



Effects of Herbal Medicine Use on Adherence to Conventional Anticancer Drugs

Christine Karungi¹, Philip Asiimwe^{1*}, Conrad Ssentongo¹, Sharon Primah Tuhaise¹ and Joseph Oloro²

¹*Department of Pharmacy, Faculty of Medicine, Mbarara University of Science and Technology, Uganda.*

²*Department of Pharmacology and Therapeutics, Faculty of Medicine, Mbarara University of Science and Technology, Uganda.*

Authors' contributions

This work was carried out in collaboration among all authors. Author CK suggested idea for topic of research. She also participated in proposal and questionnaire writing, requesting for ethical approval, data collection, dissertation and manuscript writing. Author PA participated in polishing research idea into a topic, proposal and questionnaire writing, requesting for ethical approval, data collection and statistical analysis, dissertation and manuscript writing and was as well the corresponding author for manuscript submission. Authors CS and SPT participated in polishing research idea into a topic, proposal writing, requesting for ethical approval, data collection, dissertation and manuscript writing. Author JO participated in polishing research idea into a topic, proposal editing, requesting for ethical approval, data collection, dissertation and manuscript writing. All authors read and approved the final manuscript.

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ABSTRACT

Background: Use of herbal medicines alongside conventional anticancer drugs is common among cancer patients. This may potentially cause reduced adherence to conventional anti-cancer drugs, unpredictable side effects and unknown drug-herb interactions. This in the long run could result in poor clinical outcomes.

Aim: This study was conducted to investigate how use of herbal medicines affects adherence to

*Corresponding author: E-mail: philipasiimwe24@gmail.com;

conventional anti-cancer drugs, to determine the proportion of patients using both conventional and herbal anticancer medicines and to identify the common herbal medicines used alongside conventional anti-cancer drugs by patients at the Mbarara Regional Referral Hospital Oncology unit.

Methods and Findings: A cross-sectional study was conducted in the oncology clinic of Mbarara Regional Referral Hospital found in Mbarara district, Uganda. Data was collected between 20th March and 20th April 2019 from 122 participants who met the inclusion criteria with subsequent consenting. Our primary outcome was adherence and secondary outcome was to investigate whether cancer patients use herbal medicines alongside conventional anti-cancer drugs.

Our study had 122 patients most of them belonging to the Banyankole tribe, 75 (61.5%) being males. Of the 72 (59.02%) patients who used herbal medicine, 40 (55.56%) were males and 66.67% of the herbal users reported relief from herbal medicines. Aloe Vera was the most commonly used herb. Most of the patients 77 (63.1%) showed high adherence, this was greater in the non-herbal users than in the herbal users (COR=1.62) though this was not significant (p=0.399).

Conclusion: It is most likely that majority of cancer patients use at least one herb during their course of life. The results did not show a significant relationship between herbal medicine use and adherence to conventional anti-cancer drugs. The high proportion of herbal medicine users calls for more research into the area to provide further information that can help optimize cancer treatment outcomes.

Keywords: Cancer; herbal medicine; adherence; anticancer drugs.

1. INTRODUCTION

Cancer is a condition or disease involving abnormal cell growth characterized by uncontrolled proliferation [1].

In Uganda over 5000 cancer cases are annually registered at the Uganda cancer institute (UCI). Despite being a threat, it can be prevented and controlled if detected early [1]. The incidence of cancer for every 100,000 is 320 newly diagnosed cases with 80% mortality rate and 20% survival.

Greater than 35% of patients in the United States report using herbal medicine during chemotherapy. Between 20% and 70% of patients using complimentary and traditional medicine including herbal agents. The above-mentioned patients are reluctant to disclose this practice to their health care practitioners [2].

Health care practitioners reported that 65.9% of the herbs their patients admit to using are associated with safety related health concerns. Of the above-mentioned patients 34.1% experienced potentially harmful herb-drug interactions which involve reduction in bio-availability of conventional anti-cancer drugs while 40.9% experienced directly toxic effects from plant metabolites. Only 15.9% had enhanced anticancer effects from using herbal drugs while on chemotherapy [2]. Herbal drugs like cannabinoid extract (*Cannabis sativum*),

vinca alkaloids (*Catharanthus roseus*) have been used in cancer management [3].

Almost half of the women with breast cancer report taking herbal medicine during treatment and 7% among general cancer patients report taking herbal medicine. Self-medication using herbal medicine counteract the effect of cancer treatment, alleviates symptoms of cancer and boost immune system However, herbal remedies can interfere with conventional treatment [4]. St. John's wort can increase the metabolism of cancer treatment i.e. imatinib by 44% Because of the unwanted side effects, cancer patients are advised to tell professionals if they are taking other medications [4].

Adherence is the extent to which patient's behavior coincides with medical advice [5]. Non-adherence to modern medicines is particularly common in most chronic diseases for example cancer, diabetes resulting into poor health outcomes and health care costs, increased mortality and morbidity [6].

Whereas the pathophysiology and management of cancer is well understood, a key concept in its quality of healthcare is adherence to medication [7]. There are arguments that patients living alone and those on continuous dosing regimen are most likely to adhere sub-optimally [8]. Therefore improving adherence to currently available anticancer medicines would result into

more health benefits worldwide and reduce mortality rates [9].

Cancer treatment requires adherence to drugs and success of treatment is low due to defaulting treatment i.e. termination of treatment to herbal remedies, patient not coming back when disease has elapsed, economic insufficiency and side effects [1].

Cancer complications such as difficult in breathing, weight loss, are associated with uncontrolled cancer, delayed diagnosis, non-adherence to conventional drugs and effects of chemotherapy [10].

Complementary and alternative therapies are becoming more common ways to improve quality of life due to increasing number of cancer patients and the potential risks of concurrent use such as poor clinical outcomes, drug interactions which could be harmful and wastage of public health resources must be addressed [11].

St. John's wort usually affects the pharmacokinetics of cyclophosphamide, docetaxel. Most herbs are Cytochrome P450 substrates which is a critical concern by clinicians because they impact efficacy and safety of medicines [12].

About 52% of cancer patients use more than one Complementary and Alternative Medicine while 80% of the patients use CAM together with chemotherapeutic agents in the initial phases of treatment. 50% of Chinese patients in North America use traditional herbal medicines as alternatives to conventional therapy. Media encourages herbal medicine use despite the potential risks of concomitant use [4].

A large proportion of cancer patients are estimated to use cancer medicine together with conventional therapy but data to substantiate this are still lacking. Patients taking both herbal medicine and conventional anti-cancers are usually unidentified by medical personnel.

There is therefore need for documented scientific evidence to show the impact of herbal medicine use on conventional medicine adherence among cancer patients. We therefore set to investigate whether herbal medicine use affects adherence to convention anti-cancer drugs in all cancer patients on oncology clinic at Mbarara Regional Referral Hospital.

There's little data documented regarding the different herbs used in the management of Non-Communicable Diseases and cancer in particular in Uganda, the pharmacological properties of these herbal medicines could be studied so as to prevent pharmacological interactions [13].

2. METHODS

2.1 Study Setting

The study was conducted at the cancer unit (Adult oncology ward) of Mbarara Regional Referral Hospital located in Mbarara district in western Uganda along Mbarara-Kabale high way, 266.79 km from Kampala city (Refer to APPENDIX III for more information on location.). The clinic operates everyday but receives outpatients on Tuesday and Thursday. The clinic receives over 40 patients per clinic day. The hospital covers districts of Buhweju, Ibanda, Kiruhura, Isingiro, Bushenyi, Mitooma, Ntungamo, Sheema, Mbarara, referrals from Kabale and Fort portal and some refugees from Burundi, Rwanda and Congo.

2.2 Study Design

A cross-sectional study was conducted involving both qualitative and quantitative methods of data collection over a period of 1 month from 20th March to 20th April 2019. It was a cross sectional study because the results were collected at a single sitting and presented as given by participants having different characteristics like tribal differences, locations without any investigations.

2.3 Study Population

The study population was cancer patients receiving treatment from the Mbarara Regional Referral Hospital oncology unit.

2.4 Inclusion and Exclusion Criteria

2.4.1 Inclusions

Known cancer patients on conventional anti-cancer therapy for at least 3 months.

2.4.2 Exclusion

Newly diagnosed cancer patients.

Patients who do not consent to participate in the study.

2.5 Sampling Technique and Sample Size Determination

The sample size for the study was calculated using Morgan's table for sample size determination.

The following parameters were considered:

2.5.1 Total size of population

Given the incidence rate for cancer as 320 people in every 100,000 [1] and the population coverage of Mbarara Regional Referral Hospital as 2,307,692 people [14]. The population of cancer patients at the hospital would then be: $(2,307,692/100,000)*320 = 736$.

Confidence interval: 95%

Margin of error: 5%

Using Morgan's tables for sampling, the sample size would then be: 248 participants

Sampling of individuals was done randomly as per inclusion criteria.

2.6 Study Procedure

We were introduced to the participants by a nurse in-charge at the oncology clinic. We then explained the study procedures to the participants. The study participants were asked for informed consent and enrolled into the study after explaining the details of the study procedures to the participants. The participants were interviewed using the pre-tested questionnaires and their response were recorded.

2.7 Data Collection and Analysis Plan

2.7.1 Questionnaire

This was the main method of data collection from the participants. The questionnaire had four sections socio-demographic, knowledge about potential adverse effects, beliefs, name and sources of herbal medicines. The questionnaire was administered through interview by one of the investigators.

2.7.2 Adherence tool

Adherence was measured using the standardized and widely utilized 4-item Morisky Medication Scale (MMAS-4). This was a simplified method of assessing adherence by asking the patients four unique adherence

questions and scoring their responses against values which were then totaled to give the index score. A score of zero indicates the highest level of adherence while that of four shows the lowest level of adherence [1].

Morisky medication assessment (MMAS-4) scale questions

- I. Do you ever forget to take your medicine?
- II. Do you find it necessary to stop the medicine given to you?
- III. When you feel better, do you sometimes stop taking your medicine?
- IV. Sometimes if you feel worse when you take the medicine, do you stop?

2.8 Data Processing

Data was collected and entered into Microsoft Excel 2013 and exported for analysis using IBM SPSS (version 20).

The Demographic variables analyzed were sex, tribe and education level. The clinical variables were use of herbal medicines, number of times visited the clinic, time since diagnosis of cancer, time since start of conventional anti-cancer medication, timely (or untimely) medication refill and attaining of health education about the conventional anti-cancer medicine to be used for example; counselling by health practitioners on the medicine's components, medical indication, medicine side effects, medicine interactions and herbal medicine use. The statistical application was run to obtain the frequencies and percentages of participants in particular categories of the above mentioned variables.

A pie chart to show the proportion of participants using herbal remedies concurrently with conventional medicines was generated as well as one for the percentage of participants who reported relief of symptoms after using herbal remedies. A bar graph showing patients in various adherence categories (High, Low and Intermediate) was also generated.

The effect of herbal medicine use on adherence to conventional anti-cancers was assessed using binary logistic regression which compared adherence in participants taking conventional anti-cancers solely to that in those taking both conventional and herbal anti-cancer remedies.

A binary logistic regression was done to see if herbal medicine use could be associated with

any of the Variables (Clinical and Demographic) through crude odds ratio. A multivariate logistic regression was done for some of the variables (sex, anti-cancer benefit, medication refill on time and time since start of medication) to obtain an Adjusted odds Ratio to check more accurately for association as this analysis rules out cofounders.

3. RESULTS

3.1 Introduction

This section contains a breakdown of all the results from the field survey.

3.2 Patient Demographics Statistics

Table 1 indicates that, of the 122 patients who met our inclusion criteria, 75 (61.5%) were male and the rest female. Banyankole, 83 (68.0%) was the dominant tribe and 32% of the patients belonged to the rest of the tribes. Majority of the patients 53 (43.4%) had studied upto primary level and few 3 (2.5%) up to tertiary level. Those who did not attain any education level were 32 (26.2%).

3.3 Patient Clinical Characteristics Statistics

Most patients 25 (20.5%) had visited the cancer clinic 3 times since diagnosis of cancer and only 1 (0.8%) had visited the clinic for more than 6 times since diagnosis of cancer.

Of the 122 patients, 58 (47.5%) had their cancer diagnosis after one year, 26 (21.3%) had their cancer diagnosis in less than one year and the rest (31.2%) were diagnoses with cancer after a period of more than one year.

Most patients 58 (47.5%) started their anticancer medication in a period between one and twelve months and majority of the patients 80 (66.1%) got their medication refill on time.

95 (77.9%) of the patients who participated in the study were told the reasons for taking their medications and out of 122 patients only 20 (16.4%) were told about herbal medicine use when they visited the cancer clinic during their appointments.

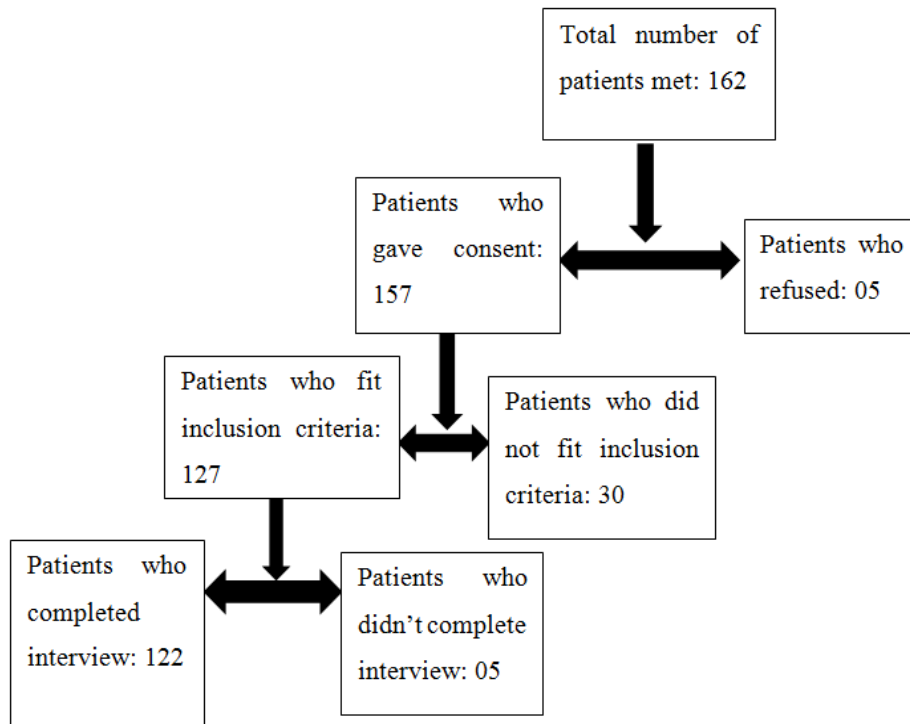


Fig. 1. A flow chart showing the trial profile of the research study. (Source: Field survey 2020)

Table 1. Patient demographic characteristics (Source: Field survey 2020)

Variable	Category	Number	Percentage
Sex	Male	75	61.5
	Female	47	38.5
Tribe	Munyankole	83	68.0
	Mukiga	23	18.9
	Mutooro	3	2.4
	Muganda	2	1.6
	Mufumbira	3	2.4
	Mukonjo	6	4.9
	Munyarwanda	2	1.6
	education level	None	32
Primary		53	43.4
O 'level		20	16.4
A 'level		5	4.1
University		9	7.4
Tertiary		3	2.5

Table 2. Patient clinical characteristics at oncology clinic of MRRH (Source: Field survey 2020)

Variable	Category	Count	Percentage
times visited the clinic	1	24	19.7
	2	18	14.8
	3	25	20.5
	4	16	13.1
	5	15	12.3
	6	23	18.9
	More than 6	1	0.8
time since diagnosis	0	26	21.3
	1	58	47.5
	2	13	10.7
	3	8	6.6
	4	8	6.6
	5	6	4.9
	6	1	0.8
	7	1	0.8
time since start of medication	1 month	9	7.4
	between 1 and 12 months	58	47.5
	Above 1 year	55	45.1
medication refill on time	Never	15	12.4
	Only sometimes	26	21.5
	Always	80	66.1
Health education on medicine components	No	59	48.4
	Yes	62	51.6
Health education on medicine indication or reason	No	26	21.3
	Yes	95	78.7
Health education on medicine side effects	No	29	23.8
	Yes	93	76.2
Health education on medicine interactions	No	52	42.6
	Yes	70	57.4
Health education on herbal medicine	No	102	83.6
	Yes	20	16.4

3.4 Adherence Patterns in Patients Interviewed

63.1% of the patients interviewed were highly adherent to conventional anti-cancer medicines as per MMAS4. 23.8% and 13.11% of the patients interviewed had intermediate and low adherence to conventional anti-cancer medicines respectively.

3.5 Relief from Herbal Medicine Use by Patients

After herbal medicine use, 66.7% patients reported to have had relief of symptoms.

3.6 Proportion of Cancer Patients' Use of Combination of Herbal and Conventional Medicine

Out of the 122 participants, 40.98% used only conventional anticancer medicine and 59.02% used both conventional anticancer and herbal medicine.

3.7 Herbal Medicines Used by Patients at the Cancer Unit

The herbal medicines used by patients interviewed included but were not limited to the following: Avocado seeds, black jack leaves, Pawpaw leaves, Cannabis and aloe vera.

3.8 The Effect of Herbal Medicine Use on the Adherence

Patients who scored high adherence on the MMAS4 were considered adherent while those who scored intermediate and low adherence were considered non-adherent.

Of those who used herbal medicine (72), 61 adhered to the conventional anticancer compared to 45 who adhered in the non-herbal medicine users (50). The patients using only conventional medication were more likely to adhere to the conventional medication (crude odds ratio =1.62) as compared to those using both herbal and conventional medication. This result is however not statistically significant (p value=0.399).

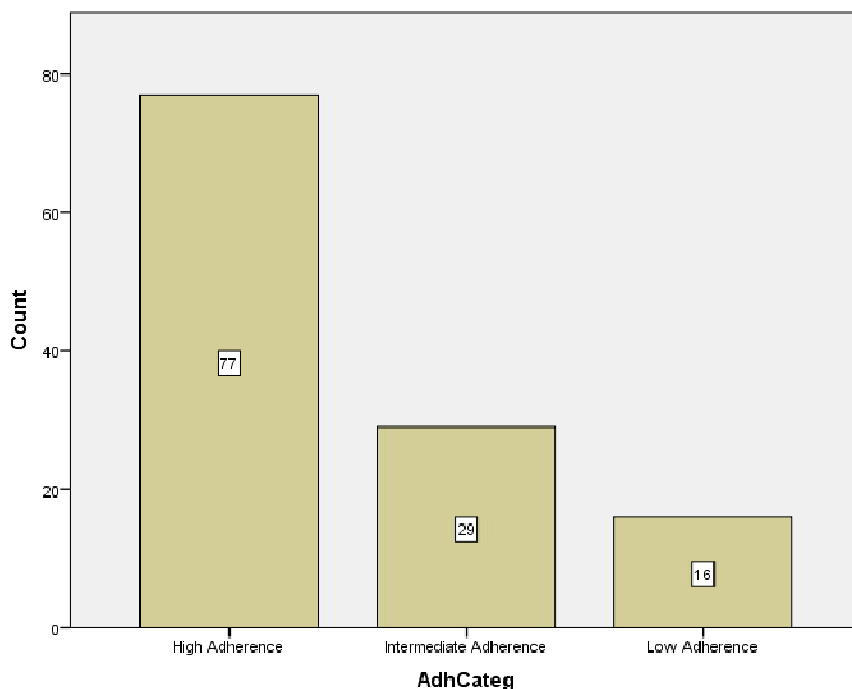


Fig. 2. Adherence patterns of Cancer patients using combination of herbal and conventional medicine at Oncology Clinic of MRRH. (Source: Field survey 2020)

Key: AdhCateg refers to Adherence Category

Out of the 122 patients, 77 showed high adherence (MMAS: 0), 29 showed intermediate adherence (MMAS:1-2), 16 showed low adherence (MMAS:3-4).

This study considered MMAS 0 as high adherence, MMAS 1 and 2 as intermediate adherence and MMAS 3 and 4 as low adherence. (Morisky & Dimatteo, 2011)

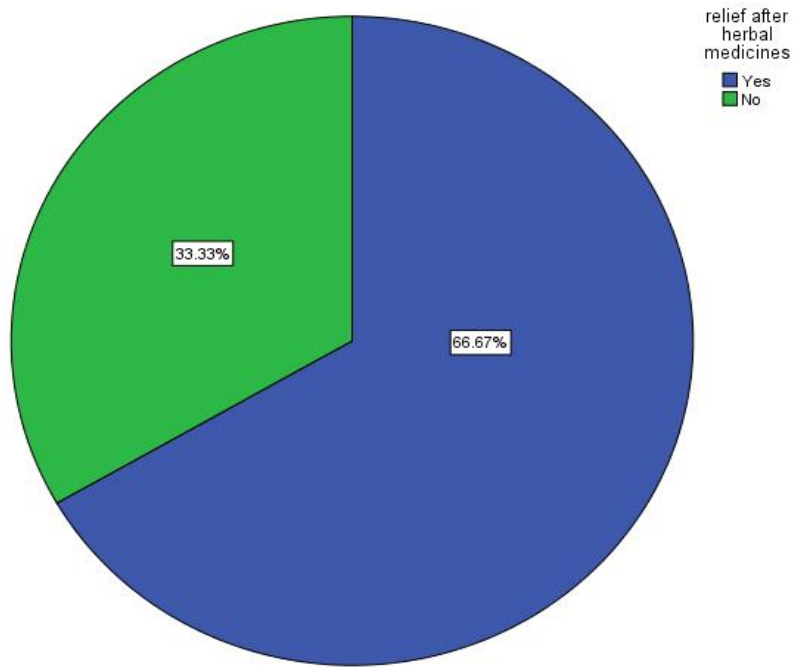


Fig. 3. Proportion of Cancer patients that got relief from using combination of herbal and conventional medicine at oncology clinic of MRRH. (Source: Field survey 2020)

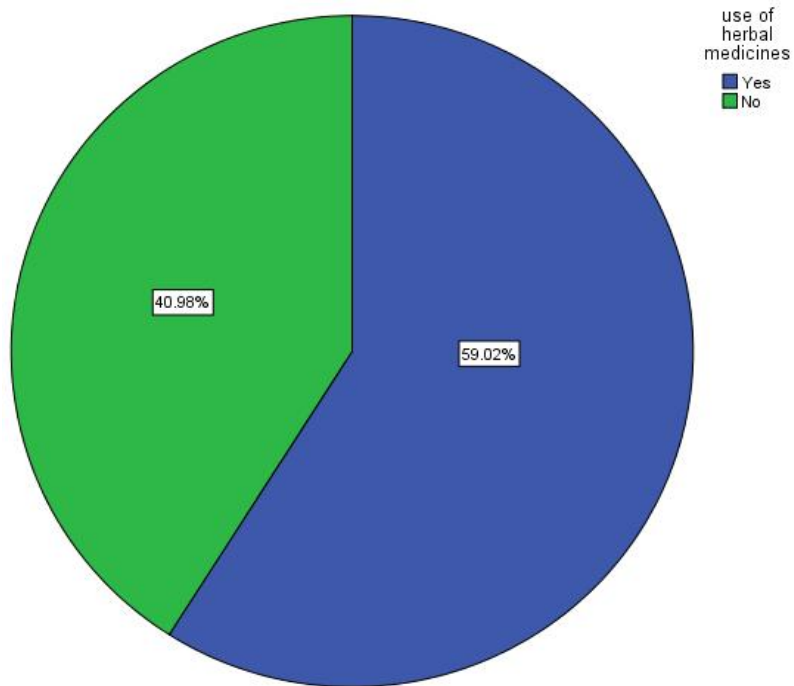


Fig. 4. Proportion of Cancer patients using combination of herbal and conventional medicine at oncology clinic of MRRH. (Source: Field survey 2020)

3.9 Factors Associated with Use of Combination Therapy

3.9.1 Uni-variate analysis

The results from uni-variate analysis in Table 5 showed no significant effect of any of the variables indicated on herbal medicine use by the patient since all p values obtained were greater than 0.05.

3.10 AOR Multivariate Analysis

Table 6 indicates that no significant findings were found among the various variables.

4. DISCUSSION OF RESULTS

The main aim of this study was to assess the impact of herbal medicine use on adherence to conventional anti-cancer drugs. We found out that 75 (61.5%) of the patients interviewed in this research study were male and the rest female.

According to [15], the ratio of incidence as per sex changes depending on the cancers for example: lung and bronchus cancer are common in males because of tobacco smoking. The incidence of many different cancers is though higher in males as compared to females which suggests the possibility of universal mechanisms (for example difference in anti-oxidative capacity) that increase male susceptibility to cancer. This can thus explain the higher percentage of males interviewed in our study.

According to a cohort study in Sweden on 39 cancers by [16] it showed that male sex is associated with increased risk of development for 34 of the 39 cancers and poor prognosis for 27 of the 39 cancers. According to the above mentioned study, women were at increased risk for development in 5 of the 39 cancers with significantly poorer survival for 2 of the 39 cancers. Identifying and eliminating factors driving the observed sex differences may reduce the global cancer burden.

Table 3. Herbal medicines used by patients at oncology clinic of MRRH. (Source: Field survey 2020)

Herbals used	Frequency	Percentage (%)
No use	51	41.80
Endenema	1	0.82
AIMS global herbal products	1	0.82
Alovera	4	3.28
Omubirizi	1	0.82
Avocado seeds	2	1.64
black jack leaves	3	2.46
Pawpaw leaves	2	1.64
Cannabis	1	0.82
Ekigolobolo	1	0.82
Oak tree	2	1.64
Guava leaves	2	1.64
Ekituutu	1	0.82
Eshabiko	1	0.82
Hibiscus	1	0.82
Unidentified	46	37.70
Kazire products	2	1.64
Mango leaves	1	0.82
Moringa	1	0.82
Omugoote	1	0.82
Omumba	1	0.82
Kamunye	1	0.82
Katengotengo	1	0.82
Sour sop	4	3.28
Total	122	100

Table 4. Effect of herbal medicine use on adherence at oncology clinic of MRRH. (Source: Field survey 2020)

Variable	Category	Adherence		COR (95% CI)	P value
		Yes	No		
Herbal use	No	45	5	1.623(0.527-5)	0.399
	Yes	61	11	1	
	Constant			.111	.000

Table 5. A Uni-variate analysis of association between various factors and combination herbal medicines with conventional therapy in patients at oncology clinic of MRRH. (Source: Field survey 2020)

Variable	Category	Herbal medicine use		COR (95% CI)	P value
		Yes	No		
Sex	Male	40	35	1.867 (0.870-4.003)	0.109
	Female	32	15	1	
	Constant			0.469	0.015
Education level	None	25	7	0.140 (0.011-1.780)	0.13
	Primary	24	29	0.604 (0.052-7.076)	0.688
	O 'level	13	7	0.269 (0.021-3.519)	0.317
	A 'level	3	2	0.333 (0.017-6.654)	0.472
	University	6	3	0.250 (0.016-3.997)	0.327
	Tertiary	1	2		
	Constant			2	0.571
Tribe	Munyakole	50	33	0.66(0.04-10.924)	0.772
	Mukiga	13	10	0.769 (0.043-13.866)	0.859
	Mutooro	3	0	0	0.999
	Muganda	2	0	0	0.999
	Mufumbira	1	2	2 (0.051-78.25)	0.711
	Mukonjo	2	4	0.5 (0.013-19.562)	0.711
	Munyarwanda	1	1		
	Constant			1	1
Time since start of medication	1 month	6	3	0.947(0.213-4.217)	0.943
	Between 1 month and 12 months	30	28	1.768(0.829-3.773)	0.14
	Above 1 year	36	19		
	Constant			0.528	0.024
Anti-cancer benefit	Yes	55	46	2.788 (0.724-10.736)	0.136
	No	7	1	0.476 (0.041-5.577)	0.555
	Not sure	10	3		
	Constant			0.3	0.067
Side effects	Yes	59	43	1.354 (0.498-3.677)	0.553
	No	13	7		
	Constant			0.538	0.187
Medication refill on time	Never	8	7	1.069 (0.354-3.232)	0.905
	Only sometimes	20	6	0.367 (0.133-1.01)	0.052
	Always	44	36		
	Constant			0.818	0.372
Discontinuation of medication	Yes	36	16	0.485 (0.228-1.031)	0.06
	No	36	33		
	Constant			0.917	0.718
Adherence	Yes	41	36	1.623 (0.527-5)	0.399
	No	31	14		
	Constant			0.455	0.144

Table 6. A multivariate analysis of association between various factors and herbal medicines use at Oncology Clinic of MRRH determined using AOR (Source: Field survey 2020)

		P value	AOR	95% C.I. for AOR	
				Lower	Upper
Step 1 ^a	Sex : Male	.153	1.851	.796	4.304
	Sex : Female				
	Medication refill on time: Always	.280			
	Medication refill on time: Never	.511	1.532	.429	5.467
	Medication refill on time: Only sometimes	.196	.456	.139	1.498
	Anticancer benefit: not sure	.121			
	Anticancer benefit: Yes	.091	4.290	.794	23.176
	Anticancer benefit: No	.950	1.092	.072	16.505
	Time since start of medication	.438			
	Time since start of medication: 1 month	.598	.651	.132	3.209
	Time since start of medication: Between 1 month and 12 months	.342	1.502	.649	3.477
	Discontinuation of medication: Yes	.594	.784	.322	1.913
	Discontinuation of medication: No				
Constant	.040	.131			
Step 2 ^a	Sex: Male	.129	1.909	.828	4.403
	Sex: Female				
	Medication refill on time: Always	.236			
	Medication refill on time: Never	.579	1.420	.412	4.902
	Medication refill on time: Only sometimes	.133	.417	.133	1.304
	Anticancer benefit: not sure	.102			
	Anticancer benefit: Yes	.080	4.488	.836	24.089
	Anticancer benefit: No	.954	1.082	.072	16.356
	Time since start of medication: More than 1 year	.413			
	Time since start of medication: 1 month	.644	.690	.143	3.332
	Time since start of medication: between 1 month and 12 months	.292	1.561	.682	3.569
	Constant	.021	.112		
	Step 3 ^a	Sex: Male	.131	1.877	.828
Sex: Female			1		
Medication refill on time: Always		.151			
Medication refill on time: Never		.471	1.564	.463	5.277
Medication refill on time: Only sometimes		.096	.388	.127	1.184
Anticancer benefit: Not sure		.098			
Anticancer benefit: Yes		.075	4.611	.859	24.745
Anticancer benefit: No		.933	1.122	.075	16.877
Constant		.031	.133		
Step 4 ^a		Medication refill on time	.166		
	Medication refill on time: Never	.636	1.332	.407	4.357
	Medication refill on time: Only sometimes	.083	.377	.125	1.137
	Anticancer benefit: Not sure	.113			
	Anticancer benefit: Yes	.097	4.023	.778	20.797
	Anticancer benefit: No	.957	.929	.064	13.462
	Constant	.081	.229		
Step 5 ^a	Anticancer benefit: Not sure	.066			
	Anticancer benefit: Yes	.078	4.091	.852	19.633
	Anticancer benefit: No	.799	.714	.054	9.497
	Constant	.038	.200		

Majority of the patients were from the Banyakole tribe 83 (68.0%) and 32% of the patients belonged to the rest of the tribes. This is because the study was conducted at MRRH in mbarara

whose coverage population is mostly banyakole. 53 (43.4%) patients had studied upto primary level and only 3 (2.5%) up to tertiary level. Those who did not attain any education level were 32 (26.2%). The high propotion of people who have studied upto primary could be associated with Universal Primary Education which according to a study by [17] in Uganda led to increased primary school enrollment.

It was found that most patients 25 (20.5%) had visited the cancer clinic three times since diagnosis of cancer and only 1 (0.8%) had visited the clinic for more than six times since diagnosis of cancer. Some of the patients who had visited the clinic less than 3 times since diagnosis gave reasons such as high cost of the cancer drugs and residing in areas far from the hospital.

Of the 122 patients, 58 (47.5%) had their cancer diagnosis in the last one year while (31.2%) had their diagnoses a period of time greater than the last one year. There was no significant relationship between period since diagnosis and herbal medicine use and this data was consistent with the multivariate analysis, in the study by [18] in the UK where period since diagnosis was not a significant predictor of herbal medicine use, this may reflect the fact that for some cancer types there may be limited herbal medicines available particularly if they are sought to alleviate specific conditions or side effects either when patient is undergoing treatment or are in the post treatment phase. According to [18] the likelihood of using herbal medicines increased with time of diagnosis where patients would consider using herbal medicines to address the long term effects of cancer treatment.

Most patients 58 (47.5%) started their anticancer medication in a period between one and twelve months and majority of the patients 80 (66.1%) got their medication refill on time.

95 (77.9%) of the patients who participated in the study were told the reasons for taking their medications and out of 122 patients only 20 (16.4%) were told about herbal medicine use when they visited the cancer clinic during their appointments. The patients who admitted to have been counseled on herbal medicine use at the oncology clinic said they were discouraged from using herbal medicines. The reasons they were given were; no known proper dose and possibility of herb-chemotherapy drug interactions as well as undocumented efficacy which was consistent with information given to cancer patients in

Uganda by Carol Kasujja because herbal remedies could render cancer treatment less effective which is life threatening [19].

This study also considered the impact of herbal medicines use on adherence to anticancer medicines and we found out that the number of patients that adhered was greater in the conventional therapy group (61) as compared to those on combined therapy group (45). This difference could however not demonstrate that herbal medicine use was associated with non-adherence due to statistical insignificance (p value = 0.399). This result is consistent with results from a study done by [20] where herbal medicine users believed doctors over prescribed medicines but no significant association was found with non-adherence. However, in some cases, [18] herbal medicine use can present significant risks such as affecting adherence with the prescribed treatment patterns which reduces treatment efficacy, or causing adverse reactions

This research study considered high and intermediate adherence patients as adherent and low adherence patients as non-adherent and out of the 122 patients, 77 showed high adherence (MMAS: 0), 29 showed intermediate adherence (MMAS:1-2), 16 showed low adherence (MMAS:2-3).

On concomitant use of conventional anticancer medicines and herbal medicines, it was found out that the majority of the patients interviewed in this study 72 (59.02%) were using herbal medicines along with their conventional anti-cancer therapy. The percentage of patients using herbal medicines is slightly higher as compared to 42% which was obtained in a study in Thailand by (Poonthananiwatkul et al., 2015). Another study done in the USA by [21] showed that the percentage of cancer patients who had used complementary and alternative medicines was 88.3%. According to a study by [22] the prevalence of herbal medicine use in Nigeria was 31.4%.

According to study in UK by [18], between 7% and 48% of cancer patients reported taking herbal medicines after diagnosis because of the possibility of side effects of conventional drugs.

This use of herbs on a large scale among patients, could be due to the following reasons less side effects as compared to conventional chemotherapy and possible immune system boosting from these products [23].

It is also important to note that of the patients using combined therapy, only 24 (33%) felt relief after using the herbal medicines which was significantly low as compared to 77% from a study done in Thailand by [24]. Only 20 patients in the study population had been counseled about using herbal medicines at the clinic when getting their medication refill. This indicates the need for oncologist to always talk to their patients about herbal medicine use while on conventional anticancer drugs.

According to study by [25] in Ethiopia, CAM use was a common practice where 154 (79%) cancer patients were CAM users, while 41 (21%) were nonusers, according to this study CAM use was higher as compared to surveys conducted in 10 European countries, This was due to referrals having limited number of oncology specialists and materials with less than 30 beds and a single radiology center, poor health care system of Ethiopia where patients needed to go through referrals starting from primary health care centers, longer waiting times for treatment and thus patients first visit traditional healers and seek alternative medical services rather than conventional.

In addition, [25] reviewed different studies conducted in western countries where CAM use among cancer patients was 40%. The prevalence of CAM use in Asia and Malaysia was found to be 98% and 60% respectively with a view of alleviating their disease and treatment side effects.

This study also considered to document the common herbal remedies the cancer patients were using and it was found out that a total of 17 different herbal remedies and products were being used by patients interviewed. However, 46 (64%) of the 72 patients using combined therapy could not identify the name of the herbal remedy they were using. The most commonly used herbs for management of cancer among patients interviewed were soursop (*Annona muricata*) (n=4; 3.3%) and *Aloe vera* (n=4; 3.3%). A study by [26] showed that HeLa cells treated with 75 micrograms of soursop extract showed 80% cell inhibition indicating anti cancer properties. Other herbs that were being used by patients included: Black jack (*Bidens pilosa*), avocado seeds (*Persea americana*), mango leaves (*Mangifera indica*), Cannabis (*Cannabis sativum*) and paw paw leaves (*Carica papaya*). This is contrary to a study done by [18] in UK which showed that the commonly used herbal medicines in cancer

patients were Evening Primrose (*Oenothera biennis*), Echinacea (*Echinacea pupurea*) and Garlic (*Allium sativum*).

Another study by [27] in Kenya documented the following plants: *Prunus Africana* (Hook. f), *Catharansus roseus*, *Harungana madagascarensis*, *Microglossa pyrifolia* among others as commonly used by cancer patients in Kenya and of the above mentioned plants, *Catharansus roseus* which contains vinca alkaloids such as vincristine, vinblastine, vindesine and vinorelbine was documented to have anticancer properties according to the study by [28].

While contemplating a relationship between various factors and herbal medicine use, a total of 9 variables were analysed using univariate analysis (Sex, tribe, education level, counseling on herbal medicine use, adherence, time since start of medication, conventional anti-cancer benefit, side effects, medication refill on time and discontinuation of medication).

None of the variables showed significant association with herbal medicine use. There are however other studies that have identified association between some of the above mentioned factors and herbal medicine use. An example is a study carried out in the Netherlands by Mathijessen, [29] where herbal medicine use was commonly associated with the female sex with reasons of little or no toxicity etc. A study done by [18] in the UK also associated use of herbal medicine with time after diagnosis and concluded that herbal medicine use increased with time after diagnosis.

From the above univariate analysis, 4 variables (sex, conventional anti-cancer benefit, time since start of medication, discontinuation of cancer medicine) were further analysed using multivariate analysis. No significant relationship between herbal medicine use and any of the factors was identified from multivariate analysis.

The insignificant p values ($p > 0.05$) from both multi and uni-variate analysis could be due to the small sample size, recall bias of patients, fear by patients to disclose their data and little time spent with the patients.

A study on patient characteristics by [30] showed that adherence was high in patients with one condition, males, older patients and those with high education rates and high income since cost

and access to medication play a role in non-adherence [30].

5. LIMITATIONS

This Study had several limitation.

Recall bias since cancer patients may not disclose herbal medicine, may not remember if they used herbal medicine. Efforts were however made to inform patients that their responses would be kept confidential.

The small sample size may have affected the significance of some of our outcome measures since sample size was calculated based on prevalence and not adherence as the primary outcome measure. Therefore, more big studies are recommended to establish these key relationships required to influence policy and practice.

6. CONCLUSION AND RECOMMENDATIONS

According to this study, it was found out that a substantial number of cancer patients (59.02%) were taking herbal medicine.

The number of adherent participants was higher in the patients using only conventional medication as compared to those using both herbal medicine and conventional medication in spite of the insignificance.

A total of 24 herbal remedies were identified to be used by patients interviewed. Majority of the patients using herbal medicines could not identify the herbal remedies they were using. Herbal medicine use was not associated significantly with any demographic or clinical patient characteristics. These herbal medicines should be studied for their pharmacological anticancer property and documented to give scientific evidence of their safety and efficacy.

There is a high potential for adverse drug interactions and as such comprehensive understanding of herbal medicine use by cancer patients is required since data to substantiate this is still lacking.

Health care professionals should increase their awareness on risks, benefits of herbal medicine to assist them make decisions regarding use of herbal medicines.

More research on a larger scale is recommended to inform policy and practice.

ETHICAL APPROVAL AND CONSENT

A letter from the head of Department of Pharmacy Research Ethics Committee was availed after approval of the research. The research investigators met the Hospital Director, submitted the letter of ethical approval and he gave administrative clearance for the research to be done at the oncology clinic. The purpose of the study was explained to the participants and an informed consent obtained before giving them questionnaires. The participants were assured of privacy and confidentiality as the study was conducted in a secluded section of the clinic. Participants were allowed to withdraw their participation at their will as long as they felt like withdrawing.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX I: CONSENT FORMS

INFORMED CONSENT FORM IN RUNYAKOLE

Mbarara University of Science and Technology

P.O BOX 1410, Mbarara Uganda. Tel: 0485661002
Faculty of Medicine, Department of Pharmacy
Website: www.must.ac.ug

ENDAGANO Y'OKWIKIRZA KUZA OMU KUBUZUBWA EBIBUZO BY'OMUSHOMO GW'OKUYONDOZA

OKWANJURA

Okukyondoza oku nigusherura okushijuma n'okumanya oku emibazi y'ebishaka eri kukora engyeri abarwire ba kokorro okuba bakumira emibazi yekijungu eyibakuhebwa aha unit ya kokorro ahari irwariro Mbarara Regional Referral Hospital.

Waterwanwa kuza omu mushono gwokukyondoza ogu ahabwokuba oyine endwara ya kokorro egi kandi nogiraguriza aha unit ya ekokoro ahari irwariro Mbarara Regional Referral Hospital. Noshabwa kuza omu kukyondoza oku nka nyekundire.

Ebitekateko n'ebitenso byawe nibyeija kuhebwa ekitinisa kandi bikwatwe nke ekihama kandi nibyeija kukoze sibwa ahabw'ebigenderwa byo'kukyondoza oku byonka. Nobasa kucwamu kuzamu kandi waba wagiremu , nabbwo nobasa kurugamu eshaha yona hatariho kutina ngu noja kufubirwa. Kwonka okuza kwawe omu kukyondoza oku nikuhereza omugisha gwo'kuta omuganda aha kumanya n'okwetegyereza oku emibazi yekishaka eri kukora engyeri abarwire ba kokorro okuba bakumira emibazi yekijungu eyibakuherwa aha irwariro.

Ninyikiriza kuza omu mushomo gwokukyondoza ogu: omukono.....
Amazina g'omukyondoza:
Omukono gw'omukyondoza:

INFORMED CONSENT FORM IN ENGLISH

We are a group of fourth year pharmacy students from Mbarara University of Science and Technology. We are carrying out a research about impact of herbal medicine use on adherence to conventional anti-cancers in patients at the Mbarara Regional Referral Hospital (MRRH) oncology clinic.

The main objective of our study is to investigate whether use of herbal medicines affects adherence to conventional anticancer medicines.

We kindly request you to answer the following questions and the information provided will be handled with utmost confidentiality. This study will benefit the community of Mbarara and the health sector at large.

We as students shall also benefit by successfully carrying out the research project and passing.

You have been chosen to participate in the study as a volunteer because you are an eligible adult. We also think that your contribution will greatly help us to get true results at the end of the research project. You can choose to participate or not to participate.

Your signature or thumb print on this form means you have accepted to take part in the study.

I..... a patient at the MRRH oncology clinic have agreed to participate in the research through filling or giving information that can be used to fill the questionnaire.

The purpose of the information I provide has been clearly explained to me.

Name of adult participant.....

Signature.....

Name of person obtaining consent.....

Signature.....

APPENDIX II

ENGLISH QUESTIONNAIRE

Mbarara University of Science and Technology
Faculty of Medicine
Department of Pharmacy

INTRODUCTION:

You have been invited to volunteer in this research study because you are eligible as per the inclusion criteria.

The main objective of this study is to investigate whether use of herbal medicines affects adherence to conventional anticancer medicines.

The findings will be used to improve people's awareness about the effect of this combined therapy on adherence to the people of Mbarara community and the health sector at large.

Instruction: Please answer truthfully and accordingly.

SECTION A: DEMOGRAPHIC DATA

1. Sex

a)Male b) Female

2. Tribe

a) Munyankole b) Mukiga c) Mutooro d) Muganda

e)Other (specify.....)

3. Education level

a) None b) Primary c) O 'level d) A 'level e) University

4. How many times have you visited the clinic in the last 6 months?

1 2 3 4 5 6

SECTION B: DRUG AND DISEASE SPECIFIC FACTORS

1. Time since cancer was diagnosed (in years)

.....

2. When did you start cancer medicine (months/years)?
(a) 1 month (b) between 1 months and 12 months (c) above 1 year
3. Do you think your hospital prescribed anti-cancer medications have helped you?
(a) Yes (b) No (c) Not sure
4. Have you ever experienced any of the side effects with your medications?
(a) Yes (b) No
5. Do you get your medication refill on time?
(a) Never (b) Only sometimes (c) Always
6. Do you receive any of the following information concerning medicines from either the doctor or the dispenser? (Indicate 1 for YES and 0 for NO)
 - Medication components
 - Reasons why you are taking the medications
 - How to recognize side effects?
 - Important interactions with other drugs
 - Use of herbal medicines
7. Other relevant medical history (chronic conditions only)
i..... ii.....

SECTION C: SOURCES OF HERBAL MEDICINES

1. Have you ever used herbal medicines?
(a) Yes (b) No
2. For how long have you been using herbal medicines since you were enrolled on conventional anti-cancer medicines?
a) <1 month b) About 6 months c) About 1 year d) > 1 year
3. Mention the local name of the herbal remedies you use alongside conventional anti-cancer medicine?
4. Do you feel any relief after taking the herbal medicines?
(a) Yes (b) No

SECTION D: ADHERENCE ASSESSMENT

Morisky medication assessment (MMAS-4) scale questions

1. Do you ever forget to take your medicine?
(a) Yes (b) No
1. Do you find it necessary to stop the medicine given to you?
(a) Yes (b) No

2. When you feel better, do you sometimes stop taking your medicine?
(a) Yes (b) No
3. Sometimes if you feel worse when you take the medicine, do you stop?
(a) Yes (b) No

APPENDIX III: LOCATION OF MBARARA DISTRICT IN UGANDA AND MAP OF MBARARA REGIONAL REFERRAL HOSPITAL





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