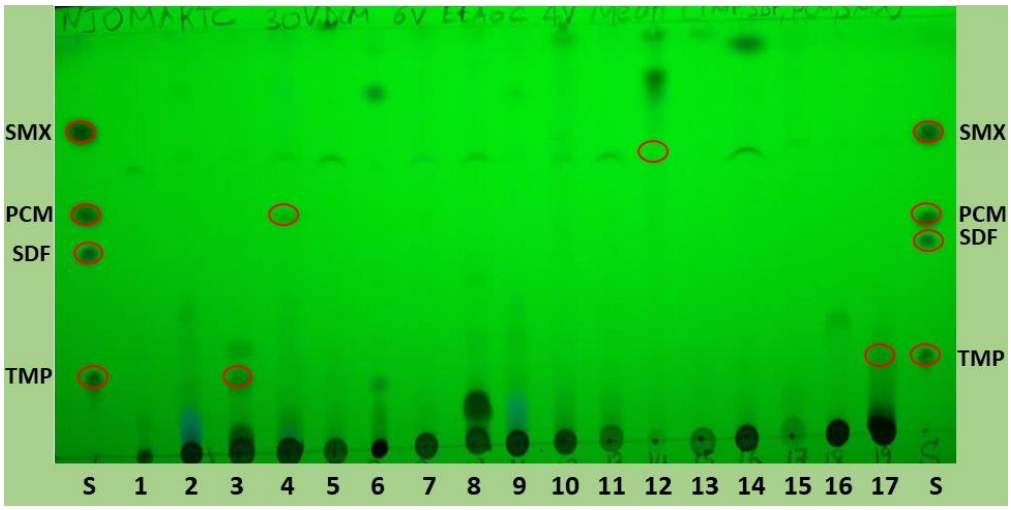


Figure 1. Chromatogram obtained at the separation of samples 1–17 and a mixture of standards, S containing, SMX—sulfamethoxazole, PCM—paracetamol, SDF—sildenafil, and TMP—trimethoprim using dichloromethane:ethyl acetate:methanol (75:15:10, *v*/*v*) and detected in UV light at 254 nm.

3. Results and Discussion

3.1. Optimization of Mobile Phase Composition for TLC Methods

Solvent development usually required 25–40 min and the pre-saturation of the TLC chamber with a mobile phase for at least 30 min, which led to a good separation with reproducible retention factor (R_f) values, as also observed in previous studies [29,30]. The attempt to separate all the twelve compounds (metronidazole, trimethoprim, sulfamethoxazole, sildenafil, paracetamol, pyrimethamine, sulfadoxine, acetyl salicylic acid, ibuprofen, diclofenac, quinine, and lumefantrine) on a single TLC plate was not successful, as several compounds had very close values of retention factor. This could be due to the similar retaining ability of the compounds rendered by the characteristics of the compounds and mobile phase [31]. Based on the tested solvents and their compositions, metronidazole, trimethoprim, sulfamethoxazole, sildenafil, paracetamol, pyrimethamine, and sulfadoxine were best separated by dichloromethane:ethyl acetate:methanol (75:15:10, *v*/*v*). The retention factors of sulfadoxine and sulfamethoxazole, as well as those of sildenafil and metronidazole, were very close, such that two different runs, with minor changes in composition (method I and II), were proposed for the best visualization, as indicated in Table 2. A slight increase in dichloromethane and a slight decrease in ethyl acetate lead to increased retention factors of metronidazole and sulfadoxine. On the other hand, acetyl salicylic acid, ibuprofen,

diclofenac, quinine, and lumefantrine were best separated by ethyl acetate:methanol:30% ammonia (75:22.5:2.5, *v*/*v*).

Table 2. Solvent composition, separated compounds, and their retention factors for the developed methods.

Method	Solvent Composition	Separated Compounds	Retention Factor
I	Dichloromethane:ethyl acetate:methanol (75:15:10, *v*/*v*)	Trimethoprim	0.15
		Sildenafil	0.39
		Paracetamol	0.60
		Sulfamethoxazole	0.79
II	Dichloromethane:ethyl acetate:methanol (77.5:12.5:10, *v*/*v*)	Pyrimethamine	0.26
		Metronidazole	0.48
		Sulfadoxine	0.84
III	Ethyl acetate:methanol:30% ammonia (75:22.5:2.5, *v*/*v*)	Acetyl salicylic acid	0.16
		Ibuprofen	0.26
		Diclofenac	0.35
		Quinine	0.60
		Lumefantrine	0.91

3.2. Application of the Optimized Method

3.2.1. Characterization of Collected Herbal Samples

Most of the products' labels (66%) did not indicate the composition and amount of the different ingredients in the products, the manufacturer's address, dosage, manufacturing, and expiry dates. None of the labels indicated the presence of the conventional drugs in the product. About 86.3% of the labelled products were marked as being a 100% natural product. Very few samples (5.9%) indicated the composition of the product, while 9.7% described the storage conditions. Relatively large number of samples (58.2%) indicated the dosage of the herbal product. Therapeutic indications were presented on all labels, and, in most cases, it was indicated that a single product can treat at least five ailments. Similar observations have been reported elsewhere [32,33]. Products packed in paper bags, used water bottles, and pieces of newspaper may raise concerns about the hygiene under which products are prepared.

3.2.2. Adulteration of Herbal Products

Out of 229 screened samples, 24.0% contained one adulterant, while 21.4% contained at least two adulterants. Samples collected from the Njombe region presented the highest adulteration rates (51%), followed by Dar es Salaam (47%), Manyara (47%), and Arusha (26). The adulterants found in the screened products were trimethoprim, sulfamethoxazole, pyrimethamine, paracetamol, sulfadoxine, metronidazole, sildenafil, lumefantrine, acetyl salicylic acid, diclofenac, ibuprofen, and quinine. This is a likely result of the ill practice of some traditional health practitioners to capture the market for their products. Adding conventional drugs to herbal preparations by untrustworthy traditional health practitioners have been noted elsewhere [7]. As indicated in Table 3, half of the samples from herbal shops, street vendors, and open markets contained adulterants. Herbal clinics and home-based practitioners, respectively, had 39% and 37% of samples that contained adulterants. A high percentage of adulteration for the products from herbal shops and street vendors may be attributed to the dealers aspiring to position their herbal product brand in the market and hence make a large profit. Similarly, the adulteration of herbal products with varieties of conventional drugs has been observed in other counties [2,3,8,18].

3.2.3. Frequency of Adulterants

The most common adulterants are listed in order of the frequency of detection (with the incidents of detection totalling above four) in Table 4. Trimethoprim (43), sulfamethoxazole (28), pyrimethamine (27), paracetamol (25), sulfadoxine (19), and metronidazole (15)

were among the most frequently encountered adulterants. Up to eight adulterants were detected in a single sample. Almost quarter of the screened products (24.0%) contained one adulterant, and 21.4% contained at least two adulterants. The presence of more than one adulterant in a product was observed by other researchers [9,34]. Trimethoprim and sulfamethoxazole occur in a combination termed as cotrimoxazole or commonly septrin. In Tanzania, cotrimoxazole is used as a prophylactic agent for HIV and AIDS patients and in diarrheal diseases for non-HIV patients [35,36]. Its high frequency of adulteration could be targeting the prevention of opportunistic infections in HIV/AIDS patients and to manage diarrhoea. A combination of pyrimethamine and sulfadoxine is recommended for intermittent preventive treatment of malaria during pregnancy [37]. The objective of its adulteration could to render clinical effectiveness for malaria treatment. The adulteration of paracetamol and metronidazole could be targeting pain and protozoa infections, respectively.

Table 3. Adulteration of herbal products according to the supplying sources.

Source	No. of Samples	No. of Adulterated Samples (%)
Herbal Clinics	51	20 (39.2)
Home-Based	40	15 (37.5)
Herbal Shops	68	34 (50.0)
Street Vendor	66	33 (50.0)
Open Market	4	2 (50.0)
Total	229	104

Table 4. Frequency of adulteration of herbal products.

Ranking of Adulteration	Detected Adulterant	Frequency of Adulteration
1	Trimethoprim	43
2	Sulfamethoxazole	28
3	Pyrimethamine	27
4	Paracetamol	25
5	Sulfadoxine	19
6	Metronidazole	15
7	Sildenafil	11
8	Lumefantrine	11
9	Acetyl salicylic acid	9
10	Diclofenac	8
11	Ibuprofen	7
12	Quinine	5

3.2.4. Distribution of Adulterants among Therapeutic Areas

Categorizing herbal products according to their claimed indications as shown in Table 5 reveal that half of the products claimed to be pain killers and almost half (47.3%) of the products claimed for bacterial infections contained adulterants. Pain and bacterial infections have been cited as most frequent health problems for which people use herbal products [38]. In addition, other studies reported that products purportedly for pain killing and fever were most commonly adulterated [39,40]. As also observed by Huang et al. [34], some adulterants appeared in categories not relevant to their claimed indication or purpose. For example, although antidiabetic conventional drugs were not screened in the products, antidiabetic products were found to contain other conventional drugs such as trimethoprim, sulfadoxine, and ibuprofen. While consumers are assuming that they are taking a natural product, they could unknowingly be exposed to dangerous complications such as unpredictable herb–drug interactions which could increase or decrease an undesirable pharmacological effect of either or both components.

Table 5. Adulterated herbal products according to therapeutic areas.

Indications	No. of Screened Samples	No. of Adulterated Samples	% Adulterated Samples
Antibacterial	55	26	47.3
Antidiabetic	19	8	42.1
Antimalarial	40	17	42.5
Pain killer	73	37	50.7
Erectile dysfunction	25	8	32.0
Others	17	8	47.1

4. Conclusions

Simple and rapid TLC methods for the detection of metronidazole, trimethoprim, sulfamethoxazole, sildenafil, paracetamol, pyrimethamine, sulfadoxine, acetyl salicylic acid, ibuprofen, diclofenac, quinine, and lumefantrine in herbal products were developed. Chromatographic separations were found to be highly reproducible, and more than 10 samples can be analysed in one run. The proposed TLC methods are simple, rapid, and flexible compared to HPLC, and they can be used for the preliminary screening of herbal products for the presence of adulterants. However, confirmation of the identified adulterants using other methods such as HPLC-MS/MS will be required. The presence of adulterants in herbal products might unknowingly be exposing consumers to conventional drugs that may lead to herb–drug interactions. The screening of the herbal products using the developed methods may contribute to the protection of herbal product consumers from unethical practices such as adulteration. We recommend further studies for the confirmation and quantitative determination of the adulterants in a wide range of products as well as a systematic toxicological analysis of the adulterants in herbal products.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical considerations.

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Conflicts of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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