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Evaluation of the microbial quality and safety of regulated and unregulated liquid herbal preparations in Benin City, Nigeria.

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Abstract

Due to people's unhappiness with orthodox treatment, prior positive experiences, family traditions, and poverty, the use of herbal drugs has expanded globally. Unhygienic production conditions are typically one of the drawbacks of herbal products. The aim of this study was to evaluate the microbial quality and safety of regulated and unregulated liquid herbal preparations in Benin City, Nigeria. Standard microbiological procedures were employed in the identification of the isolated microbes and the evaluation of the total viable bacterial count in the 50 herbal preparations that were tested. A larger proportion (36%) of the unregulated herbal preparations was contaminated with bacteria as compared with regulated ones (4%). *Klebsiella pneumoniae* was the predominant bacterium isolated from unregulated herbal products. A proportion of 2% and 26% of the regulated and unregulated herbal preparations, respectively, exceeded the World Health Organization's acceptable limit for microbial contamination. In Benin City, there are a lot of unregulated herbal remedies with microbial contamination that is higher than the WHO's permitted level for aerobic and coliform bacteria. The regulatory agencies should intensify efforts to ensure that all herbal medicines marketed in the country are lawfully registered and produced in accordance with current Good Manufacturing Practice standards.

Keywords: Good Manufacturing Practice (GMP), Herbal preparation, Microbial contaminations, NAFDAC.

Introduction

According to the World Health Organization (WHO), traditional herbal medicine includes herbs, herbal preparations, herbal materials, and completed herbal products that include plant parts or other plant materials as active components and are used to cure or prevent a variety of illnesses (Tilburt and Kaptchuk, 2008). In low-and middle-income countries, about 80% of the population utilizes herbal drugs as their main source of primary health care (Ugbomoiko *et al*., 2022; Kretchy *et al*., 2021; Umair*et al*., 2017; WHO, 2002b). In many African nations, herbal preparation is the first option for treating children at home who have a high fever caused by malaria (Aschwanden, 2001). These products are reliable, simple to use, accessible, affordable, and believed to be safer than orthodox medicine (Abualhasan *et al*., 2020; Farrington *et al*., 2019). Due to the region's rich biodiversity, there is currently a trend in Nigeria toward employing a variety of herbal preparations as alternative medicines. Traditional herbal healers in Nigeria cure a wide range of illnesses with different herbal remedies, including skin conditions, cough, seizures, neonatal fistula, diarrhea, etc. (Sofowora, 1982). The majority of these herbal products are used as concoctions, which are soups or drinks that are often created by boiling materials, or as infusions, which involve soaking plant material and letting it stand for varying amounts of time (Adeleye and Opiah, 2003).

In the developing world, the microbial safety of herbal medicines is a big concern because there are worries that they may be prepared in unhygienic ways and put consumers in danger (Rajkumar and Sriram, 2021; Abtahi and Nourani, 2017; Khattak, 2012). These risks include those related to the nervous system, the heart, and the blood (Palmer *et al*., 2003). Microbial pollutants that produce toxins are frequently to blame for these negative impacts. As a result, it is crucial to recognize the microbiological contaminants in herbal preparations as signs of their quality and safety (Schweiggert *et al*., 2005).Herbal goods may become contaminated by microorganisms at any point in the production process, from planting and harvesting to packaging, shipping, and storage (Kosalec *et al*., 2009).The packaging for these goods is frequently poor as well; the finished preparations are frequently placed in unlabeled recycled plastic bottles (Igbeneghu and Lamikanra, 2016). *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, Enterobacter spp., Bacillus spp., *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* are a few of the prevalent bacteria detected in herbal medicines (de Sousa *et al*., 2020; Yesuf *et al*., 2016).

Because of this, pharmaceutical businesses are expected to follow the guidelines of Good Manufacturing Practice (FDA, 2015), and their products must be subjected to strict quality controls. Additionally, the entire medication manufacturing process must pass quality assurance tests at every stage (Igbeneghu and Lamikanra, 2016). However, it must be acknowledged that only the large pharmaceutical firms have the resources to follow the guidelines of modern GMP (Igbeneghu and Lamikanra, 2016). Small pharmaceutical companies many of which are located in nations with struggling economies are unable to finance machinery or the hiring of qualified personnel to ensure that their goods are of consistently high quality (Okeke and Lamikanra, 2001). Nigeria's situation is made worse by the existence of a sizable informal sector, which is in charge of the small-scale production of numerous unregistered and typically unstandardized medications using crude equipment and raw plant-derived materials that are extremely vulnerable to extensive contamination (Igbeneghu and Lamikanra, 2016). The relevant regulatory organizations have no control over these unregistered herbal medications. However, they cannot be disregarded because they are widely accessible, particularly in rural areas where there is a lack of modern pharmaceutical coverage (Igbeneghu and Lamikanra, 2016). Therefore, this study aimed to evaluate the microbial quality and safety of regulated and unregulated liquid herbal preparations in Benin City, Nigeria.

Method

Study Area and Design

This cross-sectional study was carried out in Benin City. The Benin City is the capital of Edo State, located in the South-South region of Nigeria (latitude 6°20′00" N and longitude 5°37'20"E). Benin City has an estimated area of 1,204 km^2 and a population of over 1,500,000 according to the 2006 census (Encyclopedia Britannica, 2022).

Sample Collection and Preparation

Ten (10) regulated and forty (40) unregulated liquid herbal preparations were randomly purchased from 3 major areas across Benin City, Nigeria; from hawkers, herbal shops, and drug stores. These areas were Adolor, Technical, and Uselu. Details regarding the dosage and uses of each product were collected from the vendors and recorded. To avoid bias, the reason for purchasing the preparations was not made known to the vendors. All samples were transported in a sterile screw-capped bottle to the Medical Microbiology Laboratory of the University of Benin Teaching Hospital (UBTH) in a cold box within one hour of collection. The preparations were stored at 4 °C until use.

Laboratory Analysis

Identification of isolated bacterial species

Ten millilitres of the samples were centrifuged for 5 minutes at 5000 rpm. The pellets were then inoculated onto MacConkey agar, Blood agar, Eosin Methylene Blue agar, and Deoxycholate Citrate agar. For 18 to 24 hours, the culture plates were incubated at 37°C. Isolated bacteria were identified by standard microbiological procedures (Cheesbrough, 2006).

Evaluation of total viable bacterial count

The samples were mixed vigorously to homogenize and then serially diluted by ten-folds up to 10^{-5}. The microbiological analysis was performed in triplicate. One millilitre of each dilution was pipetted into each Nutrient Agar plate with a sterile pipette and incubated for 24 hours at 37°C. After the incubation period, the average number of colonies was multiplied by the dilution factor to determine the colony-forming units per milliliter (CFU/ml). The CFU/ml of the sample that was obtained was compared to WHO standards. According to the WHO criteria for aerobic bacteria, herbal preparations with > 10^5 CFU/ml were considered unsatisfactory (WHO, 2007a).

Antimicrobial susceptibility test

Isolates were cultivated overnight on nutrient agar and emulsified in 3ml of sterile physiological saline to achieve turbidity corresponding to 0.5 McFarland standards. Using a sterile, non-toxic cotton swab, the Mueller-Hinton agar plates were inoculated with the standardized inoculum. The selected antibiotic discs (Cefoxitin [30 µg], Piperacillin [100 µg], Gentamycin [10 µg], and Meropenem [10 µg]) by Thermo Scientific™, MA, USA; were placed on the agar plates and incubated at 37°C for 24 hours.

Statistical Analysis

Descriptive statistical analysis was carried out using SPSS (Statistical Package for the Social Sciences) Version 23 Software. The Chi-square test was employed to determine whether category variables were related. For all statistical tests, a P value less than 0.05 was considered significant.

Results

Characteristics and intended use of herbal preparations sold in Benin City.

Among the 50 herbal preparations tested, 15 (30%) were purchased each from the Adolor and Technical areas of Benin City, while 20 (40%) were from the Uselu area of the city. Forty (80%) of the herbal preparations were unregistered and unregulated by the appropriate Regulatory body. Thirty-nine (78%) of the herbal products were

prepared with water (Table 1). Each of the herbal preparations tested in this study has one or more therapeutic purposes according to their sellers (Table 2).

Table 1: Characteristics of herbal preparations sold in Benin City, Nigeria.

Herbal Preparation	Frequency (%)
Regulation Status	
Regulated	10 (20.0)
Unregulated	40 (80.0)
Total	50 (100.0)
Solvent	
Water	39 (78.0)
Alcohol	11 (22.0)
Total	50 (100.0)
Area	
Adolor	15 (30.0)
Technical	15 (30.0)
Uselu	20 (40.0)
Total	50 (100.0)

Table 2: Intended use of herbal preparations sold in Benin City, Nigeria.

Purpose	Herbal Preparation	
	Regulated N (%)	Unregulated N (%)
Asthma	-	1 (2.5)
Blood tonic	-	1 (2.5)
Body pain	-	3 (7.5)
Cough/Pharyngitis	1 (10.0)	3 (7.5)
Deworming	-	1 (2.5)
Diarrhoea/Dysentery/Pile	-	4 (10.0)
Immune booster	2 (20.0)	-
Malaria	-	2 (5.0)
Multipurpose	-	2 (5.0)
Reproductive health	5 (50.0)	3 (7.5)
Rheumatism/Arthritis	2 (20.0)	4 (10.0)
Skin infections	-	1 (2.5)
STIs/Gonorrhoeae	-	1 (2.5)
Stomach pain	-	5 (12.5)
Stomach ulcer	-	2 (5.0)
Tooth infections	-	1 (2.5)
Typhoid	-	3 (7.5)
UTI	-	3 (7.5)
Total	10 (100.0)	40 (100.0)

Prevalence and total viable counts of isolated bacteria species

Overall, 20 (40%) of the tested herbal preparations were contaminated with bacteria, out of which 36% were from unregulated herbal products. A total prevalence of 4% was observed each for *S. aureus*, *E. coli*, and Enterobacter spp among the tested herbal products. However, *K. pneumoniae* had a prevalence of 10%, followed by *K. oxytoca* and *P. mirabilis* with 8% each (Table 3). The microbial counts of isolated bacteria ranged from 2.8 x 10^4 CFU/ml to 3.1 x 10^4 CFU/ml and 3.8 x 10^4 CFU/ml to 12.6 x 10^8 CFU/ml for the regulated and unregulated herbal products, respectively (Data not shown).

Table 3: Bacterial species isolated from regulated and unregulated herbal preparations.

Bacteria Isolate	Herbal Preparation		
	Regulated N (%)	Unregulated N (%)	Total N (%)
S. aureus	1 (2.0)	1 (2.0)	2 (4.0)
E. coli	1 (2.0)	1 (2.0)	2 (4.0)
K. pneumoniae	-	5 (10.0)	5 (10.0)
K. oxytoca	-	4 (8.0)	4 (8.0)
P. mirabilis	-	4 (8.0)	4 (8.0)
Enterobacter spp	-	2 (4.0)	2 (4.0)
Citrobacter spp	1 (2.0)	1 (2.0)	1 (2.0)
Total	2 (4.0)	18 (36.0)	20 (40.0)

Microbial quality of the herbal preparations

In general, 2% and 26% respectively, of the regulated and unregulated herbal preparations exceeded the acceptable limit of microbial contamination according to the WHO standards (WHO, 2007a). Although not statistically significant, herbal products prepared with water were more contaminated with bacteria than those prepared with alcohol. Similarly, herbal products that are unregulated and prepared with water are 3 times more likely to exceed the acceptable microbial limit compare to those that are regulated and prepared with alcohol (Table 4).

Table 4: Microbial quality of herbal preparations in Benin City, Nigeria.

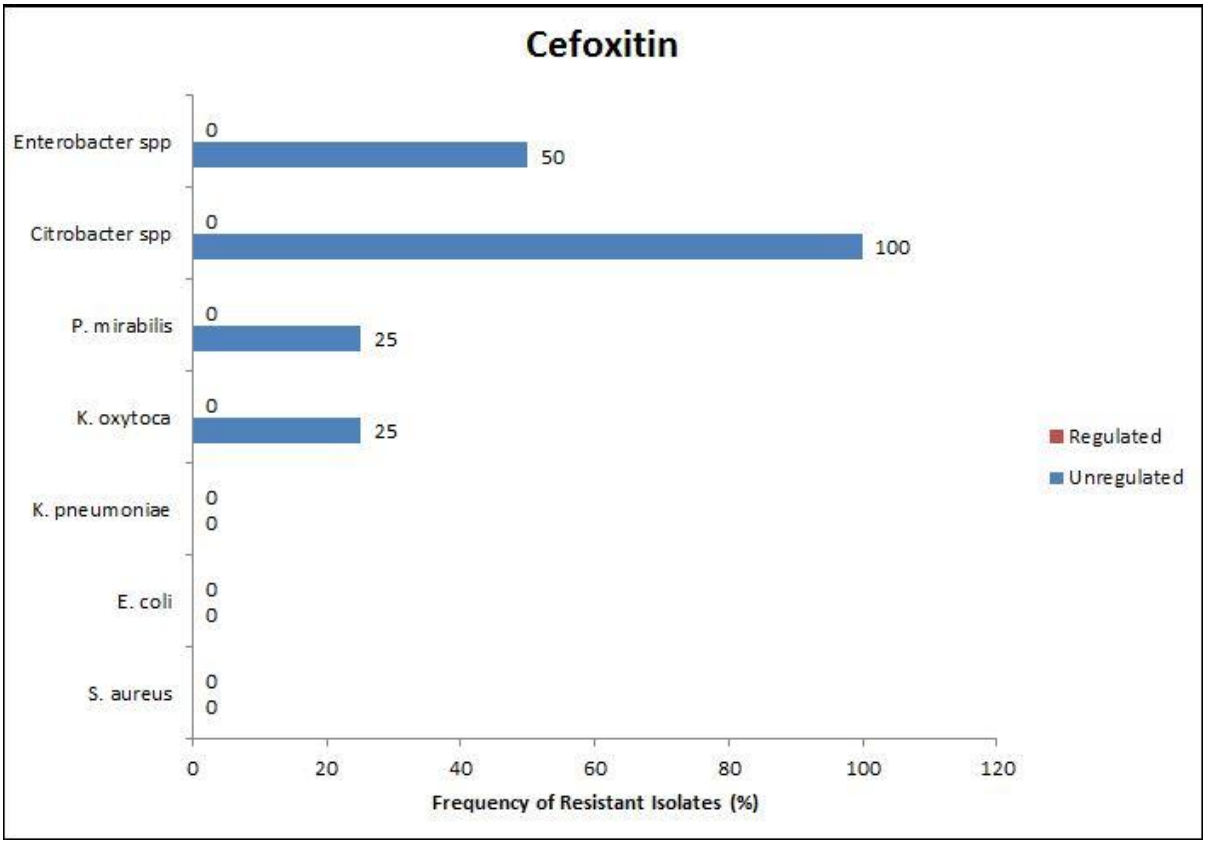
Herbal Products	Microbial Quality			
	Acceptable N (%)	Unacceptable N (%)	Odd Ratio (95% CI)	P-value
Regulation Status				
Regulated	9 (18.0)	1 (2.0)	1	
Unregulated	27 (54.0)	13 (26.0)	4.33 (0.49-37.93)	0.1852
Total	36 (72.0)	14 (28.0)		
Solvent				
Water	26 (52.0)	13 (26.0)	5.00 (0.58-43.39)	0.1443
Alcohol	10 (20.0)	1 (2.0)	1	
Total	36 (72.0)	14 (28.0)		
Area				
Adolor	12 (24.0)	3 (26.0)	0.69 (0.12-3.79)	0.6668
Technical	11 (20.0)	4 (2.0)	1	
Uselu	13 (20.0)	7 (2.0)	1.48 (0.34-6.42)	0.6001
Total	36 (72.0)	14 (28.0)		

Regulation Status and Solvent				
Unregulated and water based	23 (46.0)	13 (26.0)	3.39 (0.37-31.34)	0.2817
Unregulated and alcohol based	4 (8.0)	-	0.48(0.02-14.70)	0.6752
Regulated and water based	3 (6.0)	-	0.62 (0.02-19.59)	0.7855
Regulated and alcohol based	6 (12.0)	1 (2.0)	1	
Total	36 (72.0)	14 (28.0)		

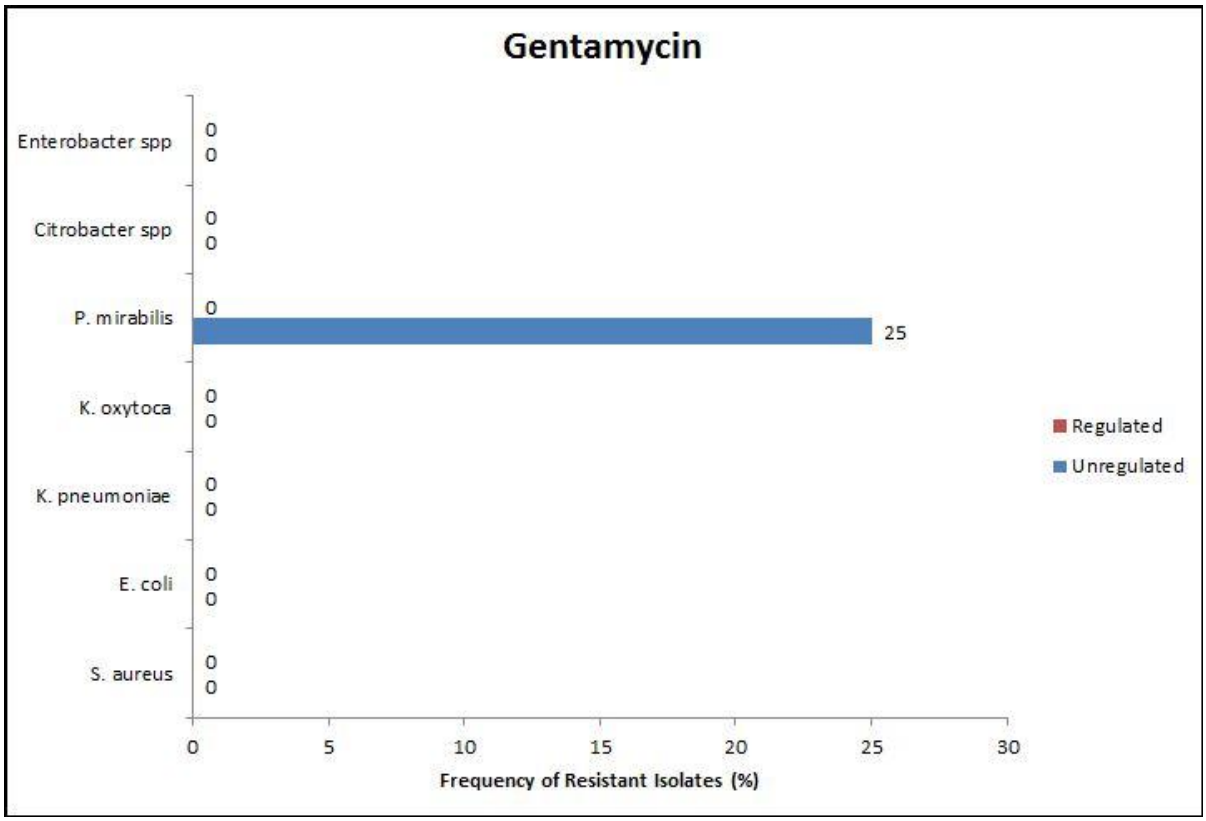
Acceptable limit: Aerobic bacteria – ≤ 10^5 CFU/ml, *Escherichia coli* – 10 CFU/ml(WHO, 2007a).

Resistance of isolated bacterial species to antibiotics

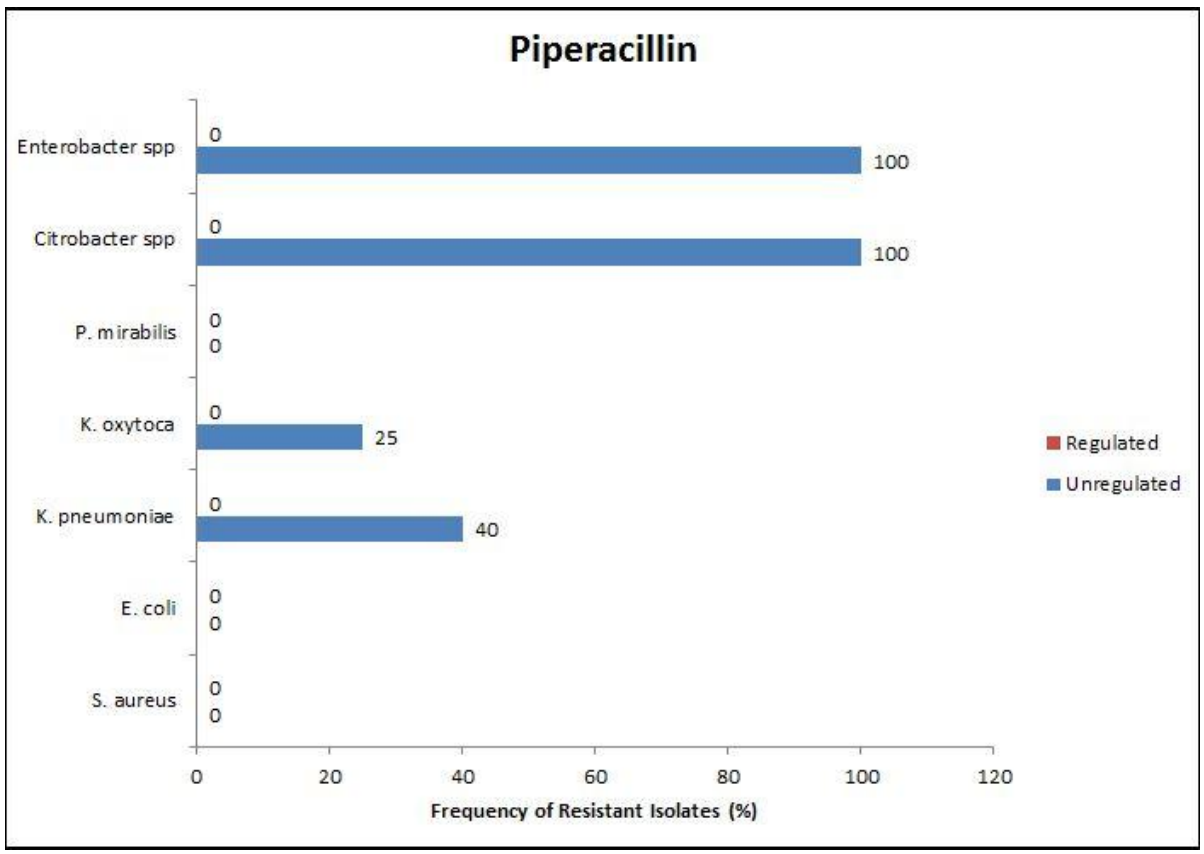
All the bacterial species isolated from the regulated herbal preparations were susceptible to all tested antimicrobials. Only 1 out of the 2 Enterobacter spp isolated from the unregulated herbal products showed resistance to Cefoxitin. However, both isolates were resistant to Piperacillin. Furthermore, 25% of the *P. mirabilis* isolated showed resistance to Cefoxitin and Gentamycin (Figure 1a-d).



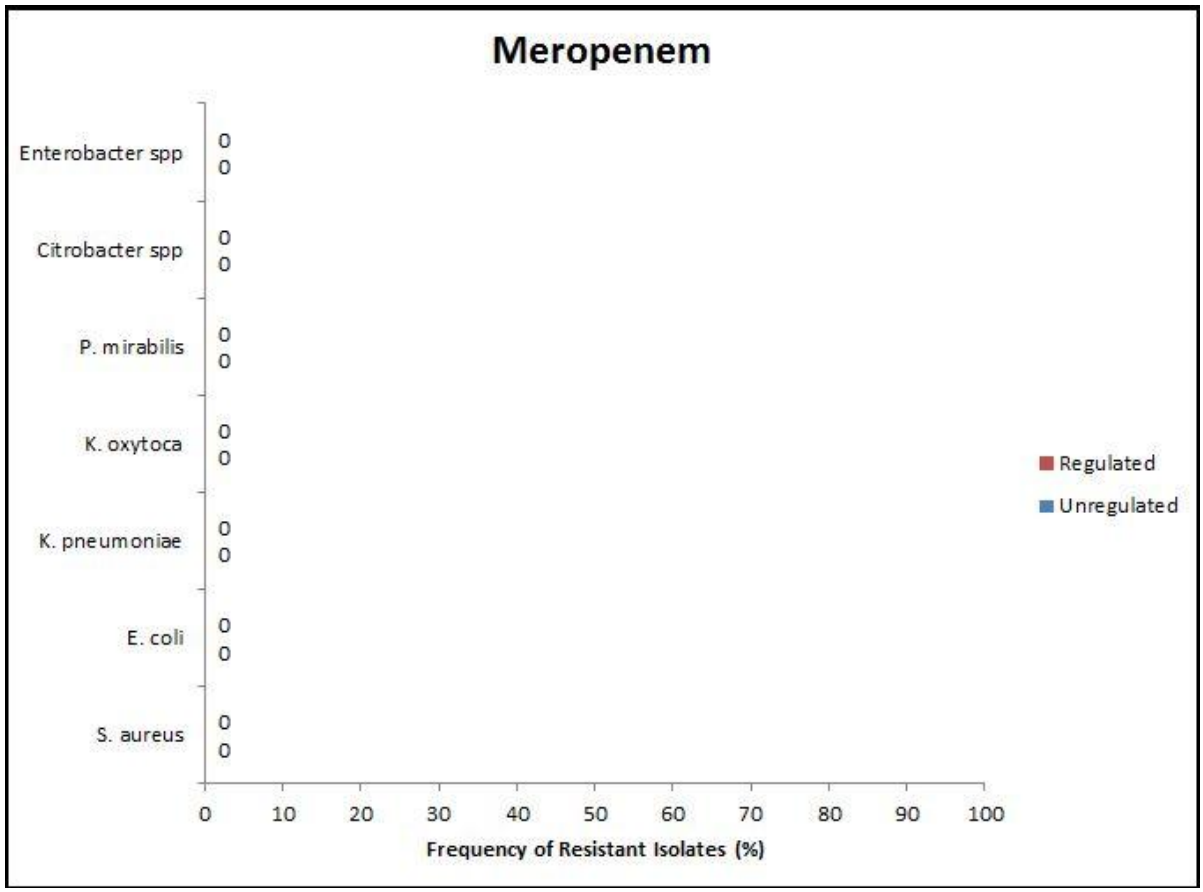
(a)


Gentamycin
Enterobacter spp
Citrobacter spp
P. mirabilis
K. oxytoca
K. pneumoniae
E. coli
S. aureus
0
0
0
0
0
25
0
0
0
0
0
0
0
0
0
5
10
15
20
25
30
Frequency of Resistant Isolates (%)
Regulated
Unregulated

(b)


Piperacillin
Enterobacter spp
Citrobacter spp
P. mirabilis
K. oxytoca
K. pneumoniae
E. coli
S. aureus
0
100
0
100
0
0
0
25
0
40
0
0
0
0
0
20
40
60
80
100
120
Frequency of Resistant Isolates (%)
Regulated
Unregulated

(c)



(d)

Figure 1(a-d): Prevalence of bacteria isolates resistant to: (a) Cefoxitin, (b) Gentamycin, (c) Piperacillin, and (d) Meropenem.

Discussion

Although herbal products are becoming more and more popular around the world, one barrier to their acceptability is the absence of a uniform quality control profile (Kunle *et al*., 2012). Lack of systems to track herbal medicine contaminants like microbes and chemicals, as well as providers' judgment of best practices, could be harmful health risk factors for herbal medicine users (WHO, 2019). These contaminations of herbal preparations both lessen their efficiency and put the health of their users in grave danger (Turkson *et al*., 2020). In the present study, 80% of the herbal preparations were unregistered and unregulated. There is a high proliferation of unregulated herbal products in many developing countries such as Nigeria owing to their cheaper cost and readily available than the regulated ones. Unregulated herbal preparations are sold by street hawkers and in many unlicensed herbal shops in Benin City, Nigeria. Poverty and ignorance of the health risks associated with the use of unregulated herbal products are major reasons for the general acceptance of these products. According to the World Health Organization, limited financial resources are a key reason people utilize herbal medicine (WHO, 2011).

Unhygienic production conditions are typically one of the drawbacks of herbal products (Nwoko and Mgbeahuruike, 2011; Oyetayo, 2008). Their negative consequences range in severity, including deaths (Justin-Temu *et al*., 2009). A prevalence of 40% microbial contamination was observed for the regulated and unregulated herbal

preparations, out of which 36% was from the unregulated herbal products. Several studies had reported higher rates of bacterial contamination than what was observed in this study (Darkwah *et al*., 2022; Kira *et al*., 2021; Kalumbi *et al*., 2020; Igbeneghu and Lamikanra, 2016). This disparity may be due to the fact that some of these studies were conducted in countries with no regulation governing the production of herbal products resulting in the proliferation of low-quality herbal products (Kira *et al*., 2021; Kalumbi *et al*., 2020). The primary duty of regulatory agencies is to make sure that patients receive medication that is guaranteed to be pure, safe, potent, and effective (Kunle *et al*., 2012). In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) is the agency responsible for regulating and controlling both local and imported herbal medicines in the country (Osuide, 2002). On the other hand, this result is in tandem with the reports of Abualhasan *et al* (2020) who reported a high rate of microbial contamination among unregulated herbal tea in Palestine. The high rate of microbial contamination observed among the unregulated herbal preparations may be due to the lack of resources to follow the guidelines of current Good Manufacturing Practices. Unregulated herbal products in Nigeria are mainly homemade, produced by individuals that are unable to purchase machinery that could ensure the high quality of their products (Okeke and Lamikanra, 2001).

The presence of *Staphylococcus aureus*in this study is lower than 8% and 49.2% reported in Tanzania (Kira *et al*., 2021) and Brazil (de Sousa *et al*., 2020), respectively. This difference in data may be due to the improvement in the packaging of herbal products over the years in Nigeria (Igbeneghu and Lamikanra, 2016). However, a lower prevalence of this pathogen had been reported in a previous study in Uganda (Walker *et al*., 2021). In our study, Citrobacterspp was isolated in 2% of the unregulated herbal products. This result is in accordance with the reports of Igbeneghu and Lamikanra (2016), but lower compared to the 30% reported in Blantyre, Malawi (Kalumbi *et al*., 2020). Citrobacter spp and *S. aureus* have been linked to food poisoning in humans (Brooks *et al*., 2013; Bai *et al*., 2012). The presence of *Escherichia coli* is an indication of fecal contamination (Edberg *et al*., 2000). This bacterium was isolated from 4% of the regulated and unregulated herbal preparations. This microorganism could be acquired by using contaminated water and containers to prepare herbal products. Utilizing plant parts that have been exposed to manure but have not been properly washed or disinfected is another possible source. Vegetables and other plant components have been documented to act as reservoirs for a variety of bacteria (Holden *et al*., 2009). *Escherichia coli* contamination has also been linked to poor harvesting and production methods (WHO, 2007b).

The rate of unregulated herbal preparations exceeding the permissible limit for microbial contamination in the present study (26%) is lower than 39.4% and 48% reported in Bangladesh (Nur *et al*., 2018) and Iran(Ameri *et al*., 2020), respectively. The high number of herbal products that fail the microbial test in these studies could be linked to the poor quality of water in some of these countries (Parvin *et al*., 2022; Fanack Water, 2021). Furthermore, in our study, herbal products prepared with water were observed to be more frequently contaminated than products prepared with alcohol. This is made worse when the product is unregulated. The use of medicinal herbal medications takes many various forms, and the manipulation and processing steps have a significant impact on the microbial quality of the finished preparation (Kneifel *et al*., 2002). Since boiling water is predicted to significantly reduce the viable counts by several log units and inactivate potential pathogens, the use of hot water extraction typically compensates for microbiological contaminations (Kneifel *et al*., 2002). In contrast, herbal preparations undergoing cold water extraction may include a significant number of microorganisms, and the ambient temperature extraction process typically promotes microbial multiplication. In general, ethanol-extracted herbal tinctures offer hygienic conditions, however, the outcome will vary depending on the concentration of alcohol used (Kneifel *et al*., 2002).

Some herbal products may pose a major health risk to users due to contamination with bacteria carrying genes for antibiotic resistance (Kira *et al*., 2021). Enterobacterspp isolated in this study showed resistance to Cefoxitin and Piperacillin. Similarly, 25% of the *Proteus mirabilis* isolated were resistant to Cefoxitin and Gentamycin. A similar incidence of bacterial resistance to widely used antimicrobials was documented in studies conducted elsewhere (Kira *et al*., 2021). This observation may be the result of the misuse of antibiotics in animals and human health practices for the prevention and management of bacterial illnesses (Rahimi and Nayebpour, 2012; Esimone *et al*., 2007; Foster, 1983). Additionally, this resistance could also result from the overuse of herbs with antimicrobial properties, which causes bacteria to become resistant to antibiotics with similar chemical structures (Kalumbi, 2019; Kalumbi, 2018; Tiwari and Tiwari, 2011).

Conclusions

There are a substantial number of unregulated herbal products in Benin City with microbial contamination exceeding the WHO acceptable limit for aerobic and coliform bacteria. Alcohol-based herbal preparations are more microbially stable than those prepared with water. The regulatory authorities should intensify efforts to see that all herbal medicines in the country are duly registered and their productions follow the guidelines of current GMP. This can be achieved by recognizing small-scale herbal product vendors as alternative health care providers in the country and providing appropriate training and financial support to them. In addition, public enlightenment focused on the health hazards associated with the use of adulterated and unregulated herbal products should be put in place and emphasized.

Conflict of Interest Statement: None

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