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A review on the role of the pharmacist in a patient-centered healthcare system: Re-aligning healthcare to people's needs

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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

Universal Health Coverage and the Crucial Role of Pharmacists

Eric Koome & Nadia Butt

Universal Health Coverage (UHC) is based on all health-related sustainable development goals and has been adopted in a number of countries while others have plans to ensure that it is realized. UHC is geared towards ensuring that people have access to the use of curative, preventive, rehabilitative, as well as palliative medical services that are of superior quality and are effective without experiencing financial constraints.

World Health Organization Resolution of 1998 recognized health as a basic human right. This resolution is echoed in Chapter IV of the Constitution of Kenya which stipulates that every person is entitled to the highest attainable standard of health care services. In line with the constitution, UHC is envisaged in the Kenya Vision 2030 under the Social Pillar which aims at improving the quality of life for all the citizens via various programs in the health sector. This pillar seeks provision of affordable, equitable and quality healthcare to all Kenyans. The realization of UHC will go a long way in ensuring improved health and protecting citizens whose financial status is compromised.

The major objectives encompassing UHC include: ensuring that there is equity in access to health services, provision of quality health services and protecting people against the financial risk associated with health services. The above objectives of UHC are tailored towards ensuring that the health condition of citizens in any country is improved. The realization of these objectives is at the hands of different stakeholders including the government, insurance companies, non-governmental institutions as well as donors.

Medicines present a major challenge for UHC. In developing countries, pharmaceuticals consume 25-65% of both public and private spending on health care. According to data claims by Jubilee Insurance, pharmaceuticals in health sector take up to 40% of health expenditure in Kenya. Such statistics show the great role that pharmacists have in the health sector ranging from their involvement in manufacturing, procurement, distribution, and dispensing to the patients in various health facilities. In addition, Pharmacists are the custodians of knowledge in areas of drugs, supplements, medical devices among others. This autonomous expertise is required in hospital pharmacy, community pharmacy, regulatory control and drug management, pharmaceutical industry, research, training of other health workers and academia. The main objective is to ensure optimal drug therapy where pharmacists play a vital role across all sectors from preparation, control and

supply of pharmaceuticals (and non-pharmaceuticals) as well as providing information to prescribers and patients on these products.

The administrative roles of pharmacists include formulation of health and drug policies regarding selection, procurement as well as distribution of drugs. They provide drug-related information during the making of formularies and other guidelines in hospitals for cost-effective management of diseases. In hospital settings, the role of pharmacists is further amplified where they offer pharmaceutical care to patients by influencing drug selection and best patient drug regimens, monitoring therapeutic response and patient compliance, as well as recognize and report adverse drug reactions (ADRs). Moreover, they are at the center of drug procurement ensuring supply of high quality and cost-effective products. As members of Drugs and Therapeutic Committees in hospitals, pharmacists are key policy-makers ensuring rational selection and use of drugs and adherence to hospital formulary by prescribers. Formularies in hospitals are developed in an attempt to lower costs of healthcare to patients.

Community pharmacists are usually the first point of contact by patients before visiting a clinic or hospital. They are responsible for being primary healthcare units. In addition to their normal role of processing prescriptions and management of minor ailments; community pharmacists' care for patients by providing drug related information, counseling them on medication use and monitoring drug utilization. Moreover they participate in health promotion, administers vaccination and while some offer domiciliary services like for patients with Parkinson's disease.

Research is also carried out by pharmacists in order to introduce new drugs or improvement on existing ones in order to make them more effective in their use in treatment of different diseases. Lastly, pharmacists are important in the field of pharmacovigilance which entails assessment, detection, and preventions of ADRs and other post-marketing drug related problems.

It is clear that pharmacists form a key part in the realization of UHC. It is imperative that pharmacists are available in all hospitals, furthermore they are required for the strengthening of the regulation of pharmacy practice. In order to make stronger systems, we must engage in pursuing a higher academic level by introducing Pharm D in our mainstream curriculum. A more thorough curriculum

that allows pharmacists to tackle the challenges associated with the community sector. This will lead to a paradigm shift to a more patient centered pharmaceutical care and a well-defined role of pharmacists in Kenya and thus the success of UHC.

Bibliography

ifty-First World Health Assembly: Geneva, 11-16 May 1998; Resolutions and Decisions Annexes. WHA51-1998-REC-1-engapps.who.int/iris/bitstream/10665/258896/1/WHA51-1998-REC-1-eng.pdf

Elijah Matolo, Dr. (Sep 2018). How to reduce cost of medication in Kenya, standard news. Retrieved from

<https://www.standardmedia.co.ke/article/2001294761/how-to-reduce-cost-of-medication-in-kenya>

Republic of Kenya, (2010). The Constitution of Kenya, Government Printers. Nairobi. Retrieved from www.kenyalaw.org/lex/actview.xql?actid=Const2010

OECD (2015), "Pharmaceutical spending trends and future challenges", in Health at a Glance 2015: OECD Indicators, OECD Publishing, Paris. DOI: https://doi.org/10.1787/health_glance-2015-5-en

Republic of Kenya, (2015). Accelerating attainment of Universal Health Coverage: The Kenya Health Sector Strategic and Investment Plan 2014 - 2018. Ministry of Health.

In-Vitro Anticancer Efficacy of Kenyan *Ruellia prostrata* (Acanthaceae) Against Breast, Prostrate and Human Hepatocellular Carcinoma Cell Lines

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Abstract

Background: According to the World Health Organization, cancer is currently a global health problem and is projected to increase devastatingly by 70% in the next two decades. Reported toxicity and high economic burden of current conventional drugs has prompted research into evaluation of medicinal plants as alternative options in the management of cancer.

Objective: The objective of this study was to evaluate *in-vitro* anticancer properties of methanolic and aqueous extracts of *Ruellia prostrata* against breast, prostate and human hepatocellular carcinoma, *vis a vis* Vero (normal) cell line using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT). Cell proliferation assay was used to evaluate the antiproliferative potential for whole plant parts of *R. prostrata*.

Methods: The experiment was done in duplicate and data analyzed by miniTab software version 17.0 and Microsoft Excel-2010. It was noted that *R. prostrata* possesses anticancer activity in both methanolic and

aqueous extracts which were not statistically significant ($p > 0.05$). The methanolic extract showed the lowest proliferation against 4T1 (breast cancer cell line) with IC₅₀ value of 17.36 µg/mL, while the highest proliferation rate was generally observed in Vero (normal) cell line with IC₅₀ of 426.32 µg/mL. Prostate cancer (22RV1) and HCC cell lines (hepatocellular carcinoma) showed higher proliferation with IC₅₀ values of 228.75 and 168.60 µg/ml respectively. Aqueous extract on the other hand demonstrated lower anticancer activity compared to the methanolic extract, with IC₅₀ values of 393.67 µg/mL, 2691.32 µg/mL, 669000 µg/mL, 107.94 µg/mL, and 45.79 µg/mL against 4T1, DU145, HCC, 22RV1 and Vero cell lines respectively.

Results and Discussion: In Conclusion, it was noted that the methanolic extracts of *Ruellia prostrata* had the highest activity against breast cancer and prostate cancer cell lines. The activity observed could be related to the presence of identified phytochemicals. To the best of our knowledge we report anticancer potential of *R. prostrata* for the first time. Therefore, extracts of *R. prostrata* can be developed further as alternative options for management of cancers of the breast, prostate, and the liver.

Keywords: Cancer cell lines, Anticancer, Extracts, Proliferation, Phytochemicals

Introduction

Cancer is a leading cause of morbidity and mortality worldwide and failure of conventional chemotherapeutic agents to meet their expected demands highlights the need for new approaches of cancer management. Toxicity of chemotherapy and the general economic burden of the disease have been implicated in the ever increasing deaths from cancer [1].

A major portion of present pharmacological research is devoted to anticancer drug design customized to fit new molecular targets, achieve economic availability and enhance better safety standards [2]. The plant kingdom, however, is a huge potential source of chemical constituents with antitumor and cytotoxic activities. This has been attributed to the enormous propensity of plants, which synthesize a variety of structurally diverse bioactive compounds [3, 4].

Evidently, several conventional drugs used in cancer chemotherapy are derived from plant species. For example, taxol and taxanes which are isolated from *Taxus* species, vincristine and vinblastine which are isolated from *Catharanthus roseus* and camptothecin which is isolated from *Camptotheca acuminata* among others [5].

The rich and diverse plant kingdom in Kenya is likely to provide novel effective anticancer agents and hence, one of the best approaches in the search of anticancer agents from plant sources is the selection of plants based on available folkloric information [6].

Ruellia is a large genus of about 300 species. The species are distributed in Mexico and Brazil as the main centers of diversity, but the genus is common elsewhere throughout the neotropics, Madagascar, and mainland Africa. A few species also occur in Southeast Asia, Australia, and temperate regions of North America and South America. *Ruellia* is known for its medicinal and ornamental properties.

From Indian folkloric medicine, *R. prostrata* is claimed to possess anti-inflammatory activity of joint disorders of varied aetiology. This Indian species is also claimed to possess hypoglycaemic, contraceptive, anti-diuretic and anti-cancer activity against cancer of the epidermis [7]. *R. prostrata* has also been established to exhibit antidiabetic, contraceptive, anti-inflammatory, antioxidant, and antibacterial activity [7 - 10]. In as much as there is no documentation on ethnobotanical use of *R. prostrata* in Kenya [11], a study on extracts of *R. prostrata* found in Kenya, confirmed its antioxidant [12] and anti-inflammatory potential [9].

However, to our knowledge, no study has been carried out in Kenya to validate their cytotoxic activity. Here, we report *in-vitro* anticancer activity of Kenyan growing *R. prostrata* breast, prostate and human hepatocellular carcinoma cell

lines. The cytotoxicity activity was established using MTT colorimetric assay based on enzymatic activity of dehydrogenase enzymes on yellow water soluble substrate 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) into formazan. Formazan is an insoluble yellow colored product that is measured spectrophotometrically in an optical density reader [13, 14]. The enzyme activity responsible for production of formazan is directly proportional to the level of cell viability and inversely proportional to the level of cell inhibition [15, 16].

Materials and Methods

Sample collection, preparation and extraction

Whole plant parts of *R. prostrata* were collected from Machakos County, taxonomically identified and voucher specimen (Ref. no. UoN/2010/598) deposited at the Department of Botany Herbarium, University of Nairobi. The collected plant materials were washed using running tap water and dried under shade for two weeks before grinding using an electric mill. A hundred grams of finely ground plant powder was exhaustively extracted using methanol, filtered and concentrated in a rotary evaporator under reduced pressure (BUCHI R-200, Switzerland). Another batch of ground sample was boiled at 60°C for 30 minutes. The mixture was filtered, and the filtrate was dried by lyophilization using a freeze dryer (Modulyo Edwards freeze dryer).

Quantitative analysis of flavonoids and phenols

Flavonoids and phenols were quantified using established standard procedures as described [17, 18]. This was done given their reported significance in anticancer activity of medicinal plant extracts [19, 20].

Cell Culture

The cell lines used in the current study included: breast cancer (4T1), prostate cancer (DU145 & 22RV1), hepatocellular carcinoma (HCC) and Vero (normal) cell lines. The cell lines were maintained as monolayer cultures in RPMI 1640 supplemented with 10% heat inactivated fetal bovine serum (FBS), and 100µg/ml L-glutamine and treated with penicillin and streptomycin. The cells were incubated at 37°C in a humidified incubator at 5% CO₂.

Cell Treatment

Upon attainment of 70-100% confluence, the obtained cell monolayer was treated with 10mM trypsin (0.25% EDTA) and re-incubated for a further 10 minutes. 5mL of growth media was added to neutralize the effect of trypsin enzyme (Gibco, USA). Thereafter, cell density was determined using trypan blue exclusion method and $A \times DF \times 10^4$ formula was used; where A is the average cell counts per square and DF represents dilution factor. The cells were seeded independently in 96-well plates at 2×10^4 cells per well at a volume of 100µl and incubated at 5% CO₂ humidified incubator at 37°C for 24 hours. Treatment was done by

adding 50µl of the extract at 7 concentrations namely 1000.00µg mL⁻¹, 333.33µg mL⁻¹, 111.11µg mL⁻¹, 37.04µg mL⁻¹, 12.35µg mL⁻¹, 4.12µg mL⁻¹, 1.37µg mL⁻¹. They were then incubated in 5% CO₂ humidified environment at 37°C for 48 hours after which the MTT viability assay was carried out.

MTT Assay

In-vitro anticancer test was done using the tetrazolium3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye reduction assay [12]. After 48 hours of cell incubation, 5mg/ml of MTT was prepared and seeded into all wells of the plates at 10µl per well and incubated for a further 4 hours. The plates were emptied and replaced with 100µl of pure dimethyl sulphoxide (DMSO). The plates were mildly shaken at room temperature and the optical density (OD) determined at 560 nm using a microplate reader spectrophotometer. The percentage cytotoxicity was calculated using the following formula:

$$\text{Percentage cytotoxicity} = \left\{ \frac{\text{Control absorbance} - \text{Test absorbance}}{\text{Control absorbance}} \right\} \times 100.$$

Results and Discussion

Solvent extraction yields

The mean percentage extraction yields of crude extracts of *R. prostrata* are recorded in Table 1.

Table 1. Mean percentage (w/w) yields (n=3) of *R. prostrata* with different solvents.

Solvent	Extraction yield in %
Methanol	4.4± 0.55
Water	27.4± 0.69
Chloroform	1.3± 0.03
Pet. Ether	0.35± 0.03
E. Acetate	0.8± 0.01

Each of the yields were derived from a mass of 100g of crude plant powder. Aqueous *R. prostrata* extracts gave the highest crude extract yield (27.4%) while petroleum ether gave the lowest yield (0.35%). The results suggest that the major phytochemicals in *R. prostrata* are mostly high in polarity and soluble in water. As described [21], polar compounds are also easier to be extracted compared to non-polar compounds.

Quantitative analysis

Phenolic and flavonoid content from quantitative analysis is expressed in mg/mL and presented in Table 2.

Table 2. The total flavonoids and phenolic content in *R. prostrata*

Phytochemical content (mg/mL)	
Flavonoid	15.3 ± 0.82
Phenolic	1.3 ± 0.37

The results obtained from this study revealed that *R. prostrata* contained substantial proportions of flavonoids and phenolics. The percentage mean value of flavonoids

content was found to be highest (15 mg/mL) compared to phenolic which showed less concentration (1.3 mg/mL).

Different concentrations of methanolic and aqueous extracts of *R. prostrata* whole plant parts in concentration ranging from 1.37-1000 µg /mL were tested for their cytotoxicity activity against breast cancer (4T1), Prostate cancer DU145 & 22RV1), human hepatocellular carcinoma (HCC) and Vero cell lines (normal cell line) and results presented in the Figure 1 and Figure 2.

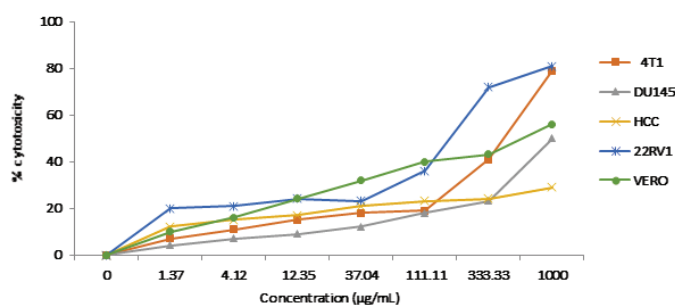


Figure 1. Anticancer activity of *Ruellia prostrata* (RPM) methanol extract on proliferation rates of 4T1, 22RV1, HCC, DU145 and VERO cell lines.

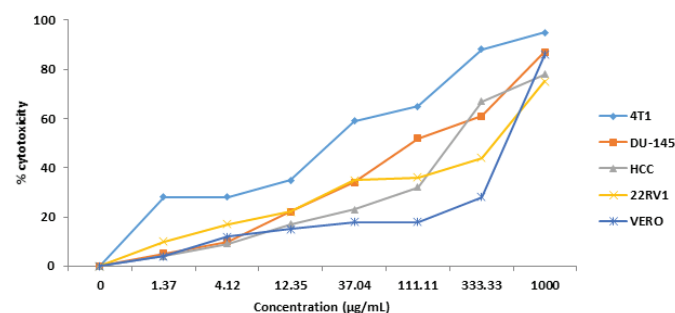


Figure 2. In vitro anticancer activity of aqueous *Ruellia prostrata* on selected cell lines

From the results presented, it was observed that aqueous and methanolic extracts of *R. prostrata* in different concentrations showed variable effects on cancerous and normal cell lines. The anticancer activity of the various concentrations of methanolic and aqueous extracts against breast, prostate and human hepatocellular carcinoma cell lines was not significantly different ($p > 0.05$). At the maximum concentration tested (1000µg/mL), the highest (95 %) cytotoxic activity was observed in methanolic extracts against 4T1 cell lines (figure 1), while the least (29 %) was from aqueous extract on HCC cell lines (Figure 2). Findings of this study showed that increasing the concentration of the extracts resulted in increased cytotoxic activity suggesting a concentration-dependent response.

The concentration required to inhibit 50% (IC₅₀) for both extracts are presented in Table 3. (Next page)

Table 3. IC₅₀ values for aqueous and methanolic *Ruellia*

prostrata extracts on selected cell lines.

IC₅₀ Values for Cancer Cell Lines in µg/mL

	4T1	DU145	HCC	22RV1	VERO
Type of extract					
Aqueous	393.67	2691.32	669000	107.94	45.79
Methanolic	17.36	96.49	168.60	228.75	426.32

Methanolic extract showed the lowest proliferation against 4T1 (breast cancer cell line) with IC₅₀ value of 17.36µg/mL, while the highest proliferation rate was generally observed in Vero (normal cell line) with IC₅₀ of 426.32µg/mL. Prostate cancer (22RV1) and HCC cell lines (hepatocellular carcinoma) showed higher proliferation with IC₅₀ values of 168.60 and 228.75µg/mL respectively. Water extracts on the other hand demonstrated a lower anticancer activity compared to the methanolic extracts with IC₅₀ values of 393.67µg/mL, 2691.32µg/mL, 669000µg/mL, 107.94µg/mL, and 45.79µg/mL against 4T1, DU145, HCC, 22RV1 and Vero cell lines respectively (Table 3). The higher IC₅₀ values of aqueous extract against the normal cell line (Vero cell line), suggests the methanol extract is safer than the aqueous extract on normal cells.

In a different study, the high anticancer activity of methanolic extracts of *Ruellia tuberosa* was reported against Ehrlich ascites carcinoma (EAC) tumor in mice (1). These findings are corresponding to our results as projected by the high activity obtained against 4T1 (breast cancer), and DU145. [22], also noted that dichloromethane extract of *Ruellia squarrosa* demonstrated anticancer activity with 58% inhibition against human prostate cancer (PC3) cell line with IC₅₀ value of 15.4 µg/mL. The IC₅₀ value is a parameter to measure level of cytotoxicity for plant crude extracts. The recommended IC₅₀ as established by the US National Cancer Institute (NCI), is an IC₅₀ value less than 30 µg/ml [23]. Thus, based on National Cancer Institute recommendation's, the results of *in-vitro* anticancer screening showed that out of two extracts tested, only methanolic extracts of *R. prostrata* showed higher cytotoxic activity against breast cancer cell lines (4T1).

As described [24] medicinal plants have many secondary metabolites with significant bioactivities, including anticancer, antioxidant, anti-inflammatory and anticancer properties. The anticancer properties of the medicinal plants are due to the presence of phytochemicals such as tannins, flavonoids, alkaloids, terpenoids, phlobatannins and reducing sugars [25]. Phytochemical analysis of *R. prostrata* whole plant parts tested positive for flavonoids, saponins, glycosides, phenolics, and terpenoids [12].

The results of the current study also showed substantial amounts of phenolic and flavonoids in *R. prostrata* extracts. The phenolic and flavonoids present in the plant extracts could be a key contributing factor for the observed anticancer activity. Other studies have also linked high phenolic content of *Ruellia* species to its anti-proliferative potential, [19, 20]. Flavonoids are phenolic compounds which largely include anthoxanthins (flavanones, flavanols,

chalcones and flavones) anthocyanins, leucoanthine and flavonoidal alkaloids [26].

Conclusion

The findings of this study showed that, aqueous and methanolic extracts of *R. prostrata* have a potential anticancer activity against cancer of breast, prostate and human hepatocellular carcinoma. It is suggested that flavonoids and phenols identified could be responsible for the observed anticancer activity. Therefore, further research on extracts from this plant should be done in order to evaluate maximum potential of *R. prostrata* in management of cancer. Further studies to isolate and characterize the bioactive constituents from the plant with a view of identification of lead compounds for novel anticancer drug development are required.

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Conflict of Interest

Authors have declared no conflict of Interest.

References

1. Nagarjuna R, Nagarathna PKM, Divya M. Evaluation of anti-cancer activity of *Ruellia tuberosa* on EAC induced mammary tumor. *International Journal of Pharmacology and Toxicology*. 2013; 1(2):36-42.
2. Xia M, Wang D, Wang M. Dracorhodin perchlorate induces apoptosis via activation of caspase and generation of reactive oxygen species. *Journal of PharmacolSci*. 2004; 95: 273-83.
3. Kim JB, Koo HN, Joeng HJ. Introduction of apoptosis by Korean medicine Gagam-whanglyunhaedoktang through activation of capase-3 in human leukemia cell line, HL-60 cells. *Journal of Pharmaceutical Sciences*. 2005; 97.
4. Inda MA, Radhika S, Motiwale L, Rao, KV. Quercetin: antitumor activity and pharmacological manipulations for increased therapeutic gains. *Indian Journal of Pharmaceutical Sciences*. 2006; 68(4): 465.
5. Costa-Lotufo LV, Khan MT, Ather A, Wilke DV, Jimenez PC, Pessoa C, de Moraes MO. Studies of the anticancer potential of plants used in Bangladeshi folk medicine. *Journal of Ethnopharmacology*. 2005; 99(1): 21-30.
6. Kintzios SE. Terrestrial plant-derived anticancer agents and plant species used in anticancer research. *Critical reviews in plant sciences*. 2006; 25(2): 79-113.
7. Unny R, Cauwan A, Joshi Y, Dobhai M, Gupta R. A revas the source of contraceptive principles.iew on potentiality of medicinal plants. *International Journal of phytotherapy and phytopharmacology*. 2003;

- 10(2-3):233-260.
8. Kalia A, Borar R, Thakar J. Anti-oxidant potential fractionation from methanol extract of aerial parts of *Ruellia prostrata* poir (Acanthaceae). *International Journal of Pharmaceutical Sciences and Research*. 2011; 2(4):1015-1022.
 9. Jeyachandran RB, Cindrella L. In vitro antibacterial activity of three Indian medicinal plants. *International Journal of Biological Technology*. 2010; (1):103-106.
 10. Kokwaro JO. Medicinal plants of East Africa Kenya: East Africa Literature Bureau. Genus *Ruellia*: pharmacological and phytochemical Importance in ethnopharmacology. 2009.
 11. Wangia O, Jennifer A, Francis W, Patrick G, Cheruiyot K, Japheth K. Anti-oxidant activity of aqueous and organic extracts from Kenyan *Ruellia prostrata*. *IJPSR*, 2017;8(3), 1282-1286.
 12. Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *Journal of immunological methods*. 1983;65(1-2), 55-63.
 13. Patel S, Gheewala N, Suthar A, Shah A. In-vitro cytotoxicity activity of *Solanum nigrum* extract against Hela cell line and Vero cell line. *International journal of pharmacy and pharmaceutical sciences*. 2009; 1(1):38-46.
 14. Mantani N, Imanishi N, Kawamata H, Terasawa K, Ochiai H. Inhibitory effect of (+)-catechin on the growth of influenza A/PR/8 virus in MDCK cells. *Planta Med*, 2001;67, 240-243.
 15. Berridge MV, Herst PM, Tan, AS. Tetrazolium dyes as tools in cell biology: new insights into their cellular reduction. *Biotechnology annual review*, 2005; 11:127-152.
 16. Rasineni GK, Siddavattam D, Reddy AR. Free radical quenching activity and polyphenols in three species of *Coleus*. *Journal of Medicinal Plants Research*. 2008; 2(10):285-291.
 17. Otang W, Grierson D, Ndip R. Phytochemical studies and antioxidant activity of two South African medicinal plants traditionally used for the management of opportunistic fungal infections in HIV/AIDS patients. *Alter. Med*. 2012; 12(10):12-43.
 18. Balasundram N, Sundram K, Samman S. Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food chemistry*. 2006; 99(1):191-203.
 19. Chu YF, Sun J Wu XZ, Liu RH. Antioxidant and antiproliferative activities of common vegetables. *Journal of Agricultural and Food Chemistry*. 2002; 50: 6910-6916.
 20. Pin KY, Chuah AL, Rashih AA, Mazura MP, Fadzureena J, Vimala S, Rasadah M.A. Antioxidant and anti-inflammatory activities of extracts of betel leaves (*Piper betle*) from solvents with different polarities. *J. Trop. For. Sci*. 2010; 22: 448-455.
 21. Khurram A, Muhammad U, Bashir A. Anticancer activity of *Ruellia squarrosa* against human prostate cancer cell line. *Bangladesh Journal of Pharmacology*. 2015; 10, 97-99.
 22. Suffness M, Pezzuto JM (). Assays related to cancer drug discovery. In: Hostettmann K, (ed.). *Methods in Plant Biochemistry: Assay for Bioactivity*. Vol, London: Academic Press, pp. 1990; 6:71-133.
 23. Wu J, Wu Y, Yang BB. Anticancer activity of *Hemsleya amabilis* extract. *Life Sci*, 2002; 71 (18):2161-2170.
 24. Balakrishnan N, Sharma A. Preliminary phytochemical and pharmacological activities of *Luffa cylindrical* fruit. *Asian J Pharm Clin Res*. 2013; 6, 851-856.
 25. Houghton, P. Chromatography of the chromone and flavonoid alkaloids. *Journal of Chromatography*, 2002; 75-84.

Prevalence of Nutritional and Herbal Medicine use and its Impact on Warfarin Dose and Response in a Tertiary Referral Hospital in Kenya

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Abstract

Background: Warfarin is the most extensively prescribed oral anticoagulant drug in Kenya and the rest of the world,

owing to its demonstrated efficacy and affordability. Dosing and the response to warfarin are complicated by the fact that it is affected by nutrition status as well as commonly used herbal products.

Objective: To determine the prevalence of nutritional and herbal medicine use and its impact on warfarin dose and response among outpatients on anticoagulation therapy.

Study Area and Setting: Kenyatta National Hospital Anticoagulation Clinics.

Study Designs: Cross-sectional study.

Participants and Sample sizes: One hundred and eighty patients aged ≥ 18 years, who voluntarily signed informed consent to participate. Patients had to be on long term warfarin therapy (≥ 28 days), did not suffer from uncontrolled hypertension, peptic ulcer, and inherited coagulopathies or liver diseases. Mentally challenged patients and pregnant women were excluded.

Methods: The participants' clinical data such as details of sociodemographic characteristics and dietary habits such as type of food consumed, frequency of consumption, herbal and nutritional supplementation were obtained through direct patient interviews. The data on clinical indication and warfarin doses were acquired from patients' medical records. Warfarin response was determined by measurements of international normalized ratios (INRs), whose therapeutic range was set at 2-3 as recommended in the international guidelines.

Data Management: Data was analyzed using IBM Statistical Package for Social Sciences version 23. Frequencies were done to describe the prevalence of use of the nutritional and herbal substances. Student t-test and Chi-square tests were used to determine the strength of associations between warfarin maintenance doses and consumption of various foods or nutritional supplements as well as INR therapeutic levels, while setting the threshold for statistical significance at $p \leq 0.05$.

Results: Patients were generally middle aged at 43.4 (± 13.2) years, and majority, 77.0% ($n=138$) were females and in the 3rd to 5th decades (55.5%) of their lives. The median duration of warfarin therapy was 753 (range 31-11433) days. The mean maintenance dose of warfarin was 6.17 ± 2.75 mg per day. The prevalence of use of garlic and ginger herbal medicine was 18.9% and 12.2%, respectively. Majority of patients (70%) were consuming vegetables and fruits for 3-7 times in a week. Dietary and herbal medicine use did not significantly impact on warfarin doses and level of anticoagulation ($P > 0.05$).

Conclusion: The prevalence of herbal medicine use among the patients on long term warfarin therapy is low. Dietary habits did not affect warfarin dose and response. Similar correlation studies with the inclusion of conventional drugs and comorbidities may improve warfarin dosing and determine anticoagulation response among patients.

Keywords: Anticoagulation, herbal medicine use, nutritional supplements, warfarin response, warfarin dose, Kenya.

Introduction

Warfarin interacts with many commonly used medicines and some foods when co-administered [1]. Studies have indicated that the pharmacokinetics or pharmacodynamics effects of warfarin may be altered by consumption of some foods or herbal medicine [2]. The interactions observed may necessitate warfarin dose titrations or cause harmful consequences ranging from minor changes in international normalized ratios (INRs) to fatal effects such as gastrointestinal haemorrhage [3] or other forms of bleeding [4].

Some foods such as green leafy vegetables have been reported to interact with warfarin [5]. Furthermore, foods that contains large quantities of vitamin K reduce the anticoagulant effects of warfarin [1]. Warfarin also interacts with many herbs such as Ginkgo, Ginseng, Ginger and Garlic, when supplemented in the diet [6]. Similar effects have been reported with starflower oil or fish oils and St. John's Wort [7] as well as cranberry juice [8,9]. These products may necessitate lowering of warfarin dose as they are known to increase bleeding episodes in patients taking warfarin (10). As such, studies have recommended that healthcare workers and patients be made aware of these interactions for optimal anticoagulation control [5].

Despite its effectiveness, dosing of warfarin is complex because it is known to interact with many commonly-used herbs and some foods [1]. In addition, warfarin has a narrow therapeutic index and hence high propensity to cause drug-food interactions. Consequently, in order to optimize the therapeutic effect, especially in patients who are taking herbs or certain foods, without risking dangerous side effects such as bleeding, close monitoring of the degree of anticoagulation is required [11] by frequent blood testing for the INRs [12,13]. As such patients should be screened for use of herbs or certain foods before initiating therapy so as to achieve optimal anticoagulation. Information on the effects of use of some foods and herbs among patients on warfarin therapy would reduce healthcare costs associated with the management of the disease [14] through patients advice and optimal anticoagulation. The magnitude of utilization of the various dietary intake as well as the nutritional remedies requires to be estimated.

Methods

Study Design and Area

This was a cross-sectional study carried out at Kenyatta National Hospital (KNH) from January 2018 to December 2018. KNH is the largest teaching and referral hospital in Kenya. The study was conducted among adult outpatients on long term warfarin therapy at the specialized anticoagulation clinics. These clinics are the focal points for all patients requiring coagulation management at the hospital including those who have been discharged at the referrals from peripheral health facilities. The clinics comprised of cardiothoracic surgery, haemato-oncology as well as cardiac. The sites formed the ideal catchment area for the study population.

Study Population

Patients' aged ≥ 18 years on warfarin and undergoing long term anticoagulation management at the specialized clinics, were eligible. Patients who switched to other treatments such as rivaroxaban and fondaparinux or were advised not to take warfarin by their physicians at the time of the study were not entitled to participate. Patients who were not adhering to warfarin therapy were not eligible. Healthy volunteers, pregnant mothers and mentally challenged patients were also excluded.

Sample Size and Sampling Method

The primary outcome was the prevalence of herbal medicine use among patients with chronic diseases. Related studies have shown varying prevalence of use of herbal supplements in such patients. For instance, previous studies had indicated that the prevalence of herbal medicine use among patients on chronic diseases such as diabetes mellitus was at 7.2% [15]. In USA, the prevalence of use of herbal medicine among patients on warfarin anticoagulation therapy was at 17% [16]. Using the average (12.1%) of the two prevalence and related equation [17] for estimation of sample size for such epidemiological surveys, a minimum sample of 163 participants was calculated. However, a 10% was added to cater for the data losses to get a sample size of least 180 participants. Convenient sampling was used to recruit participants until the number required was achieved.

Study Methods

Study approval under reference number KNH-ERC/A/569 was granted by Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH/UoN-ERC). Authority to conduct research at the anticoagulation clinics was also approved by the respective departments before commencement of the study.

Participants were taken through the screening for eligibility and then detailed consenting process informing them about the study. The eligible participants signed the informed consent after which they were taken through the questionnaire to capture their demographic characteristics including age, weight, occupation, marital status, denomination, smoking and alcohol consumption status. Patients were also interviewed on the details of type of diet and the frequency of consumption per week as well as information on use of herbal and nutritional supplements. The nutritional and herbal products assessed included Vitamins E, K and C as well as garlic, ginger, red clover, sweet clover, St. John's Wort, glucosamine & chondroitin, Coenzyme Q10, alfalfa, aloe vera gel or Ginkgo biloba extracts. Information which the patients could not provide such as the clinical indication of warfarin therapy, doses and duration of use were retrieved from the medical records and medication charts. To determine the level of response to warfarin therapy, venous blood samples were drawn for the determination of INRs at UoN's Department of Haematology and Blood Transfusion Laboratory.

Therapeutic response of warfarin was assumed when INR was in the range of 2-3 as recommended in international guidelines [18].

Data Entry and Statistical Analysis

A database, resembling the questionnaire, was created using the IBM Statistical Package for Social Science version 23 computer software, where all the raw data was entered, cleaned and analyzed. Each questionnaire had a unique alphanumeric number which was linked to the database to avoid confusion and duplication of data. Preliminary analysis was done by determining the distribution structure of the variables so as to eliminate the outliers or the unusually entered values. Frequencies were then run for socio-demographic characteristics such as participants' age, gender, body mass index, occupation and marital status as well as the nutritional and herbal medicine use. Proportions were computed for the frequencies of consumption of various food types as well as the outcome variable of the INRs.

Associations were done between the predictor variables (frequency of consumption of foods, herbal medicine use) and the outcome variables (warfarin maintenance doses and level of INRs) using students t-tests and Pearson's or Spearman's correlation tests. P-values and Chi square tests were used to estimate the strength of association between predictor and outcome variables. The threshold for statistical significance was set at $P \leq 0.05$ with values whose $p \leq 0.05$ being considered statistically significant.

Results

A total of two hundred and nine participants were screened. However, data were analyzed from 180 participants because twenty-nine were not eligible due to: age < 18 years ($n=2$), declined to participate ($n=5$), missing data in files ($n=15$) and non-adhering to warfarin ($n=7$).

The sociodemographic characteristics of the study population are presented in Table 1.

Table 1. Characteristics of the Study Participants (N=180)

Variable	Category	Frequency (N=180)	Mean (%)
Sex	Male	42	23.0
	Female	138	77.0
Age categories (years)	19-30	31	17.2
	31-50	100	55.5
	51-64	37	20.6
	65 and above	12	6.7
Mean Age(\pm SD) years; Range		43.4(\pm 13.2); 19-87	
Body Mass Index	≤ 25	58	32.2
	> 25	90	50.0
	Missing data	32	17.8
Marital status	Single	39	22.0
	Married	118	66.0
	Divorced	11	6.0
	Widowed	12	7.0

Employment status	Unemployed	55	31.0
	Salaried	53	29.0
	Self employed	64	36.0
	Student	8	4.0
Highest academic level	College/ University	35	19.0
	Secondary	81	45.0
	Primary	41	23.0
	Non-formal	23	13.0
Clinical indications of Warfarin	Heart Related Diseases	75	41.7
	VTEs	101	56.1
	Both Heart Disorders and VTEs	4	2.2
Doses of Warfarin Prescribed	Mean initial dose (mg) (SD)	6.03 (SD±4.90)	
	Mean maintenance dose (mg)(SD)	6.17 (SD±2.75)	
Duration of Warfarin Therapy(Days)	Mean(range)	753 (31-11433)	

Key: SD Standard Deviation; VTEs-Venous Thromboembolic Events

The mean age of the study participants was 43.4 (±13.2), with a range 19-87 years. Approximately three-quarters of the study participants were females and two-thirds were married. More than half (55.5%) were aged between 31-50 years and half had exceeded their ideal body weights. Patients had been on warfarin for a median duration for approximately two years. The mean initial and maintenance daily warfarin doses were 6.03 mg (±4.90) and 6.17 mg (±2.75), respectively. The main clinical indication for anticoagulation was VTEs at 56.1% (Table 1).

Table 2. Prevalence of nutritional and Herbal Supplements in the Study Population (N=180)

Nutritional supplements and herbal preparation	Use	Frequency (n)	Percentage
Vitamin E (Greater than 400 IU per day)	No	179	99.4
	Yes	1	0.6
Vitamin C (greater than 500 mg per day)	No	177	98.3
	Yes	3	1.7
Vitamin K supplements	No	178	98.9
	Yes	2	1.1
Garlic herbal	No	146	81.1
	Yes	34	18.9
Ginger herbal	No	158	87.8
	Yes	22	12.2
Green tea herbal	No	179	99.4
	Yes	1	0.6

Approximately ninety percent of the study patients were not using herbal or nutritional supplements which are likely to interact with warfarin. However, 18.9 % and 12.2 % of the study participants were using garlic and ginger, respectively. Additionally, none of the patients was using supplements such as red clover, sweet clover, St. John's Wort, glucosamine & chondroitin, Coenzyme Q10, alfalfa, aloe vera gel or Ginkgo biloba extracts which were investigated in the study (Table 2).

Table 3. Types and Frequency of Dietary intake by the Study Patients (N=180)

Dietary Type	Frequency of Consumption	n	Percentage
Vegetables (N=135)	<3 Times a Week	31	23.0
	3-7 Times a Week	102	75.6
	>7 Times a Week	2	1.5
Proteins (N=78)	<3 Times a Week	21	26.9
	3-7 Times a Week	56	71.8
	>7 Times a Week	1	1.3
Carbohydrates (N=73)	<3 Times a Week	7	9.6
	3-7 Times a Week	60	82.2
	>7 Times a Week	6	8.2
Fruits (N=124)	<3 Times a Week	19	15.3
	3-7 Times a Week	103	83.1
	>7 Times a Week	2	1.6

Most of the patients were moderating consumptions of various food types as over 70% were consuming either food type (vegetables, proteins, carbohydrates or fruits) for 3-7 times per week. Higher frequencies of intake of any food type for >7 times per week were rare (Table 3).

Associations between the frequencies of consumption of various food types as well as herbal supplements and the mean daily maintenance doses of warfarin across the clinical conditions of the patient are shown in Table 4.

Table 4: Associations between frequency of consumptions of food types, herbal supplements and Mean maintenance doses of warfarin across the clinical conditions.

Clinical Condition	Consumption	n	Mean Warfarin maintenance dose,	Group Difference
Fruits				
Heart Diseases	<3 Times a Week	12	5.20±1.9	$t_{(57)}=-0.99$; P=0.3284
	3 Times and above /Week	47	5.78±1.8	
	VTEs	<3 Times a Week	9	
	3 Times and above /Week	58	6.63±3.0	$t_{(65)}=-0.96$; P=0.3390
Vegetables				
Heart Diseases	<3 Times a Week	15	6.21±1.7	$t_{(64)}=1.40$; P=0.1665
	3 Times and above /Week	51	5.46±1.8	
	VTEs	<3 Times a Week	17	
	3 Times and above /Week	54	6.47±2.5	$t_{(69)}=-0.23$; P=0.8181
Proteins				
Heart Diseases	<3 Times a Week	12	5.40±1.3	$t_{(35)}=-0.07$; P=0.9459
	3 Times and above /Week	25	5.44±1.8	
	VTEs	<3 Times a Week	10	
	3 Times and above /Week	33	6.33±2.5	$t_{(41)}=-0.83$; P=0.4116
Carbohydrates				
Heart Diseases	<3 Times a Week	3	5.42±1.9	$t_{(31)}=0.36$; P=0.7191
	3 Times and above /Week	30	5.08±1.5	
	VTEs	<3 Times a Week	4	
	3 Times and above /Week	38	6.37±2.3	$t_{(40)}=-1.67$; P=0.1028
Garlic Supplements				
Heart Diseases	No	64	5.66±2.1	$t_{(75)}=0.14$; P=0.8898
	Yes	13	5.57±2.1	
VTEs	No	84	6.11±2.6	$t_{(103)}=-0.44$; P=0.6597
	Yes	21	6.39±2.8	

Ginger supplements				
Heart Diseases	No	68	5.69±2.1	$t_{(75)}=0.57$; P=0.5687
	Yes	9	5.27±1.6	
VTEs	No	92	6.17±2.6	$t_{(103)}=-0.01$; P=0.9925
	Yes	13	6.17±2.6	

Key: SD-Standard Deviation; t- Student-t-test; VTEs-Venous thromboembolic Events

The frequency of consumption of the various food types did not statistically significantly impact on warfarin maintenance doses ($P > 0.05$). However, patients consuming vegetables at varying frequencies per week required higher warfarin maintenance doses than other category of foods across the clinical conditions. In addition, patients suffering from VTEs and consuming various food types for 3 or more times per week required slightly higher mean warfarin maintenance doses per day compared to those presenting with heart diseases (Table 4).

There were no statistically significant associations between consumption of garlic and ginger supplements with warfarin maintenance doses ($P > 0.05$). However, participants with VTEs and using either of the supplements required slightly higher maintenance doses than their counterparts suffering from heart diseases (Table 4).

Some foods may also interact with warfarin and thereby affect its response, in terms of the measured INRs. As such, associations between frequency of consumption of foods and the level of INRs were determined.

Table 5. Association between the frequency of consumption of food types, nutritional supplements and Level of INRs

Type of Food/Supplement	Consumption	INR Range			Group Difference
		<2 n (%)	-3 n (%)	3 n (%)	
Fruits	<3 Times a Week	9(52.9)	4(23.5)	4(23.5)	$\chi^2_{(2,116)}=1.63$; P=0.4417
	3 Times and above /Week	46(46.5) 3	8(38.4)	15(15.2)	
Vegetables	<3 Times a Week	15(55.6) 7	(25.9) 5	(18.5)	$\chi^2_{(2,123)}=1.27$; P=0.5308
	3 Times and above /Week	46(47.9) 3	6(37.5)	14(14.6)	
Proteins	<3 Times a Week	9(47.4)	6(31.6)	4(21.1)	$\chi^2_{(2,72)}=1.63$; P=0.4418
	3 Times and above /Week	23(43.4) 2	4(45.3)	6(11.3)	
Carbohydrates	<3 Times a Week	3(50.0)	2(33.3)	1(16.7)	$\chi^2_{(2,65)}=0.38$; P=0.8268
	3 Times and above /Week	27(45.8) 2	6(44.1)	6(10.2)	
Garlic herbal preparations	No 6	5(48.1%) 4	7(34.8%) 2	3(17.0%)	$\chi^2_{(2,164)}=0.80$; P=0.6695
	Yes	15(51.7%)	11(37.9%)	3(10.3%)	
Ginger herbal preparations	No 7	0(48.3%)	52(35.9%)	23(15.9%)	$\chi^2_{(2,164)}=0.15$; P=0.9266
	Yes	10(52.6%)	6(31.6%) 3	(15.8%)	

Key: INRs-International Normalized Ratio; χ^2 -Chi-Square

There were no statistically significant associations between the frequency of consumption of various food types and the patients' level of INRs ($P > 0.05$). The proportions of patients with therapeutic response to warfarin therapy remained below 40% regardless of the frequency of consumption of any particular food type (Tables 5).

Approximately a third of the patients had INR of 2-3 across the use of the nutritional supplements. Additionally, less than 20% were over-anticoagulated ($INR > 3$) while almost half were under-anticoagulated ($INR < 2$). However, there

were no statistically significant associations between the use of various nutritional supplements and level of INRs ($p > 0.05$) (Table 5).

Discussion

The present study explored the prevalence and relationship between consumption of foods, nutritional supplements and herbal remedies versus warfarin response as measured by maintenance dose requirements and level of INRs. The prevalence of herbal products use was low as almost a fifth (18.9 %) and 12.2 % of our study population was using garlic and ginger supplements, respectively. Studies have indicated varying prevalence of use of herbal products among patients on warfarin anticoagulation. For example, in USA, the prevalence of use of herbal medicines among similar patient population was 17% (16). Related studies have reported higher prevalence of up to 50% [19].

Several herbal supplements have been implicated in the action and response to warfarin therapy [20–23]. For instance, use of ginger [22] and garlic [23] have been associated with over-anticoagulation in patients using vitamin K antagonists. Another study indicated that users of herbal remedies were more likely to have INRs outside range than non-users [19]. Despite their consumption by few patients in our study, there were no statistically significant associations between their use and warfarin maintenance doses as well as the response as measured by the level of INRs. Perhaps the proportions of patients using the herbal supplements were relatively small to elicit statistically significant associations with warfarin response. There is also a possibility that the previous studies done on patients' knowledge on anticoagulation [24,25] and adherence [26] in the same study setting had significant improvement on the dietary measures to undertake to improve on warfarin anticoagulation therapy.

Studies have indicated that some diets may interact with warfarin [27–29] and their frequency of consumption among patients using warfarin is important for counseling purposes. In particular, frequent consumption of vegetables and fruits with high levels of vitamin K, such as green leafy vegetables, may interact with warfarin necessitating higher warfarin maintenance doses. Although there were no statistically significant associations between the frequency of consumption of various food types and warfarin doses, the data revealed that patients with VTEs and taking various food types for more than three times per week required higher mean warfarin maintenance doses. This suggested that there were possible minor interactions between the various food types and warfarin.

Generally, compared to other food types, patients who were taking vegetables at varying intervals per week, required higher warfarin maintenance doses across the clinical indications of warfarin anticoagulation. Most green leafy vegetables contain vitamin K, which is an antagonist to the action of warfarin. As such, patients consuming high levels of green leafy vegetables were likely to require higher warfarin maintenance doses to achieve sufficient anticoagu-

lation. This may explain why patients who were regularly consuming vegetables generally required higher warfarin doses than the ones taking other food types.

It is unclear why patients with VTEs and consuming garlic or ginger supplements required slightly higher warfarin maintenance doses than their counterparts suffering from heart diseases (>6.2 vs. <5.6 mg per day). Probably these were the general findings for patients with VTEs. Additionally, the frequencies of their consumption and the quantities consumed thereof were not measured to assess the degree of any possible clinical significance with warfarin maintenance doses as well as level of anticoagulation. It is possible that the quantities consumed as well as the frequencies of consumption were not significantly impacting on warfarin maintenance doses and the level of anticoagulation.

Herbal supplements such as ginkgo biloba [21,23] and ginseng [23] as well as red clover, St John's Wort, alfalfa, aloe vera, vitamin C, E and K have been shown to interact with warfarin thereby producing varying response but the use of these products among our study patients was infrequent. As such, there were no statistically significant differences with warfarin maintenance doses or the response as measured by INRs. Besides, patients may have forgotten to give adequate information because the data collected relied upon recalling on their use of herbal remedies. However, it is worth noting that use of herbal remedies is increasingly becoming common in developing countries among patients with chronic diseases [30] and therefore, this finding should not be underestimated.

The major limitation in this study is that data on nutritional and herbal medicine use was collected through direct patients' interviews and the participants could have overrated or underrated their experiences.

Conclusion and Recommendations

The frequency of herbal medicine use among patients on long term warfarin therapy was less than 20%. There were no statistically significant associations between foods, nutritional and herbal supplements with warfarin dosing and response among patients on anticoagulation therapy. Further studies should correlate other conventional drugs and comorbidities with warfarin doses as well as response.

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Author Contributions

DN Conceptualized the idea and wrote the proposal with the help of GO, AN and EA. DN collected the data. DN and AK analyzed data. AN and EA assisted in interpretation of the data. All authors reviewed the manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

1. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165(10):1095–1106.
2. Choi S, Oh D-S, Jerng UM. A systematic review of the pharmacokinetic and pharmacodynamic interactions of herbal medicine with warfarin. *PLoS One.* 2017;12(8):e0182794.
3. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug–drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *Can Med Assoc J.* 2007;177(4):347–351.
4. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. *Am J Med.* 2000;109(6):481–488.
5. Pham DQ, Pham AQ. Interaction potential between cranberry juice and warfarin. *Am J Health Syst Pharm.* 2007;64(5):490–494.
6. Lininger SW. AZ guide to drug-herb-vitamin interactions: how to improve your health and avoid problems when using common medications and natural supplements together. Three Rivers Press (CA); 1999.
7. Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of Warfarin-Related Bleeding Events and Supratherapeutic International Normalized Ratios Associated with Complementary and Alternative Medicine: A Longitudinal Analysis. *Pharmacotherapy.* 2007 Sep;27(9):1237–47.
8. Aston JL, Lodolce AE, Shapiro NL. Interaction between warfarin and cranberry juice. *Pharmacother J Hum Pharmacol Drug Ther.* 2006;26(9):1314–1319.
9. Suvarna R, Pirmohamed M, Henderson L. Drug point: Possible interaction between warfarin and cranberry juice. *BMJ.* 2003;327(7429):1454.
10. Leite PM, Martins MAP, Castilho RO. Review on mechanisms and interactions in concomitant use of herbs and warfarin therapy. *Biomed Pharmacother.* 2016;83:14–21.
11. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy1. *J Am Coll Cardiol.* 2003;41(9):1633–1652.
12. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E, et al. The pharmacology and management of the vitamin K antagonists. *Chest.* 2004;126(suppl 3):204S–233S.
13. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants:

- an update. *J Thromb Thrombolysis*. 2011 Feb 27;31(3):326–43.
14. Moura C, Prado N, Acurcio F. Potential drug-drug interactions associated with prolonged stays in the intensive care unit. *Clin Drug Investig*. 2011;31(5):309–316.
 15. Elsa OM, Kuria K, Nyamu D, Mwangangi E. Utilization of Herbal Medicines among Diabetic Patients Attending Kenyatta National Hospital Outpatient Clinic. *J Complement Altern Med Res*. 2017;1–18.
 16. Zuckerman IH, Steinberger EK, Ryder PT, Haines S. Herbal Product Use Among Anticoagulation Patients. *Am J Health Syst Pharm*. 2002;59(4):379.
 17. Barlett JE, Kotrlik JW, Higgins CC. Organizational research: Determining appropriate sample size in survey research. *Inf Technol Learn Perform J*. 2001;19(1):43.
 18. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2):e44S–e88S.
 19. Chan H-T, So L-T, Li S-W, Siu C-W, Lau C-P, Tse H-F. Effect of herbal consumption on time in therapeutic range of warfarin therapy in patients with atrial fibrillation. *J Cardiovasc Pharmacol*. 2011;58(1):87–90.
 20. Jiang X, Blair EY, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic-pharmacodynamic modeling approach. *J Clin Pharmacol*. 2006;46(11):1370–1378.
 21. Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol*. 2005;59(4):425–432.
 22. Krüth P, Brosi E, Fux R, Mörike K, Gleiter CH. Ginger-associated overanticoagulation by phenprocoumon. *Ann Pharmacother*. 2004;38(2):257–260.
 23. Vaes LP, Chyka PA. Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: nature of the evidence. *Ann Pharmacother*. 2000;34(12):1478–1482.
 24. Mariita K, Nyamu DG, Maina CK, Karimi PN, Menge TB. Patient factors impacting on oral anticoagulation therapy among adult outpatients in a Kenyan referral hospital. *Afr J Pharmacol Ther*. 2016;5(3).
 25. Iqbal S. Effect of a Designed Warfarin Based Education Program on Patients' Knowledge and Anticoagulation Control among Adult Outpatients Attending Clinics at Kenyatta National Hospital. [Mpharm Thesis]. School of Pharmacy, University of Nairobi; 2017.
 26. Mariita K, Nyamu D, Maina C, Karimi P, Mugendi G, Menge T. Patient Associated Factors that Affect Adherence to Warfarin Therapy in a Tertiary Referral Hospital in Kenya. *East Cent Afr J Pharm Sci*. 2015;18:67–74.
 27. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug–drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *Can Med Assoc J*. 2007;177(4):347–351.
 28. Fugh-Berman A. Herb-drug interactions. *The Lancet*. 2000;355(9198):134–138.
 29. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J Thromb Thrombolysis*. 2011;31(3):326–343.
 30. Bodeker G, Ong C-K. WHO global atlas of traditional, complementary and alternative medicine. Vol. 1. World Health Organization; 2005.

A review on the role of the pharmacist in a patient-centered healthcare system: Re-aligning healthcare to people's needs

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Abstract

Background: Patient-centered care model of healthcare acknowledges inter-profession team-based care and the need of care that is respectful of and responsive to individual patient preferences, needs and values. The

contribution of the pharmacist in this paradigm can provide important benefits within primary healthcare systems through collaborative medication therapy management, providing education and drug information, promotion of patient self-management, improved effective communication and personalized medicine.

Aim of the Review: The main aim of this review was to assess the impact of the pharmacist in a collaborative patient centered healthcare system.

Method: The review involved keyword searches of electronic databases, including MEDLINE, PsycINFO and Google Scholar. Review search terms included 'patient centered healthcare', 'role of pharmacist in patient centered healthcare', 'impact of pharmacists' intervention on medication discrepancies' and 'collaborative healthcare'. Using the search outputs, the impact of pharmacists in collaborative patient-centered healthcare system is described.

Results: Inclusion of pharmacists in collaborative healthcare programs have shown improved management of chronic diseases and reduced healthcare cost. A number of publications reported the importance of the pharmacist as valuable health care personnel in the collaborative healthcare model albeit others recognizing limitations and the need for the pharmacist to know more about the patient population and the unique healthcare provider needs of every team.

Conclusion: Contributions of pharmacists to the Health Care team is essential toward improving the quality of patient care, improving the coordination of medicines and pharmaceutical care, ensuring rational use of medicines and reducing medicines waste. The pharmacist being able to identify distinctiveness of every health provider in a team and patient needs to facilitate improved participation may well be a stimulus for further research.

Introduction

Health systems are moving toward a more inter-professional approach to primary care. Patient-centered care is a model of health care delivery that facilitates comprehensive and coordinated care. The model supports active involvement of patients and their families in decision-making about individual options for treatment. As the third largest professional group in national health systems, the pharmacy profession has a significant and unique role to play in the healthcare of the people of a nation and in re-engineering healthcare services to deliver more patient-centered care. The Pharmacist provides care through patient encounter, documentation and evidence-based practice [1]. Integration into team-based primary health care provides both challenges and fresh opportunities. Pharmacists' professional identities develop into valued role models contributing concretely to patient care even though occasionally they feel underutilized [2].

Patient-Centered Care

Patient-Centered Care advocates have described patient-centered care as that which honors patients' preferences, needs, and values; applies a biopsychosocial perspective rather than a purely biomedical perspective; and forges a strong partnership between patient and clinician [3, 4]. Similarly, Greene et al (2012) describes patient-centered care as care that "honors and responds to individual patient

preferences, needs, values, and goals" [5].

Contributions of pharmacists to the inter-professional team-based care activities that support and strengthen the patient-centered care model in areas such as collaborative drug therapy management; health information technology; personalized medicine; and the integration of advocacy and community-engagement into the profession are essential toward improving the quality of care, cost-effectiveness, and the patient experience [6]. It is essential for patients that their medicines and pharmaceutical needs are overseen and coordinated at all points of the health and social care pathway to ensure they can benefit from their medicines and suffer no harm. Since medicines are one of the most common interventions today, used in pain control and disease management, patients must access the pharmacy team, with the pharmacy profession taking greater responsibility for medication outcome. This is only possible when they work in partnership with patients to coach them to achieve their health goals at all points of their care journey. Furthermore, given that the role of the pharmacist has evolved from that of a compounder and supplier of pharmaceutical products towards that of a provider of services and information and ultimately that of a provider of patient care; it is imperative that pharmacists become patient-centered and collaborative towards re-aligning pharmaceutical practice to meet people's needs.

Inclusion of pharmacist in Patient-Centered Care health systems

The changing role of pharmacy practice have seen a trend for pharmacy practice move away from its original focus on medicine supply towards a more inclusive focus on patient care. As Health systems move toward a more inter-professional approach to primary care, this team-based paradigm has had a significant impact on the role of pharmacists within primary health care systems. Pharmacist-provided direct patient care has favorable effects across various patient outcomes, health care settings, and disease states. Incorporating pharmacists as health care team members in direct patient care provide viable solution to help improve health care. Consequently the America pharmacists are included as part of the healthcare workforce that focuses on preventive medicine, health promotion, disease prevention, and patient self-management [7, 8].

Clinical pharmacists are integrated into many Primary Care Trusts in the United Kingdom [9, 10] and similar practice settings around the world [11, 12, 13]. These practices have seen Pharmacists bring value to these teams by improving medication use through individual patient assessments and population-based interventions, providing education and drug information to other team members and enhancing public health and emergency preparedness practice [11]. At the same time physicians appreciate the benefits of working with pharmacists' colleagues to provide reliable drug information thus leading to increased security in prescribing [14]. The role of specialist pharmacists as collaborative prescribers in mental health and as integral

members of the multidisciplinary team is also recognized and accepted [15].

Medication therapy management and improved healthcare cost

Research has shown that patient-centered interactions promote adherence and lead to improved health outcomes [16]. Preventable adverse drug events that lead to hospital admissions occur due to inappropriate use of medications, contributing to increased health cost. Pharmacist-led Medication therapy management (MTM) can be applied to many medical conditions and can provide long-term cost saving to the health care system [17]. Particularly because they empower patients to optimize their medication use. Pharmacists providing medication therapy management are able to identify and resolve drug therapy problems through medication therapy review, personal medication record, medication-related action plan, intervention, referral, documentation and follow-up. Besides, they provide services that seek to enhance patient care by improving communication and collaboration among pharmacists and other health care professionals.

In Canada, research show that Pharmacists provide care for patients with diabetes improving patient outcomes such as glycemic control [18] and blood pressure control [19] in patient-centered MTM program. Such improvements tend to decline 3 months after an intervention has been completed [20] corroborating the value of the pharmacist in the team. A study by Moore *et al*, 2013 emphasizes that t pharmacist-managed medication therapy management program to reconcile the medication therapies of high-risk patients and improve adherence, as measured by medication possession ratios (MPR), is effective in reducing total health care costs. The participants in this patient-centric, high-touch MTM program significantly increase medication adherence levels and reduce the use of inpatient hospital services, as compared with a matched control group [21]. Patient outcomes can also be improved through one-on-one medication counseling by specially trained clinical pharmacists [22].

A controlled study to evaluate the effect of adding pharmacists to primary care teams on the management of hypertension and other cardiovascular risk factors in patients with type 2 diabetes shows that significantly more patients with type 2 diabetes achieve better blood pressure control when pharmacists are added to primary care teams [23, 24]. This suggests that pharmacists can make important contributions to the primary care of these patients. Another study by Al Mazroui *et al* (2009) demonstrates that the pharmaceutical care programme results in better glycaemia control and reduces cardiovascular risk scores in Type 2 diabetes patients over a 12-month period [25].

A systematic review assessing team-based care for Blood Pressure (BP) control supplemented with a Community Guide update also suggest that team-based care is effective in improving BP outcomes. Team-based care increase the proportion of people with controlled BP and

reduce both systolic and diastolic BP, especially when pharmacists and nurses are part of the team [26]. Pharmacist interventions alone or in collaboration with other healthcare professionals improve BP management; Systolic blood pressure improves with pharmacists' interventions. Other outcomes may also improve however more high-quality studies are needed for a comprehensive quantitative assessment. Further research may address the most efficient, cost-effective, and least time-consuming intervention [27, 28].

Barriers of inclusion

Pharmacists commonly encounter barriers to integrating into primary care teams; some may experience a lack of role clarity, for example, other team members' expectations regarding the pharmacists' responsibilities are frequently unclear [12, 15, 29]. In addition, patients often do not understand the role of the pharmacist in this setting [30]. Pharmacists are also typically unfamiliar with the roles of other team members creating difficulties in the collaboration. They often rely on other team members to assist in their integration, creating additional work for nurses and physicians [31]. Other barriers include physician resistance, lack of pharmacist assertiveness, inadequate pharmacist support, lack of space and inadequate pharmacist training [15, 29, 31].

Aim of the review

This review article aims to establish the impact of pharmacist in a collaborative patient centered healthcare system and investigates the state of knowledge by healthcare team on the role of the pharmacist in a patient-centered healthcare system.

Method

This was a narrative review of existing articles selected from reviews and original works published in open journals in the internet. The review involved keyword searches of electronic databases, including MEDLINE, PsycINFO (psychology and related behavioral and social sciences), and Google Scholar. Review search terms included 'patient centered healthcare', 'role of pharmacist in patient centered healthcare', 'impact of pharmacists' intervention on medication discrepancies' and 'collaborative healthcare'. The review included case studies, descriptive studies, systematic reviews describing role of pharmacists in patient centered/ collaborative care, as well as meta-analysis of randomized controlled trials narrating the effect of pharmacists' as team members on patient care.

Studies reporting integration of pharmacists in home based care, physicians' family practice teams and the need for collaborative care in healthcare systems as well as publications focusing on patient centered-care as a method of satisfying the needs of the patient were reviewed and summarized. The impact of pharmacist in collaborative healthcare systems and the knowledge of other members of healthcare teams on the role of the pharmacist in a

patient-centered healthcare system are described.

Results

The studies in the review included a wide range of health-related research, including basic and biomedical research, clinical trials, as well as public health research. Contribution of the pharmacist in patient centered care is recognized widely and healthcare systems are glad to include pharmacists in the healthcare team. Physicians also appreciate the role and value pharmacists bring to clinical practice. The present review demonstrates the involvement of pharmacists in hospital care and medication reconciliation may improve the quality of the patient medical care and reduce healthcare cost. The importance of integrating a pharmacist into an interdisciplinary team for medication management is adequately reported in literature [32 – 35]. However, Pharmacists occasionally encounter barriers to integrating into primary care teams due to lack of role clarity as pharmacists themselves and other team members are often unclear on what impact to expect in collaborative healthcare as regards the pharmacists' responsibilities. Other notable barriers include physician resistance, lack of pharmacist assertiveness, inadequate pharmacist support, lack of space and inadequate pharmacist training.

Discussion

Pharmacy is an ancient and honorable profession that deals with the latest, up-to-date technological advances for the benefit of mankind. Today's status of the profession results from an evolution over thousands of years. Pharmacists are healthcare professionals who, through the training they undergo, are empowered to dispense prescription medication, provide information about the drugs and ensure patients can use medications safely and effectively. For these reasons, pharmacists are able to make major contributions in Patient-centered health care delivery to facilitate comprehensive and coordinated care that supports collaborative involvement of Healthcare providers and, Patients & their families in decision-making about individual options for treatment. Patient-centeredness has been recognized as a desirable attribute of health care and collaborative drug therapy management as well as personalized medicine addressing pharmacogenomic research. These are among the activities that support and strengthen Patient-Centered Care model [5]. Information technology systems that create bidirectional data flow and facilitate communication enhance pharmacist collaboration and communication with other care team members on behalf of a patient to ensure safe, effective, and coordinated care.

Interestingly, majority of studies reviewed were conducted in Australia, United Kingdom, America and Canada. There is paucity of information on the African region although in Kenya, for example, the universities embrace clinical pharmacy education and major hospitals in the country now appreciate the inclusion of clinical pharmacists in

collaborative healthcare management systems. As with any healthcare system, limitations to the effectiveness of collaborative care are expected to occur due to the different practice areas of the team members and different patient needs. This may slow down efforts of team members in collaborating successfully.

Conclusion

This review demonstrates the positive impact of pharmacists working in collaboration with patients and physicians who appreciate the value of including a pharmacist in a patient-centered healthcare system. Inclusion of pharmacists in collaborative healthcare programs is necessary for improved management of chronic diseases and reduced healthcare cost. Contributions of pharmacists to the Health Care team is essential toward improving the quality of patient care, improving the coordination of medicines and pharmaceutical care, ensuring rational use of medicines and reducing medicines waste. This is because Pharmacists are healthcare professionals who, through the training they undergo, are empowered to dispense prescription medication, provide information about the drugs and ensure patients can use medications safely and effectively.

In the case of screening and prescribing however Pharmacists need to exploit their own strengths and the potential opportunities for these services, and reduce any weaknesses and threats possibly by including effective communication, piloting services, and the integration of some services into medical practices [15, 36].

Overall, improving the uptake of patient-centred services must begin with government policy makers, pharmacy organizations and employers recognizing pharmacists' career preferences and shaping future opportunities in the best interests of pharmacists [37].

It is recommended that as every team has unique provider needs and patient populations, pharmacists should invest time and energy learning about the team they are joining. Determining the specific medication-related needs of the team and patient population will make it easier to provide pharmacist services that add value. This is also an important step necessary to develop a pharmacist's job description [22].

To create patient-centered professionals, students should train in a patient-centered curriculum that is rich with patient care experiences. Similarly, to create team-ready professionals, students should train extensively in inter-professional health care teams. Expanded experiential education can help student pharmacists prepare for increased patient care roles in settings such as the patient-centered medical home and also help as practitioners advance the profession of pharmacy.

Conflict of interest

Author declares no conflict of interest

Reference

1. Mills, A. Patient-Centered Care for Pharmacists. *The Canadian Journal of Hospital Pharmacy*, 2013; 66(2), 134.
2. Pottie K, Haydt S, Farrell B, Kennie N, Sellors C, Martin C, Dolovich L. Pharmacist's identity development within multidisciplinary primary health care teams in Ontario; qualitative results from the IMPACT project. *Res Social Adm Pharm*. 2009; 5(4):319-26.
3. Stewart M. Towards a global definition of patient centred care. *BMJ* 2001 Feb 24;322(7284):444-5.
4. Mead N, Bower P. Patient-centredness: a conceptual framework and review of the empirical literature. *SocSci Med* 2000 Oct;51(7):1087-110.
5. Greene SM, Tuzzio L, Cherkin D. A Framework for Making Patient-Centered Care Front and Center. *The Permanente Journal*, 2012;16(3): 49-53.
6. <http://www.aacp.org/advocacy/engage/casestudies/pages/expandingpharmacistroleinpcmh.aspx>, Accessed 27th January 2016.
7. Mehta B, Kliethermes MA, Moczygemba LR, Andanar D, Bode LE. Pharmacists' roles in patient-centered medical homes. *J Am Pharm Assoc* (2003) 2014; 54:217-224.
8. Chisholm-Burns MA, Kim Lee J, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, Graff Zivin J, Abraham I, Palmer J, Martin JR, Kramer SS, Wunz T. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. *Med Care*. 2010; 48(10): 923-33.
9. Bradley F, Elvey R, Ashcroft DM, Hassell K, Kendall J, Sibbald B, Noyce P. The challenge of integrating community pharmacists into the primary health care team: a case study of local pharmaceutical services (LPS) pilots and interprofessional collaboration. *J Interprof Care* 2008;22:387-98.
10. Silcock J, Raynor DK, Petty D. The organisation and development of primary care pharmacy in the United Kingdom. *Health Policy* 2004;67:207-14.
11. Dolovich L, Pottie K, Kaczorowski J, Farrell B, Austin Z, Rogroque C, Gaebel K, Sellors C. Integrating family medicine and pharmacy to advance primary care therapeutics. *ClinPharmacolTher*. 2008; 83:913-7.
12. Farrell B, Pottie K, Haydt S, et al. Integrating into family practice: the experiences of pharmacists in Ontario, Canada. *Int J Pharm Pract* 2008; 16:309-15.
13. Isetts BJ, Schondelmeyer SW, Artz MB, Lenarz LA, Heaton AH, Wadd WB, Brown LM, Cipolle RJ. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. *J Am Pharm Assoc* (2003) 2008;48:203-11.
14. Pottie K, Farrell B, Haydt S, Dolovich L, Sellors C, Kennie N, Hogg W, Martin CM. Integrating pharmacists into family practice teams: physicians' perspectives on collaborative care. *Can Fam Physician*. 2008; 54(12):1714-1717.
15. Wheeler A, Crump K, Lee M, Li L, Patel A, Yang R, Zhao J, Jensen M. Collaborative prescribing: a qualitative exploration of a role for pharmacists in mental health. *Res Social Adm Pharm*. 2012; 8(3):179-92.
16. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: Definitions and applications to improve outcomes. *Journal of the American Academy of Nurse Practitioners*, 2008;20(12), 600-607.
17. de Oliveira RD, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. *J Manag Care Pharm*. 2010;16 (3):185-95.
18. Johnson JA, Lewanczuk R. Opportunity knocks: a diabetes strategy for pharmacists in Canada. *Can Pharm J*. 2009;142(1):84.
19. Cioffi ST, Caron MF, Kalus JS, Hill P, Buckley TE. Glycosylated hemoglobin, cardiovascular, and renal outcomes in a pharmacist-managed clinic. *Ann Pharmacother*. 2004 May;38(5):771-5.
20. Cranor CW, Bunting BA, Christensen DB. The Asheville Project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. *J Am Pharm Assoc*. 2003;43(2):173-84.
21. Moore JM, Shartle D, Faudskar L, Matlin OS, Brennan TA. Impact of a Patient-Centered Pharmacy Program and Intervention in a High-Risk Group. *J Manag Care Pharm*. 2013;19(3):228-36.
22. Jorgenson D, Dalton D, Farrell B, Tsuyuki RT, Dolovich L. (2013). Guidelines for pharmacists integrating into primary care teams. *Canadian Pharmacists Journal* : CPJ, 2013;146(6), 342-352.
23. Scot HS, Sumit RM, Ross TT, Richard ZL, Richard S, Jeffrey AJ. Effect of Adding Pharmacists to Primary Care Teams on Blood Pressure Control in Patients With Type 2 Diabetes, A randomized controlled trial. *Diabetes Care* 2011;34:20-26.
24. Simpson SH, Majumdar SR, Tsuyuki RT, Lewanczuk RZ, Spooner R, Johnson JA. Effect of adding pharmacists to primary care teams on blood pressure control in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2011 Jan;34(1):20-6.
25. Al Mazroui NR, Kamal MM, Ghabash NM, Yacout TA, Kole PL & McElnay JC. Influence of pharmaceutical care on health outcomes in patients with Type 2 diabetes mellitus. *British Journal of Clinical Pharmacology* 2009; 67: 547-557.
26. Proia KK, Thota AB, Njie GB, Finnie RK, Hopkins DP,

- Mukhtar Q, Pronk NP, Zeigler D, Kottke TE, Rask KJ, Lackland DT, Brooks JF, Braun LT, Cooksey T, and the Community Preventive Services Task Force. (2014;). Team-Based Care and Improved Blood Pressure Control: A Community Guide Systematic Review. *American Journal of Preventive Medicine* 47(1), 86–99.
27. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part II: Systematic review and meta-analysis in hypertension management. *Ann Pharmacother.* 2007; 41(11):1770-81.
 28. Santschi V, Chiolero A, Colosimo AL, Platt RW, Taffé P, Burnier M, Paradis G. Improving Blood Pressure Control Through Pharmacist Interventions: A Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2014; 10:3(2):e000718. <http://doi.org/10.1161/JAHA.113.000718>.
 29. Kozminski M, Busby R, McGivney MS, Klatt PM, Hackett SR, Merenstein JH. Pharmacist integration into the medical home: qualitative analysis. *J Am Pharm Assoc* 2003; 51:173-83.
 30. Assa-Eley M, Kimberlin CL. Using interpersonal perception to characterize pharmacists' and patients' perceptions of the benefits of pharmaceutical care. *Health Commun.* 2005; 17:41-56.
 31. Dobson RT, Henry CJ, Taylor JG, Zello GA, Lachaine J, Forbes DA, Keegan DL. Interprofessional health care teams: attitudes and environmental factors associated with participation by community pharmacists. *J Interprof Care* 2006; 20:119-32.
 32. Hawes EM, Maxwell WD, White SF, Mangun J, Lin FC. Impact of an outpatient pharmacist intervention on medication discrepancies and health care resource utilization in posthospitalization care transitions. *Journal of primary care & community health* 2014; 5: 14-18.
 33. Farley TM, Shelsky C, Powell S, Farris KB, Carter BL. Effect of clinical pharmacist intervention on medication discrepancies following hospital discharge. *International Journal of Clinical Pharmacy* 2014; 36(2): 430-436.
 34. Chisholm-Burns MA, Lee JK, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, Zivin JG, Abraham I, Palmer J, Martin JR, Kramer SA, Wunz T. US Pharmacists' Effect as Team Members on Patient Care Systematic Review and Meta-Analyses. *Medical Care* 48; (10): 923-933.
 35. Coleman EA, Parry C, Chalmers S, Min S. The Care Transitions Intervention: Results of a Randomized Controlled Trial. *Arch Intern Med.* 2006; 166(17):1822-1828
 36. Hatah E, Braund R, Duffull S, Tordoff J. General practitioners' perceptions of pharmacists' new services in New Zealand. *Int J Clin Pharm.* 2012; 34(2): 364-73.
 37. Grindrod KA, Marra CA, Colley L, Tsuyuki RT, Lynd LD. Pharmacists' preferences for providing patient-centered services: A discrete choice experiment to guide health policy. *Ann Pharmacother.* 2010; 44(10): 1554-64.



HERBAL MEDICINES REQUIRE REGULATION LIKE CONVENTIONAL MEDICINES

Stanley Ndwigah

The use of herbal medicines is increasing and gaining popularity throughout the world. People take herbal remedies to treat various diseases ranging from malaria, to diabetes and cancer. Their use is not regulated in many low-income countries, including Kenya. The herbal products are freely available, thus people are more liable to self-medicate and neglect to inform their doctors, even though herbal remedies can cause side effects or react with prescription drugs. This is because consumers have a widespread misconception that “natural” always means “safe” and a common belief that herbal remedies are harmless and carry no risk, because they are “not chemicals” like conventional medicines. These herbal medications must be regulated and the population must be informed about their risks.

The quality and safety of herbal medicines is poorly understood. Several studies have reported that herbal medicines have various toxic and pathogenic contaminants. In this context the term “contaminants” can be defined as the intentional or unintentional presence of undeclared ingredients which impact adversely on the safety of the product.

Among the potential contaminants are toxic botanicals, microorganisms (germs), microbial endotoxins, mycotoxins, pesticides, fumigation agents, toxic metals and animal substances. Potential harmful germs include *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and *Pseudomonas aeruginosa*. Other detrimental effects are attributable to problems of quality, for example, adulteration with undeclared pharmaceutical substances such as sildenafil (Viagra®) for aphrodisiacs and amoxicillin for antibiotics. Adverse events may also arise from the mistaken use of the wrong species of medicinal plants, incorrect dosing, and errors in the use of herbal medicines by both health-care providers and consumers.

Herbal medicines have side effects, because plants have “active ingredients” just like conventional medicines. For example coffee contains caffeine which keeps people awake and is the primary reason why we drink coffee. Similarly, all herbs contain compounds which are also used in traditional medicines. A good example is Cinchona species which contains quinine, an antimalarial used for treatment of severe malaria; at high doses it can cause cardiac arrhythmias, blindness and even death. The fact that it is a plant does not make Cinchona any safer!

Other plants are inherently toxic and can kill due to the molecules they contain. *Abrus precatorius* has attractive seeds which contain abrin, which is a very potent poison and causes nausea, vomiting, convulsions, liver failure, and death. Ingesting a single seed can kill an adult human. Abrin is classified as a “select agent” under U.S. law, and it has no antidote.

In Kenya, the Pharmacy and Poison Board (PPB), which is the Government drug regulatory body, doesn’t register all herbal medicinal products. Some are listed as food supplements by Kenya Bureau of Standards. This is partially because some people market these products as food supplements and also stiff opposition from some especially traditional health practitioners who think that herbal medicine practice is a cultural practice that should be regulated by Ministry of Culture and Social Services. Hence, herbal medicines can be purchased from outlets ranging from health food stores, roadside stalls to retail outlets, and even herbalists homes thus relevant and important evaluation of their safety lacks.

A lot of unethical practices have been documented, such as advertising in print and electronic media, peddling of products with no therapeutic benefits, and unsubstantiated medicinal claims.

For these reasons, the PPB needs full support from stakeholders in healthcare and all Kenyans to ensure that only good quality, safe and efficacious herbal products are marketed. The PPB can contribute towards their accessibility, cost effectiveness and appropriate use within the current state of knowledge. Although it is hard (as many argue) to determine efficacy of herbal medicines, the PPB needs support at least to ensure safety of herbal products.

My advice to Kenyans is to avoid unlicensed herbal medicines, particularly those sold on the streets, unlicensed shops and the internet. Secondly you should completely avoid any drug claiming to be “100 % safe” or “safe because it is natural”. Herbs can have side effects and some even kill! And lastly consult your doctor or pharmacist in case you are in doubt about any product you buy.

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PHARMACEUTICAL SOCIETY OF KENYA

Become A Member

In order to become a member with the Pharmaceutical Society of Kenya (PSK), you must provide your registration number. This information will be verified by the Secretariat before any member has access to their account.

Qualification

Member PSK (MPSK)

A graduate pharmacist registered by the Pharmacy and Poisons Board (PPB)

Fellow PSK (FPSK)

A full member who has rendered distinguished service to the society or in the field of pharmacy or who has made outstanding original contribution to the advancement of pharmaceutical knowledge or who has attained exceptional proficiency in a subject embraced by or related to the practice of pharmacy

PSK is a closed society. Membership is by annual subscription. Paid up members' benefits include:

- Elect representation to elective and nominated positions
- Stand for elective and nominated positions
- Access to Professional networks both locally and internationally
- Publish on the Pharmaceutical Journal of Kenya (PJK)
- Access to members empowerment programmes

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