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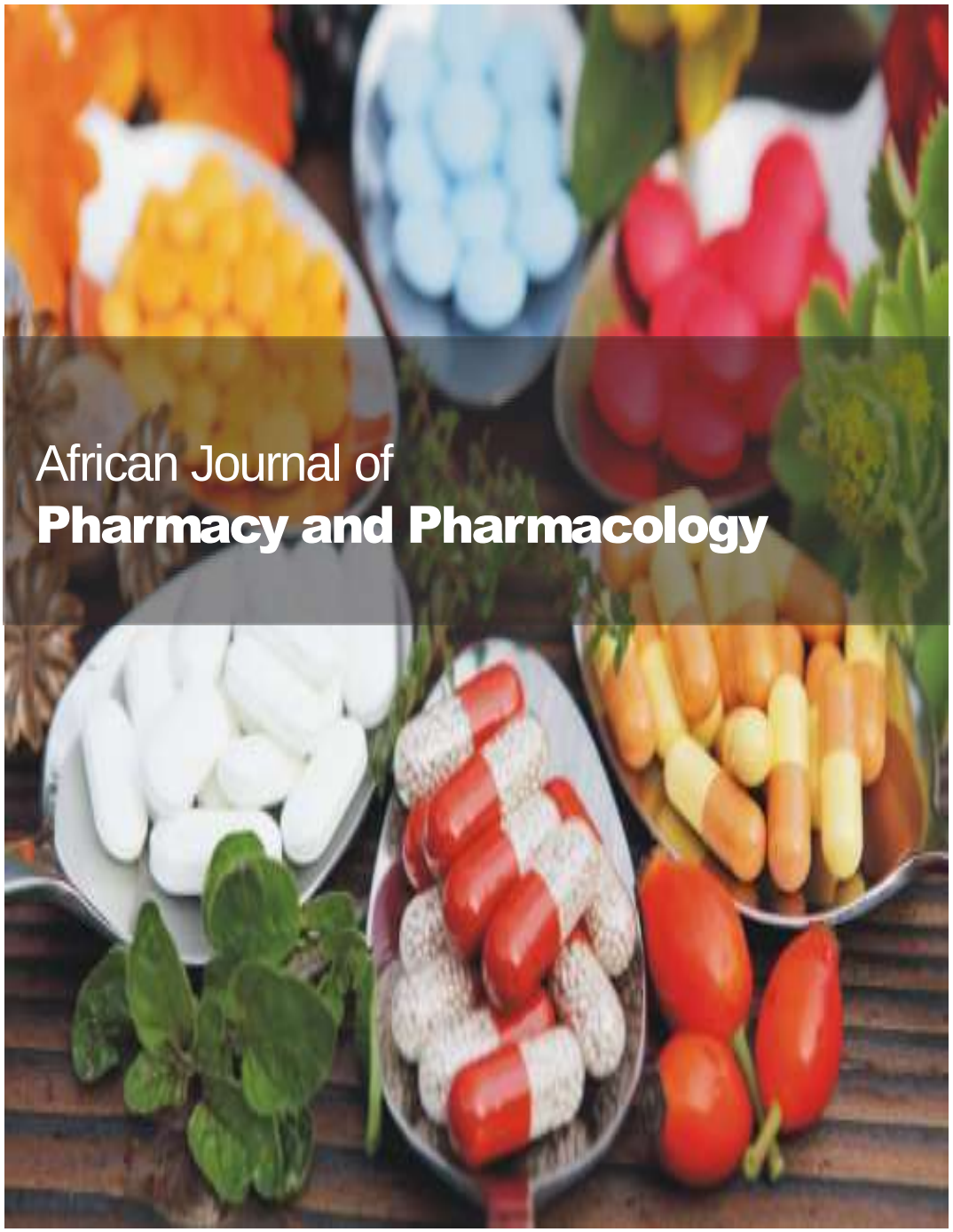

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Full Length Research Paper

Anti-fertility activity of aqueous root bark extracts of *Asparagus africanus* Lam and *Annona senegalensis* Pers combination on female Sprague Dawley rats

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Many rural and poor women have now resorted to use of potential medicinal plants as a means of fertility control. *Asparagus africanus* Lam and *Annona senegalensis* Pers are some of the plants used for this purpose. The efficacy and safety of many of such plants, however, have not been verified. Therefore, screening for anti-fertility activity of potential medicinal plants, would thus provide alternative safe and affordable contraceptive, if effective and less toxic. This study aims to carry out phytochemical screening, acute toxic effects and antifertility activity in female rats of the aqueous extracts of *A. africanus* Lam and *A. senegalensis* Pers combination. Acute toxicity test was done according to Lorke's methods and antifertility activity of the extracts by use of the method described by Khanna and Chaudhary, with modification for our local use. The percentage inhibition of conception of the extract was compared with those of the controls. Phytochemical screening revealed the presence of known anti-fertility principles such as saponins, alkaloids and phenolic compounds. Acute toxicity studies indicated that the extract was non-toxic up to the highest dose of 12.8 g and the antifertility activity of the aqueous crude extract was found to be dose dependent. This study therefore demonstrated that the aqueous root extract of *A. africanus* Lam and *A. senegalensis* Pers combination has antifertility activity and is safe at the doses employed in this study.

Key words: Anti-fertility, rats, phytochemical screening, acute toxicity, *Asparagus africanus*, *Annona senegalensis*.

INTRODUCTION

Uganda has one of the fastest growing populations in the world with a fertility rate of 6.7 and an annual population growth rate of 3.2%. This is due in part to low contraceptive use as a result of lack of access to safe and affordable contraceptives *(UDHS 2011)*. The capacity to address the world wide incidence of

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unintended pregnancy and abortions lies in the ability to discover an alternative effective, safe and affordable contraceptive (WHO). The current contraceptive methods are associated with serious adverse effects such as: thromboembolic events, hepatic tumors, breast cancers, cardiovascular diseases, uterine cervical cancer, breakthrough bleeding, spotting, amenorrhea, diabetes mellitus, gall bladder disease, continuous change in healthy body metabolism (that is, causes migraine headaches, weight increase, moodiness, and loss of libido), hypertension, depression, abortion (Kahlenborn, 2006; Giannitrapani, 2006) which are inconveniencing and less satisfactory probing in adherence and acceptability problems. Despite plants are extremely exploited in traditional healing systems, only in some cases their therapeutic potential in human has been substantiated (Rad et al., 2013; Sharifi-Rad et al., 2013, 2014a, b). Screenings for anti-fertility activity of potential medicinal plants provided alternative safe and affordable contraceptive (Farnsworth, 1975). There are several plants that have been known to possess contraceptive activity (Mukund et al., 2012). *Asparagus africanus* Lam and *Annona senegalensis* Pers, locally known as "Ogwaro" and "Obwolo" respectively are some of the traditionally used anti-fertility plants in Abim, Uganda. However, there were no reports on both ethno botanical and pharmacological profile of these plants. *A. africanus* Lam (Liliaceae) is an erect armed herb that grows up to 5 ft high. The plant is widely distributed in tropical Africa. In traditional medicine, the plant is used for the treatment of headache, backache, stomach pain and as an aid in childbirth (Msonthi and Magombo, 1983), heamaturia, heamorrhoids (Desta, 1993), malaria, lishmaniansis, bilharziasis, syphilis and gonorrhoea (Oketch-Rabah et al., 1992). The root extract is applied externally for the relief of pain, rheumatism and chronic gout (Watt and Breyer-Brandurijk, 1962). It is also used as a diuretic, for sore throat and otitis (Oliver, 1960). Three steroidal saponins have been isolated from the roots of *A. africanus* (Debella et al., 1999). *A. senegalensis* takes the form of a small tree, growing between two and six meters tall. Occasionally, it may become as tall as 11 m. The plant is widely distributed in tropical Africa. It is among medicinal plants that have been documented to possess antibacterial effects (Muanza et al., 1994). It is also used in the treatment of wounds and infectious diseases such as diarrhea (Suleiman et al., 2008), periodontal and other oral infections (More et al., 2008). Furthermore, the anticonvulsant, sedative and muscle relaxant (Okoye et al., 2010) as well as anti-inflammatory (Okoye et al., 2011) effects of the root bark extract and fractions of *A. senegalensis* have been reported. This study was carried out to determine the antifertility activity of the crude extract of *A. africanus* Lam and *A. senegalensis* Pers root combination, with particular emphasis on phytochemical screening, determining the toxicity profile and evaluating the anti-fertility effects using experimental models in rats.

MATERIALS AND METHODS

Study site

The study was carried out in the Pharmaceutical Chemistry Laboratory, Biochemistry Laboratory and Animal Research Facility of Mbarara University of Science and Technology.

Study design

This was an experimental short term prospective research study.

Plant collection and extract preparation

The roots of *A. africanus* Lam and *A. senegalensis* Pers were collected from Abim district, North Eastern Uganda in January 2014. The plants were identified by a botanist at the Department of Plant Biology, the Herbarium section at Makerere University, Kampala main campus and authenticated and assigned the voucher numbers by a botanist at the Department of Plant Biology, Faculty of Science, Mbarara University of Science and Technology (Oscar P'Okello Okidi 001 and 002, respectively). The roots of the plants were washed and shade dried at room temperature for a period of 21 days, crushed using mortar and pestle to reduce the size and then blended using a blender to powder of which 400 g of the combined plant material in the ratio of 1:1 was cold macerated in distilled water for 24 h, filtered with filter paper (Whatman No.1) and the solvent evaporated using an oven at 65°C for 4 days resulting in the recovery of a brownish dark solid.

Experimental animals

Cyclic virgin female Sprague Dawley rats, 3 months old (200±10 g) were used for the acute toxicity testing and anti-fertility activity while the male rats were used for mating in the anti-fertility assay. All animals were housed in standard cages with uniform conditions of lighting (12 h dark: 12 h light cycle) and at room temperature. Animals were fed on pellet and tap water. Animals were handled in this study as per the National Institute of Health guidelines (1978) for the care and use of laboratory animals.

Phytochemical screening

Identification of the chemical constituents of the aqueous roots bark extract of *A. africanus* Lam and *A. senegalensis* Pers combination was carried out as per the method described by Trease and Evans (2009).

Determination of oral median lethal dose (LD_{50})

The acute toxicity (LD_{50}) was determined in female rats by the method of Lorke (1983) using the oral route. The test was performed in one phase. Animals in the three different groups received oral administration of one of 5000, 8000, and 12,800 mg/kg (n=3) and observed for 24 h for mortality (number of deaths) and general behavior. The rats were further observed for fourteen more days for delayed toxicities and deaths.

Table 1. Phytochemical screening results of the aqueous root extracts of *Asparagus africanus* Lam and *Annona senegalensis* Pers combination.

Phytochemical	Test method	Deduction
Free amino acids	Amino acid test	Present
Alkaloids	Dragendorrf's test	Present
Terpenoids	Liebermann-Burchard test	Present
Reducing sugars	Fehling's test	Present
Tannins	Ferric chloride test	Present
Phenolic compounds	Ferric chloride test	Present
Flavonoids	Ammonia test	Absent
Saponins	Frothing test	Present
Proteins	Million's test	Absent

Anti-fertility assay

Anti-fertility activity was carried out using the method described by Khanna and Chaudhary (1968) with minor modifications. Five groups of 3 months old virgin female rats (n=5) were used. Three experimental groups received the aqueous extract (test sample) in doses of 125, 250 and 500 mg/kg body weight every 12 h. While the positive control received injectaplan (0.33 ml, that is, 50 mg) intramuscularly once, the negative control group received distilled water. Rats receiving the aqueous extract in each of the experimental groups were continuously treated as in Day 1 up to Day 5. All animals were allowed to mate with proven fertility male rats (n=3) on Day 6 for five (5) days, that is, up to Day 10 while maintaining daily treatment of the rats as per the previous days. The male rats were withdrawn from each group on Day 11 and administration of the aqueous extract continued to Day 13. The rats were then anaesthized, dissected and the uterus observed for the presence of fetus within the uterus to confirm for pregnancy on Day 21. The number of pregnant and non-pregnant animals was recorded and the antifertility activity determined (Kong et al., 1989).

Data analysis

The number of non-pregnant rats between the three extract treated groups (125, 250 and 500 mg/kg), distilled water and Depo-Provera (50 mg) were entered into Excel sheet, exported into Graphpad prism version 6 software and analyzed using Kruskal Wallis test followed by Dunn's multiple comparison test at 95% Confidence Interval. Results have been presented in table format. Those results with p-value ($P \leq 0.05$) were considered statistically significant.

Ethical consideration

This work was approved by the Faculty Research and Ethics Committee of the Faculty of Medicine, Mbarara University of Science and Technology.

Deep anesthesia was achieved during operation to determine whether the rats were pregnant or not using chloroform. The NIH guidelines for handling animals in teaching and research were clearly followed.

RESULTS

Phytochemical screening

Phytochemical screening of aqueous extract indicated the presence of free amino acids, terpenoids and saponins, alkaloids, reducing sugars, phenolic compounds and tannins. However flavonoids and proteins were not detected (Table 1).

Determination of oral median lethal dose (LD_{50})

The oral LD_{50} of the aqueous extract was not calculated as the extract did not cause any mortality unto a dose of 12,800 mg/kg body weight. However rats showed signs of clinical toxicity such as poor appetite, inactivity and drowsiness.

Acute toxicity test results

At the highest dose used of 12800 mg/kg body weight, inactivity, drowsiness and poor appetite were noted but no death during the 14 days of observation.

Anti-fertility assay

Treatment of animals with aqueous extract resulted in a significant dose-dependent inhibition of conception (Table 2). Table 2 shows that there was a dose dependent increase in antifertility activity of the extract, with 500 mg/kg of extract giving the same effects as the standard drug Depo-provera.

DISCUSSION

The current study has indicated that the combined

Table 2. Comparison of the antifertility effects of water (Control), extract and Depo-Provera.

Test	Number	Mean Rank Diff	Adjusted P-value at 95% CI
Control vs. Extract (125 mg/kg)	5	5	0.7868
Control vs. Extract (250 mg/kg)	5	10	0.0393
Control vs. Extract (500 mg/kg)	5	12.5	0.0050
Control vs. Depo-Provera (50 mg)	5	12.5	0.0050

aqueous extracts of *A. africanus* Lam and *A. senegalensis* Pers has significant antifertility effects. In the phytochemical screening, the presence of saponins, alkaloids and phenolic compounds which have been reported to possess anti-fertility activity, may support the claimed anti-fertility effects of the aqueous extract as reported to have contraceptive activities (Shibeshi et al., 2006; Padmashali et al., 2006; Ramya et al., 2011).

The combined aqueous extract of the roots of *A. africanus* and *A. senegalensis* did not cause any mortality up to a dose of 12,800 mg/kg orally and was thus considered to be non-toxic. However, milder signs of toxicity such as poor appetite, inactivity, and drowsiness were observed.

Administration of aqueous crude roots extract to the three experimental groups of female virgin rats at three dose levels of 125, 250 and 500 mg/kg body weight twice a day for 13 days showed significant dose-dependent anti-fertility effect (Table 2) by inhibition of conception suggesting that the extract has anti-fertility effect. This finding is consistent with those of Shibeshi et al. (2006) and Ramya et al. (2011) that showed similar results in female virgin rats following treatment with *Achyranthes aspera* and *Dodonea viscose* Linn, respectively. Based on the results of the present study with animal models, it can be concluded that the combined aqueous crude roots extract of *A. africanus* Lam and *A. senegalensis* Pers when administered orally has effective dose-dependent anti-fertility activity and reasonable safety. However, the study has limitations, in that it was conducted using a combined crude extract of the two plants that contains many anti-fertility components and quantitative determination of principal active ingredient responsible for observed effects was not done. It is also not possible at this point to tell if this effect was due to components from one plant or a synergistic effect of the two plants. Further studies should therefore be done using the same method to determine the reproducibility of this result, which will confirm this activity. Also, study on the possible mechanism as well as investigation on the fractionated isolates should be pursued. There is also need for standardization of the preparations being used by the local people in the community.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Good practice guidance to support safe oral medication preparation and administration through feeding tubes

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The objective of this work is to elaborate good practice guidance, aimed at preparing and administering drugs through feeding tube. This study was performed at a secondary level hospital in the interior of São Paulo state, Southeast Region of Brazil. For the first phase, a literature review was carried out in the following databases: LILACS, MEDLINE, Web of Science, and MICROMEDEX® Solutions. A manual search was also carried on other sources. In a second phase, the guide was refined for the hospital through meetings. Out of 104 references found, seven were read in full. The most employed technique for drug preparation was a simultaneous crushing of solid formulations. Participants identified a need to standardize techniques for drug preparation and administration through feeding tube, and the importance of using best practice guidance for patient safety was acknowledged.

Key words: Feeding tube, medication errors, hospital, good practice.

INTRODUCTION

Medication errors related to feeding tube route happen more often than reported or recognized. These errors are often the result of administering medications that are incompatible with administration via, preparing the medications improperly, and/or administering a drug using improper administration techniques (Seyede et al., 2017) (ISMP, 2010). Errors occurring in oral medication preparation and administration can lead to an occluded feeding tube, reduce the effects of drugs, lead to unsuccessful treatment, and increase the risk of potential adverse drug reactions (Emami et al., 2012; Seyede et al., 2017). Potential leading causes of these errors include lack of drug knowledge among physicians, inadequate training of nurses and lack of pharmacists participation in

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medical setting (Johnson et al., 2018).

Previous study showed that 40.5% of medications were not administered in appropriate dosage forms via feeding tube; 58% pharmacists, 17% nurses and 24% doctors were aware of the fact that enteric-coated tablets should not be crushed owing to the risk of tube occlusion and lack of efficacy when they are administered via feeding tube (Demirkan et al., 2017). Brazilian study identified that the technique mostly used to prepare the medicines was to grind (50%); 4.1% nursing staff let the tablets to dissolve in the water and then medicate the patient. It is revealed that enteral medication preparation and administration practices are inconsistent and nurses are still using unsafe practices that may compromise patients' care (Anderle et al., 2018).

In response to this scenario, World Health Organization (WHO) identified *Medication Without Harm* as the theme for the third Global Patient Safety Challenge with the aims to reduce severe avoidable medication-related harm by 50% in the next 5 years and propose solutions to address many of the obstacles the world faces today to ensure the safety of medication practices (WHO, 2017). One solution may be related to the development of protocols and evidence based guides (Figueiredo et al., 2018) that can provide clear and easily accessible information for the general and standard rules on how to prepare and administer oral medications through feeding tubes safely. To reduce these risks, guides for the safe administration of drugs via enteral feeding tube are now available (Neto et al., 2016); however, there is a gap between the best evidence available and clinical practice. Thus, the aim of this study is to develop a good practice guidance (GPG) for safe oral medication preparation and administration through feeding tubes in order to support prescribers, nurses and pharmacists to provide high quality care for patients in hospital setting.

MATERIALS AND METHODS

This article is the result of an initiative between the research team and a Brazilian public hospital. This is a descriptive study, composed of two phases and conducted in one general medium teaching hospital, between April 2014 and December 2015. The hospital has a 50 bed medical ward, four operating rooms, and encourages scientific production of high level research. The medical ward was chosen because it provides care for adult patients in various medical specialties and most of the patients have chronic conditions, thus many require enteral nutrition and medications through enteral feeding tube. This study was approved by the Research Ethics Committee (n° 412.833), according to the Resolution n° 466/2012, of the National Council of Ethics in Research of the Brazilian Ministry of Health. Healthcare professionals were informed of the research and asked to voluntarily sign the consent form. Participants were informed that the results will be used for publication and researchers guaranteed their confidentiality and anonymity. The study was conducted in two phases, as described as follows:

Phase 1: Development of good practice guidance

Based on the results of a previous investigation (Gimenes et al., 2017), a good practice guidance (GPG) for safe oral medication preparation and administration was developed, based on an integrative review. The population, intervention of interest, comparison and outcomes (PICO) strategy was used (Santos et al., 2007). Thus, the PICO question for the review was: "In adults requiring feeding tube (P), which techniques should be used to prepare and administer oral medications (I), (C) to avoid medication adverse events related to feeding tube (O)?

A search from the literature was conducted in October 2014 in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Web of Science. A manual search was also carried out on the website of the National Health Surveillance Agency (ANVISA), Brazil, in national and international guidelines, in textbooks related to the subject, in theses and dissertations, and in the MICROMEDEX® Solutions database, which provide health professionals with up-to-date clinical information about the medicines. Descriptors and keywords used for searching included: "adults"; "enteral administration of drugs"; "intubation, gastrointestinal"; "medication errors". These descriptors or keywords were combined using the Boolean conjunctions "AND" and "OR". A data collection tool adapted from Ursi (2005) was used to analyze the evidence. The studies were selected, analyzed and the results were synthesized. Data extraction from the selected studies was initially performed by the principal investigator and subsequently, by two reviewers who acted as independent validators (Favretto et al., 2012).

Only original articles published in English, Portuguese or Spanish were included in this review. Studies of children or infants and literature reviews were excluded. The strategy for selection of the studies is illustrated in Figure 1. Based on the results of this integrative review, the first version of the GPG was developed by the research team to address the continuing need to refine the techniques associated with oral medication preparation and administration through feeding tubes. This guide was composed of a title; objective; target audience; methodology; risks / critical points for patients; expected results; basic recommendations for safe oral medication preparation and administration through feeding tube; and a table containing explicit instructions for oral medication preparation of standardized drugs within the hospital. Table 1 exemplifies these instructions.

Phase 2: Refinement of the good practice guidance (GPG)

The first version of the GPG was presented and reviewed with the multidisciplinary team of the hospital, that included the research project coordinator, one nurse research fellow, one nursing manager, a nurse member of the Hospital Infection Control Committee, a nurse member of the training program, a pharmacist, a nutritionist, and a secretary. The reviewing process involved four meetings with the multidisciplinary team; they were held from April 2015 to August 2015 to discuss the guide and improve the processes of oral medication preparation and administration through enteral feeding tube, according to the hospital's individual requirements. The meetings took place in the hospital, so that the project coordinator could assist the team in action planning; they were accompanied by a nurse research fellow of the research project and had a maximum duration of 60 min each. The members of the multidisciplinary team exchanged experiences and knowledge to solve the task.

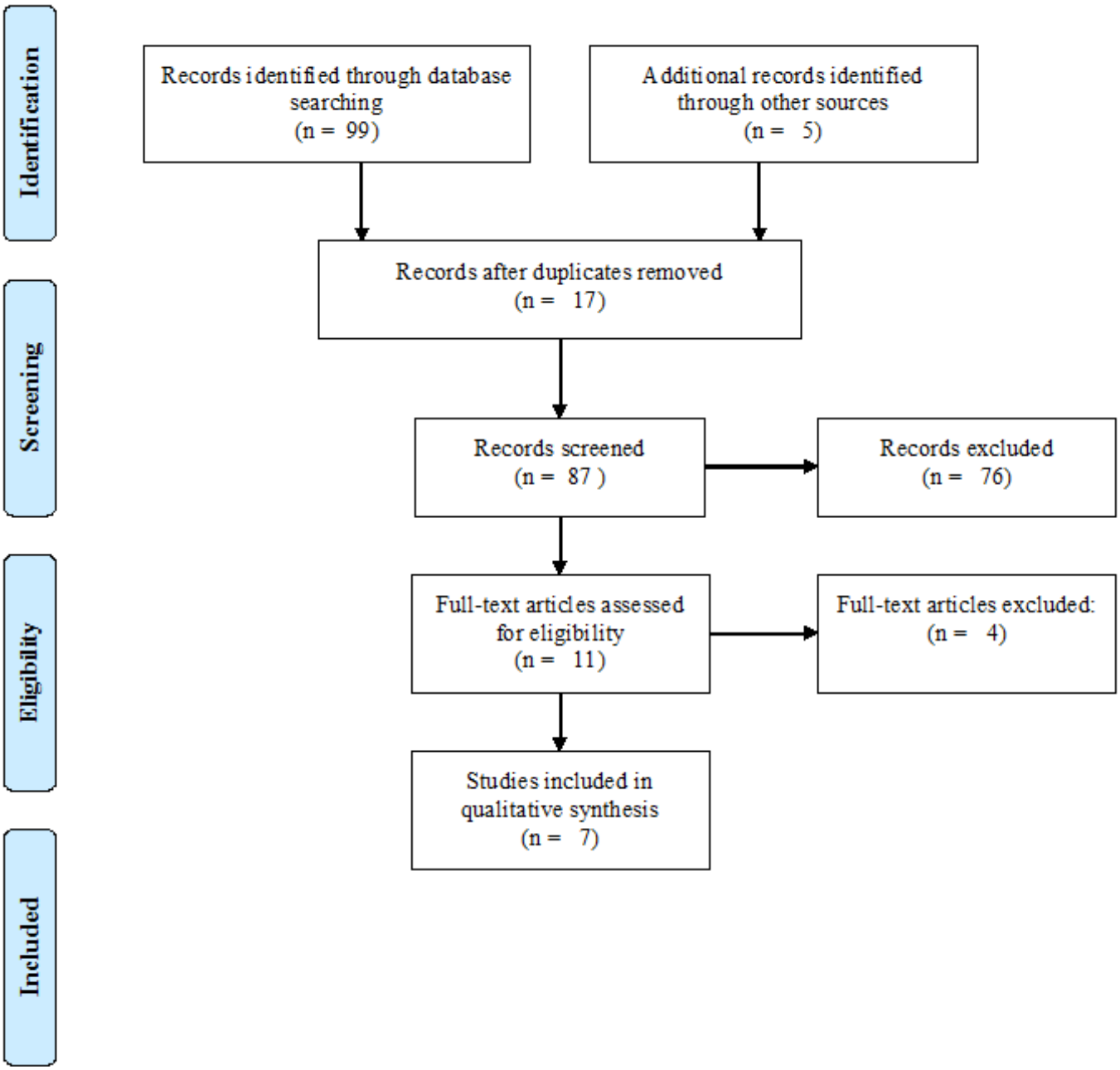

Figure 1. PRISMA flow diagram.
Source: (Moher, Liberati, Tetzlaff, & Altman, 2010).

RESULTS

Phase 1: Literature revision

Seven primary qualitative studies were included in the integrative review. The most commonly used techniques in the preparation of drugs via feeding tube were simultaneous grinding of solid drugs (Heydrich et al., 2009; Mota et al., 2010) and the reconstitution of the drugs in tap water (Mota et al., 2010). Since these drugs are administered concomitantly to patients, the probe is not washed before and after administration (Heydrich et al., 2009; Mota et al., 2010; Ramos et al., 2013). The main drug incident was feeding tube obstruction (Phillips and Endacott, 2011; Lisboa et al., 2011; Renovato et al., 2010) and the authors recommended the development of

Table 1. Examples of specific recommendations for preparing standardized drugs, contained on the GPG's first version.

Medicine	Can be crushed? (Yes/No)	Recommended technique	Recommendation for enteral nutrition
Captopril (25 mg tablet)	Yes	Crush until turning fine and homogeneous powder and reconstitute in 10 ml of distilled water*	Pause enteral nutrition 30 minutes before administering the tablet*
Esomeprazole	No	Reconstitute in 25 ml of distilled water*	Do not administer along with diet. Patient should be fasted*

*Source: White and Bradnam, (2015).

ongoing training programs for the nursing team as a strategy to reduce adverse events associated with medications. They also suggested that health services stimulate the joint work of multidisciplinary teams and the elaboration of protocols for good practices in the preparation and administration of drugs via feeding tube (Van Den et al., 2006; Mota et al., 2010).

Phase 2: Meeting good practice guidance (GPG)

In the first meeting, two doctors, three registered nurses, one pharmacist and one nutritionist participated. The objectives were to present the first version of the GPG and to discuss the suggestions proposed by the researchers. We addressed aspects related to patient safety, among them, replacing the plastic mortar used in the crushing of solid drugs with ceramic or glass mortar. The researchers also suggested to the pharmacist to label those medicines that should never be crushed; the standardization of reconstitution of solid forms and the dilution of oral liquid formulas with filtered water, since professionals used distilled water, saline or filtered water to reconstitute / dilute the drugs. The team also discussed cost-related issues involving the replacement of plastic mortar and considered it important to standardize the reconstitution / dilution of oral medications, depending on the hospital's individual requirements.

In the second meeting, three nurses and one pharmacist participated. The objectives were to discuss the items included in the GPG and to adapt them to the hospital's individual requirements. There was disagreement among participants in the group regarding the need to crush and reconstitute / dilute the drugs separately; to test the positioning of the tube before administering the drugs; and the simultaneous administration of the drugs with the enteral diet. For some participants, these recommendations would not be feasible in view of the disproportion between the number of drugs scheduled for the same time and the number of nursing professionals responsible for the preparation and administration of drugs. However, other participants pondered the importance of all nursing professionals to understand the importance of these recommendations for patient safety. Therefore, the recommendations were maintained in the guidance. The participants presented the need to elaborate a second table containing specific information on medicines that can be reconstituted / diluted with other medicines and on those that should not be administered simultaneously with enteral diets. They also discussed the importance of using color scheme in the table containing specific recommendations for the preparation of the medicines, in order to draw the attention of the team regarding the recommendations.

The third meeting was attended by four nurses and one pharmacist. The objective was to present and review the second version of the GPG that presented the drugs grouped according to pharmacological groups and with a color scheme and symbols to draw the attention of the professional to the particularities of each medicine. Once again, the group discussed the importance of not crushing, reconstituting / diluting and administering multiple medications simultaneously; as well as the need to respect the intervals between administration of the drug and enteral diet infusion. Other changes were suggested by participants in the group, such as: red color would be used to signal medications that should never be crushed, and yellow to signal medications that should not be administered along with the enteral diet.

The participants also decided that the medications would be presented in alphabetical order, and not according to the pharmacological group, in order to facilitate the understanding by mid-level nursing professionals. In the space for the observations of the medicines, the participants decided that the standard recommendations for medication preparation (crushing to a fine and homogeneous powder and reconstituting in 10 ml of distilled water) and / or specific recommendations as described in the literature (reconstitute the tablet in distilled water and administer at the end of the effervescence). Regarding the interruption of the enteral diet, it was decided to establish a standard pause before and after the drug administration (30-min pause before and after the drug administration), so as not to delay the infusion of the diets for the patients. At the end of the

Table 2. Synthesis of GPG development and refinement process.

Process of constructing and refining the protocol		
Previous research*	**First version**	**Final version**
Drug reconstituted in distilled water, 0.9% saline or filtered water.	Perform reconstitution in potable water.	Perform reconstitution of drug(s) in distilled water.
Liquid pharmaceutical form diluted, without volume measurement.	Dilute liquid drugs with high osmolarity/viscous drugs in 60 to 90 ml of potable water.	Dilute liquid drugs with high osmolarity/viscous drugs in 60 to 90 ml of distilled water (question nurses/doctors when patient is under water restriction).
Solid pharmaceutical form (pill/tablet/dragee/capsule) crushed simultaneously, without observing commitment of biopharmaceutical aspects.	Crush solid drugs separately and verify if capsules can be open without commitment of biopharmaceutical aspects.	For solid drugs, observe standard reconstitution: crush until obtaining a thin and homogeneous powder, and reconstitute in 10 ml of distilled water. For capsules, verify if these can be opened. Specific drugs which do not follow standard reconstitution: observe the recommended technique for drug preparation.
Feeding tube were not tested for correct positioning before drug administration.	Confirm correct positioning of NGT/NET before drug(s) administration, using the following technique: inject 20 ml of air with a syringe through the tube; perform abdominal auscultation with stethoscope, under the xiphoid process; aspirate injected air and observe characteristics of aspirated contents.	Confirm correct positioning of NGT/NET at least once a day: inject 20 ml of air with a syringe through the tube; perform abdominal auscultation positioning the stethoscope under the xiphoid process; aspirate injected air; observe and register characteristics of aspirated contents.
-	-	Recommendation for use of surgical gloves and masks during drug preparation, when indicated, was included.
-	-	Recommendation for using the red color, in order to indicate drugs that must never be crushed and administered through NGT/NET was included.

Source: Author.

third meeting, the participants suggested that they decided to meet to finalize the adaptation of the medication list to the hospital's context and to send the researchers, by electronic mail, to finish the GPG. Five nurses and one pharmacist attended the fourth meeting. The objective was to present the final version of the GPG for the multidisciplinary team of the hospital. At this meeting, more adjustments were required, such as using only the red color to signal the particularities in the preparation / administration of the drug. Table 2 presents an overview of the entire process of the GPG development and refinement for the preparation and administration of medication through feeding tubes.

DISCUSSION

The objective of the study is develop a good practice guidance for the preparation and administration of medicines via feeding tube, based on the results of the integrative literature review. It was verified that the trituration of solid drugs was the technique most used by the nursing team to prepare the drugs in the studies included in the integrative review. Concomitant preparation and administration of the medicinal products may result in physico-chemical interactions capable of rendering drug therapy unfeasible. In addition, nursing professionals use various substances (water, juices, teas) in the reconstitution / dilution of medications. However, this practice compromises biopharmaceutical aspects, which may result in feeding tube obstruction and serious adverse events in the patient (Phillips and Endacott, 2011).

The nursing staff use plastic crush solid dosage forms. This fact is relevant when considering some important points: 1) change in the dose to be administered, since

fragments of the drug can be adhered in the pestle; 2) possible physico-chemical interactions between the components of the pharmaceutical formulation and the material of the pestle; and 3) drug interactions as a consequence of the simultaneous grinding of several drugs (Heydrich et al., 2009). Safety in health care means avoiding, preventing and improving adverse outcomes and damages generated by the health care process. It also includes the reduction and mitigation of unsafe acts within the healthcare system, as well as the use of good practices to achieve optimal outcomes for patients. In this context, it is fundamental to standardize the techniques of drug preparation and administration feeding tube through good practice guidance (Goedecke et al., 2016).

Good practices regarding preparing and administering oral drugs through feeding tube have recently been addressed at an international level. A study conducted in France verified how drug administrations through tubes occurred in 46 health care units in the country; 1,110 nurses took part in the study, and two-thirds of them said to crush tablets and capsules at least once a month, while 28% reported performing this practice on a daily basis. In addition, 71% of the total stated that they never asked pharmacists their doubts about crushing of medications. Although considering preparation and administration of drugs an innocuous procedure, this is a common practice that can bring risks for patients (Clauson et al., 2016).

Main risks that may happen during administration of drugs through enteral tubes are related to interactions between medications administered simultaneously or between drugs and enteral diet; destruction of enteric drug protection resulting from incorrect crushing; complications due to erroneous administration of substances outside the gastrointestinal tract; and obstruction of enteral tubes due to incorrect handling. Therefore, discussing this issue in different health care environments becomes necessary, so that professionals involved in preparing and administering medications through enteral tubes are able to understand the risks involved in this care, and can provide better safety to patients (Silva and Guaraldo, 2016; Marquez et al., 2018).

Simultaneously crushing medications is a common procedure in clinical practice and, in many cases, medicines are crushed using the same pestle. In one previous study, the researchers verified improvements, after implementing good practice guidance for crushing medication in elderly patients. Authors observed that 90% of nurses performed this type of procedure during the preparation of drugs. After implementation of system improvements, there was reduction of nonconformities to 70%, especially regarding the crushing of enteric coated pills. They also found that, after utilizing the good practice Thus, it was observed that recommendations of the guide contributed to improvements in the care practice of elderly patients (Goedecke et al., 2016) (Bourdenet et al., 2015).

Elaboration of guidance to guide good practices of different procedures in health care environments is necessary due to the importance of improvements in the care and to patients' safety. However, it is fundamental to think of strategies according to each hospital's individual requirements, with some changes being feasible for some environments and infeasible for others. In this study, through discussion groups with a multidisciplinary team, improvements were made in the GPG, appropriate to the hospital's context. It is important to reinforce that elaboration of good practice guidance must be substantiated in literature reviews, so that care practices can be based on the best scientific evidences. Literature reviews can improve guides, so these can be used as a tool during medication preparation and administration through feeding tubes, with decrease in medication errors, thus improving drug therapy and patients' safety (Johnson et al., 2018), (Shawn and Paul, 2018). Use of guides for improvement of nursing care requires a constant review of them according to recent literature, so that new knowledge is applied in clinical practice. Therefore, the process of implementing these guides in assistance seeks constant evaluation of expected results from new evidence that emerges from scientific research (Kenny and Goodman, 2010).

The knowledge of nursing teams regarding the process of drug administration via enteral tube is important, in order to perform these procedures safely and to achieve positive results of the drug therapy. In addition, it must be considered that there is a distance between academic theory and the knowledge of health teams, such as crushing modified-release pills, with consequent increase or decrease in absorption. A lack of training of the teams (doctors, pharmacists and nursing) was observed, with constant doubts presented by them and a lack of materials for consultation on the safe and effective execution of pharmacotherapy through tubes. These point to the need for formulating formal material of consultation, such as manuals, folders, explanatory videos and posters, to guide conducts, as well as the implementation of continuing education programs for the employees involved (Godoi et al., 2016). Therefore, it is necessary to elaborate guides that help nursing professionals to know the good practices in the process of preparation and administration of drugs by enteral tubes, as well as to stimulate the study and the search for knowledge for improvements in the care of patients (Johnson et al., 2018).

Study limitations

The study presented limitations. The good practice

guidance was developed with a multidisciplinary team. However, there was no participation of mid-level nursing professionals. In addition, the guide was refined based on the requirements of a general mid-sized hospital and may not reflect the context of other health care institutions.

Conclusion

The good practice guidance for safe oral medication preparation and administration through feeding tubes was developed through joint collaboration between researchers and the multidisciplinary team and relied on scientific evidence of best practice and on ethical principles. It is a comprehensive resource to support safe practices and it optimally utilizes the skills of healthcare teams. The development of a robust document to support safe medication practices should consider the hospital's individual requirements to promote adherence by all healthcare professionals. In addition, training programs should be planned to educate healthcare teams in accepting full responsibility and accountability for the decision to use the guide. The next step is to evaluate the impact of the GPG on medication errors and patients' outcomes.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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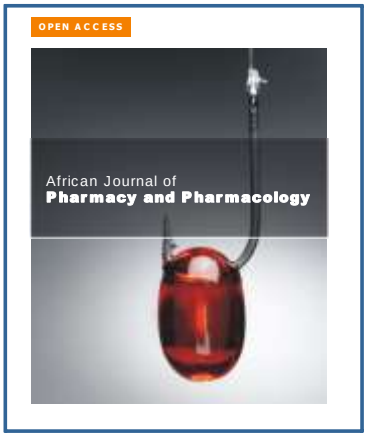

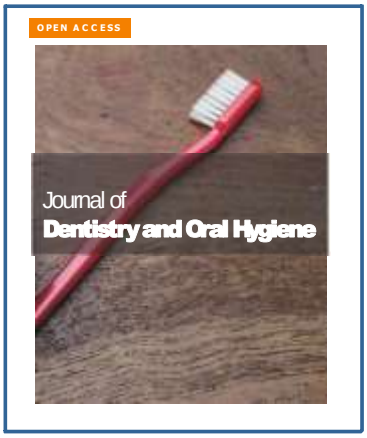

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