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Experience of Health professionals in the implementation of Clinical trials of Traditional Herbal Medicines: A cross-sectional study in Mali

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Abstract

Objective: The objective of this study was to determine the experience of health professionals in clinical trials of traditional herbal medicines in Mali.

Material and methods: This was a cross-sectional study conducted from June to December 2022 among healthcare professionals in three randomly selected localities: the district of Bamako and the regions of Koulikoro and Sikasso. Data were collected by direct interview using an anonymous questionnaire. The Chi-square ($\chi 2$) test was used to assess factors associated with participation in clinical trials of traditional medicines.

Results: The involvement of healthcare professionals in clinical trials of traditional medicines was low (3.5%) and was associated with age ($p=0.021$). The obstacles to conducting these trials reported by healthcare professionals were lack of funding and failure to take account of the specificities of traditional medicines in clinical trial regulations. Some healthcare professionals suggest ethnomedical evaluation of recipes proposed by traditional practitioners and the use of reverse pharmacology as alternatives.

Conclusion: Research into traditional medicines could be given greater impetus by the long-term funding of clinical trials and by less costly alternatives such as the ethnomedical evaluation of recipes proposed by traditional healers and reverse pharmacology.

Keywords: Traditional herbal medicines (THMs), clinical trials, healthcare professionals, Mali World Health Organization (WHO), Sampling

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1. Introduction

In 1978, at the Alma-Ata conference on primary health care, the World Health Organization (WHO) recommended the integration of traditional medicine (TM) into the health systems of member countries. (1) In Africa, TM is one of the primary sources of healthcare, even though the health authorities rely on conventional medicine, whose services are generally not widely available and/or accessible. (2) Accessibility to quality medical products also remains a major challenge for healthcare policies. (3-5) It is in this context that the use of traditional herbal medicines (THMs) to treat various diseases is on the increase, due to their availability, affordability and promising efficacy. (6,7)

However, this use is not without risks for people. Studies have reported cases of adulteration, toxicity and adverse effects attributable to THMs. (8-11) The evaluation of medicines as part of clinical research is a

means of generating solid evidence for their safe use. (12) This research should also be applied to THMs in order to select products of interest for further investigation in ethnopharmacology and to promote precautions for the use of local treatments. (13) This is why the WHO recommends clinical trials similar to conventional medicines for new THMs and those already known, in the case of new indications, galenic forms or methods of administration. (14)

Despite these recommendations, few THMs have been the subject of clinical trials in Africa. (15-17) The West African Health Organization (WAHO) has also pointed out that the majority of the few clinical studies that have been conducted in the region do not meet international standards. With this in mind, in 2013 it proposed a regulatory procedure for authorizing clinical trials in traditional medicine, with the creation of a technical committee to review the dossiers. (18)

In addition, the need for medicines adapted to the difficult conditions in which medicine is practised in Africa (reduced availability of care, limited resources, etc.) should encourage more clinical studies to improve therapeutic strategies. (19) These studies would encourage the large-scale approval of THMs and their survival on the international market alongside conventional medicines. (20) They could also complement the efforts of conventional medicine to achieve universal health coverage. However, an analysis carried out in 2011 among clinicians and scientists in 14 African countries revealed a lack of methodology and experience in clinical trials in the field of TM. (21)

At national level, research into plants has been dynamic since the years of independence under the aegis of the National Research Institute for Traditional Medicine and Pharmacopoeia (NRITMP), the former Department of Traditional Medicine (DTM). The NRITMP's research has resulted in seven Improved Traditional Medicines (ITMs) being placed on the Malian market and included in the National List of Essential Medicines (NLEM), while other marketing authorization (MA) applications are underway. (5,22,23) ITMs are medicines derived from TM recipes, with quantified dosages, defined toxicity limits, confirmed efficacy and controlled quality. Their development involves ethnobotanical surveys and phytochemical, toxicological, pharmacological, galenical and clinical studies. (24) In the past, some ITMs have been the subject of clinical studies, particularly in hospitals. (25–29) However, there is no recent evidence of clinical trials of THMs in Mali. (30) It is in this context that this study aims to determine the experience of health professionals in the implementation of clinical trials of THMs in Mali in order to identify obstacles and propose alternative measures.

2. Material et Methods

2.1 Scope, type and period of the study

This was a cross-sectional study, which took place in the District of Bamako and the Regions of Koulikoro and Sikasso from June to December 2022.

The three localities were randomly selected from the 10 regions of Mali and the District of Bamako using Excel's ALEA.ENTRE.BORNES formula.

2.2 Study population and inclusion criteria

The study focused on healthcare professionals. All healthcare professionals working in public and private healthcare establishments who were present on the day of the survey and who agreed to participate were included in the study.

For the purposes of the survey, the list of healthcare institution staff was used as a sampling frame for the random selection of participants.

Sampling

The sample size was calculated using the StatCalc function in EpiInfo 7.2.5.0. The parameters used were the expected frequency of 57%, (31) the margin of sampling error of 5% and the cluster effect of 1. The sample size was calculated simultaneously for two groups of practitioners (health professionals and traditional healers). However, only healthcare professionals were included in this study.

Thus, each group was considered as a cluster. The size of each group was 188, i.e. a total of 376 people. We allowed for a loss rate of 2% per group, i.e. 384 for the two groups, rounded to 385 participants.

Sampling was then proportional to the size of the population in each locality. The number of inhabitants in the selected localities was 2,559,000 in Bamako, 3,424,001 in Koulikoro and 3,736,002 in Sikasso, giving a total of 9,719,003 inhabitants. (32) Next, demographic and health statistics from the Ministry of Health, which count 8,833 health professionals, were used to adjust the number of participants per locality. By applying these proportions and adjustments, we obtained a sample size of 192 participants in this study, i.e. 50 in Bamako, 68 in Koulikoro and 74 in Sikasso.

2.3 Data collection techniques and tools

Data collection was carried out by a team of two people, including the principal investigator (a pharmacist) and a pharmacy intern (a student at the end of the study). Data were collected by direct interview using paper questionnaires and a pen. The information collected related, among other things, to participation in a clinical trial of traditional herbal medicines, healthcare professionals' perceptions of clinical trials, alternative methods of assessing the safety and efficacy of traditional medicines, and collaboration between conventional and traditional medicine practitioners. The survey was extended by interviewing participants with experience in clinical trials of THMs.

2.4 Ethical considerations

The study protocol was approved by the Ethics Committee of University of Science, Technique and Technology of Bamako under No. 2020/275/CE dated 07 December 2020. In practice, an information sheet was made available to study participants. It included information on the title, the research team, a description

of the project, the collection procedure, the benefits and risks associated with the study, voluntary participation, data confidentiality, the right to withdraw, and telephone contacts for the principal investigator and the chairman of the ethics committee. The free and informed consent of each participant, obtained on a signed consent form, was a prerequisite for inclusion in the study. Anonymity and confidentiality of personal information were guaranteed during data collection and processing.

2.5 Data entry and analysis

Epi Info version 7.2.4.0 was used to enter and analyze the data collected from the questionnaires. The interview data was analyzed and summarized according to the objectives previously set. Descriptive statistics such as numbers, frequencies and averages were used to present the results of the analysis. The Chi-square ($\chi 2$) test was used to identify associated factors, with a p value < 0.05 being considered statistically significant.

3. Results

3.1 Socio-demographic characteristics of participants

A total of 173 participants agreed to take part in the study during the survey period, giving a participation rate of 90.1%. More than half of the sample were men (63.6%), with a sex ratio of 1.7:1. The average age was 40.5±7 years and the age groups most represented were 30-44 years (58.4%) followed by 45-59 years (30.1%). Professional experience was between 11 and 20 years for 43.4% of participants. Healthcare professionals were generally general practitioners (42.2%) and state nurses in 20.2% of cases.

Table 1. Socio-demographic characteristics of participants

Variable	n	%
Localities		
– Bamako	46	26.6
– Koulikoro	61	35.3
– Sikasso	66	38.1
Structures		
– Hospital	15	8.7
– Health center	155	89.5
– Pharmacy	1	0.6
– Non-governmental organization	1	0.6
– Industry	1	0.6
Age in years		
– Less than 30	19	10.9
– [30 - 44]	101	58.4
– [45 – 59]	52	30.1
– 60 and more	1	0.6
Professional experience in years		
– <5	14	8.1
– [5-10]	66	38.1
– [11-20]	75	43.4
– >20	18	10.4
Gender		
– Woman	63	3.4
– Man	110	63.6
Marital status		
– Single	8	4.6
– Married	165	95.4
Profession		
– General practitioner	73	42.2
– General pharmacist	1	0.6
– Specialist doctor	27	15.6
– Specialist pharmacist	1	0.6
– State nurse	35	20.2
– Medical assistant	4	2.3
– Other	32	18.5

3.2 Participants' involvement in clinical trials and perceptions of their practice

The survey revealed that 3.5% (6/173) of participants had been involved in 3 clinical trials of THMs. Only age was associated with involvement in clinical trials of traditional herbal medicines ($p = 0.021$).

Table 2. Factors associated with the participation of healthcare professionals in clinical trials of THMs

Variable		Frequency, n (%)		
		Not implicated	Implicated	*P value*
Localities				
	Bamako	42(91.3)	4(8.7)	*0.408*
	Koulikoro	61(100.0)	0(0.0)	
	Sikasso	64(97.0)	2(3.0)	
Age in years				
	Less than 30	19(100.0)	0(0.0)	*0.021*
	[30 - 44]	96(95.0)	5(5.0)	
	[45 – 59]	52(100.0)	0(0.0)	
	60 and more	0 (0)	1(100.0)	
Professional experience in years				
	<5	14(100.0)	0(0.0)	*0.707*
	[5-10]	64(97.0)	2(3.0)	
	[11-20]	72(96.0)	3(4.0)	
	>20	17(94.4)	1(5.6)	
Gender				
	Woman	63(100.0)	0(0.0)	*0.081*
	Man	104(94.5)	6(5.5)	
Marital status				
	Single	8(100.0)	0(0.0)	*0.371*
	Married	159(96.4)	6(3.6)	

The majority of participants (97.1%) thought it was necessary to conduct clinical trials on traditional herbal medicines using the same scientific methodology as that used for conventional medicines. The main reasons given for this need were: "*to assess the quality and adverse effects in order to minimize the risk associated with their use*" (28.3%), "*to know the contraindications and exact doses to be administered" (23.1%), "to prove their efficacy and safety*" (20.8%), "*to assess their toxicity and to prove the claims made by certain traditional practitioners in relation to THMs*" (22.0%).

3.3 Barriers to conducting clinical trials

The main barriers to conducting clinical trials of THMs in Mali mentioned by healthcare professionals who have already been involved in such a study are: "*compliance with current regulatory requirements ... as this requires a great deal of financial and material resources to implement*" (50.0%), "*the problem of funding to continue research up to the clinical trial stage and to support its implementation*", "*research is generally funded by external projects and the State intervenes very little*" (16,7%).

A few healthcare professionals (2.9%) felt that the methodology used for clinical trials of conventional medicines is not very relevant for THMs and could be replaced by ethnomedical evaluation of the recipes proposed by traditional healers and reverse pharmacology.

3.4 Collaboration of health professionals with traditional healers and knowledge of ITMs

Only 37% and 13.9% of the healthcare professionals surveyed respectively stated that they collaborated with traditional healers and referred certain patients to traditional healers. The main pathologies concerned by this referral were hepatitis (62.5%) and fractures (12.5%). More than half of healthcare professionals were aware of the existence of ITMs on NLEM (60.1%) and the points of sale (60%) for these products. In addition, 37.6% of healthcare professionals had already prescribed or advised the use of ITMs from the NLEM.

4. Discussion

In the present study, more than half the participants were men (63.6%). Professional experience was between 11 and 20 years for 43.4% of participants. Yaméogo et al. in 2019 found a similar result for practitioners of modern medicine, 43.4% of whom had between 1- and 20-years' professional experience. (33)

4.1 Participants' involvement in clinical trials and perceptions of their practice

Only 3.5% of health professionals surveyed were involved in clinical trials involving THMs. In contrast, in the study by Willcox et al. in 2012, 57% (n=58) of researchers at universities and research centers in 14 African countries had already participated in a clinical trial involving THMs. (31) This result could be explained by the nature of the structures in which the health professionals surveyed work and their relatively small number (173) across the country. Health professionals' perception of the need to conduct clinical trials on traditional herbal medicinal products was essentially motivated by the adverse effects and potential toxicity risks of these products reported in certain studies. (8,10)

4.2 Barriers to conducting clinical trials

Among the barriers identified by the participants was the fact that the specific characteristics of THMs were not considered in the regulations governing clinical trials in Mali. Article 4 of Decree No. 2017-0245/P-RM, which sets out the conditions for biomedical research on human beings, states that "*the drafting of a biomedical research protocol must comply with an outline that conforms to international standards*". And Article 20 of law n°09-059/ governing biomedical research also states that "*biomedical research may only be carried out by a*

competent team, in a place equipped with material and technical resources adapted to the research and compatible with the safety requirements of the persons undergoing the research". (34,35) Strict application of the methodological framework (randomization, use of placebos, etc.) must therefore comply with international standards, which require material and financial resources, as well as highly qualified staff to ensure the scientific validity of the results. However, the State plays very little part in funding research, which very often comes from external financial partners within the framework of time-limited projects.

This lack of a sustainable funding mechanism for research into herbal medicines was in fact identified as a major obstacle by the participants. This result is in line with that of Wilcox et al. in 2012, (31) where the lack of funding was also reported by researchers. Furthermore, the WAHO guidelines for the regulation of traditional medicines state that inadequate funding makes it almost impossible to conduct scientific studies similar to those carried out for conventional medicines. (18) In addition, the lack of a binding Community and/or regional regulatory framework for clinical trials of THMs that is adapted to the realities of West Africa could act as a brake on their development. With regard to the more general regulation of THMs, the lack of Community and/or regional regulatory provisions was also reported by Dori et al. in 2019. (36)

To overcome the reported barriers, some participants thought that ethnomedical evaluation of the recipes proposed by traditional practitioners would be a good alternative to trials. However, without standardized treatment and appropriate follow-up, the results could be questionable due to patients' habits of using THMs in conjunction with other drugs. On the other hand, reverse pharmacology, which consists of modifying the drug discovery and development process on the basis of traditional knowledge, (37,38) could be a more credible alternative for proving the quality and safety of remedies used in the community in a relatively shorter period of time, compared with the long years spent researching conventional medicines. This approach was used in Mali by Willcox et al. (2011), for example, to produce a new standardized plant-based antimalarial after six years of research. (39) It has also been used in the Republic of Palau (Oceania) and Senegal (Africa) to identify effective traditional treatments for diabetes and hypertension. (40,41)

4.3 Collaboration of health professionals with traditional healers and knowledge of ITMs

The collaboration of healthcare professionals with traditional healers is a factor that may arouse their interest in further research into THMs. However, in this study, it was relatively low (37%) as in that of Kroa et al. in 2014 (27%). (42) This could be due to health professionals' mistrust of the recipes proposed by traditional practitioners, as reported by Oseni et al. in 2020. (43) The inadequacy or absence of notions of traditional medicine in the training of certain healthcare professionals could also explain this low level of collaboration. In Burkina Faso in 2019, Yaméogo et al. found that herbal medicines had not been included in the initial training of the doctors surveyed. (33)

The main reasons for referral of patients to traditional healers were hepatitis (62.5%) and fractures (12.5%). In the study by Ouoba et al. in 2022 on compliance with legal and ethical requirements for the practice of TM in Burkina Faso, (44) the conditions for referral of patients to biomedicine were 36.4% for chronic diseases and 54.5% for serious diseases. Furthermore, the lack of training in TM for healthcare professionals and the low level of collaboration between traditional and modern practitioners could indicate the relatively low prescription and/or advice of ITMs (37.6%) registered in Mali and listed on the NLEM. (5)

4.4 Study limitations

For reasons of budget limitations and residual insecurity in several regions, the study covered only three localities in Mali. Also, as the data collection tool was a questionnaire, the responses could be subjective. Despite these limitations, the results of this study could provide food for thought on the regulation of clinical research and alternative methods of evaluating traditional remedies in a context of limited resources.

5 Conclusion

This study showed the low level of involvement of healthcare professionals in the implementation of clinical trials for THMs in Mali. The barriers to the conduct of clinical trials of traditional medicines identified were mainly the lack of material and financial resources and the fact that the specific characteristics of these products were not considered in the regulations governing clinical trials at national level.

Some healthcare professionals believe that ethnomedical evaluation of recipes proposed by traditional healers and reverse pharmacology can be credible alternatives to traditional clinical trials. As far as ethnomedical evaluation is concerned, collaboration between healthcare professionals and traditional healers needs to be strengthened in order to obtain convincing results. In addition, to boost clinical trials of THMs, it would be advisable to ensure long-term funding for research projects in traditional medicine, and to review the regulations to include simplified, lower-cost studies for health products with long experience of use in the community.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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