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FEATURE ARTICLE:

**PREVALENCE AND PREVENTIVE STRATEGIES
OF NEPHROTOXICITY IN PATIENTS RECEIVING
CISPLATIN BASED REGIMEN IN A KENYAN
REFERRAL HOSPITAL**

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Hurlingham Woodlands Road, Opp. Department of
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P.O. Box 44290-00100 GPO Nairobi, Kenya
Tel/Fax: +254 20 2738364/18
Mobile: +254 722 817 264/723 310 942
E-mail: pskjournal@gmail.com
Website: www.psk.or.ke

DESIGN AND LAYOUT

Commwide Concepts
P.o. Box 12227-00100, Nairobi.
Tel: 0710 262 294
E-mail: commwideconcepts@gmail.com

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The Pharmaceutical Society of Kenya (PSK) is a representative organization that was formed enabling Pharmacists' to employ their professional expertise in the care of patients.

Established in 1964, PSK has its roots in the Pharmaceutical Society of East Africa, which was registered in 1950. Since its formation, PSK continues to promote a common standard for professional conduct and code of ethics for its members, as well as advocate for the welfare of Pharmacists.

EDITORIAL

Review Articles: How should they be written?

Orwa J. A.

Email: jenorwa@gmail.com

Review articles summarise previously published material in an attempt to understand the current state of a topic. Scientific literature review articles use database searches to retrieve results of research, and have as their main goal the objective and theoretical discussion of a specific topic. There are two main types of review articles: systematic and narrative reviews, each with a specific purpose and justification. In both types of reviews the objective of the review must be precisely defined and stated. Review articles submitted to the Pharmaceutical Journal of Kenya (PJK) for publication are often narrative reviews.

Narrative review consists of critical analysis of the literature published in books and electronic or paper-based journal articles. It is a review of what is considered relevant for the topic and the aim of the review, but without a specified methodological plan as for a systematic review. In a narrative review, an unstructured *Abstract* of less than 200 words may be most relevant. In the *Introduction* section a survey of relevant literature and the aim and goal for the review should be presented. The headlines in the review have to be chosen according to the need of that particular review. There is usually no *Method* section. The *Discussion* section could be structured along the lines for an original report keeping in mind that the limitation and its scientific message should be discussed. A long reference list is normally acceptable in a narrative review paper. Narrative literature review articles have an important role in continuing education because they provide readers with up-to-date knowledge about a specific topic.

A Systematic review on the other hand, is carried out according to a specified methodological plan to minimise bias and omission of relevant studies. A systematic review is a literature review focused on a research question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question. Systematic reviews of high-quality randomized controlled trials are crucial to evidence-based medicine.

A systematic review paper should have a structured **Abstract** of no more than 200 words using headlines as *Objective*, *Data Sources*, *Study Selection*, *Data Extraction*, *Data Synthesis* and *Conclusions*. *Objective* gives a precise statement of the primary objective for the review. In *Data*

Sources, the author presents data sources used. *Study Selection* describes criteria used to select studies for detailed review. *Data Extraction* describes how extraction was made, including assessment of quality and validity. In *Data Synthesis* the author presents the main results of the review and state major identified sources of variation between studies. *Conclusion* should give a clear statement of the conclusions made, its generalisability and limitations.

The **Introduction** of the paper could be similar to an original report, but without any longer literature survey, only reviewing previous structural reviews and stating the reason and aim of the present review.

The **Methodology** may have subheadings corresponding to the Abstract (*Data Sources*, *Study Selection*, *Data Extraction*) and should include clearly defined and reported inclusion and exclusion criteria, and specification of databases and other formal register, conference proceedings, reference lists and trial authors, which are used as sources. The full search strategy should be given so that it is easy to reproduce.

The **Results** corresponds to Data synthesis in the Abstract and may present tables with long lists of selected articles. It should also state the major identified sources of variation between reported studies, as differences in treatment protocols, co-interventions, confounders, outcome measures, length of follow-up, and dropout rates. Tables and figures must be self-explanatory and have an appropriate title or caption. The methods for synthesis of evidence should be pre-determined. Sometimes it may not be possible to pool the data, but a synthesis of best evidence ought to be given.

The **Discussion** should be structured similar to an original report. The findings should be discussed with respect to the degree of consistency, variation, and generalisability. New contribution to the literature based on the review conducted and where information is insufficient must be stated. Providing the limitations of the review would be helpful. Suggest the need for new studies and future research agenda.

Systematic literature review thus uses rigorous methodology to prevent shortcuts and bias in conducting a review. Meta-analysis is a statistical method to integrate the

results of the selected studies included in a systematic literature review. Systematic literature review articles are considered original work because they are conducted using rigorous methodological approaches.

Further Reading

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Prevalence and Preventive Strategies of Nephrotoxicity in Patients Receiving Cisplatin Based Regimen in a Kenyan Referral Hospital

Mwai G.O.^{1*}, Nyamu D.G.², Menge T.B.³, Karimi P.N.²

¹ Ministry of Health, Siaya County Referral Hospital, P. O. Box 144-40600, Siaya, Kenya.
Mob: +254 721351130. Email: jeffogy@yahoo.com;

²Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi,
P.O Box 19676-00202, Nairobi, Kenya,

³Kenyatta National Hospital, P.O. Box 20723 – 00202, Nairobi, Kenya

*Corresponding author

Abstract

Cisplatin administration is associated with nephrotoxicity. There is scant literature on the renal toxicity profiles and their preventive strategies in Kenyatta National Hospital. A retrospective cohort study design was used to study the nephrotoxicity profiles and preventive strategies among three hundred and sixty seven adult patients in Kenyatta National Hospital's radiotherapy clinic.

There was female preponderance of 62.6%. The median age of the study population was 51 years (ranging from 18-91). Prevalence of renal toxicities was found to be 58.5%, mostly grade 2 nephrotoxicity, with mean glomerular filtration rate of 59.3 ml/min/1.73m² (±20.6). At a patient's fifth visit, the

odds ratio of developing grade three nephrotoxicity was twice as compared to the first visit (p=0.008). Postponement of doses of cisplatin retarded progression of nephrotoxicity in terms of deranged renal functions (p<0.0001). Medication change from cisplatin to carboplatin (p=0.181) and hydration with normal saline (p=0.486), however, did not prevent nephrotoxicity.

More than half of the patients exhibited nephrotoxic profiles despite employing preventive strategies suggesting that better ways of preventing nephrotoxicity ought to be sought.

Keywords: Cisplatin, Nephrotoxicity, Preventive Strategies, Normal Saline.

Introduction

Africa, Asia, Central and South America account for a higher (70%) global cancer burden [1, 2]. Cisplatin forms the backbone of the majority of chemotherapeutic regimens used in many malignancies [3]. Its main side effects include acute and chronic renal insufficiency, renal magnesium wasting, electrolyte disturbances [4], and changes in glomerular filtration rates (GFRs) which are reversible or irreversible. Studies have shown that the prevalence of cisplatin nephrotoxicity is high, occurring in about one-third of patient undergoing cisplatin treatment [5]. Although cisplatin nephrotoxicity is dose related and cumulative, it is known that the therapeutic efficacy of cisplatin increases with increasing dose [1].

Cisplatin administration and exposure to kidney cells and tubules (especially the proximal tubule) are associated with the activation of inflammatory reactions, vascular and ischemic injury to the kidney. This is mainly due to multifactorial and multidimensional processes compromising the activation of signal transduction pathways, leading to the damage and cell death of the renal tubule epithelium [6]. In a study, Daugaard *et al.* found that there was a severe progressive decrease in GFR during treatment with cisplatin. The Glomerular Filtration Rate remained decreased for up to 2 years after termination of treatment [7].

Preventive strategies against development of nephrotoxicity include adequate hydration and magnesium and potassium replacement [1]. In addition, dose limiting nephrotoxicity of cisplatin may be reduced by fractionation of the dose, slower rate of infusion, forced diuresis and hydration [2, 8, 9]. Other cytoprotectants include the use of amifostine, N-acetylcysteine [7, 10, 11] and lipoplatin [12]. Moreover, early prediction of predisposition to renal function impairment and taking precautions early are crucial [13].

Continued use of cisplatin may lead to renal toxicity and adequate preventive measures need to be employed. Although hydration with a normal saline solution is thought to be the single most important preventive measure, the amount and duration of hydration is still controversial [14]. The main objective of this study was, therefore, to assess the nephrotoxicity profiles and preventive strategies in patients receiving cisplatin in Kenyatta National Hospital (KNH).

Methodology

Ethical approval to carry out the study was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC) and approval (Reference P 167/03/2014) was granted on 15 June 2014. The study design was a retrospective cohort study which was conducted at the Radiotherapy clinic, KNH. Patients who met the criteria were included in the study. One hundred and thirty eight male and two hundred and twenty nine female patients with a diagnosis of cancer on a

cisplatin based regimen, who had received at least two courses of therapy and any form of preventive strategies to nephrotoxicity were included. Patients aged less than 18 years, and for those whom cisplatin administration was contraindicated, and for patients whose files did not have the laboratory measurements of urea, electrolytes and creatinine were excluded from the study.

Sample size estimation was based on a previous local study [15] which evaluated GFR of pediatric population on cancer chemotherapy. At 95% confidence interval, the minimum sample size estimated using Cochran's formula [16] was 367 patients' files with an over age of 3% to cater for data losses (missing age, sex, urea and creatinine). All files of cancer patients treated in the year 2012 and 2013 meeting the inclusion criteria were identified and computer generated random numbers were used to pick 367 files for data abstraction.

Predesigned data collection forms were used to abstract participants' socio-demographics, diagnosis, the number of visits/ chemotherapy courses given, strategies used for the prevention of development of nephrotoxicity, and laboratory test results for tracking the effects of chemotherapy. Patients were retrospectively followed from the first to sixth visit. A database was created using MS ACCESS version 2010. The data were exported to SPSS version 21.0 and analyzed. The profiles of nephrotoxicity and preventive strategies were estimated using simple proportions. Each individual patient was categorized according to nephrotoxicity grades (0-4) [17]. Those with GFR over 90 (Grade 0) and GFR between 60-90 (Grade 1) were considered not to have developed nephrotoxicity. However, patients with GFR between 40-69 (grade 2), between GFR 20-39 (grade 3), and GFR<20 (grade 4) were considered to have developed nephrotoxicity. The median time for the development of nephrotoxicity during follow-up was determined using Kaplan Meier survival curve. Nephrotoxicity preventive strategies included use of oral hydration (before and after chemotherapy), varying doses of normal saline, and postponement of scheduled drug due to deranged laboratory parameters and change of cisplatin to carboplatin due to deranged renal profile.

During multivariate analysis, we adjusted for confounders and effect modifiers in the model to determine the relationship between nephrotoxicity and preventive strategies independently. This was achieved using binary stepwise 'backward' multinomial logistic regression.

Results

Of 367 patients studied, the majority (62.6%) were females. The mean and median ages were 50 years (± 13) and 51 years (range 18-91 years) respectively. The mean weight was 60kg (± 13). The median height and body surface area were 164cm (range 114-191) and 1.6 kg/m² (range 1.1-2.3) respectively. Most participants were aged between 50-60 years with females being majority in all age ranges, except in the lowest 18 to 30 years (Table 1). The majority of

patients had cervical (41.5%) and ovarian (12.7%) cancer.

Table 1. Study participants' profile

Characteristic		n	%
Gender	Male	137	37.4
	Female	229	62.6
Age	18-30	29	8
	31-40	66	18.3
	41-50	81	22.4
	51-60	108	29.9
Residence	Urban	149	44.3
	Rural	187	55.7
Education level	Informal	72	21.0
	Primary	90	26.2
	Secondary	103	30.0
	College	78	22.7
Marital status	Married	242	67.2
	Single	48	13.3
	Divorced	8	2.2
	Widowed	54	15.0
	Separated	8	2.2
Employment status	Employed	96	27.2
	Not employed	221	62.6
	Student	19	5.4
	Retired	17	4.8

Profiles of Nephrotoxicity among the Study Participants

There were fluctuations in mean serum urea, creatinine concentrations, electrolytes and other hematological parameters from visits 1 to 6. However, the mean serum bicarbonate levels and platelets fell in each consecutive visits as shown in Table 2 below.

Grading of Nephrotoxicity

The overall mean Glomerular Filtration Rate (GFR) achieved was 59.3ml/min/1.73M² (±SD 20.6). The number of patients with grade 0 and 1 nephrotoxicity declined from visit 1 through visit 6, whereas the number of those suffering nephrotoxicity grades 2-4 increased from visit 1 to visit 6. Overall, 6.5% of the patients developed grade 0 nephrotoxicity, 35% developed grade 1, 43.8% developed grade 2, while 14.7% developed grade 3 (Table 3).

Table 2. Mean hematological test parameters at each visit (course of therapy)

Mean [Std dev]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Urea(mg/dL)	5 [7]	5 [5]	5 [7]	6 [9]	8 [29]	6 [7]
Creatinine(mmol/L)	86 [56]	67[103]	101[103]	47 [54]	38 [59]	103 [46]
Na(mEq/L)	138 [7]	139 [6]	138 [8]	137 [11]	138 [12]	138 [7]
K(mEq/L)	4 [1]	4 [1]	4 [1]	4 [1]	4 [1]	4 [1]
Mg(mEq/L)	3 [1]	0 [0]	2 [0]	0 [0]	0 [0]	7 [7]
CL(mmol/L)	103 [6]	100 [6]	109 [37]	101 [7]	103 [6]	101 [6]
BUN(mmol/L)	2 [2]	2 [1]	2 [1]	4 [14]	3 [4]	2 [1]
HCO ₃ (mmol/L)	29 [19]	4 [3]	2 [0]	0 [0]	0 [0]	0 [0]
WBC(*10 ⁹ /L)	8 [5]	6 [4]	6 [3]	6 [4]	6 [4]	5 [3]
N(*10 ⁹ //L)	5 [4]	4 [6]	5 [9]	6 [12]	4 [7]	4 [9]
L(*10 ⁹ //L)	2 [1]	2 [1]	2 [1]	2 [1]	2 [1]	2 [1]
RBC(*10 ¹² /L)	5 [1]	4 [1]	4 [1]	4 [1]	4 [1]	4 [1]
Hb(g/dl)	12 [2]	12 [2]	12 [2]	12 [2]	12 [2]	11 [1]
Platelets(10 ³ /mm ³)	372 [166]	361 [166]	328 [136]	311 [190]	291 [149]	278 [136]

Key: Na: Sodium, K: Potassium, Mg: Magnesium, CL: Chloride, BUN: Blood Urea Nitrogen, HCO₃: Sodium Bicarbonate, WBC: White Blood Cell count, N: Neutrophils, L: Lymphocytes, RBC: Red Blood Cells, Hb: Hemoglobin.

Table 3. Grading of Nephrotoxicity According to the Estimated GFR

		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4											
GFR(ml/min/1.73m2)		(>90)		(60-89)		(20-39)		(40-59)		(<20)											
		n	%	O	R	n	%	OR	n	%	O	R	n	%	OR	n	%	O	R	P-value	
Visit 1	33	11.3		Ref	123	42.0		Ref	95	32.4		Ref	41	14.0		Ref	1	0.3		Ref	
Visit 2	20	7	.9	R	ef 8	5	33.7	1.4	105	41.7	0.7	37	14.7	0.8	5	2.0		1.0			
Visit 3	18	8	.6	R	ef 6	8	32.5	1.3	79	37.8	0.7	40	19.1	1.2	4	1.9		0.8			
Visit 4	15	8	.6	R	ef 5	4	30.9	1.2	71	40.6	0.8	34	19.4	1.1	1	0.6		0.2			
Visit 5	9	7.0		Ref	36	28.1		1.3	43	33.6	0.7	34	26.6	1.9	6	4	.7	1	.3	0.008	
Visit 6	7	8.6		Ref	21	25.9		1.0	36	44.4	1.0	15	18.5	1.0	2	2.5		1.0			
Overall	22	6	.5		119	35.0			149	43.8	5	0	14.7	0	0	.0					

*Ref: The GFR grade zero and for visit one are taken as reference values; OR-Odds Ratio

At visit five, the odds ratio of developing grade 3 nephrotoxicity was twice as compared to visit one (Table 3). Chi square for trend of nephrotoxicity was significant at P=0.008.

The median time for development of nephrotoxicity using the Kaplan-Meier survival curve was the fourth cycle [95%

CI 3.782-4.218]. Sixteen percent of patients were censored after visit one compared to ninety percent at visit six. This was due to death, lack of follow up, transfers out and postponing doses due to deranged renal function.

(see figure next page)

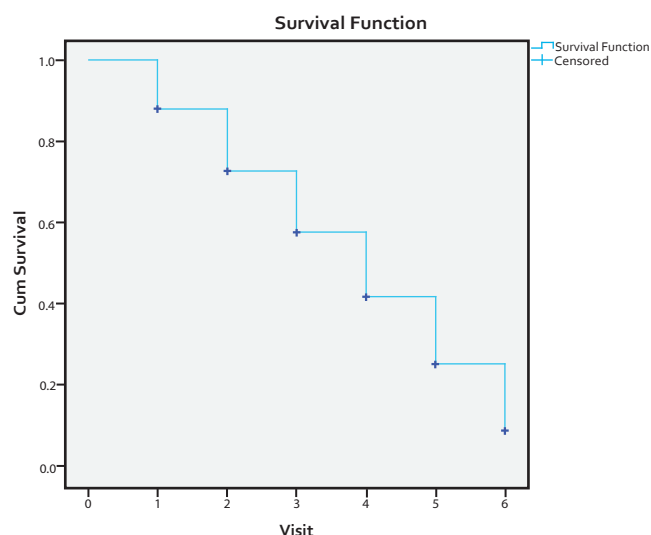


Figure 1. Kaplan Meier Survival Curve for the Development of Nephrotoxicity throughout the Various Visits

Table 4. Median Survival

Median Survival			
Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound
4.000	0.111	3.782	4.218

Strategies Used to Prevent the Development of Nephrotoxicity

Preventive strategies towards the development of nephrotoxicity included postponement of cisplatin doses due to deranged renal function (33.2%), change of cisplatin to carboplatin (3.5%), oral hydration (100%) and intravenous hydration with normal saline (100%). The dose of normal saline used ($p=0.487$) and the change of regimen from cisplatin to carboplatin ($p=0.181$) did not confer protection to development of nephrotoxicity. However, postponement of the regimen conferred protection from progression of damage to kidneys ($p<0.0001$) (Table 5).

Table 5. Association between Strategies and Development of Cisplatin Nephrotoxicity

Preventive Strategy		Nephrotoxicity				Chi square	P value
Normal Saline Dose	No	Nephrotoxicity (%)	Nephrotoxicity Developed (%)	n			
1L	38	22.5	131	77.5	1.441	0.487	
2L	44	26.7	121	73.3			
3L	0	0.0	2	100.0			
Drug Postponed	No	82	36.1%	145	63.9%	47.863	<0.0001
	Yes	2	1.8%	111	98.2%		
Regimen changed	No	83	25.3%	245	74.7%	1.792	0.181
	Yes	1	8.3%	11	91.7%		

Discussion

We found the prevalence of nephrotoxicity in our study patients to be 58.5%. This was similar to a study by Vaibhav Sahni et al who reported the prevalence of renal dysfunction

in patients to be as high as 60% [18]. Blachey et al reported that nephrotoxicity may occur in as many as 50% to 75% of patients receiving cisplatin [19]. In a local study, Muthoni et al found the prevalence of nephrotoxicity in pediatric cancer patients on chemotherapy at KNH to be 37% [15]. Our findings differed with Hartmann et al who found reduction in glomerular filtration rate occurring in 20% to 30% of patients [5, 18]. The possible explanation of the difference in the prevalence in the latter study may be due to the differences in populations being studied. The high prevalence of nephrotoxicity in patients using cisplatin could be attributed to renal tubular injury caused by cisplatin [20].

Our study has revealed that nephrotoxicity increased with subsequent cycles of chemotherapy. In addition, our study showed fluctuations in urea, creatinine, hemoglobin, potassium, white blood cells and a drop in platelets with subsequent courses of cisplatin chemotherapy. Daugard et al [7] in their prospective study on cisplatin nephrotoxicity, an experimental and clinical study, found that there was severe progressive decline in GFR observed during treatment and this decreased GFR remained for up to 2 years after termination of treatment. Moreover, studies done by Yao et al, Gomez et al and Launey-Vacher et al found hematological parameters as being the most common derangements associated with cisplatin administration [1, 11, 21]. The observed changes in the laboratory values were probably due to cumulative renal tubular injury caused by cisplatin [20]. Employment of various preventive strategies to nephrotoxicity has been controversial. For example, studies have cited that prevention of nephrotoxicity can be achieved through identification of patients at high risk of chemotherapy induced nephrotoxicity, adequate volume infusion, early detection of renal damage, avoidance of concurrent use of other nephrotoxic drugs, serial monitoring of renal function, and electrolyte repletion when necessary [18]. Other studies have shown that despite saline infusion, nephrotoxicity remained frequent in patients receiving cisplatin regimen [22]. Tiseo et al, who investigated a short hydration regimen, found that normal saline reduces cisplatin nephrotoxicity [23]. Our study has revealed that the dose of normal saline used ($p=0.487$) could not confer protection to cisplatin induced kidney damage. In other studies, sodium chloride showed protection against nephrotoxicity caused by cisplatin metabolites only at low doses of platinum [24], although the amount and duration of hydration remained controversial [23].

A number of recommendations have been made regarding the prevention of nephrotoxicity. For instance, cessation or reduction of chemotherapy should be considered for patients who have an elevation of serum creatinine levels during cisplatin combination chemotherapy [25]. Secondly, in patients who are at high risk for drug toxicity, the dosage of the drug should be adapted to renal function, and the use of nephrotoxic therapies avoided whenever possible [26]. Despite the fact that carboplatin is equally effective as cisplatin and has the advantage of being less nephrotoxic, our study showed that changing cisplatin to carboplatin ($p=0.181$) was not renal protective. Dose of cisplatin was postponed due to renal toxicity ($p<0.0001$) and deterioration of renal function halted.

Patients who had postponement of dose seemed to have more nephrotoxicity (98.2%) when compared with those

whose dose was not postponed (63.9%), giving an impression that postponing dose leads to greater nephrotoxicity. Alternatively, it may be suggestive that the dose was postponed because of renal toxicity. This, however, is a limitation to this kind of retrospective study. In addition, being retrospective in nature, the quality of data in the patient's files could not be ascertained. However, we ensured that only the files with as much information as possible were used for the study. Secondly, a few patients were eliminated from the study as these patients lacked follow up during the course of therapy as they may have received chemotherapy in other hospitals. Finally, serum magnesium measurement, a measure of kidney function, was not routinely done.

Conclusions and Recommendations

Nephrotoxicity was found to be high (58.5%) in our study population and the profiles of nephrotoxicity increased with the number of cycles of administration. The most common preventive strategies to nephrotoxicity were use of normal saline and oral hydration. Whereas, the dose of normal saline was not found to be statistically significant towards prevention of development of cisplatin nephrotoxicity, deterioration of nephrotoxicity was halted in patients postponing the dose of cisplatin due to renal toxicity.

Despite the fact that patients receiving cisplatin based regimens were put on preventive strategies for nephrotoxicity, more than half exhibited nephrotoxic profiles suggesting that better ways of preventing nephrotoxicity ought to be sought.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors took part in drafting the protocol and the interpretation of results. Data were extracted from patient files by OG. Data analysis was carried out by OG with the help DG and a biostatistician. All authors were involved in drafting and approving the final review, with OG being the coordinating author. All authors read and approved the final manuscript.

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Impact Of Medication Related Problems on Individualized Dispensing at Kenyatta National Hospital

Rugendo A.B.¹, Karimi P.N.^{1*}, Amugune B.K.², Maima A.O.³

¹Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, P.O. Box 30197-00100, Nairobi. Email:ndirang@yahoo.com

³Department of Pharmaceutical Chemistry, University of Nairobi, P.O. Box 30197-00100, Nairobi
School of Pharmacy & Health Sciences, USIU-Africa, P.O. Box 14634-00800 Nairobi

*Corresponding author

Abstract

Medication related problems occur when the outcome of medicine use is not optimal. This often results in a significant strain on the health delivery system and contributes to mortality, morbidity and escalation of healthcare costs. Potential and actual medication related problems can occur at any stage of the medicine use process.

This study assessed the effects and/or challenges of implementing individualized in-patient dispensing systems and medication related problems in Kenyatta National Hospital's medical wards. A quasi experimental study design was applied and a systematic random sample of 236 patient files before, and 207 files after, the introduction of individualized dispensing system were selected. An incidental sample of 25 health workers were surveyed on challenges faced. Descriptive and inferential data analysis was performed.

Challenges faced included inadequate medicine storage facilities, patient management software anomalies, delay in ordering patient medicines and increased workload. There was a high prevalence of medication related problems (97.5 % vs.95.7 %) with potential drug interactions (80.9 % vs. 69.9 %) and non adherence (80.9 % vs.91.3 %) being most common.

There are several challenges encountered in implementation of individualized dispensing and many medication related problems at Kenyatta National Hospital.

Keywords: medication related problems, medication error, non adherence, adverse drug reactions and medication order.

Introduction

Medicines play an important part in preventive and curative healthcare, forming a huge cost of current spending. Because of their association with harmful effects, there is need for judicious use of medicines with elaborate systems to ensure safety to patients [1]. Medication related problems (MRPs) or drug therapy problems however do arise, and are said to occur when the outcome of medicine use is not optimal. MRPs result in a significant strain on the health care delivery system, contributing to mortality and morbidity, escalate cost of treatment, and result in increased hospital stay. MRPs are categorised as: untreated indication, treatment without indication, improper drug selection, too little drug, too much drug, non-compliance, adverse drug reaction and drug interaction [2]. However, majority of these MRPs are preventable and strategies should be instituted to minimise them [3].

Medicine management in hospitals is a process involving medicines selection, procurement and storage, prescription, dispensing, administration and monitoring in order to optimise patient health outcomes. Potential and actual MRPs can occur at any stage in the aforementioned medicine use cycle [4]. At the Kenyatta National Hospital (KNH), medicines selection is a multidisciplinary process spearheaded by the Medicines and Therapeutics Committee that develops and maintains a hospital formulary that forms the basis of medicine procurement.

The objectives of this study were: to evaluate the challenges faced, to compare the types of medication related problems in the medical wards of KNH, to compare the frequency of medication problems in the medical wards of KNH before and after introduction of individual

dispensing system, and to describe the mechanisms currently used to resolve medication related problems.

Methodology

Two study designs were employed to address the various aspects of this study. A cross section study was carried out to determine the challenges faced in implementing individualized dispensing. A quasi experimental design was used to compare the prevalence of medication related problems before and after introduction of individualized dispensing at the medical wards. The target population for the quasi experimental design was files of patients admitted in the medical wards. The workforce for evaluating the challenges encountered comprised of a pharmacist, nurses and pharmaceutical technologists attached to the medical wards at KNH.

An incidental sample of 40 health care workers was picked to study the challenges faced during the implementation process and interviewed about their experiences after consenting. The responses were entered into a researcher administered questionnaire. The data on medication related problems was abstracted using a questionnaire from a random sample of 236 patient files before and 207 patient files after the introduction of individualized dispensing. The treatment chart was assessed for MRPs while the medical and nursing notes were evaluated for reports of adverse drug reactions. Laboratory reports were examined for evidence of normality of hepatic and renal functions by use of Child-pugh scores and estimated glomerular filtration rates. For the challenges, a questionnaire was administered by the researcher, and the information later entered into an excel spreadsheet. Data analysis was performed using Statistical Package for Social Scientists (SPSS) version 2.0. Ethical approval was sought and granted by the KNH/ UON Research and Ethics Committee and the head of the department of Internal medicine and therapeutics of KNH before data collection.

Results

Health care workers

A total of fourty questionnaires were distributed to recruited participants. Twenty five questionnaires were returned fully completed representing a response rate of over 50%. The average age of the respondents was 40.9 years and nurses were the majority (Table 1).

Table 1. Socio-demographic characteristics of healthcare workers

Trait	Category	Frequency	Percentage
Gender	Male	18	32
	Female	17	68
Age	20-29	3	12
	30-39	7	28
	40-49	11	44
	50-59	4	16
Designation	Nurse	22	88
	Pharmaceutical technologist	2	8 %
	Pharmacist	1	4 %

The major challenges faced in the implementation of

individualized dispensing systems by the healthcare workers were determined as percentages from the total number of respondents and depicted in Figure 1 below. Inadequacy of storage facilities was the main challenge and the least was lack of adequate procedures.

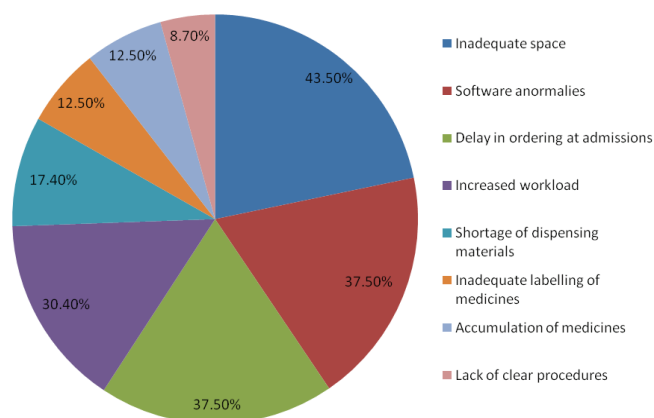


Figure 1. Challenges associated with individualized dispensing systems

Individual patient cabinets were not available but there was improvisation with use of cupboards and small baskets to accommodate the patient medicines.

Socio demographic characteristics of patients

Some 443 files were sampled, out of which 236 were before and 207 after implementation of the individualized dispensing system. Females comprised of 51.3 % and 52.7 % before and after study groups, respectively (Table 2).

The average age for the first group was 31.4 years (range 13 to 84 years) and the second group had an average age of 36.9 years (range 13 to 102 years). Majority of the respondents in both groups had primary and secondary level of education while the lowest category had no formal education as shown in Table 2.

Table 2. Socio-demographic characteristics of the patients

Characteristic	Category	Frequency (%)	
		Before	After
Gender	Male	1115(48.7 %)	98(47.3 %)
	Female	121(51.3 %)	109(52.7 %)
Education level	None	12(5.1 %)	31(15 %)
	Primary	73(30.9 %)	84(40.6 %)
	Secondary	61(25.8 %)	64(30.9 %)
	College	90(38.1 %)	28(13.53 %)

Prevalence of diseases

The highest number of patients had HIV, followed by kidney disease, neurological conditions, tuberculosis and gastrointestinal diseases among others as shown in Figure 2.

The least common was venous thromboembolism. Approximately 22.6 % of all the study participants in both study groups had a degree of renal impairment (eGFR<60ml/min/1.73m²) while 5.3 % vs. 8.2 % (before and after) had some degree of hepatic dysfunction with a Child-pugh score of ≥ 7 .

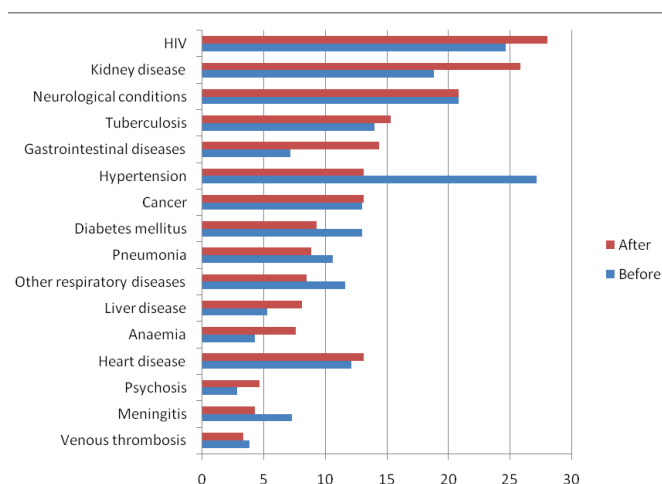


Figure 2. Prevalence of diseases before and after introduction of individualized dispensing system

Types of medication problems

Prescribing errors were common, with drug-drug interactions being the most frequent in both study groups followed by dosage regimen where most patients had no duration indicated (Table 3). Almost all patients had frequency and route of administration correctly indicated and approximately 10 % of patients requiring dose adjustment for renal and hepatic impairment was not done appropriately, and the difference between the two study groups was not statistically significant ($p=0.423$).

However there were statistically significant differences for some traits namely indicated treatment duration, non adherence and adverse drug reactions. Non adherence was reported in a majority of patients with 80.9 % in the before group and 91.3 % in the after group [$p=0.002$] and adverse drug reactions were reported in a minority of patients with 11% before and 8.7% in the after group.

Table 3. Types of medication errors

Trait	Categories	Frequency before	Frequency after	P value
Dose	High	3 (1.3 %)	2 (.1 %)	0.423
	Low	0	2 (.1 %)	
	Correct	207 (88.1 %)	177 (85.5 %)	
	Adjusted 2	5 (10.6 %)	26 (12.6 %)	
	Missing	1 (.4 %)	2 (.1 %)	
	Correct	228 (96.6 %)	200 (96.6 %)	
Duration	Wrong	0	0	0.000
	Missing	195 (83 %)	149 (72 %)	
	Indicated	41 (17 %)	58 (28 %)	
Drug-drug interaction	Yes	191 (80.9 %) 1	65 (69.9 %)	0.825
	No	45 (19.1 %)	41 (17.4 %)	
Contraindications	Contraindications	5 (3.5 %)	5 (4.5 %)	0.689
	Serious	48 (33.3 %)	42 (37.5 %)	
	Minor	91 (63.2 %)	65 (58 %)	
Adverse drug reactions	Yes	26 (11 %)	18 (8.7 %)	0.017
	No	210 (89 %)	189 (91.3 %)	
Adherence	Yes	45 (19.1 %)	18 (8.7 %)	0.002
	No	191 (80.9 %)	189 (91.3 %)	

The proportion of patients who had at least one medication related problems was 97.5 % before and 95.7 % after

introduction of individualized dispensing system.

The main reasons for non-adherence are shown in Table 4. Non apparent explanation for non-adherence was statistically significant between the two study groups ($p=0.000$).

Table 4. Reason for non-adherence

Drug pair	Frequency Before	Frequency After
Ceftriaxone/Anticoagulants	39 (16.5 %)	31 (15 %)
Sulfamethoxazole/Specific anticoagulants	19 (8.1 %)	17 (8.2 %)
Heparin/Warfarin	12 (5.1 %)	9 (4.3 %)
Macrolides/Anticoagulant	8 (3.4 %)	15 (7.2 %)
Ceftriaxone/calcium	5 (2.1 %)	4 (1.9 %)

Potential Drug interactions

Potential drug - drug interactions had a prevalence of 80.9 % in the before group with 69.9 % in the after group but the difference between the two groups was not statistically significant [$p= 0.825$]. The minority of interactions were categorized as serious while the majority were considered minor, as shown in the Table 5.

Table 5. Drug- drug interactions

Patient Category	Category	
	Serious	Minor
Before	87 (36.8%)	149 (63.2 %)
After	87 (42 %)	120 (58 %)
Total	174 (39.2 %)	269 (60.7 %)

The average number of drug interactions in the first group was 5.82 while the second group had an average of 5.94 per patient and the difference was statistically significant [$p= 0.005$]. The most common drug pairs involved in the interactions were: ceftriaxone/specific anticoagulants, sulfamethoxazole/anticoagulants, heparin/warfarin and macrolides/anticoagulants while the contra-indications reported in both study groups involved ceftriaxone and calcium salts (Table 6).

Table 6. The most common interacting drugs

Reason	Frequency Before	Frequency After	P Value
Non availability	120 (50.8 %)	110 (53.1 %)	0.630
Delay in administration	75 (31.8 %)	82 (39.6 %)	0.086
Patient factors	20 (8.5 %)	16 (7.8 %)	0.786
No IV access	19 (8.1 %)	30 (14.6 %)	0.030
Non apparent	45 (19.1 %)	93 (44.9 %)	0.000

Prevalence of adverse drug reactions

The patients with documented adverse drug reaction were 11 % before and 8.7 % after introduction of individualized dispensing system and the difference was statistically significant [$p= 0.017$]. The most common adverse drug reactions were hyperkalemia, hepatotoxicity and nephrotoxicity.

Drug Availability

The mean drug availability was 87.5 % before and 86.92 % after introduction of individualized dispensing system,

but the difference between the two study groups was not significant [$p=0.746$]. The majority of the patients received all the drugs that were prescribed while 3 % of patients in both study arms received less than half of the prescribed drugs as shown in the Figure 3 below.

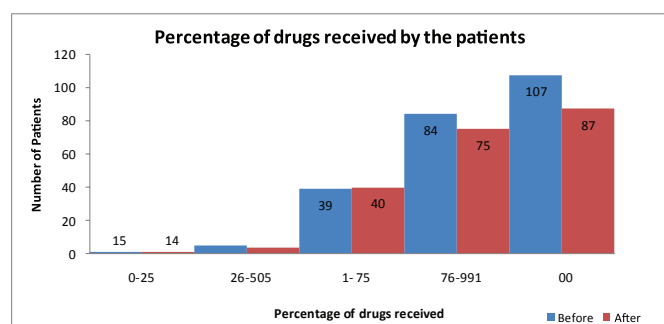


Figure 3. Percentage of drugs received by the patients

Bivariate analysis

There was an association between age and the presence of a medication related problem. The patients aged below 39 years were least affected, peaking at age 40-49 years, and lowest at age 50-59 years. The male to female ratio for prevalence of medication related problems in this cohort of patients was 1:1.24 which was not statistically significant [$p=0.084$].

The number of drugs per prescription had an effect on the prevalence of medication related problems with 1-3 drug category per prescription having the lowest prevalence while the 8-11 category had the highest prevalence of medication related problems [$p<0.001$]. The number of disease conditions had an association with presence of medication related problems; patients with more than two conditions had a higher prevalence.

Mechanism currently used to resolve medication related problems

Twenty four healthcare workers revealed there are mechanisms currently in use to resolve medication related problems. They included consultations with other members of the healthcare team (45.8 %), ensuring adequate stocks of medicines (41.7 %), and prescribing of once or twice daily formulations (8.3 %).

Discussion

The medication related problems evaluated were found to be prescribing errors, drug interactions, non-adherence and frequency of adverse drug reactions. The study demonstrates a high prevalence of medication related problems both before and after change of medicine distribution system which was similar to a study conducted in the same institution in 2012 [5]. The implementation of individualized dispensing system is faced with challenges that hinder complete realization of individual medication order benefits. Provision of resources is vital to the successful implementation of change in the hospital medicine distribution system; this was evident in the study results that cited inadequate medicine storage facilities and patient management software as some of the main challenges. Of importance is the critical role of human resource mix of adequate numbers and skills, at a ratio of 1 and 3 pharmacist/ pharmaceutical technologists per 100 hospital beds, respectively. This constraint was highlighted by the number of respondents who reported increased

workload and delay in ordering medicines as main challenges. Comparatively the ratio of healthcare workers to population in US health facilities is higher [6, 7].

The study did not show a statistically significant difference in the frequency of medication related problems in the two study groups, however there was a noticeable increase in the number of treatment charts with indications of treatment duration, and a reduction in reported frequencies of adverse drug reactions in the after study group. There was no significant difference in dose and medication frequency errors which was similar to findings of another study [8]. Potential drug-drug interactions were reported by a majority of study participants, but the prevalence was higher than that previously reported in Kenya and Pakistan [7, 9].

The majority of patients reported non-adherence to the prescribed medication which differs markedly with the 2012 study [5]. The proportion of respondents with documented adverse drug reaction had a statistical difference between the two study groups. This prevalence was comparable to Kenyan and Nigerian studies [5, 10].

Most of the patients received all the drugs that were prescribed while 3 % of patients in both study arms received less than half of the prescribed drugs. Drug shortage still continues to plague the public health sector; strict adherence to the hospital formulary system coupled with higher resource allocation could ameliorate this situation. Mechanisms currently used to resolve medication related problems were consultations with other members of the healthcare team, ensuring adequate stocks of medicines and prescribing of once or twice daily formulations.

Studies elsewhere have reported robust methods with wide acceptance for identifying and resolving medication related problems that involve multidisciplinary teams including pharmacists [11, 12]. The use of electronic aids has been shown to improve detection of drug related problems.

There are several challenges encountered in implementation of individualized dispensing and many medication related problems at Kenyatta National Hospital.

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Review of the Status of Alternative Medicine Practice in Kenya

Muriuki B.^{1*}, Midiwo J.O.², Mbugua P.M.³, Gikunju J.K.⁴

¹ Nairobi Technical Training Institute, P.O. Box 30039-00100, Nairobi, Kenya. Email: gakombi@yahoo.com.

² Department of Chemistry, University of Nairobi, P.O. Box 00100-30197, Nairobi, Kenya. Email: jimidiwo@uonbi.ac.ke.

³ Department of Medical Physiology, School of Medicine, College of Health Sciences, University of Nairobi, P.O. Box 00100-30197, Nairobi, Kenya. Email: mungaigits607@yahoo.co.uk.

⁴ Department of Medical Laboratory Sciences, Jomo Kenyatta University of Agriculture and Technology, P.O. Box 62000, Nairobi, Kenya. Email: jgikunju@jkuat.ac.ke.

*Corresponding author

Abstract

The non mainstream medical practices in Kenya vary widely along cultural, religious and geographical lines. The methods adopted range from material administration, non-invasive physical and invasive surgical procedures to psychological and spiritual based procedures. The material-medical practice or herbalism may be the only one that can be subjected to uniform registration and regulatory procedures. Kenyan herbal medicine practice has largely remained uncontrolled and unregulated despite the fact that a large proportion of the Kenyan population could be relying on the same. Although some substantial data on alternative medical products has been generated by institutions and individual scientists, lack of necessary coordination has rendered practical progress, value addition and utilization difficult. There is now a constitutional requirement for formal incorporation of traditional and alternative medicine into the mainstream health sector and its implementation may enable

development of efficient regulatory mechanism for herbal medicine. This article is a summarized review of the current status of alternative medicine practice in Kenya. Issues of regulation and registration are mainly reviewed in the context of herbal or alternative material medicine.

Keywords: Traditional Medicine; Alternative Medicine; Herbalist; ethnomedicine.

Introduction

Complementary or alternative medicine refers to a broad set of healthcare practices that are not well integrated into the dominant healthcare system [1, 2]. A medical procedure or practice is in this review taken to be one that conforms to the World Health Organization's (WHO) and Kenya's Ministry of Health (MOH) definition of a drug [3]; a procedure or practice performed with the intention of medically benefiting the recipient. A cultural procedure like non hospital male circumcision is hence taken to be an

alternative surgical procedure with some medical benefit [4]. This may however not have been accepted widely as a medical procedure [3].

A medical procedure or practice hence restores “health” as defined by (WHO) as a state of complete physical, mental and social well-being [5, 6].

Some African TM practices are based on spiritual, psychological, culture and taboos and

“Satisfactory healing involves not merely recovery from physical symptoms, but also the social and psychological re-integration of the patient into his/her community” [7].

Herbalists usually dispense “multi-drug” regimens that are difficult to subject to the evaluation methods of conventional drug development pipelines [8].

However, non-herbalist con-people have infiltrated the practice [9, 10] and contaminated herbs have been reported probably due to poor harvesting and processing practices [11]. The issue of some herbalists mixing their products with conventional drugs [12] needs to be investigated especially because of its possible contribution to drug interactions, toxicity, resistance and/or tolerance [8, 9].

The shortcomings in herbal medical practice could be addressed through regulatory and legislative measures [2, 9, 12, 13, 14, 15, 16, 17].

The World Health Organization (WHO) has been publishing useful guidelines on quality control methods on medicinal plant materials [2] and their integration into the mainstream health care services [18].

The existing guidelines on evaluation methods are usually silent on how issues of Intellectual Property Rights (IPR) could be handled during product registration. The pharmacy and poisons (amendment) bill, 2014 actually proposes to ensure that IPR issues will not hinder their activities [19]. The implementation of IPR policies could be discouraging. In a study on IPR issues at the Kenya Industrial Property Office (KIPO) in Kenya, the major findings were that patent records at KIPO were not well-managed or organized, and access to patent information was problematic [20].

Some researchers on traditional medicine have identified IPR issues as some of the impediments in efforts aimed at integrating Kenyan traditional medicine into the mainstream health sector [8,21].

The WHO and the World Intellectual Property Organization (WIPO) encourage development of National policies and guidelines on issue of intellectual property rights (IPR) that can be applicable to traditional or cultural knowledge. *“However, intellectual property rights in the context of traditional medicine are a very complex issue”* [22].

The adoption of the Swakopmud Protocol on the Protection of Traditional Knowledge and expressions of Folklore, in 2010 by members of the African Regional Intellectual Property Organization (ARIPO) is an indicator that ARIPO member countries (Kenya included) are becoming more proactive in efforts aimed at the protection of knowledge and innovations of traditional healers [16].

Although figures suggest rampant utilization of Traditional Medicines (TM) in Kenya [10], the coverage of TM in Government official documents on health provision and medicinal agents is usually limited to efficacy and safety with little on policy guidelines in other related issues like conservation, production, domestication, commercialization and the necessary collaboration between alternative and conventional medical practitioners [16,10, 23].

This is worrying because an alternative should not be ignored by a world already faced with a shortage of conventional medical practitioners [10] and rising cases of microbial resistance towards available conventional drugs [2,17,24]. For instance, drug resistance is the major challenge in the conventional treatment of TB [25, 26] and malaria, a challenge whose solution could be found in AM [17]. Toxicities associated with conventional drugs and drug interactions in multi-drug regimens are real and current issues of concern that may raise questions on the effectiveness of the current post marketing pharmacovigilance national program.

Kenyan Alternative Medical Practices

The alternative, traditional or non-mainstream Kenyan medical practices are multidimensional, complex and usually shrouded with secrecy. Classification, stratification or niche definition of particular practices within the medical ecosystem is not easy. Other studies have used medication procedures as the basis of classification [21]. Using similar criteria four major classes of AM practitioners were identified in this review; *pure-material-herbal, pure-physical, pure spiritual/faith based and spiritual-material-herbal*.

Pure-material-herbal practitioners dispense material medical products mostly derived from plants [21]. Their products may also contain animal products like fats and oils from particular animal species, bee honey, cattle bile juices, eggs from particular bird species etc [7, 21]. Their medications may also include mineral additives like magadi soda, ashes from particular plant materials or some mineral rock products [7, 27].

This group may be sub classified further on the bases of knowledge acquisition into traditional, modern trained and untrained-sales people.

The traditional pure-material-herbal practitioners are those whose medical knowledge has been transmitted verbally down generations [10, 16]. They are usually honest people and hence rightly referred to as the true herbalists [9]. The true herbalists *“practice in accordance with ubuntu philosophy that require a THP not to provide services for material gain”* [9].

Majority is now of advanced age [9] and they usually don't depend purely on their medical practices for daily living; they are also crop farmers, herders or business operators [10]. A few have formal outlets for their products; others display their products in the local food markets. Others treat their patients at home [16] while others trek from one center to another searching for willing customers. They usually interact with their customers through local vernacular languages or through the national Kiswahili language. Their medications are mainly administered orally [11] and a few through sniffing of steamed substances, and

others through cuts and/or body piercing [7].

They may treat a range of well defined to undefined conditions; from well defined pains (back pain, migraines, stomach aches and rheumatic pains), well defined infections (sexually transmitted, respiratory infections, open wound infections, topical fungal infections) to unclearly defined conditions characterized by symptoms like general body weakness and rheumatic disorders [7, 10].

The *modern trained pure-material-herbal practitioners* constitute a relatively new generation of practitioners who have received formal training on well established herbal practices especially from China and India. They usually operate from major urban centers and are usually registered with a Government department. Others have acquired some hands-on training on local herbal medicine from real herbalists after which they “modernize” the same through some training on conventional medicine [10, 21] either informally through private tutors or formally in some tertiary institutions; in their adverts, they pose as well trained and knowledgeable in all matters medical. They use anatomical models or pictures of various body parts to emphasize their skills. Their adverts will also portray pictures of laboratories equipped with modern diagnostic kits to enhance customer confidence.

The *untrained-sales people* constitute a range of practitioners whose source of medical knowledge cannot be traced to an authoritative recognized system or body. In her study on oral health herbal materials, Waiganjo (2013), sub classified this cadre of practitioners as traders [11]. Their products range from food products, nutritional supplements, and nutraceuticals to herbals. Usually they have only acquired minimal text book knowledge about their products but they aggressively market the same as much needed and potent medical products. Some have well established clinics which they “safely” call “Nutritional Clinic” or “Natural products Clinic” probably as a way of avoiding scrutiny from medical regulatory bodies. Others have small pharmacy-like outlets while others obtain temporally licenses from town authorities to market their products in small tents along pavements [11]. Others market their products to commuters in public transport vehicles. Others make arrangements with churches on Sundays to market their magical herbal products and sell to Christians immediately after worship. Others sell their products from the boots of cars or vans packed from one market center to another. Their sales strategy usually involves use of loud speakers and pre-recorded information about the ailments they “treat”. The very aggressive ones even include entertainers like acrobats to enable quick crowd gathering and quick sales. Disease conditions are described in a fun-filled atmosphere and buyers could be pre-arranged to encourage potential but public shy customers to also buy the products.

The *pure-physical* form of alternative medicine is a traditional form of medical practice that utilizes non material physical procedures that range from surgical [26] to massage [21]. The practices were more common in the past and they aimed at treatment, prophylaxis or initiation. Simple physical procedures did not require specialists; back-massage was readily provided by children stepping repeatedly on the back of an adult. More complex

physical procedures were performed by specialists [9, 10]; traditional surgeons specialized in head, dental, dermal and others have been documented from various communities; craniotomy has been practiced by the Kisii and Turkana people of Kenya in the treatment of diseases thought to be located inside the skull [16]. Midwifery is also mainly physical with minor surgical procedures [7,10]. Male and female circumcision was conducted by specialized surgeons. Some specialists could fix dislocated joints and even fix fractured bones [10, 11]. Uvulectomy was only conducted by specialists (*The Star Wednesday, 15 July 2015*) just like traditional dental procedures. Others could physically diagnose the cause of death through postmortem surgical procedures that were usually conducted in graves and just prior to burials. Surgical practitioners are rarer than other AM providers [10].

The *Spiritual /Faith Based* medical practices are practiced at varied levels of the community and they are derived from varied beliefs and worldviews. “*Spiritual or faith healers are viewed by many Kenyans as an important source of relief for stress, depression, or mental problems*” [10]. At institutional levels, especially Christian based churches, spiritual “healing” is practiced through prayers and the laying of hands [21]. Some are reputed to be so successful that patients are withdrawn from referral hospitals to be taken for spiritual healing in well advertised crusades. The turn outs are so big and some patients have reportedly died while waiting for their turn to heal in such meetings (*The Standard, Thursday January, 1st 2015*). Christian spiritual healing became more rampant in the 1990s with catchy adverts on print and electronic media to ensure a large following. The practice is however facing challenges with inquisitive minds and a less friendly press highlighting every loophole and failure. A prominent Nairobi based “spiritual healing” pastor was recently so vividly exposed in the print and electronic media that the Director of Public Prosecution ordered a probe into his wayward ways. For Kshs. 310/=, the pastor could “cure” all manner of diseases including HIV/Aids.

The *wagangas* and diviners [7] may also be included under spiritual healers; they promise cure to varied conditions including love, financial, work, family and witchcraft [16] related issues. Majority of those who advertise their trade in Nairobi, usually on electricity posts or any available space proclaims to be “doctors”, “professors” or “prominent traditional healer” usually of Tanzania or *Ukambani* origin. Majority operates from rental hotel rooms and their continued persistence indicates they have some following. They are however not as affluent as the Church based spiritual healers. Some prominent politicians have been rumored to have sought the service of a *mganga* at some time. Some success stories attributed to *waganga* services include the return of stolen properties and control of amorous spouses.

At the family level disease conditions may be resolved through spiritual based counseling [16]; individuals could suffer illness because they failed to live family values by disregarding or disrespecting the elderly, some clan practice or by not abiding with ancestral directives or desires. They may have failed to pay dowry, shown disrespect to an important relative (especially aunts and

uncles) or failed to respect the wishes of dead relatives (especially parents and grandparents). This could be the explanation especially when disease conditions fail to respond fast enough to normal treatment. A ceremonial goat or sheep could be slaughtered to resolve a medical condition. Some terminal conditions like cancer and deaths perceived as untimely could be explained as ancestral punishment or punishment from "the gods" [16]. Some researchers have defined this type of counseling based AM practice as psychotherapy [16] or mental therapy [21].

The *spiritual-material-herbal* form of AM/TM utilizes spiritualism and/or rituals that may utilize non consumable articles/paraphernalia along with consumable material medicines. Such practitioners have been classified as herbalist-diviners in some studies [17] or ritual-herbalists in others [17]. The spiritualism in this practice is based on cultural and traditional beliefs and recognized taboos that are usually unacceptable by the major Christian based spiritualism. In one study it was described as; *"Spiritual therapy attempts to bring peace and harmony between the living and the spiritual world, especially spirits of the ancestors, which are believed to live on after death and continue to influence events in the living world"* [16]. The country-wide spread of Christianity may have reduced the influence of the *spiritual-material-herbal* practice. However prayers are still considered an important component of disease management whether one is on herbal or conventional medication [10, 16]. Prayers for the sick are conducted in hospitals, in churches and at home.

The Referral Niche of the Kenyan Herbalist

"People who seek traditional medicine treatment are more likely to have chronic complaints and to have seen several doctors. THPs are a last resort for patients with long-term health problems, who may be unhappy with the outcome of biomedical treatment" [7].

Popularity of herbal drugs may have been driven by the reported failure or toxic effects [28] associated with some conventional medicines [9]; HIV/Aids was for a long time described as terminal before ARVs were introduced. Issues of toxicity and even withdrawal of some anti retroviral drugs [29] have been reported in the local press. The statutory public withdrawal of conventional cough syrups from hospitals in 2009 must have been well received by herbalists. The drugs were then described as useless and potentially harmful to children (*Daily Nation, Friday, March 13 2009*). Advocates of herbal medicines have maintained that they have been used successfully for ages and have not been associated with toxic effects. The resulting popularity has led to sudden increase in the number of herbal drug manufactures [30]. It is also claimed that herbal therapy is better than modern treatment because it addresses afflictions in a broader manner that aims at diagnosing all possible causes including physical, cultural, social and spiritual [7,13,31]. It has been estimated that 80% of the world's population depend on alternative approaches as their primary medical care [7, 24]. Successful treatment of prominent members of society, especially presidents could guarantee survival of a traditional practice (*The Star Wednesday 15 July 2015*).

The issue of disease diagnosis is not a major challenge

to Kenyan herbalists; they occupy an almost exclusively referral niche in the country's health sector; most of their patients actually refer themselves to herbal medicine after perceived or real inability to get cure from the mainstream health services [7, 16]. Traditional surgeons also receive such patients (*The Star Wednesday 15 July 2015*). In most cases and especially for conditions recognized as "chronic" or "terminal" by conventional health systems, the patient paying a visit to the herbalist comes along with more than sufficient medical information about their ailments [7, 16]; TB patients will have tested positive in a mainstream health facility and already started their free DOTs TB medication. They will then refer themselves to the herbalist for varied reasons; the treatment is taking too long, a colleague on similar treatment died, adverse drug effects are too much to bear, the herbalist's advert is too good to be ignored, depression has set in making clear and sound judgment impossible. Whatever the reason for their self-referral, the patients are correctly informed about their ailments and the herbalist need not waste time and resources on laboratory tests; the patient had visited a reputable health facility and tested positive for TB, HIV/Aids, hypertension, gout, rheumatoid arthritis, diabetes, ovarian cysts, etc.

The herbalist will dispense the necessary medicine and give an appointment for a future visit to monitor treatment progress. On improvement the patient could be referred to a mainstream health facility for laboratory tests [16]. The referral system is informal but very much similar to the formal referrals practiced in Senegal and other African countries [17]. Proof of cure makes the herbalist more confident and the practice is proudly advertised through print and electronic media. Some patients may get well and not report the same to the herbalist; they may only inform relatives and friends who could be the next customers to the herbalist. Some patients may fail to get cured but public discrediting of a failed herbal remedy is rare.

A few herbalists have good understanding of conventional medical procedures and their clinics have modern diagnostic equipments [21]. They also employ conventionally trained medical diploma holders as assistants in their trade. The trainees could in future open shop as well educated herbalists if they manage to learn enough from their master herbalist.

Advertising in the print and electronic media is becoming a common practice especially for the urban based herbalists [9]. For a fee, media houses readily transmit the herbalists' claims while cautioning listeners that what is being aired is purely the advertiser's view and not the view of the media house. The frequency and period at which some herbalists appear in some national television or radio stations is an indicator of rewards in the herbal medical practice. Advertisement through expensive and highly visible bill-boards is also becoming popular especially in Nairobi.

Regulatory Policy on Herbal Medicines; Migration from Cultural to Medical

Since independence herbalists have never been formally recognized by the Government's Ministry of Health [8, 16]; those who bothered to register with the Government did so with Government's ministry responsible for cultural affairs. Their trade was hence perceived to be equivalent to cultural music, art or history.

As early as 1995 Sindiga *et al* [13], recommended the enactment of statutes to facilitate the operation of traditional medicine in Kenya. They identified financing of traditional medicine, registration and certification, training of practitioners, quality control, and research and development as measures necessary in improving traditional medicine in Kenya. By 2010, the recommendations had been effected fully and some Kenyan scientists were still advising for creation of more awareness, policies and official recognition of traditional herbal medicine [8].

In 2008, the Government's Ministry of Health (MOH) developed a National Pharmaceutical Policy (KNPP) document [14] that recognized the necessity of integrating traditional medicine (TM) into the healthcare system. The KNPP-2008 document quoted the WHO estimates on Africans utilizing TM as 80% and hence the need to develop "policy and legislative framework necessary to guide their use" in Kenya. The definition of "Traditional Medicines" in the KNPP-2008 document was not precise enough but it implied human and veterinary medicines that "includes Traditional, Complementary/Alternative & Herbal Medicines (TCAM)".

Efforts on implementation of the policy include the drafting of guidelines for registration of herbal medicines by the Pharmacy and Poisons Board [12]. The new regulations aimed at stopping fraudulent herbalists from practicing but they are loaded with complex and highly technical and scientific language that is beyond the understanding of most Kenyan herbalists [12].

The Pharmacy and Poisons Board (Amendment) Bill -2014 [19] proposed to create a more powerful regulatory authority with a new office of the "Director General" to replace that of "Chief Pharmacist" and heavier penalties for noncompliance. The bill did not propose to include a TM/AM practitioner or specialist in the new authority's board. The proposed board would be constituted by mainstream medical personnel and representatives from the Health Ministry, veterinary services, the Law Society of Kenya, a University training pharmacists, and a financial or accounting officer.

The proposed amendments did not cover any specific issue on TM or AM.

The failure by the official documents to clearly define and thoroughly describe TM/AM is an indicator that TM/AM practitioners, specialists or scholars may not have participated as stakeholders in the development of the documents. The non inclusion of TM stakeholders in policy development is also apparent in the Kenya Health Policy 2014–2030 document; although matters related to abortion appear three times in the glossary section of the document (*Abortion, Unsafe abortion, Trained health professional in the context of provision of legal termination of pregnancy*), there is not a single term related to AM or TM [3]. Such a recent document would be expected to conform to constitutional requirement of recognizing TM [32] and WHO's guidelines on the importance of integrating AM/TM into the mainstream health sector [18].

The draft Health Bill 2014 was more recognizing, proactive, accommodating, tolerant and inclusive towards TM/AM [33]. The Bill was more precise on the recognition of alternative medicine as a constitutional requirement that

should be implemented by the Health Ministry.

However, the proposed registration was still prejudicial that TM is subordinate to mainstream medicine especially on referral matters; "The national government department of health shall develop policy guidelines for referral mechanisms and a system of referrals from practitioners of traditional and alternative medicine to conventional health facilities" [33]

The bill acknowledged that no policies have been developed on TM/AM [33] and it rightly recognized the need to develop standardization methods for TM; "The national government department for health shall, in consultation with key stakeholders develop policies for standardization of traditional and alternative medicine practice" [33].

A localized definition of "African traditional medicine and alternative medicine" would have reduced ambiguity and enabled establishment of boundaries for policy implementation.

The bill proposed to regulate what was obviously not well defined; "The regulatory body in consultation with the National government department for health shall set the minimum standards of practice for African traditional medicine and alternative medicine" and that "The regulatory body shall be responsible for registration, licensing and standards compliance of practice in traditional and alternative medicine" [33].

It however becomes apparent that the "African traditional medicine and alternative medicine" is mainly "Kenyan material-herbal medicine" because it may be the only form of Kenya's alternative medicines capable of availing medical materials for scientific analysis.

At almost the same time that the Health Bill 2014 and PPB amendment bill 2014 were being developed, a group of herbalists had drafted a bill intended to enable self regulation of their practice [34]. They intended to persuade parliament to pass the bill that would enable them escape scrutiny by the PPB.

The bill appears to have been drafted for the elite THPs and it would discriminate others to subordinate positions; "No person shall be appointed as chairperson of the council unless such person is-

(a) A traditional health practitioner of not less than eight years standing; and

(b) The holder of a diploma, or degree in traditional health practice"

The criteria for appointment of two THPs to the disciplinary committee was:

"(i) one shall be in the public service;

(ii) one shall be from the private practice".

The document did not define a herbalist in the public or private service.

The authors of the document failed to recognize matters related to collaboration with Conventional health practitioners (CHPs), definition of the scope of TM and hence scope of registration, regulation and discipline issues.

The Disconnect between Conventional and Alternative

In America, *"Many people are confused about alternative medicine, and I do not blame them...one must realize that while treatments may look like alternatives to us, they have long been part of the medical mainstream in their culture of origin..."* [24].

In Kenya, *"some of our scientists and medical fraternity believe that all herbal medicines are harmful...some conventional medical professionals often oppose integration of herbal with conventional..."* [8]

A stakeholders meeting on the National Health draft bill 2014 [33] was held at the Kenya School of Government in July, 2014 under the stewardship of the Commission for the Implementation of the Constitution (CIC). Herbalist representatives had been invited through the *Center for the Empowerment of the Local Herbalist (CELOH)*. Other participants were mainly from the mainstream health service providers, health research and a few from the legal fraternity and academia. Matters pertaining to conventional medicine were amicably discussed with participants showing mutual respect. All this changed when it was time to discuss the section on alternative medicine; the disconnect between CHPs and THPs was evident. Some conventional medicine representatives made deliberate efforts to trivialize, water-down and not accord any serious thought to the idea of constitutional recognition of alternative medicine in Kenya. A question on whether a CHP could refer a patient to a herbalist was received with contemptuous gleans by some participants. This waded only after a renowned pharmacist informed the forum that he had witnessed such referrals during a visit in China. He went on to expound on how conventional and alternative medicine is practiced in a parallel manner in China. The Chinese referrals have been documented by some TM researchers [8], while some African countries have now started similar referrals [17].

Similar disconnect was noted about American doctors by Everret [24]; *"in the opinion of most doctors, there is not a definitive answer on the value of alternative medicine. I would like to see us undertake the study and research that could provide definitive answers to prudent questions about the usefulness of complementary and alternative medicine for our society"*. As Everret was making these observations, the American Herbal Pharmacopoeia (AHP) had just been founded in 1995 [15]. One of the objectives of the AHP was *"to break down the many barriers and fears that prevent the complete integration of herbal medicines into our health care system and our lives ... AHP's primary role is to develop quality control monographs and authenticated reference materials for analytical work and to produce tools such as microscopic characterization of botanical medicines that can be used in the quality assessment of herbal products"*.

The Kenyan herbalist generally respects and even envies the conventional practitioner [16]. The latter, however, in general appears to have little or no respect and trust for the former [16,8]. While the herbalist thirsts and even makes effort to acquire conventional medical knowledge (Daily Nation, Feb. 8 2010.), the conventional health professional generally treats herbalism like an outdated cultural practice with no position in modern medical practice [10]. This is

despite the fact that THPs in Kenya far outnumber CHPs or allopathic providers [10]. Even the Traditional Birth Attendants who had initially been integrated in the MOH's Division of Reproductive Health are reportedly no longer recognized [10].

The new trend in aggressive and untrammled print and electronic advertisement by alternative medical practitioners [9] and their push for establishment of their own authority [34] could be an indicator that they are now ready to be challenged by the current apparently weak and probably "easy to manipulate", regulatory mechanisms.

A renowned medical practitioner and a regular medical-issues columnist with a local daily has expressed displeasure with frequent untrammled adverts by a Nairobi based herbalist; one of his recent columns was purely an expression of frustration and disappointment that the regulatory bodies could allow such adverts to be transmitted. The columnist was concerned that the herbalist was using the title "Doctor" and promising to treat and successfully heal terminal illnesses within weeks. The columnist recognized that the herbalist has a sizeable number of faithful patients; *"many Kenyans have visited his clinics... some of his clients swear by him, and insists that he cured them of one disease or the other"*.

The herbalist referred to above appears to be doing extremely well since he can afford prolonged periods of advertising on national television and the print media. The herbalist also advertises on expensive bill boards that are usually associated with the affluence of politicians or big companies. The advertisements are laced with conventional medical terminologies and even some authoritative statistical information on popularity of herbal medicine. He even appeals for a speedy review of some medical terminology because he is able to "treat" what conventional medicine may have described as "terminal or chronic"; he specifically promises to treat hypertension in twenty five days and advises listeners not to opt for what he describes as life-long treatment with conventional antihypertensives.

Some conventional scientists also hold a similar view that herbal medicine can successfully treat some conditions that are problematic with conventional medicine [8]. In some of his print adverts the herbalist claims to have established collaborations with some conventional scientists in order to generate scientific data on his remedies (People Daily, June 19 2015).

The columnist's views are that it is impossible to regulate *"herbalists and traditional healers"* and blames the Ministry of Health for sitting back and watching as *"Kenyans are literally killed by medical charlatans in the name of cure-all herbalists"*. The medical practitioner offers a *"simple solution to this menace"* as *"accountability mechanism, whereby anyone making claims of cure must be made to produce the evidence to back his claims"*. This might be practically very difficult to implement [8]; regulatory authorities may succeed by applying the elastic yardstick, casuistry, such that every herbalist is treated uniquely and not judged according to rigid conventional regulations; panel members involved in the development of the WHO analysis manuals for herbal products recognized the difficulties

of reaching general consensus on all issues pertaining to herbal medicine and recommended use of common sense in unique situations [2].

The columnist's disapproval of the use of titles like "doctor" by advertising AM practitioners could be one of the most difficult regulatory aspects in the practice of AM in Kenya. The Kiswahili equivalent of "doctor" is "dactari". The title may be used alone or with further descriptive terms coined in to indicate a specialization - "dactari wa meno", "dactari wa kienyenji", "dactari wa mifugo", "dactari wa kilimi".

To a good proportion of the ordinary Kenyan, the title "Doctor" or "dactari" implies anybody in the health sector; nurses, medical laboratory technologists, pharmacists, pharmaceutical technologists, physicians, clinical officers, veterinarians, holders of medical, nursing, nutritional, herbal, or veterinary diplomas and certificates etc.

All such personnel may acknowledge verbal recognition through the title "doctor" even when the title is misleading. It is however only the alternative medical practitioners who will go to the extent of mentioning or printing the misleading authoritative titles before their names; it is usual for the least schooled practitioners to adopt the most authoritative titles with "professor" and "doctor" being the more popular preferences.

The non recognition and non registration of herbalist by the Ministry of Health since independence [8, 16] has contributed to the delay in establishing regulatory mechanism for alternative medical practices in Kenya. The registration of herbalists with the Government's ministry responsible for cultural affairs was an indicator that their trade was perceived to be equivalent to cultural music, art or history; it was not "scientific" but a subjective practice whose parameters were shrouded in secrecy. The herbalist has hence remained free to conduct his business without scientific scrutiny from the Government's Ministry of Health because the Ministry is not responsible for regulating cultural affairs. The herbalist can use whatever title he desires because it is only himself who can define the parameters upon which such title are acquired "culturally". What, for instance, would a regulator do to a "professor" herbalist who claims to have been bestowed the title by some long dead ancestors, or a "dactari wa kiriti" who has performed uvulectomy for more than 60 years and with a president in his list of past uvulectomees? (*The Star Wednesday 15 July 2015*).

The situation in some other African countries like Mali is quite different; there actually exists a "Department of Traditional Medicine" in the Ministry of Health [8]. In such countries the collaboration between THPs and CHPs has resulted in improved health indicators for diseases like malaria [8].

In the past herbalism also suffered stigma because it did not earn the necessary approval from the more dominant Christian-based followers [8]; the boundaries between the Kenyan pure-material-herbal, spiritual-herbal and pure-spiritual healing practices were not clearly defined. A Christian visiting a herbal clinic could be tarnished as having sourced for witchcraft or other "unchristian" evil spiritualism.

Commenting on similar issues with regard to American's alternative medicine [1], Micozzi made the following remarks, "Allopathic medicine is considered the 'scientific' healing art while the alternatives are considered 'non-scientific'. However, perhaps what is needed is not less science, but more science in the study of alternative/complementary medicine. ... Quantum physics and contemporary biology-ecology may be needed to understand alternatives. ... If biomedicine cannot explain scientific observations of alternatives, then the biomedical paradigm will be revised. ... when homeopathy or acupuncture is observed to result in a physiological or clinical response that cannot be explained by the biomedical model, it is not the role of the scientist to deny this reality, but rather to modify our explanatory models to account for it. ... science must account for all that is observed, not just part of it. That is why physics has moved beyond Newtonian mechanics - biology beyond typology."

Pharmacopoeial Characterization and Specification of Herbal Products

Although the popularity of traditional medicine has continued to rise both in the developing and industrialized countries, there has been a mismatch in the generation and documentation of objective scientific data and only a few plant materials have been characterized and specified in official publications [2]. While the WHO has published guidelines on analysis of herbal plant materials, panel members involved in the development of the WHO analysis manuals recognized the difficulties of reaching general consensus on all issues pertaining to herbal medicine and recommended use of common sense in unique situations [2]. Compilation of conventional pharmacopoeial monographs on Kenyan herbal products would be an impossible undertaking for scientists adopting methodologies used to develop pharmacopoeias in the industrialized countries [8]. In most cases a Kenyan herbal product is a powdered mixture containing materials from several different plants; different plant barks, leaves, roots, twigs, flowers, seeds or fruits are harvested and dried before undergoing miller-grinding. The resulting powders are then mixed in different ratios to formulate different drugs for varied ailments. The powder products are usually dispensed in sealed plastic containers and the patient guided on how to reconstitute the drug in either hot water, boiling water, tea or milk. Liquid and paste formulations are also available [11]. Only the owner herbalist has information on the exact composition of each product. The requirement by the regulatory body to disclose drug content is met with hostility.

Pharmacopoeia characterization of herbal products must generate monographs suited to the particular product and not merely guided by some set standards [15]. Some AM researchers advocate simplification of evaluation procedures into the monitoring of safety and efficacy in the course of therapy [16] as opposed to rigorous and expensive scientific trials.

Scientific Contributions in the Evaluation of Herbal Products

Kenyan researchers on natural products have been researching and documenting varied pharmacological, ethnomedical and chemical information on many plant materials of known ethnobotanical importance. Such

studies include the characterization of benzoquinones isolated from some ethnomedically important *Myrsinaceae* species [36, 37], the characterization of anthraquinones isolated from some ethnomedically important *Rumex* species [38], the characterization of flavanoids isolated from some ethnomedically important *Polygonum* species [39]. The scientists usually document in vitro pharmacological activities of extracts and compounds from plant materials that have been traditionally used for their antimicrobial properties (anthelmintic, anti-bacterial, anti-fungal) analgesic and antiinflammatory activities (chest pains, stiff joints), purgative activities among others. Other scientists have documented ethnomedical uses of various plant materials [10, 39] as well as generating data on safety of medicinal materials [11]. Scientists at Kenya Medical Research Institute (KEMRI) have generated data on AM [40, 41] and they are currently aiming at commercial production of herbal medicines [41].

The practical utilization of such scientific information with regard to evaluation and standardization of herbal products is not commonly known or documented; the necessary collaboration between the laboratory scientists, herbalists, conventional health professionals (pharmacists, physicians, veterinary doctors) and Government policy makers does not exist.

Universities and research institutions in which such research findings on natural products are usually reported do not appear to have been proactive in guiding, persuading and influencing policy makers on the need for practical application of available data in the standardization, evaluation and development of pharmacopoeial specifications on herbal products. The physicochemical and in vitro pharmacological data available on ethnomedically important plant materials could be used to establish regulatory references or standards for evaluation of herbal products. However, it currently appears that each research, academic or regulatory authority operates in an autonomous and non collaborative manner with regard to issues related to AM.

In their 2014 amendment bill [19], the PPB proposes to be the sole regulator of clinical research- *"No person shall conduct a clinical trial in Kenya whether for investigation of new drugs or for new indications unless he has been granted approval by the Authority"*. The bill is silent with regard to the expected clinical trials contribution by universities, research institutions, other health regulatory national bodies and hospitals. Some AM researchers feel that a clinical trial for a herbal medicine that is already in use is an unnecessary, complex and expensive demand on herbalists [8].

It is not clear how the PPB will for instance relate with the National body that is constitutionally mandated to monitor and approve scientific research in the country, the National Commission for Science, Technology and Innovation (NACOSTI). One of NACOSTI's objectives as outlined in their January, 2014 Service Charter [42] is *"To commission relevant research, document, store and disseminate research results and encourage their application"*

In the past, herbalists were advised to take their products to the Kenya Medical Research Institute (KEMRI) for analysis before applying for practice registration certificate from the

Ministry of Culture. It is reported that herbalists were not happy with the arrangement and they even felt cheated [22]. Many herbalists may have lost confidence with conventional researchers; *"During the survey a number of THMPs offered examples of negative experiences with local and international researchers. A common complaint was that they had provided plant material for analysis and were never given any information in return"* [10]

The Kenya Medical Research Institute (KEMRI) has recently realigned its *"Traditional Medicine and Drug Development Programme (TMDDP)"* to *"be a leading programme in the promotion of Traditional Medicine and Drug Development. The Center's aim is "To identify and develop effective traditional/alternative medicines and drugs for use against human diseases"* [42]. It remains to be seen whether a close working relationship between KEMRI and PPB will result in the registration of herbal products that have been subjected to clinical trials. This major achievement would serve as practical prototype of future AM research that would have significant value addition to the practice of herbal medicine in Kenya.

Kenyatta University is another institution that has adopted a more proactive role on AM issues. Its Department of Pharmacy & Complementary/Alternative Medicine is *"responsible for the training of professional pharmacists and natural medical practitioners both at the undergraduate and postgraduate levels, to meet the needs of the country"* [43].

Other institutions that have shown interest in AM include UoN, ICIPE, KALRO, KEFRI, and CELOH.

Such efforts are in line with WHO's recommendations; *"Given the increasing popularity of traditional medicine globally, it is imperative that medical and other healthcare personnel collaborate with THPs to understand traditional medicine practices and products"* [23]. Elsewhere in Africa, fruitful collaborations between THPs and CHPs have been reported in Mali, Senegal, Uganda and South Africa [23].

"...so many people have relied on these approaches for so long that they may have something of value to offer. Let us begin with the necessary research so that we could have substantive answers in the near future"- Everret [24], former Surgeon General of the United States and Chairman, National Museums of Health and Medicine Foundation, Washington, DC.

"We live in a world filled with opportunities to observe the practice of alternatives. It only remains to apply scientific standards to their study. In the meantime, patients are now waiting for mainstream physicians to understand the mechanisms of alternatives" [1].

The Center for the Empowerment of the Local Herbalist (CELOH) is a local non-profit making organization that was founded in 2010 with the major aim of generating, documenting and preserving scientific data on Kenyan herbal medical practice. One of organization's achievements is the generation of scientific data on some herbal products to enable owner herbalists apply for product registration with the PPB. Some chromatographic, pharmacological (potency and toxicity) and morphological data on some gastrointestinal and antimicrobial products has been generated.

A Herbalist's TB Remedy; The In Vitro Anti-TB Activity of Some Extracts of the Herbal Product CE2013X

The herbal product CE2013X had been delivered to CELOH scientists for data generation to enable registration of the product by the PPB. The code name CE2013X has been adopted for the purposes of conforming to legal and ethical issues. The herbalist had claimed to have used the product in TB treatment and hence the need to establish its in vitro anti-TB activity. TB treatment by Kenyan herbalists is relatively rare in comparison to other conditions like malaria, gastro intestinal diseases and arthritis [10].

Methodology and Results

The herbal product, CE2013X, is a brown finely divided powder with a faint cocoa-like aroma.

Sohxlet extraction of dry powder drug was performed using water, ethanol and chloroform at the Department of Chemistry, University of Nairobi.

2mg/ml stock solutions of three extracts were prepared in the corresponding extracting solvents (ethanol, water and chloroform) and further dilution done with MGIT media components. H37Rv and MDR Mycobacterium tuberculosis isolates were obtained at the Central Reference Laboratory for TB in Nairobi (CRL). They were subcultured to obtain viable growth before inoculation. Procedures detailed by Muriuki et al [44] were adopted to generate in vitro anti-TB activity of the extracts, a 1:1:1 mixture of the three extracts and four conventional TB treatment drugs.

The results are summarized in Table 1 below.

Table 1. MIC values of extracts and conventional drugs.

Substance	MGIT MIC (H37Rv) µg/ml	MGIT MIC (MDR) µg/ml
Isoniazid	0.8	2.7
Ethambuto	2.5	15
Streptomycin	3.25	2.5
Rifampicin	7.5	30
Ethanol extract	25.6<MIC<102.4	MIC>102.4
Water extract	1.6<MIC<1.6	0.1<MIC<0.4
Chloroform extract	6.4<MIC<25.6	1.6<MIC<6.4
Mixed extract	0.4<MIC<1.6	0.1<MIC<0.4

The experimental data on the herbal drug CE2013X appears to support the owner herbalist's claim of successful herbal TB treatment; the activity of the mixed extract was better than that of any of the four conventional drugs.

Experimental data on an antiulcer herbal medication also appeared to support the owner herbalist's claim on treatment of ulcers.

Although the drugs appears to be potent towards ailments, this conclusion must await further studies to answer critical questions such as; are the results reproducible with every batch of the product?, is the drug a pure herbal product or one adulterated with conventional drugs?, what are the pharmacokinetic profiles of the drug in man?, can the

herbalist's claims be established by collecting data from individual cases that have been treated with the drugs?

Conclusion and Recommendations

The review of the status of Kenyan alternative medicine has identified major gaps that need to be addressed especially in giving a local definition to the practice and the establishment of boundaries for what can be scientifically regulated. With the new and broader freedoms guaranteed by the new constitution, Kenyan medical field will experience serious challenges especially from die hard comen determined to make money from medically ignorant masses. The Kenyan conventional physicians in collaboration with relevant scientists and Government Departments must extend a hand of recognition to the genuine and honest herbalist to enable the establishment of order in the Kenyan AM practice. Most of the herbal medicine research undertaken by universities and other research institutions serve the purpose of research funding and academic promotion with hardly any significant scientific impact to the AM practice. As an illustration, the in vitro anti-TB data reported here may remain as such unless a cooperative approach by all the stakeholders mandated to ensure better health care for all Kenyans is adopted.

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Assessment Of The Pharmaceutical Manufacturing Industry In Kenya In Regard To Self Sufficiency In Essential Medicines

Vugigi S. K.^{1,2}, Ogaji I. J.^{2,3} and Thoithi G. N.⁵

¹ Elys Chemical Industries Ltd., P.O. Box 40411-00100, Nairobi, Kenya. Email: qa@elys.co.ke

² Department of Pharmacy and Complementary/Alternative Medicine, School of Medicine, Kenyatta University, P.O. Box 43844-00100, Nairobi, Kenya.

³ Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, University of Jos, P M B 2084-930001, Jos, Plateau State, Nigeria

⁴ Department of Pharmaceutical Chemistry, School of Pharmacy, College of Health Sciences, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya.

*Corresponding author

Abstract

Kenya National Pharmaceutical Policy (2012) encourages local production of essential medicines. Pharmaceutical manufacturing industry in Kenya currently consists of 30 companies accredited by the Pharmacy and Poisons Board of Kenya. The aim of this study was to assess the contribution of the pharmaceutical manufacturing industry in Kenya towards essential medicines demand.

Dosage forms produced locally, registered pharmaceutical products and pharmaceutical lists in Kenya were evaluated. Subsequently, pharmaceutical equivalents of 150 locally manufactured essential medicines were determined.

Solid dosage forms were the majority (54.9%) of local products. Locally manufactured products accounted for 14.5% of registered products. Local firms manufactured 38.4% of products listed as essential medicines. Ninety one percent (91.0%) of products stocked by Kenya Medical Supplies Authority were essential medicines. The overall percentage of local pharmaceutical equivalents was 32.4%.

Kenya depends heavily on imported pharmaceutical products for her essential medicines needs.

Key words: Essential medicines, local pharmaceutical industry, pharmaceutical product, self sufficiency.

Introduction

The goal of the manufacturing sector in Kenya is to develop a robust, diversified and competitive industry by strengthening local production [1]. In pursuit of this, the ministry of health has developed a pharmaceutical policy [2] that aims to ensure access to quality medicines and to encourage self sufficiency in essential medicines through local production. The government envisions implementation of this policy by encouraging adherence to Good Manufacturing Practice (GMP) standards, creation of incentive schemes and ensuring an enabling environment for investment in local pharmaceutical production.

The local pharmaceutical industry in Kenya is engaged in secondary and tertiary manufacture of products for human and veterinary use. Most of the products manufactured are non-sterile and include tablets, capsules, syrups,

suspensions, ointments and creams. Pharmacy and Poisons Board (PPB) regulates pharmaceutical manufacturing activities through issuance of license to manufacture and accreditation certificate for GMP compliance. PPB also authorizes marketing of pharmaceutical products through a product registration process and subsequent annual product retention for which a fee must be paid. The PPB maintains a database of products registered and retained in Kenya. Kenya government, through Kenya Medical Supplies Authority (KEMSA), is currently the major purchaser of local and imported pharmaceutical products in Kenya. It has been estimated that KEMSA's purchases constitute 30 per cent of all prescription drugs in the Kenyan market [4]. The Government allocation meets 65% of KEMSA budgetary requirements [7]. Kenyatta National Hospital (KNH), a public and the largest hospital in Kenya, procures a substantial quantity of these pharmaceutical products.

A principal prerequisite of self sufficiency in essential medicines is the capability of the local industry to manufacture the essential medicines in sufficient quantities to meet the populace demand [8]. The contribution of the local industry towards the essential medicines demand can be established by evaluation of production lines, dosage forms and the range of products. Dominance of local products on the PPB list of registered products, the Kenya essential medicines list [9] and stock lists of KEMSA, the major public procurement agency and KNH, may also be construed as measures of capability. The prevalence of local products in the Kenyan market can be demonstrated by the available pharmaceutical equivalents (PEs).

There are no publications on the prerequisites of self sufficiency in essential medicines in Kenya, upon which to assess and forecast local sufficiency in essential medicines. Furthermore, no literature is available on pharmaceutical equivalents to locally manufactured products. The aim of this study was to assess the contribution of the local pharmaceutical industry to the demand of essential medicines in Kenya. This work reports on dosage forms, production lines and range of products manufactured in Kenya, registered and retained pharmaceutical products, products on Kenya essential medicines list which can be locally manufactured, products on KEMSA and KNH stock lists that can be produced locally and pharmaceutical equivalents of locally manufactured essential medicines.

Methodology

Research design

Data on the contribution of the local Pharmaceutical Manufacturing Industry to the demand of essential medicines in Kenya was obtained by scanning official pharmaceutical documents and databases. Data on manufacturing activities in the local industry was collected from the 30 licensed pharmaceutical manufacturers during this study. Information on growth profile of Kenyan pharmaceutical industry was obtained from Kenya pharmaceutical gazette notices. Data on range and primacy of local pharmaceutical products was obtained from Pharmacy and Poisons Board database, Local pharmaceutical manufacturer's product lists, Kenya essential medicines list and pharmaceutical products stock lists from KEMSA and KNH.

Profile of local pharmaceutical industry growth

Preliminary investigation was carried out from literature [11] to establish the growth profile of local pharmaceutical industry since inception. A search in the Kenya Gazette Notices [12] for licensed pharmaceutical manufacturers from 1963 to 2014 was performed to determine growth trend in the local pharmaceutical industry.

Dosage forms and production lines

Data on dosage forms, production lines, types of and range of products manufactured by each local facility were obtained from manufacturers' product lists.

Registered and retained pharmaceutical products

Information on local and imported pharmaceutical products registered and retained in Kenya was obtained from the PPB database [12]. The percentage of the registered and retained products that was locally manufactured was determined. The ratio of retained products to the registered was computed for both local and imported products.

Pharmaceutical product lists

Pharmaceutical product lists were analysed to identify products that could be manufactured by the local industry. The Kenya Essentials Medicine List (KEML) was examined to determine products that could be manufactured in Kenya. Information on pharmaceutical products procured in Kenya was obtained from stock lists of KEMSA and KNH. The stock lists were examined to identify products that could be manufactured locally.

Pharmaceutical equivalents (PEs)

Subsequent analysis was carried out on 150 essential medicines that were locally manufactured to find out the available local and imported pharmaceutical equivalents in Kenya. The products evaluated were categorized according to the KEML pharmacological classification namely analgesics, antiallergies, antibacterials, anticonvulsants, antidiabetic, antifungals antimalarials, anthelmintics, antiretrovirals (ARVs), beta-lactams, dermatological preparations, gastrointestinal agents, other antibacterial drugs and other central nervous system (CNS) acting drugs. The PEs were determined for both registered and retained products. The percentage of PEs retained on the market relative to the registered products was calculated for both local and imported products and the prevalence of locally

manufactured products was deduced from the overall percentage of local pharmaceutical equivalents on the market.

Results And Discussion

Profile of local pharmaceutical industry growth

The pharmaceutical industry in Kenya currently consists of 30 firms licensed and current Good Manufacturing Practice (cGMP) accredited by the PPB to manufacture human and veterinary products [13]. This industry exhibited a steady growth from the year 1963 until 2012 as shown in Figure 1. The drop in 2014 may be attributed to the exclusion of non mainstream manufacturers such as Kenya Veterinary Vaccine Production, and firms previously licensed as pharmaceutical manufacturers but were not accredited by the PPB to manufacture. The ownership structure is predominantly indigenous, with one company, GlaxoSmithKline, being a multinational. The presence of foreign multinational manufacturers has diminished mainly due to mergers, unfavorable business conditions and also the free market policy adopted by Kenya as a prerequisite to the structural adjustment loan with the World Bank in the 1980's [14].

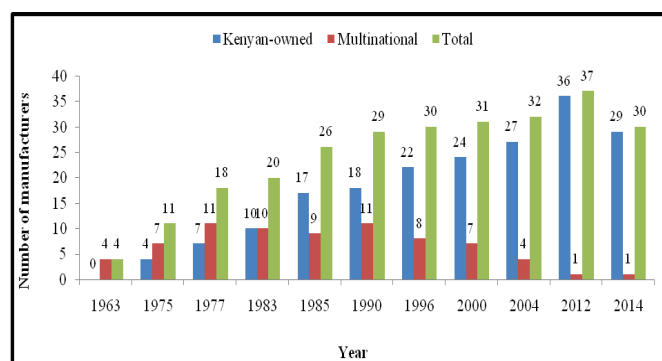


Figure 1: Trends in the Kenyan pharmaceutical manufacturing sector from 1963 to 2014

Dosage forms and production lines

Table 1 shows dosage forms, production lines and the number of products manufactured in the local industry. The β -lactam products were categorized differently due to the molecular structure of these compounds which cause allergy in some individuals [15] and hence, the segregation from other products.

The pharmaceutical industry in Kenya manufactures mainly non-sterile products (97.3%) comprising of solids, semisolids and liquid preparations. Sterile products demand compliance to very stringent cGMP standards and high levels of preventive maintenance practices, with enormous financial investment. Viable sterile manufacturing requires high capacity production and a large market for these products, which are not guaranteed for the local industry.

Solid dosage forms were the majority followed by liquids, accounting for 54.9% and 32.1%, respectively. It was observed that established firms manufactured the three dosage forms whereas new start-up firms, under five years in operation, manufactured mainly liquid and semisolid preparations; this may be due to the relative simplicity of manufacturing machinery and processes involved.

The development of a dosage form is a function of market demand among other factors. The demand for solid dosage forms by government and other procurement agencies is high due to ease of administration, transportation and stability [16][17].

Table 1. Dosage forms, production lines and products manufactured in Kenya

Dosage Form	Production lines		Manufactured products
Solids T	ablets	Non β -Lactam tablets	614
		B-Lactam tablets	5
	Capsules	Non β -Lactam capsules	111
		β -Lactam capsules	44
	Dry syrups	Non β -Lactam dry syrups	42
		B-Lactam dry syrups	31
Semisolids		Creams and ointments	159
Liquids	S	syrups and suspensions	496
Others		Sterile products	42

Registered and retained pharmaceutical products in Kenya

Table 2 shows the number of products at various facilities in the local industry registered by PPB in 2014. There was a huge disparity in the number of products registered from each facility, ranging from 1 to 250 products. The number of products registered depended on the size of the facility, whether the facility was well established, availability of technology and access to funds for upgrading. Ten facilities, mainly new start-up, had less than 10 products registered. Eight facilities had more than 100 products registered accounting for 72.3% of the registered locally manufactured products in Kenya.

Table 2. Products registered from each facility by Pharmacy and Poisons Board in 2014

Number of products registered	Number of Companies
Less than 10	10
10 to 50	9
50-100	3
100-200	6
200-250	2

In year 2014, 7466 of the 12313 registered pharmaceutical products were retained at the PPB as indicated in Table 3. Local products accounted for 14.5% of the registered products and 21.5% of retained products in the market. Local manufacturers retained 90.2% of the registered products whereas only 55.6% of the imported products were retained. Examination of the data obtained seems to indicate that foreign manufacturers may register some products, especially those listed as essential medicines, in readiness for government tenders and strategically retained them at the opportune time.

Table 3. Products registered and retained by Pharmacy and Poisons Board in 2014

Institution	Number of products on stock list		
	Sterile	Non sterile	Total
KEMSA	601	20	180
KNH 2	873	13	600

Pharmaceutical equivalents

Pharmaceutical equivalents on the Kenyan market for 150 locally produced essential medicines were evaluated. Table 5 presents the local and imported pharmaceutical equivalents for 14 analgesic products available on the Kenyan market. Paracetamol tablets 500 mg and diclofenac tablets 50 mg had the highest number of pharmaceutical equivalents. Three products namely aspirin tablets 300 mg, ibuprofen syrup 100 mg/5 ml and paracetamol syrup 120 mg/5ml had more local PEs than imported products. This may be attributed to the logistics of importation of liquid preparations which are usually bulky, and also to the fact that the new start-up companies in Kenya manufactured mainly liquid dosage forms. The percentage of local PEs for the rest of the products in this category accounted for less than 30%. Diclofenac tablets are usually enteric coated, a technique that the new start-up manufacturers have not ventured into, hence the low percentage of local PEs. Ibuprofen tablets 200mg was manufactured by 8 established local manufacturers, who were capable of carrying out the sugar coating process. There was no local PE for ibuprofen tablets 600 mg which may be attributed to the low demand for this strength. The same trend was observed for the retained products as local manufacturers retained almost all the products registered. Most foreign manufacturers retained less than 50% of the products registered. The probable reason was that most of the analgesic products were cheap and foreign manufacturers registered them in readiness for government tenders as illustrated by diclofenac tablets 25 mg, indomethacin capsules 25 mg and mefenamic acid capsules 250 mg. The imported PEs dominated the market. The overall percentage of the registered and retained analgesics PEs on the Kenyan market that were manufactured locally was 24.0 % and 35.7 %, respectively.

Table 5. Analgesics pharmaceutical equivalents in the Kenyan market in 2014

Product	Number of registered products		Number of retained products		%Retained Registered	
	Imported L	ocal I	mported	Local I	mported	Local
Aspirin tablets 300 mg 6	7	1	7		17.0	100.0
Diclofenac tablets 100 mg 2	3	4	164		70.0	100.0
Diclofenac tablets 25 mg 2	6	3	1	0	4.0	0
Diclofenac tablets 50 mg 5	1	4	404		78.0	100.0
Diclofenac tablets 75 mg 6	1	4	1		67.0	100.0
Ibuprofen syrup 100 mg/5ml 9	1	4	4	6	44.0	43.0
Ibuprofen tablets 200 mg 3	5	8	138		37.0	100.0
Ibuprofen tablets 400 mg 3	4	6	196		56.0	100.0
Ibuprofen tablets 600 mg	9	0	1	0	11.0	0
Indomethacin capsules 25 mg 3	4	8	4	4	12.0	50.0
Mefenamic capsules 250 mg 2	0	5	3	3	15.0	60.0
Mefenamic tablets 250 mg 9	1	4	1		44.0	100.0
Paracetamol tablets 500 mg	381	6	271	6	71.0	100.0
Paracetamol syrup 120 mg/5 ml	9	154	1	5	44.0	100.0
Total	309	92	141	75		

Table 6 represents the β -lactam PE registered and retained by PPB. The proportion of local products was less than 30%, except for flucloxacillin capsules 250 mg and flucloxacillin powder 125 mg/5ml. The two products have limited demand due to their pharmacological characteristics, hence the registration of few imports. Amoxycillin dry powder 125 mg/5ml, a broad spectrum drug, had the largest number of PEs on the market due to high

demand of this product especially for pediatric use. The β -lactam ring is associated with hypersensitivity reaction and the manufacturing activities of β -lactams require an independent air handling unit to avoid cross contamination of non β -lactam products. It is almost impossible to achieve this separation and containment, therefore β -lactams are usually manufactured in a separate facility. Only the established companies manufactured β -lactams and hence the low presence of local products on the market. The overall percentage of registered and retained β -lactams PEs in Kenya that were manufactured locally was 23.7 % and 37.2%, respectively.

Table 6. Beta lactam pharmaceutical equivalents in the Kenyan market in 2014

Product	Number of registered products		Number of retained products		% Retained Registered	
	Imported L	ocal I	mported	Local	Imported	Local
Amoxycillin dry syrup 125 mg/5ml 6	0	11 1	3	5	22.0	45.0
Amoxycillin capsules 500 mg	31 1	1	16 6		52.0	55.0
Amoxycillin capsules 250 mg	49 1	1	39 6	8	0.0	55.0
Ampicillin dry syrup 125 mg/5ml 3	2	9	2	6	6.0	67.0
Ampicillin capsules 250 mg	48 1	0	9	6	19.0	60.0
Ampicillin capsules 500 mg	31 7	5	4		16.0	57.0
Cefuroxime capsules 250 mg	18 1	1	4	1	78.0	100.0
Fludoxacin capsules 250 mg	3	3	2	3	67.0	100.0
Fludoxacin dry syrup 125 mg/5ml 3	2	3	2		100.0	100.0
Total	275	65	103	39		

Pharmaceutical equivalents for 8 antimalarial products in Table 7 indicate that less than 25% of antimalarial products registered and retained were locally manufactured. The procurement of artemisinin combination therapy (ACT) antimalarials in public institutions during this period was donor funded; the requirement by the donors is that these products be sourced from manufacturers with international cGMP accreditation. None of the local manufacturers had this accreditation. Quinine, being the second line treatment drug [18] for uncomplicated malaria, was not in high demand and therefore not attractive for importers. Doxycycline is used for other pharmacological indications in addition to malaria prophylaxis, hence the high overall percentage of local PEs.

Table 7. Antimalarial pharmaceutical equivalents in the Kenyan market in 2014

Product	Number of registered products		Number of retained products		% Retained Registered	
	Imported L	ocal I	mported	Local	Imported	Local
Artemether Injection 300 mg/ ampoule	20 0	1	4	0	70 0	
Artemether/lumefantrine tablets 40/240 mg	4	0	3	0	75 0	
Artemether/lumefantrine tablets 15/90 mg 1	0	0	0	0	0	
Artemether/lumefantrine liquid 15/90 mg 6	0	6	0		100 0	
Artemether/lumefantrine tablets 20/120 mg	15 5	1	5	2	100 4	0
Artemether/lumefantrine tablets 80/480 mg 2	0	2	0		100 0	
Doxycycline tablets 100 mg 1	7	9 5	9	2	9 4	100
Quinine tablets 300 mg	14 1	1	4	4	28 6	36 4
Total	79	25	49	15		

Table 8 presents the six antihypertensive products examined. Methyldopa tablets 250 mg had the highest percentage (19.4%) of local PEs followed by amlodipine tablets 5 mg (19.2%). Few local manufacturers had endeavored in the manufacture of antihypertensive products, probably due to inadequate research and product development units for designing a product with consistent release properties of the active pharmaceutical ingredient (API), in order to eliminate the risk of inaccurate dosage. The overall percentage of the registered and retained antihypertensives PEs on the Kenyan market that were manufactured locally was 13.1% and 14.4 %, respectively.

Table 8. Antihypertensive pharmaceutical equivalents in the Kenyan market in 2014

Product	Number of registered products		Number of retained products		% Retained Registered	
	Imported L	ocal I	mported	Local	Imported	Local
Amlodipine tablets 5mg	21 5	2	1	5	100.0	100.0
Atenolol tablets 50mg 5	2	4	28 4		53.8	100.0
Enalapril tablets 5mg 3	7	5	32 3		86.5	60.0
Methyldopa tablets 250 mg	25 6	7	5		28.0	83.3
Nifedipine tablets 10mg 3	5	4	22 1		62.9	25.0
Propranolol tablets 40mg	23 5	4	2		17.4	40.0
Total	193	29	114	20		

A total of 168 ARV products had been registered in Kenya by 2014. Seven local manufacturers had registered at least one ARV product. The local industry manufactured mainly single API formulation products such as zidovudine and stavudine tablets. Two companies, Universal Corporation and Cosmos Limited, have ventured into formulation of Fixed Dose Combination ARVs. The overall percentage of local PEs in this class was 19.2 %. Lack of product development technology and patent rights on some of these products contributed to the dominance of imported PEs in Kenya. Procurement of ARVs, like the artemisinin combined therapy (ACT) was donor funded, and apart from one facility that had been prequalified for one product (lamivudine/zidovudine); the rest did not meet the donor requirement for facility cGMP prequalification. Despite this requirement, the local industry was positioning itself to manufacture these products since donor funds were not assured.

Similar analysis was carried out on locally manufactured antiallergies, antibacterials, anticonvulsants, antifungals, anthelmintics, dermatological preparations, diuretics and gastrointestinal agents. Table 9 presents a summary of the pharmaceutical equivalents for all the pharmacological classes studied. The imported brands dominated the Kenyan market for both the registered and retained products. The overall percentage of local PEs in Kenya was 32.4% for the registered and 41.9 % for the retained products. Apart from dermatological preparations, other CNS products and anti-tuberculosis products, the percentage of the local products was less than that of imported products. The higher percentage of local PEs for dermatological preparations was due to the fact that prevalence of dermatological conditions in Kenya is relatively low compared to other diseases, and this market may not be lucrative for exporters. The other CNS

products evaluated were metoclopramide, amitriptyline hydrochloride, chlorpromazine, haloperidol, benzhexol hydrochloride, loperamide and fluoxetine tablets. These products were not in high demand and were registered by 4 manufacturers. The high percentage of local PEs is due to the fact that there were no imported PEs for benzhexol hydrochloride and amitriptyline hydrochloride. The percentage of the anti-tuberculosis products was higher for local products because old molecules such as rifampicin, isoniazid, pyridoxine, pyrazinamide and ethambutol were only registered by local manufacturers. More than 75% of antimalarial, antiretroviral, analgesic, antihypertensive, antacid, antidiabetic and diuretic pharmaceutical equivalents on the market were imported. The percentage of locally produced PEs for antimalarial and antiretroviral products was less than 20% due to the prequalification requirements for donor funded procurement. Deficiency in pharmaceutical technology expertise in this industry contributed to the manufacture of similar products. The dominance of imported pharmaceutical equivalents in Kenya and the inability of the local industry to manufacture the majority of essential medicines may have contributed to the high market share of imported pharmaceutical products. A study carried out on the pharmaceutical industry in Kenya in 2008 showed that the market share of the local pharmaceutical industry based on sales was 28% [19]. This is comparable to the overall percentage (32.4%) of local PEs in Kenya for the registered products which was obtained in this study.

Table 9. Summary of pharmaceutical equivalents for various products in Kenya in 2014

Pharmacological class	% Registered		% Retained	
	Imported L	ocal I	mported	Local
Analgesics	76.0	24.0	64.3	35.7
Antiallergics	58.9	41.1	42.3	57.7
Antidiabetics	75.5	24.5	55.8	44.2
Antituberculosis medicines	36.1	63.9	37.9	62.1
Anticonvulsants	66.7	33.3	45.8	54.2
Antifungals	67.8	32.2	55.1	44.9
Anthelmintics	62.6	37.4	49.2	50.8
Antihypertensives	87.1	12.9	82.3	17.7
Antimalarials	88.5	11.5	86.0	14.0
Antiretrovirals	80.8	19.2	91.1	8.9
Beta-lactam antibiotics	76.3	23.7	62.8	37.2
Dermatological preparations	41.3	58.7	32.7	67.3
Diuretics	76.7	23.3	63.6	36.4
Gastrointestinal medicines	84.6	15.4	47.1	52.9
Other antibacterials	56.8	43.7	43.4	56.6
Other CNS acting drugs	36.5	63.5	54.2	45.8
Other drugs	77.7	22.3	74.2	25.8
Average	67.6	32.4	58.1	41.9

The negative impact of dominance of imported products on local production has led some countries such as Ghana and Nigeria to prohibit importation of 44 and 18 essential medicines, respectively, [20][21] in order to promote self sufficiency in essential medicines through local production. The government of Kenya therefore, should consider providing interventions aimed at sustaining the local pharmaceutical industry in order to promote local sufficiency in essential medicines and support the

development of a viable local industry that is competitive, reliable, innovative, productive, responsible and strategic as envisaged in Kenya Vision 2030.

Conclusion

Despite the capability of the local industry to manufacture a significant percentage of non-sterile essential medicines as established in this study, Kenya depended heavily on imported drugs for her essential medicines needs. A shift towards self sufficiency through local production will require government intervention by a review of Health and Industrial policies in order to provide incentives that will substantially promote local production. The recommended incentives include inhibition of importation of pharmaceutical products that the local industry has capacity to manufacture, encouragement of sterile production by assurance of a local market and eligibility for weighted tax reduction for companies that are engaged in research in order to encourage development of new products.

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Sunscreen Creams

Mungoma M.*

¹ Department of Medical Sciences, Technical University of Mombasa, P.O. Box 90420 - 80100, Mombasa, Kenya

*Email: mikemungoma@yahoo.com

Abstract

Background: Sunscreen creams contain varying concentrations of UV filters in their formulations inhibiting direct exposure to damaging UV radiation which have a potential for toxicity, raising concerns over their safe use. Environmental toxicity from sunscreen creams is emerging with evidence of toxic ingredients reaching aquatic life, soil and possibly the food chain to man.

Aims of the study: This is a review highlighting the pros and cons of sunscreen use. It explores the controversies surrounding the use of sunscreen creams eliciting the benefits as well as the doubts around their efficacy in skin protection. By examining controversies, recent developments and the array of approaches surrounding the sunscreen use, this review confronts these opposing views and explains the contribution of ingredients and individual use as a stratified and very context-sensitive subject and provides a comprehensive picture on the potential toxicity of suncreams.

Search Methods: An electronic search of PUBMED database was undertaken on sunscreen articles. Cohort studies, retrospective studies, in vivo and in vitro studies and randomized controlled clinical trials referring to potential toxicity were evaluated.

Data Collection and Analysis: Data was extracted from articles and significant findings filtered to highlight the controversies surrounding the use of suncreams.

Main Results: Suncreams contain organic compounds known as UV filters which absorb UV radiation, reducing

the adverse effects of sunlight exposure. Benzophenone-2 (BP-2) has an increased potential for ecological toxicity particularly on marine life. It similarly is toxic to both male and female reproductive systems. However the use of suncreams for protection against photodamaging effects of sunlight has been proven.

Conclusions: This review suggests that sunscreen potential toxicity to humans requires further exploration. There are several layers of arguments that are confounded by variation in use of end users. However its use in vulnerable people including those suffering albinism and those exposing themselves to long hours under the sun is supported.

Key words: Ultra Violet (UV) filters, zinc oxide, nano particles, reactive oxygen species

Introduction

A sunscreen cosmetic has been defined as "any cosmetic product containing Ultra Violet (UV) filters in its formulation in order to protect the skin from the solar deleterious UV-light, avoiding or minimizing the damage that this radiation might cause on human health"[1]. Different jurisdictions have their own cosmetic legislations and permissible substances are reviewed and modified from time to time based on research findings from older and current formulations.

However health practitioners continue to prescribe and encourage consumers to use sunscreen creams as a way of reducing skin damage produced by ultraviolet radiation (UVR) from sunlight. Sun protection factor (SPF) is used as a

useful assessment of primarily UVB (290–320 nm) filters. But the SPF test does not comprehensively assess the complete photoprotective profile of sunscreen creams especially against long wavelength UVA1 (340–400 nm). Following acute, subchronic and chronic animal or human toxicity studies there is suggestion that they do not pose a great risk to human health. In contrast their protective effect plays an important role in reduction of UV rays exposure [2].

Basal and squamous cell carcinoma and cutaneous malignant melanoma can be induced with UV radiation making sunlight exposure a concern. DNA damage is the major consequence of UV radiations that is dependent on wavelength. Etiologically important UV wavelengths, which cause photoaging and photocarcinogenesis include UVA (315–400 nm), UVB (280–315 nm), and UVC (200–280 nm). UVB is primarily responsible for induction of DNA damage because DNA maximally absorbs radiation at wavelengths of 245–290 nm. This can trigger cell-cycle arrest, activation of DNA repair, cell death, mutation and neoplastic transformation as well as immunosuppression. The formation of cyclobutane pyrimidine dimers (CPDs) between adjacent thymine (T) or cytosine (C) residues and formation of pyrimidine (6–4) pyrimidone photoproducts (6–4PPs) through direct absorption of UV photons by the DNA bases (14) and (15) is the underlying cellular mechanism of toxicity. Mutations can result from these lesions. A study establishing these mechanisms of toxicity was carried out on PC12 cell lines derived from rat pheochromocytoma tumor cells. These results were extrapolated to humans effectively due to the ability of these cells to divide rapidly, their differentiation ability, and the presence of sodium, potassium, and calcium channels and other membrane receptors found in human skin cells. The study sought to establish the toxicological effects of different wavelengths (250, 270, 290, and 310 nm), doses of UV radiation on cell viability, DNA structure and DNA damage repair mechanisms. Results confirmed a decrease in cell survival rate 24 h after UV irradiation in a dose-dependent manner at all wavelengths (except at 310 nm) with 250 nm showing the highest cell killing ability [3].

The application of sunscreen creams has recently been studied among low sun exposed and high sun exposed subjects in Berlin and Monegasque respectively. Findings from the study reveal that extended sun exposure significantly reduces the cutaneous carotenoids and collagen/elastin concentration. The study also concluded that application of sunscreen is effective in protecting cutaneous carotenoids and collagen/elastin from being damaged subsequent to sun exposure [4].

The argument whether to retain sunscreen creams or look for other alternatives that would not predispose consumers to the deleterious direct effects contents of the creams or phototoxic effects of UV radiation from the sun remains debatable. The present assessment highlights arguments for and against the continued use of sunscreen cream providing findings from studies and reviews on the subject.

Effects of Solar radiation and Sunscreen cream use

Sunscreen creams are popular and regularly used to protect

people from the deleterious effects of ultraviolet (UV) radiation on then skin. They contain organic compounds known as UV filters which absorb UV radiation, reducing the adverse effects of sunlight exposure. The efficacy of these creams has been questioned over time following analytical studies suggesting an attenuation of protective capacity due to photo-induced decomposition as well as absorption through the skin [5].

Sunscreens are regulated by the Food and Drug Administration (FDA) as over-the-counter drugs, determining safety and effectiveness for photo protection. There are several types of sunscreens including inorganic sunscreen drugs that are photo stable and protect against UV radiation by reflecting, scattering, or absorbing UV, depending on the particle size. These have to spread as a thick coat to offer protection. But reduction of particle size into the micronized or ultrafine form improves cosmetic acceptability by lessening the scattering of visible light and it also shifts the protection toward shorter wavelengths and toward absorbency function. Examples of commonly used sunscreens are microfine zinc oxide that protects from the UVB to the UVA1 (340–400 nm) range. Zinc Oxide is more effective than microfine titanium dioxide, which is more protective in the UVB and UVA2 (320–340 nm) range [6].

Nanoparticles have a potential of causing neurological damage by inducing cellular reactions if released in a prolonged manner. These microscopic particles provoke protective substances in cells which in the long run become offensive to the cell. Titanium dioxide (titania), a common ingredient in sun creams is generally considered non-toxic. It absorbs ultraviolet light. Nanoparticles of this powder appear transparent making it very suitable for application on the skin. Chemical reactivity increases with reduction in particle size. Nano particles have an increased tendency to cross the blood brain barrier and their safety has not been proven fully. Titania particles, 30 nanometres in size across were used in a study on cultures of mouse microglia which are protective cells of neurons in the brain that act by engulfing foreign particles as well as release reactive oxygen species (ROS) to destroy invading substances. ROS are known to damage neighbouring cells [7].

In vitro studies on rat striatum exposed to commercially available titania showed a reduction of immunohistochemically stained neurons as well as microscopic evidence of neuronal apoptosis after 6-hr exposure which was associated to generation of ROS [8].

Environmental exposure to residues of sun cream degradation remains a toxicological concern. Following a study on the chemical evolution during artificial aging in water of four sunscreens containing titanium dioxide based nanocomposites, results indicated up to 30% of the total nano- titanium dioxide in sun creams were released into aquatic environments. In seawater a big fraction of this aggregate and sediment increasing potential of exposure through consumption [9]. According to Dondi [5], chemicals in sunscreen creams can bioaccumulate in aquatic animals and this is attributed to their lipophilicity. Persons living along sea shores and lakes that consume large quantities of fish have a predisposition to titanium

dioxide reaching their general circulation. In vivo studies on mice injected intravenously with a single dose of titanium dioxide nanoparticles at varying dose levels demonstrated a potential for acute toxicity effects in the brain, lung, spleen, liver, and kidney. In fact death of mice was observed in the highest dose (1387 mg/kg) group after 2 days following administration. However there was no significant hematological or genetic toxicity [10].

A study on *Daphnia magna* populations in a multi-generational study over six generations exposed to titanium dioxide for 21 days was carried out to assess its effects on mortality, individual growth, reproduction and population growth rates. Size distribution of nano particles of titanium dioxide in the single test media was analysed by dynamic light scattering (DLS) and transmission electron microscopy (TEM) whereas their concentrations were measured using ICP-MS. The study revealed that mortality and individual growth were significantly affected with increasing exposure duration and concentration. There was a decrease in reproduction over generations in all treatment groups (1.19–6 mg/L) but not in the control. A population collapse after five generations was noted at concentration levels of 1.78 mg/L chronic exposure [11]. These results would raise concern over long term use of sunscreen creams and with new knowledge of epigenetics, the possibilities of heritable long term effects of titanium dioxide exposure.

UV filters have a potential for endocrine disruption. In vitro studies have revealed that six filters namely benzophenone (Bp)-1, Bp-2, Bp-3, 3-benzylidene camphor (3-BC), 4-methylbenzylidene camphor (4-MBC) and octyl-methoxycinnamate (OMC) increased uterine weight in immature rats, findings which can be extrapolated in humans. Similarly 4-Methylbenzylidene camphor and 3-BC were observed to delay male puberty. Acute subcutaneous administration of estrogen 10 or 50 µg/kg to adult 4-MBC-exposed offspring that were previously gonadectomised revealed a lowering in estrogen sensitivity in the uterus. Two out of eight tested UV filters demonstrated anti androgenic activity in MDA-kb2 breast cancer cells. They antagonized dihydrotestosterone (DHT)-induced luciferase activation [12]. The use of sunscreen creams containing these substances could contribute to developmental toxicity in humans.

Sunscreen creams are frequently being introduced to surface waters by users who would swim or bath in them. This may be smaller in quantity as compared to soaps and detergents but bears significant consequences to environmental toxicology. A study was carried out in 1998 in two Swiss lakes that are located in a densely populated area. This was a suitable location for the study given the recreational activities such as swimming, bathing and boating. Lake Hüttnersee was smaller yet had more swimmers whereas Lake Zurich was larger and considered more typical with respect to possible loading with UV filters. The study assumed that release of UV filters was directly dependent on the population of swimmers or bathers at the lake, amount of sunscreen product applied on average by the swimmers, composition of the products with respect to UV filters and the fraction of the UV filters released to the water. UV filters concentrations were

established in water samples taken at different depths and UV filters were also detected in semipermeable membrane devices (SPMDs). Concentrations of UV filters in water from Lake Zurich ranged from less than 2 ng l⁻¹ to 29 ng l⁻¹, and higher at Hüttnersee, ranging from less than 2 to 125 ng l⁻¹. They were highest in the summer explainable by the higher number of swimmers and bathers at the time. These were also detected in semipermeable membrane devices (SPMDs) deployed in the lakes at concentrations of 80–950 ng SPMD⁻¹, indicative of potential for bioaccumulation [13].

Benzophenone-2 (BP-2) is a common UV filter found in sunscreen creams. In vitro as well as in vivo studies have demonstrated estrogenic properties of this compound. A study to establish the toxic effects on reproduction in fish was carried out on mature fathead minnows (*Pimephales promelas*). These fishes were exposed to 0.002, 0.1, 1.2, 5.0 and 9.7 mg/L BP-2 for 15 days. Benzophenone-2 accumulated in the fish up to 3.1 µg/g body weight. A significant dose-related effect was observed on the gonads of male and female fish. In addition, spermatocyte and oocyte development was significantly inhibited in male and female fish, respectively at concentrations of 1.2 mg/L and higher. The testes of exposed males had decreased numbers of spermatocytes and the ovaries of exposed females had lesser mature and more atretic follicles. These results would be important by extrapolation to human beings and would be significantly considered if fish that may have bioaccumulated high levels of Benzophenone-2 was consumed in the food chain by humans [14]. If these compounds have similar affinities to reproductive organs in humans, it is likely that similar effects would occur. A study on the effects of BP-2 on human sperms carried out between 2005-2009 in 413 men revealed a reduction in sperm concentration, immature sperm formation and tail abnormalities. This UV filter was associated with decreased hypo-osmotic swelling as well as a higher acrosome area [15]. The hypo-osmotic swelling property of sperms is a key indicator of sperm robustness and fertility potential [16].

Sunscreen creams play an important role in health

Sunscreen creams formulation have evolved over time and pharmaceutical formulations that enhance protection against UV radiation while minimizing toxic effects have been developed. Suncreams that contain titanium or zinc oxide nanoparticles have better spreadability on skin in comparison to those containing conventional titanium or zinc oxide particles, respectively. Suncreams containing zinc oxide nanoparticles and titanium dioxide nanoparticles confer a higher in vitro sun protection factor (SPF of 3.65 for ZnO nanoparticles and 4.93 for TiO₂ nanoparticles) as compared to that of sunscreen creams containing conventional zinc oxide particles (SPF = 2.90) and conventional titanium dioxide (SPF = 1.29) [17].

Nitroxide compounds have similarly shown promise as UV filters that have a potential of preventing photo-aging and photo-carcinogenesis. These are stable free radicals bearing an unpaired electron on the nitroxide (N–O) function included in an aromatic or aliphatic ring system.

In vitro studies on fibroblasts exposed to UV radiation demonstrated the production of Reactive Oxygen Species (ROS). These are responsible for a cascade of intracellular events that end at observable photo damage in skin cells. The increased testing and formulation of multiactive ingredients will not only enhance the protection of the skin from UV radiation but also scavenge reactive oxygen species generated from photo-decomposition of unstable UV-absorbers or of other ingredients in the formulation. This alternative development would strengthen the case for continued use of sunscreen creams [18].

Sunscreens can reflect, scatter or absorb UV radiation eg zinc oxide and titanium dioxide (inorganic) or they can just absorb UV radiation eg cinnamate and salicylate (organic). Sunscreen creams are formulated to protect against acute effects of solar UV radiation eg sunburn cell formation in the skin, cutaneous DNA damage, immunosuppression and reactivation of latent Herpes Simplex Virus. They also prevent chronic effects such as actinic keratoses and Squamous Cell Carcinoma and a potential of decreasing the incidence of Basal Cell Carcinoma. Long term application of sunscreen creams upto 8 years is known to prevent Squamous Cell Carcinoma following a study where it was applied to the head, neck, hands and forearms. Other related studies have revealed that sunscreen creams can reduce the risk of Cutaneous Malignant Melanoma. Despite mutagenicity observed in yeast cells exposed to titanium dioxide and irradiated with UV-B, there is neither sufficient evidence showing skin absorption of products containing titanium dioxide nor evidence of toxicity in man exposed through this route. Concerns have been raised regarding vitamin D deficiency states resulting from sunscreen use although it has been demonstrated that this would only occur in controlled scenarios but would not occur in real life because a fraction of the UV photons would still be transmitted through the sunscreen and that 0.5mg/cm² on average would be applied by people which is far less than the 2mg/cm² used in toxicity testing experiments. In addition, studies have shown that people who use sunscreens expose themselves to the sun longer than non-users further decreasing chances of vitamin D deficiency [19].

A study by Dominique [20] on the effects on sunscreen use showed that UV exposure reduced delayed type hypersensitivity, an indicator of immunity in the body. Importantly the use of a broad spectrum sunscreen reduced local UV-induced immunosuppression [20].

Albinism, a genetic defect that makes the body unable to produce or distribute melanin, a natural substance that gives color to your hair, skin, and iris of the eye can predispose patients to phototoxicity. Frequent use of suncreams is not an option requiring daily application especially in temperate regions like Sub-saharan Africa. An evaluation of the effects of a sunscreen formulation on the skin of albino hairless mice subjected to simulated solar light (SSL) in terms of morphological changes revealed effective protection against deleterious effects of light. This suggests that their use in special groups including albinos

may be beneficial in preventing skin damage and skin cancer associated with UV radiation from the sun [21].

Despite all concerns regarding the toxicity of titanium dioxide and zinc oxide nanoparticles being incorporated into sunscreen creams, there hasn't been any convincing evidence of its permeability into the skin. This is demonstrated by a summary of test results from different studies in the two tables below for Titanium dioxide and Zinc oxide respectively that show minimal to no penetration through the epidermis.

Table 1. Titanium dioxide skin penetration studies [22]

Study	Material + coating	Particle size	Design	Results
Tan et al, 1996	TiO ₂ . No coating specified	Not specified	Human skin, in vitro	No penetration into skin
Lademann et al, 1999	TiO ₂ Al ₂ O ₃ , stearic acid coated	150-170 nm	Human skin biopsy	Penetration into upper layers of stratum corneum; Approx. 1% of particles in ostium of follicle
European Union, 2000	TiO ₂ Anatase and rutile coating	14 nm-200µm	Human skin, tape stripping or biopsy; pig skin, in vitro	Penetration limited to stratum corneum
Pflucker et al, 2001	TiO ₂ SiO ₂ , Al ₂ O ₃ , SiO ₂ + Al ₂ O ₃ coating	10-100 nm	Human skin, in vitro	Penetration into upper layers of stratum corneum
Schulz et al, 2002	TiO ₂ SiO ₂ ± Al ₂ O ₃ coating	10-100 nm	Human skin biopsy	Particles in and on upper layers of stratum corneum
Gottbrath and Muller-Goymann, 2003	TiO ₂ No coating information	Not specified	Human skin, tape stripping	Particles in and on upper layers of stratum corneum
Menzel et al, 2004	TiO ₂ No coating information	45-150 nm	Pig skin, in vitro	Particles in stratum corneum; minimal penetration into stratum granulosum
Mavon et al, 2007	TiO ₂ SiO ₂ coated	20 nm	Human skin, in vitro	Penetration in upper layers of stratum corneum

Zinc oxide skin penetration studies

Table 2. Table showing Zinc Oxide skin penetration tests [22].

Study	Material + coating	Particle size	Design	Results
Pirot et al, 1996	ZnO No coating information	Not specified	Human skin, in vitro	0.36% Penetration in 72 h
European Union, 2003	ZnO	Not specified	Human non-psoriatic and psoriatic skin; pig skin, in vitro	No change in plasma zinc levels; in vitro, penetration <1% of dose; most ZnO recovered from stratum corneum
Cross et al, 2007	ZnO	15-30 nm	Human skin, in vitro	No penetration in epidermis or dermis; <0.03% of applied Zn recovered in stratum corneum

However these results are not conclusive because they failed to account for inter species variation as well as disruptions on the skin that could be traumatized or diseased. People who have been sunburned may have a tendency to apply sunscreen creams on the burnt skins hoping to prevent further effects of the sun. The physiological changes that occur on the skin after sun burns may alter permeability of the skin and may increase permeability of these compounds predisposing to potential toxicity. The above studies were carried out in controlled

situations and further studies may need to be carried out in real world scenarios taking into account varying times of exposure, thickness of skin in different anatomical surfaces which could receive the same amount of sun screen creams [22].

Conclusion

Sunscreen creams are applied on skin and may produce local exposure but application to the face, lips and around the eyes may also produce systemic exposure. Ultraviolet filters play an important role in protecting people against untoward effects of UV radiation. Sunscreen creams undergo rigorous safety evaluations prior to their marketing as well as being subjected to post marketing surveillance. The safety of titanium dioxide and zinc oxide in sunscreens remains controversial especially with current evidence suggesting that they are non-toxic, do not penetrate into or through normal or broken human skin, hence pose no risk to human health. The Threshold of Toxicological Concern (TTC) is a promising tool used to assess the safety of substances present at trace levels as well as minor ingredients of plant-derived substances which have been included in sun screen creams. In vitro toxicity testing can overestimate human systemic exposure to sun screen cream ingredients because of the absence of metabolism in cadaver skin or misclassification of skin residues which, in vivo, remain in the stratum corneum or hair follicle openings. These are outside the living skin. In general the safety assessment of these creams and their ingredients is based on science and their respective regulatory status including other issues, such as the ethics of animal testing. But there is consistent evidence showing that the sunscreen creams are safe and offer multiple benefits to quality of life and health of the consumer. However an international harmonization on the status and safety requirements of these creams needs to be established urgently given the progressive destruction of the ozone and hotter summers propelling increased use of these creams. Despite the controversies surrounding sun creams the benefits outweigh the risks currently and therefore should not be removed from our shops.

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If the decision is what is classified as 'Minor Revision' or 'Major Revision,' the author shall have 14 days to resubmit the revised manuscript.

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