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Microbiological Quality of Over-The-Counter (OTC) oral Drug Preparations Obtained From Some Retail Pharmacies in Katsina State, Nigeria

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Abstract: Over the counter (OTC-drugs) oral preparations being classified as non-sterile pharmaceutical products are easily prone to microbial contamination. The presence of microbial contaminants in these products may cause spoilage resulting in physical and chemical changes, as well as risk of infection or potential health hazard to the patients. A study aimed at evaluating the microbiological quality of some OTC drugs commonly dispensed to patients in Katsina was conducted from April, 2017 to March, 2019. One hundred and twenty-five (125) samples of four different OTC drugs on sale were evaluated for microbial quality using standard procedures as described in the official monograph of the British and United Stated pharmacopoeia. Incidence of microbial contamination was observed in 60 (48%) of the tested samples with 23 (18.4%) of the tested preparations having microbial count exceeding the USP and BP acceptable limit for the microbiological quality of non-sterile oral dosage forms. *Bacillus species* were the predominant contaminants recovered from the tested products. The study revealed a considerable level of microbial contamination in the examined products and thus highlighted the need for the manufacturers of these products to pay more attention and adhere strictly to the guidelines of the current good manufacturing practices.
Keywords: Microbial contamination, Non-sterile, OTC, British and United States pharmacopoeia.

INTRODUCTION

Pharmaceutical products are manufactured purposely with the intention to treat a target medical condition. Nevertheless, several factors could compromise this goal, one of them being possible contamination with pathogenic and non-pathogenic microorganisms (Okunlola *et al*., 2007).

Non-sterile preparations, although not required to be sterile as described by most pharmacopeia, are however required to pass the microbial bioburden tests and tests for the absence of certain specified indicator pathogens. These include preparations for routes of administration such as oral, topical, and rectal (Rania *et al.*, 2013; British pharmacopoeia, 2016).

Factors such as manufacturing raw materials, manufacturing water, manufacturing environment, packaging materials, and personnel have been implicated as potential sources of contaminants in pharmaceutical products (Khanom *et al,* 2013; Rana *et al.,* 2014) and this implies that pharmaceutical preparations can be contaminated at the point of production, packaging by the manufacturer, storage, distribution, dispensing or during usage by the consumers (Osungunna *et al.*, 2016).

Microbial contamination of pharmaceutical products presents a lot of problems that ranged from spoilage resulting in physical and chemical changes, risk of infection or potential health hazard to the consumer as well as product recalls and business loss (Calistus *et al.*, 2011; Oviasogie *et al.,* 2015).

Owing to the impaired manufacturing conditions such as irregular and inconsistent monitoring of equipment, personnel, and environment by most pharmaceutical companies, microbial limits testing of raw material and finished product is a critical step for the quality control analysis of nonsterile pharmaceutical products (Atata and Biyaosi, 2016).

Due to the increasing number of immunocompromised patients, increased attention needs to focus on the quality of oral pharmaceutical products being administered to these patients (Manu-Tawiah *et al*., 2001).

The presence of even a low level of pathogenic microorganisms, higher levels of opportunistic pathogens or bacterial toxic metabolites can be fatal to immunocompromised patients and in infants with an immature immune system (Shukla *et al*., 2004; Mugoyela and Mwambet, 2010).

Over the counter drugs such as paracetamol, vitamin C, antacids and cough syrups are widely used among the general population, the microbiological safety of these drugs is an important public health concern. This study was therefore aimed at investigating the microbiological quality of non-sterile OTC drugs available on sale in various retail outlets in Katsina State, Nigeria.

MATERIALS AND METHODS

Collection of Drug Samples

Samples of non-sterile OTC oral drug preparations were purchased on sight and anonymously by adopting the method of Kolawole *et al.* (2002). The samples were obtained from different hospital pharmacies and retail patent medicine stores within the state. The samples comprised of paracetamol, cough syrups, antacids and vitamin C consisting of different dosage forms such as tablets, syrups, and suspensions. For each of the sample collected, the batch number, NAFDAC registration number, date of manufacture, date of expiry, dosage form was noted. All the samples collected and analyzed were within their shelf lives.

Preparation of Test Samples

Prior to the opening of the samples, the outer surfaces of sample containers were cleansed with 70% v/v ethanol as described by Rania *et al*, (2013) and Shaqra *et al,* (2014). Sample preparation was conducted according to the United States Pharmacopeia (USP 41, 2018). A 1 in 10 dilution was prepared by dissolving 10g (tablets) or diluting 10 ml (syrups and suspensions) of the product to be examined in 90ml of Trypticase Soy Broth (TSB).

Microbial Enumeration Tests: microbial enumeration test was carried out as described by the United States Pharmacopeia (USP 41, 2018). One (1ml) of test samples were inoculated onto plates of Casein Soya Bean Digest Agar (CSBDA) and incubated at 37°C for 3–5 days, and Sabouraud-Dextrose Agar (SDA) at 25°C for 5–7 days. Duplicate plates for each level of dilution were prepared and incubated. Arithmetic mean of the counts was taken and the counts were expressed as the number of colony-forming units per milliliter or gram of the sample (CFU/mL or g).

Detection and isolation of specific microbial contaminants

Various differential and selective media such as Mac-Conkey agar, Eosine Methylene blue (EMB) agar, Mannitol Salt Agar, Cetrimide agar and Xylose Lysine Deoxycholate agar were used to isolate specific bacterial contaminants. Gram-staining and microgen identification kits namely; Bacillus-ID system, Staph-ID system and Microgen^{TM}GnA+B-ID system (Microgen Bioproducts Ltd, UK) were utilized for further identification of the isolated bacterial contaminants according to the manufacturers' instructions.

Fungal growths from the SDA plate were identified using the standard procedure described in a guide to the identification of medically important fungi by Davise (2012). The growth of the specific fungus was identified based on their colonial morphology, and further identification was achieved by lactophenol cotton blue stain and microscopically based on their cellular morphology and differentiation.

Identification of Isolated Contaminants using PCR and 16S rRNA Gene Sequencing

Representative bacterial contaminants were further identified by PCR amplification of the 16S rRNA gene and Sanger sequencing method and phylogenetic analysis.

Genomic DNA was extracted using the boiled lysis method (Kargar *et al.*, 2014; Lindsey *et al.,* 2017).

Amplification of the 16S rRNA gene was carried out using the universal primers 27F (5'-AGA GTT TGA TCC TGG CTC AG-3') and 1492R (5'-GGT TAC CTT GTT ACG ACT T-3') Senthilraj *et al.*, (2016).

A 50 µl reaction mixture which consists of 25 µl of One Tag Quick-Load 2X Master Mix with standard buffer, 1µl each of the Forward and Reverse primers, 5 µl of the extracted DNA (DNA template), and then 18 µl of Nuclease-free water was prepared. Negative control which consists of the Master Mix, Primers, and the Nuclease-free water was used throughout the PCR assay.

DNA amplification was conducted in a thermocycler (BIO-RAD, Applied Biosystems USA) with the following PCR conditions; initial denaturation at 94°C for 2 minutes, then 35 cycles of denaturation at 94°C for one minute, annealing at 46°C for 1.0 minutes and extension at 72°C for one minute, then final extension at another 72°C for 5 minutes and at infinite hold at 4°C.

Agarose Gel Electrophoresis

After PCR amplification of the 16s rRNA gene, one percent (1.0%) agarose gel was prepared and loaded with the amplified PCR products, 5 µl 100bp ladder and the negative control. The loaded gel was run at 90V for 30 minutes. After this, the gels were visualized using a Benchtop UV-Transilluminator (BioDoc-It 220 Imaging System, USA).

16S rRNA Gene Sequencing and Phylogenetic Analysis

The amplified PCR products were sequenced using the 16S rRNA Sanger Sequencing method at Inqaba Biotec West Africa. The sequences thus obtained were compared with other sequences deposited at the NCBI database to identify close sequence matches through BLAST searches using the BLAST software available at the National Center for Biotechnology Information website; http://www.ncbi.nlm.nib.gov/BLAST/blast. Evolutionary relationships among bacterial strains were inferred by comparing the sequences of the 16S rRNA genes of the identified bacterial strains with the 16S rRNA gene sequences of other related species downloaded from the gene bank of NCBI. Using MEGA X software, the sequences were aligned by multiple sequence alignment technique using CLUSTAL W and a phylogenetic tree constructed by employing the neighbor-joining method (Adesoji *et al.,* 2015; Senthilraj *et al.*, 2016).

RESULTS

During the study period, one hundred and twenty-five (125) samples of non-sterile oral drug samples were collected and examined for microbiological quality. Result of the microbiological examination showed that sixty, (60) samples, comprising 48.0% of samples had microbial contamination with the highest incidence of microbial contamination observed in vitamin C samples, where 17 (13.6%) were contaminated, followed by paracetamol and antacid samples, while the lowest incidence of contamination was observed in cough syrup samples as shown in table 1.

Table 1: Incidence of microbial contamination among the tested samples

Drug type	Total Samples Tested	No. of Contaminated Samples	% Contamination
Paracetamol	40	16	12.8%
Cough syrups	26	11	8.8%
Antacids	29	16	12.8%
Vitamin C	30	17	13.6%
Total	**125**	**60**	**48%**

Incidence of microbial contamination among the different dosage forms as shown in table 2 revealed that syrups samples were the most contaminated, 32 (25.6%) while tablets were the least contaminated.

Table 2: Incidence of microbial contamination among the different dosage forms

Dosage forms	Number of tested samples	No. of Contaminated Samples	% Contamination
Tablets	32	12	9.6%
Syrups	68	32	25.6%
Suspensions	25	16	12.8%
Total	**125**	**60**	**48%**

Microbial enumeration (CFU/mL or g) and bioburden level in the tested samples which comprised of total aerobic microbial count (TAMC) and total yeast and mould count (TYMC) as presented in table 3, showed that the proportion of the samples that had a total aerobic microbial count greater than 1000 CFU/mL or g of the samples was 18 (14.4%). Antacids and paracetamol samples had the highest number of samples that exhibited a total aerobic microbial count greater than 1000 CFU/mL or g.

Similarly, 5 (4.0%) of the samples had a total yeast and mould count greater than 100 CFU/mL or g of the samples. Samples of vitamin C had the highest number of samples that exhibited a total yeast and mould count greater than 100 CFU/mL or g.

Table 3: Microbial Bioburden Level (CFU/mL or g) in the Tested Samples

Drug type	Total Aerobic Microbial Count (TAMC)			Total Yeast and Mould Count (TYMC)		
	< 100	100 – 1000	> 1000	10	> 10-100	> 100
Paracetamol	5	4	5	3	1	2
Cough syrups	5	2	3	0	0	0
Antacids	2	0	8	0	2	0
Vitamin C	2	7	2	0	0	3
Total (%)	**14 (11.2)**	**13 (10.4)**	**18 (14.4)***	**3 (2.5)**	**3 (2.5)**	**5 (4.0)***

***- indicate the proportion of samples with counts above the USP limit**

Microbial contaminants recovered from the tested dosage forms

In general, a total of 72 microbial contaminants were isolated from the 60 contaminated samples of the tested preparations. The majority of the microbial contaminants recovered were bacteria and a few fungal isolates. Of the bacterial species recovered from the tested dosage forms, Gram-positive bacilli namely *Bacillus* species accounted for the majority of isolates.

The majority of the fungal isolates recovered from the tested non-sterile pharmaceutical products were moulds belonging to genera *Aspergillus and Penicillium.* While candida species accounted for the majority of the yeast isolates recovered.

Moreover, of the total bacterial and fungal isolates recovered, 13 were identified as USP and BP indicator or objectionable pathogens. The predominant USP indicator pathogen isolated was *Staphylococcus aureus,* 07 (34.8%), followed by *Pseudomonas aeruginosa,* 03 (30.4%) and *Candida albicans,* 02 (26.1%) and one *Escherichia coli* isolate as shown in ta ble 4.

PCR-based Detection of Representative Bacterial isolates

The gel electrophoresis of PCR amplification of the 16S rRNA gene of the bacterial isolates showed positive results with bands size of approximately of 1500 bp in length as depicted on Plate 1.

The phylogenetic analysis of the 16S rRNA gene sequences and NCBI blast search placed the isolates to the genus *Pseudomonas, Enterobacter* and *Bacillus* showing higher sequence similarity that ranged from 96 to 100 % compared with sequences of related bacterial strains in GenBank of NCBI (Table 5).

Figures 1 and 2 are phylogenetic trees showing evolutionary relationship of 16S rRNA sequences of isolates of *Pseudomonas aeruginosa* and *Bacillus* species recovered from non-sterile oral drug formulations as compared with the sequences of related bacterial strains in the NCBI.

Table 4: Microbial Contaminants recovered from the tested samples

Drug type	Microbial contaminants recovered
Paracetamol	*Bacillus spp, Micrococcus spp, Staphylococcus simulans, S. intermedius, Penicillium, Aspergillus niger*
Cough syrups	*Bacillus licheniformis, B. subtilis, Enterobacter spp, Micrococcus spp, Candida spp*
Vitamin C	*Bacillus licheniformis, B. circulans, Staphylococcus xylosus, Enterobacter spp, Pseudomonas aeruginosa, Pluralibacter gergoviae, Escherichia coli*
Antacids	*Bacillus spp, Staphylococcus aureus, S. xylosus, S. simulans, Acinetobacter spp, Pseudomonas aeruginosa, Candida albicans, Aspergillus niger, A. flavus*

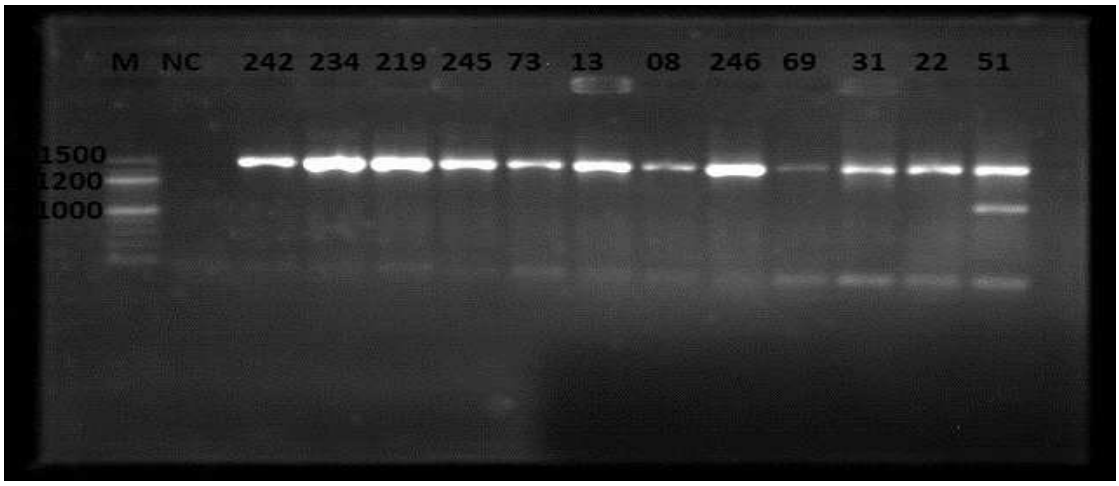


Plate 1: Agarose gel electrophoretogram of the amplified 16S rRNA gene (approx. 1500bp), lane M (100-bp DNA ladder), lane NC (Negative control), and lanes 242-51 (Test organisms).

Table 5: Bacterial strains identified through 16S rRNA sequencing and BLAST search

S/N	Isolate Code	Representative species (Accession number)	Percentage Similarity
1.	070	*Pseudomonas aeruginosa* strain (MK720218.1)	100%
2.	219	*Pseudomonas aeruginosa* strain HPRTGC207 (MH393917.1)	100%
3.	234	*Pseudomonas aeruginosa* strain NG4 (MN238694.1)	99.86%
4.	221	*Pseudomonas aeruginosa* strain (MK537388.1)	99.85%
5.	232	*Pseudomonas aeruginosa* strain (MK616103.1)	99.85%
6.	242	*Pluralibacter gergoviae* strain Rizhao_605 (MN249556.1)	99.87%
7.	69	*Enterobacter cloacae* strain (KX450926.1)	95.90%
8.	08	*Bacillus cereus* strain PR90 (MN232174.1)	99.87%
9.	73	*Bacillus subtilis* strain Cd4 (MK256680.1)	99.81%
10.	22	*Bacillus cereus* strain (MN232137.1)	98.73%

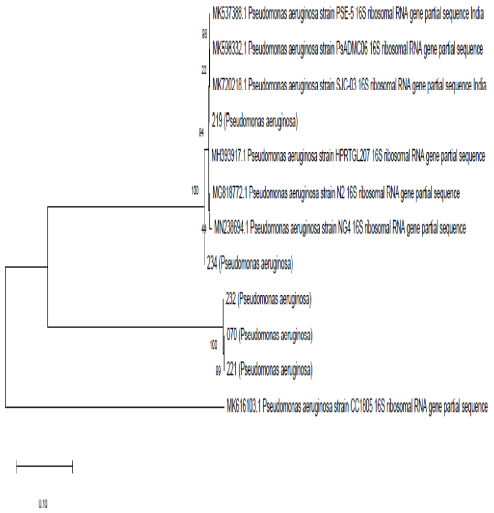


Figure 1: Phylogenetic relationship of 16S rRNA sequences of *Pseudomonas aeruginosa isolates (219, 234, 232, 070 and 221)* from Non-sterile oral drug formulations compared with the sequences of related *Pseudomonas* strains in the NCBI

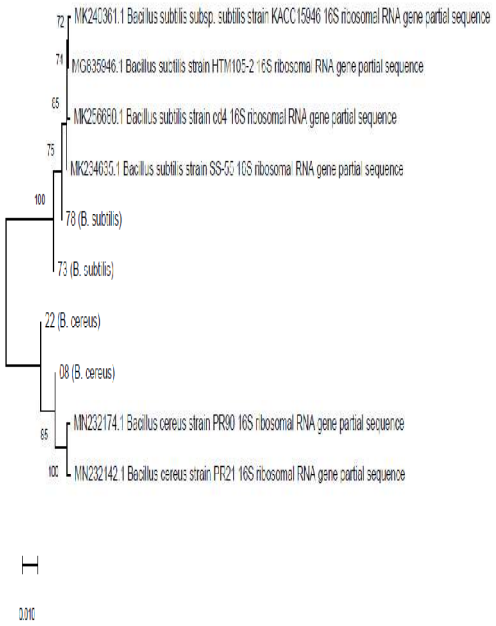


Figure 2: Phylogenetic relationship of 16S rRNA sequences of *Bacillus isolates (78, 73, 22, and 08)* from Non-sterile oral drug formulations compared with the sequences of related *Bacillus* strains in the NCBI

DISCUSSION

In this study, the incidence of microbial contamination in non-sterile pharmaceutical products in Katsina, Nigeria was observed in 60 (48.0%) of the tested samples. This implies that a greater proportion of the tested products were microbiologically contaminated. The implication of these findings is that the public is exposed to microbiologically contaminated pharmaceutical preparations with a potential of increased treatment failure, in addition to the dissemination of pathogens to consumers (Aisha *et al,* 2007).

The incidence of microbial contamination observed in this study is consistent with the report of the previous study by Mugoyela and Mwambete (2010) in Darussalam, Tanzania and that of Osungunna *et al.*, (2016) which found that 50% of their tested samples were contaminated. A much higher incidence of microbial contamination has been reported such as Ewansiha *et al.*, (2014) reported contamination in 90% of pharmaceutical products sold in Yola Metropolis, Adamawa, Nigeria. Moreover, Adeshina *et al.*, (2009) and Kabir *et al.,* (2013) reported the presence of microbial contamination in all the samples tested.

On the other hand, lower incidences of microbial contamination in pharmaceutical products have been reported. Zeitoun *et al.*, (2015) reported a 36.5% incidence of microbial contamination of pharmaceuticals and cosmetics in Egypt. Similarly, Shaqra *et al,* (2014) in Jordan demonstrated that out of 66 items investigated, only 18 items (27.3 %) were contaminated while 48 (72.7 %) were free from microbial contaminants. Furthermore, Rania *et al,* (2013) in Egypt had similar observation, were 27.6% of the examined products were microbiologically contaminated. Similarly, a study on the microbial quality of selected non-sterile pharmaceutical products commonly sold in retail outlets in Dutsinma metropolis, Nigeria by Kilani and Olaifa (2017) reported that 28.9% of the products were contaminated.

Different bioburden levels of microbial contamination such as those that are either within or have exceeded the limit for microbial quality of non-sterile oral dosage forms there-in established by USP, 2018 and BP, 2017 have been reported. In the present study, 23 (18.4%) of the tested preparations had microbial count exceeding the USP and BP acceptable limit for the microbiological quality of non-sterile oral dosage forms.

Adeshina *et al.*, (2009) in their study reported that all the preparations tested were contaminated with fourteen (14) preparations exceeded the official tolerance limit of permissible microorganisms specified for syrups and suspensions. Similarly, Obi and Nwannunu (2010) who investigated tablets dispensed to patients by counting found that all brands they studied harboured microbial count in excess of 10^5 CFU/g. In a similar study, Moniruzzaman *et al.* (2012) reported microbial contamination in antacids and paracetamol samples from different drug stores of Dhaka, Bangladesh, with 75% of the antacid and 60% of the paracetamol samples showing microbial count exceeding the USP limit.

On the other hand, lower bioburden levels of microbial contaminants were reported by Akerele and Ukoh (2002) as well as Nwambete *et al,* (2010) where in all the samples examined, the aerobic bacterial counts were within the standard limits for non-sterile preparations. Similarly, Kilani and Olaifa (2017) and Gad *et al,* (2011) reported that the proportions of the tested samples containing viable aerobic bacterial count of >1000 CFU/ml was minimal; it was 5% in paracetamol tablets and 5.8 % in syrups and 10 % in suspensions respectively. Shaqra *et al,* (2014) demonstrated that out of 66 items investigated, only 10.6 % of the items contained bacterial count between 10^2 and 10^3 CFU/g.

In the present study, the contamination rate was lower in solid dosage forms especially tablets than in the liquid dosage forms particularly syrups and suspension.

The observed differences in the contamination rate may be attributed to the lower water activity of tablets which is usually < 0.60 compared to the syrups and suspensions. Low water activity is inhibitory to the growth of most microorganisms especially members of the family, Enterobacteriaceae, as well as aerobic and anaerobic spore formers, but allow the growth of certain vegetative microorganisms, such as *Staphylococci* and *Micrococci*, especially *Staphylococcus aureus* which grow below a water activity of 0.86 (Gad *et al.,* 2011).

In addition to the low water activity, the harsh procedures and other manufacturing processes typically used in the processing of oral solid dosage particularly tablets which are detrimental to microbial growth is another factor that probably contributed to the low microbial counts obtained in tablets and other solid dosage (Shaqra *et al.,* 2014).

The presence of microbial contamination in the tested sample may probably result from unhygienic practices, and non-adherence to good manufacturing practices, poor state of the manufacturing environment, unhygienic manufacturing equipment, unhygienic handling of the products and lack of microbiological in-house control Oviasogie *et al*., (2015).

CONCLUSION

The study has successfully revealed a significant level of microbial contamination in the examined products, with 23 (18.4%) of the tested preparations failing to comply with the USP and BP acceptable limit for the microbiological quality of non-sterile oral dosage forms.

It is recommended that manufacturers of pharmaceutical products should strictly adhere to the guidelines of the current good manufacturing practices and ensure quality control processes during the manufacture, storage, and distribution of these products. And the regulatory agencies such as NAFDAC should intensify efforts towards ensuring the circulation and sales of standard drugs to the populace. Patients and consumers of pharmaceutical products are reminded of the need to maintain hygienic practices during the usage and storage of products to minimize the introduction of contaminants.

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