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Evaluation of Honey as a Topical Agent for Acute and Chronic Wound Infection

Nkechi V. Enwuru[1], Chijioke E. Ezeobiora[1], Charles C. Ezeaku[2], Calistar O. Ibedionu[1]

[1]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmacy, University of Lagos
[2]Department of Pathology, National Orthopedic Hospital, Lagos

Corresponding Author: Ezeobiora Chijioke Emmanuel

ABSTRACT

Background: Globally, health care providers are challenged by the rising rate of resistance of bacterial pathogens to antibiotics in wound infection. A retrospective cross-sectional study was conducted to determine the antibiotic susceptibility patterns of the causative bacteria in infected wounds and the antibacterial activity of local honey on these bacterial strains.

Methods: Samples of infected wound swabs were collected from 100 patients. The samples were inoculated on appropriate media and incubated at 37°C for 24hrs. After incubation, bacterial colonies were identified by Gram stain and biochemical tests. The Kirby-Bauer disk diffusion and agar well diffusion methods were used for antibiotic testing and antibacterial activity of honey at concentrations of 100%, 50%, 25% and 12.5% respectively.

Results: The prevalence of bacterial wound infection was 89%. Among these 89%, 65% were Gram negative bacteria with *Pseudomonas aeruginosa* (22.5%) being the most prevalent and 24% were Gram positive. All isolates were resistant to ampicillin, augmentin, cefuroxime and ceftazidime. Multiple drug resistance was recorded among all bacterial isolates tested. The antibacterial effect of honey on wound isolated pathogens was shown to be higher with average resistance of 31.2% than that of antibiotics (79%) used in this study.

Conclusion: This study confirms that honey possesses excellent antibacterial activity and may serve as a good alternative to curtail the further spreading of multidrug resistant (MDR) and pro-drug resistant (PDR) isolates in management of infected wounds.

Keywords: Wound infections, Bacteria, Antibiotic resistance, Honey.

INTRODUCTION

The loss of skin integrity by mechanical injuries exposes subcutaneous tissues and provides moist, warmth and nutritious environment that is conducive for microbial colonization and proliferation[1]. The mechanical disruption of the skin results in a wound[2]. Wound infection is mostly poly-microbial, involving numerous microorganisms that are potentially pathogenic[1]. Intact skin protects the tissues and prevents subsequent microbial colonization[3]. Wound infection prolongs the wound healing time which adversely affects patient's hospitalization period, therapeutic and economic outcome[4].Wound infection constitutes a major barrier to healing and can have an adverse impact on the patient's quality of life as well as on the healing rate of the wound. Infected wounds are likely to be more painful, hypersensitive and can produce offensive odors, resulting in increased discomfort and inconvenience to the patient[5]. Bacteria pathogens colonizing wounds can break the protective barrier to cause systemic sepsis[6]. Study had it that 70-80% of deaths among surgical patients are due to infection of the wound acquired in the hospital[7]. Bacterial infections in wound patients are common and difficult to control, particularly in the hospital environment[8].

Infected wound tends to aggravate in patients with disorders like diabetes, obesity and cardiovascular diseases. The most common bacteria isolates in wound are; *P. aeruginosa, E. coli, Klebsiella spp.* and *Acinetobacter spp., Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus faecalis, Streptococcus pyogenes, Proteus mirabilis, Klebsiella spp., Enterobacter, Candida albicans and C. tropicalis*.[9,10].

At present, a number of antibiotics in use are becoming ineffective to control bacterial pathogens due to wide spread of antimicrobial resistance[10,11]. It is therefore imperative to source for alternative methods to treat MDR-bacterial pathogens.

Honey was used to treat infected wounds as long as 2000 years ago before bacteria were discovered to be the cause of infection. More recently, honey was reported to have inhibitory effect to over 60 species of bacteria including aerobes and anaerobes, Gram-positives and Gram-negatives[12]. Its antibacterial activity is due to the osmotic effect and hydrogen peroxide content[13].

Wound infection poses a major concern among healthcare practitioners, not only in terms of increased trauma to the patient but also in view of its burden on financial resources and the increasing requirement for cost-effective management within the healthcare system[14,15,16]. Routine surveillance for hospital-acquired wound infections is recommended by both the Centers for Disease Control and Prevention and the Surgical Infection Society. The role of Laboratory is to find the source of infection, identify microorganisms, provide antibiotic susceptibility pattern which in turn provides guidance for most appropriate regimen thus controlling antibiotic usage and stemming the spread of antibiotic-resistant bacteria. The study is to determine the etiology of wound and compare the antibacterial activity of the honey and the antibiotics on the isolated pathogens.

MATERIALS AND METHODS

Study design

This was a retrospective cross-sectional study spanning seven months from April to October 2018. One hundred records of wound swabs samples obtained from patients with different kinds of wound, receiving treatment at the Lagos University Teaching Hospital (LUTH) and Orthopedic Hospital Igbobi, Lagos were analyzed.

Study area

The LUTH and Orthopedic hospital are tertiary health institution situated in Lagos metropolis.

Exclusion/inclusion criteria

The sample records were scrutinized in such a way that all patients with suspected wound infections were added to the study. Wound infection was suspected if a wound was not healing well, getting bigger, exuding pus or fluid. Patients who are terribly ill and undergoing antibiotic therapy within two weeks prior to the study were excluded.

Ethics approval and consent to participate

Full approval for this research was given by the Lagos University Teaching Hospital Health and Research Ethics committee (LUTHHREC). The Health Research Committee assigned approval no: **ADM/DCST/HREC/APP/2337**.

Sample collection

Sample collection was conducted by medical officers in the out-patient clinic and in the wards using commercially available sterile cotton swabs and following existing departmental guidelines. Only one swab per patient was collected after carefully cleaning the wound with sterile water to prevent surface contamination. Samples (pus, aspirates, swabs etc.) were taken from surgical and diabetic wounds using sterile cotton swab[17]. The samples were immediately put in screw capped bottles containing Brain Heart Infusion (BHI) transport medium[18].Soon after collection, each sample was transported to the microbiology laboratory for processing. The honey samples were collected from local sources in screwed capped bottles and stored in laboratory.

Sample Culture Procedure

The collected swab samples were inoculated onto MacConkey agar (Oxoid Ltd.), Mannitol Salt Agar (MSA), Eosin Methylene Blue Agar (EMBA), cetrimide agar and incubated at 37°C for 18–24h. All the plates were incubated aerobically and initially examined for growth after 24h, and the ones without growth were further incubated for up to 48 hrs. The Bacterial isolates were stored on a Mueller Hinton agar slant at 4°C prior for identification.

Bacteria Identification and Antibiotic Susceptibility Testing

Bacteria isolates were identified according to the standard microbiological techniques, such as the colonial morphology, Gram stain reaction and biochemical tests. The biochemical methods used for identification test include catalase, coagulase, oxidase, Triple sugar iron agar (TSI), Sulphide indole motility (SIM), citrate utilization and urease tests according to the standard guidelines[19].

The susceptibility to antibiotics was determined by the Kirby-Bauer disc diffusion method and interpreted according to the recommendations of the National Committee for Clinical Laboratory Standards (CLSI method)[20]. The isolates were tested against the following antibiotic ofloxacin (30 μg), nitrofurantoin (50 μg), gentamicin (10 μg), erythromycin (15 μg), ciprofloxacin (5 μg), cefuroxime (30 μg), chloramphenicol (30 μg), tetracycline (30 μg), ampicillin (10 μg), ceftazidime (30 μg) and augmentin (30/5 μg) (Oxoid England).

Standard strains used for Quality Control of the procedure were *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) and *Pseudomonas aeruginosa* (ATCC 27853).

Preparation of Honey Solutions

Hundred percent pure honey (100% v/v) was obtained after filtering using sterile gauze. To get 50% honey solution (v/v), 0.5 ml of honey was diluted in 0.5 ml sterilized distilled water. Further serial dilutions 0.25 ml of honey and 0.75 ml of sterile distilled water were added to obtain 25% honey solutions (v/v), respectively.

Antibacterial activity of Honey

This was determined using agar well diffusion technique. An overnight culture of bacterial isolate was adjusted to 0.5 McFarland standards to yield approximately 1.0 x 10^8 colony forming unit (cfu)/ml. A 1 ml bacterial suspension was mixed with 25ml of molten Mueller Hinton agar in 96mm diameter petri dish and allowed to set.

Five 8 mm well was cut into the agar using a sterilize cork borer. A 50 μl of honey with the concentration of 75%, 50%, and 25% was added to the wells in the plate. The plates were incubated at 37°C for 24 h. After incubation, the mean diameters of inhibition zones were measured in millimeters and the results were recorded.

RESULTS

A total of 100 study participants with wound infection were included in the study. Among these, 54 (54%) were males and 46 (46%) were females with the age range of 0 to 70 years.

Frequency of Bacterial Etiologic Agents of Wound Infection

Table 1: Frequency distribution of bacterial isolates from infected wounds

Bacterial Isolates	Number	Percent (%)
Staphylococcus aureus	21	23.6
Pseudomonas aeruginosa	20	22.5
Klebsiella oxytoca	19	21.3
Escherichia coli	12	13.5
Proteus mirabilis	11	12.4
Streptococcus pyogenes	3	3.4
Acinetobacter buamannii	2	2.2
Citrobacter spp.	1	1.1
Total	89	100

A total of 89 samples (89%) yielded significant bacterial growth indicative of wound infection, while 11 samples did not yield significant growth. No sample yielded more than one organism. Gram-negative bacilli were the most prevalent bacteria isolated 65 (73%) compare to Gram-positive bacteria 24 (27%). *Staphylococcus aureus* were the most frequently isolated bacteria accounting for 21 (23.6%) followed by *P. aeruginosa* 20 (22.5), *Klebsiella* spp. (19; 21.3%), *E. coli*12 (13.5%), *Proteus* spp. 11 (12.4%), *Streptococcus spp.* 3 (3.4%), *Acinetobacter baumannii* 2 (2.2%) and *Citrobacter spp*. 1 (1.1%)(table 1).

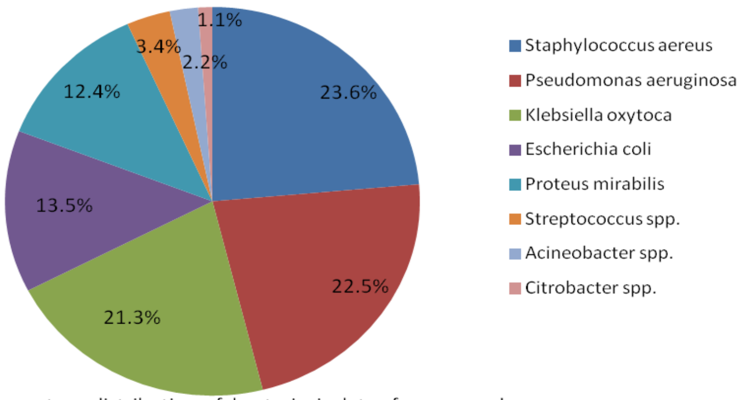

Figure 1: Percentage distribution of bacteria isolates from wound

Antimicrobial Susceptibility Patterns of Bacterial Isolates from Wound Culture

The bacterial isolates exhibited a high resistance to the antibiotics tested, with most isolates having resistance levels of between 33.3% and 100%.

The predominant Gram-positive isolate, *S. aureus,* showed high resistance to erythromycin, tetracycline 19 (90.5%) and ciprofloxacin 15 (71.4%). However, it was found to be sensitive to gentamicin 15 (71.4%) and chloramphenicol 10 (47.6%). All the *Streptococcus pyogene* were resistance to ciprofloxacin and tetracycline while erythromycin was sensitive in two of the three (66.6%) isolates. All the Gram-positive isolates were multidrug resistant.

All the Gram-negative isolates were 100% resistance to augmentin, cefuroxime, ceftazidime and ampicillin. However, majority of its strains was sensitive to gentamicin 13 (65%) while few of the isolates were sensitive to ciprofloxacin 5 (25%), ofloxacin 6 (30%) and Nitrofurantoin 7 (35%). Most Gram-negative isolates were sensitive to nitrofurantoin; *Pseudomonas aeruginosa* 7 (35%), *K. oxytoca* 16 (84.2%), *E. coli* 10 (83.3%) and *P. mirabilis* 8 (72.7%). All isolates of *Acinetobacter baumannii* and *Citrobacter spp* were resistant to all the tested antibiotics.

The antimicrobial susceptibility patterns of the Gram-positive and Gram-negative bacteria isolates were also presented in Tables 2 and 3, respectively.

Table 2: Antibiotic susceptibility profile of Gram-positive organisms isolated from wound

Antibiotics	Susceptible		Intermediate		Resistant	
	frequency	percentage	frequency	percentage	frequency	percentage
CN	15	62.5%	1	4.2%	8	33.3%
ER	2	8.3%	2	8.3%	20	83.3%
TET	0	0%	2	8.3%	22	91.7%
CHLOR	12	50%	0	0%	12	50%
CIP	6	25%	0	0%	18	75%

CN- gentamicin, ER-erythromycin, TET-tetracycline, CHLOR- chloramphenicol, CIP-ciprofloxacin

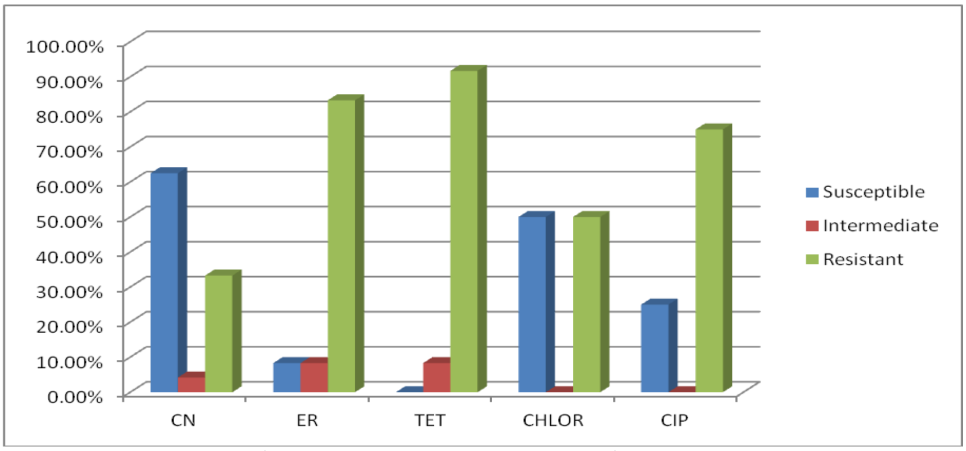

Figure 2: Antibiotic susceptibility profile graph indicating percentages of Gram-positive organisms that are susceptible, intermediate and resistant to different antibiotics.

Table 3: Antibiotic susceptibility profile of Gram-negative organisms isolated from wound.

Antibiotics	Susceptible		Intermediate		Resistant	
	frequency	Percentage	frequency	percentage	frequency	percentage
NIT	39	60%	2	3.1%	24	36.9%
OFL	17	26.2%	3	4.6%	45	69.2%
AUG	0	0%	0	0%	65	100%
CPR	9	13.8%	7	10.8%	49	75.4%
GEN	28	43%	0	0%	37	56.9%
CRX	0	0%	0	0%	65	100%
CAZ	2	3.1%	0	0%	63	96.9%
AMP	0	0%	0	0%	65	100%

Keys: *NIT- nitrofurantoin, OFL - ofloxacin, AUG - augmentin, CPR - ciprofloxacin, GEN-gentamicin, CRX - cefuroxine, CAZ - ceftazidine, AMP - ampicillin.*

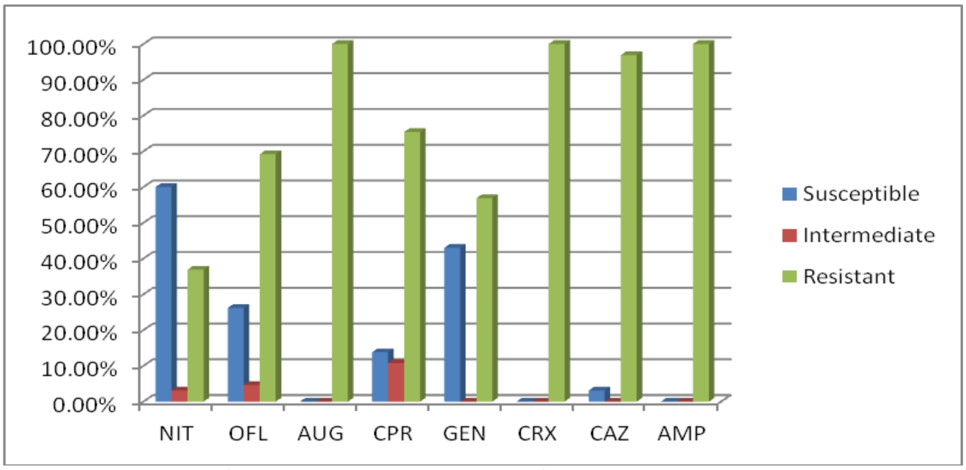

Figure 3: Antibiotic susceptibility profile graph indicating percentages of Gram-negative organisms that are susceptible, intermediate, and resistant to different antibiotics.

Percentage resistance of different wound isolates to different antibiotics

Table 4: Average antibiotic resistance exhibited by wound isolates

organisms	Percentage resistance of antibiotics to wound isolates											Average resistance
	CHLOR	CIP	ER	CN	TET	NIT	OFL	AUG	CRX	CAZ	AMP	
S. aureus	47.6%	71.4%	90.5%	28.6%	90.5%	-	-	-	-	-	-	65.7%
S. pyogene	66.7%	100%	33.3%	66.7%	100%	-	-	-	-	-	-	73.3%
P. aeruginosa	-	75%	-	35%	-	65%	70%	100%	100%	100%	100%	80.6%
K. oxytoca	-	63.2%	-	57.9%	-	15.8%	52.6%	100%	100%	100%	100%	73.7%
E. coli	-	83.3%	-	41.7%	-	16.7%	75%	100%	100%	83.3%	100%	75%
P. mirabilis	-	90.9%	-	100%	-	27.3%	100%	100%	100%	100%	100%	88.6%
Acinetobacter spp.	-	100%	-	100%	-	100%	100%	100%	100%	100%	100%	100%
Citrobacter spp.	-	0%	-	100%	-	100%	0%	100%	100%	100%	100%	75%

Keys: *CHLOR - Chloramphenicol, CIP - Ciprofloxacin, ER - Erythromycin, CN - Gentamicin, TET- Tetracycline, NIT - Nitrofurantoin, OFL - Ofloxacin, AUG - Augmentin, CRX - Cefuroxime, CAZ - Ceftazidime, AMP - Ampicillin.*

Different wound isolates showed varied levels of resistance to the tested antibiotics. The percentages of each organism's resistance against different antibiotics were recorded and average resistance calculated.

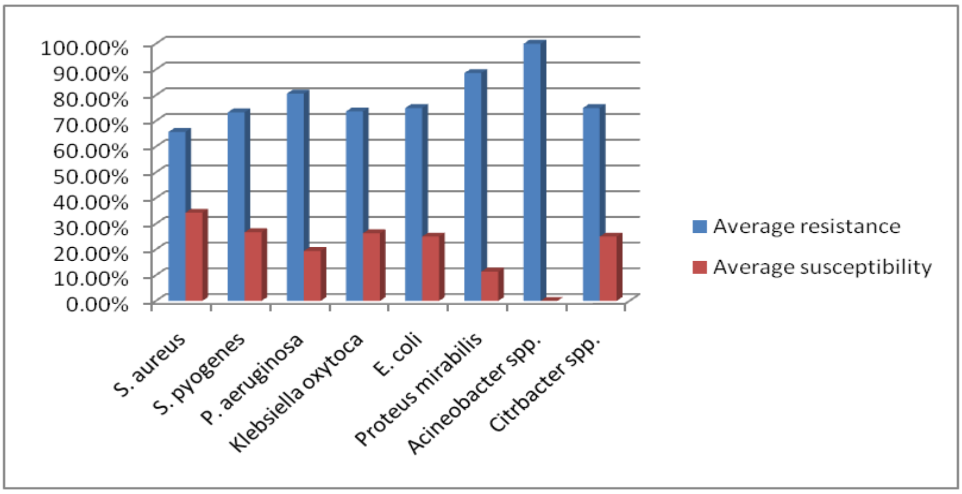

Figure 4: A graph representing the average antibiotic resistance and susceptibility of wound isolates.

Antibacterial Activities of Honey on Isolated Wound Organisms

The average resistance to the honey exhibited by bacteria isolates from wound was lower when compared to the resistance pattern exhibited by these bacteria isolates to antibiotics. The average resistance and susceptibility pattern of honey against isolated bacteria is presented below:

Table 5: Average resistance and susceptibility of bacteria isolates to honey

organisms	Concentrations of honey								Average resistant	Average susceptible
	100%		50%		25%		12.5%			
	freq S	freqR	freqS	freqR	freq S	freqR	freqS	freq R		
S. aereus	18	3	16	5	12	9	11	10	32%	68%
S. pyogenes	3	0	2	1	1	2	1	2	41.6%	58.4%
Klebsiella spp.	16	3	14	5	12	7	10	9	31.6%	68.4%
P. aeruginosa	17	3	16	4	10	10	8	12	36.3%	63.7%
E. coli	11	1	8	4	7	5	6	6	33.3%	66.7%
P. mirabilis	11	0	11	0	11	0	11	0	0%	100%
Acinetobacter spp.	2	0	2	0	1	1	1	1	25%	75%
Citrobacter spp.	1	0	1	0	0	1	0	1	50%	50%

Freq S-frequency of susceptible organism, Freq R- frequency of resistant organism

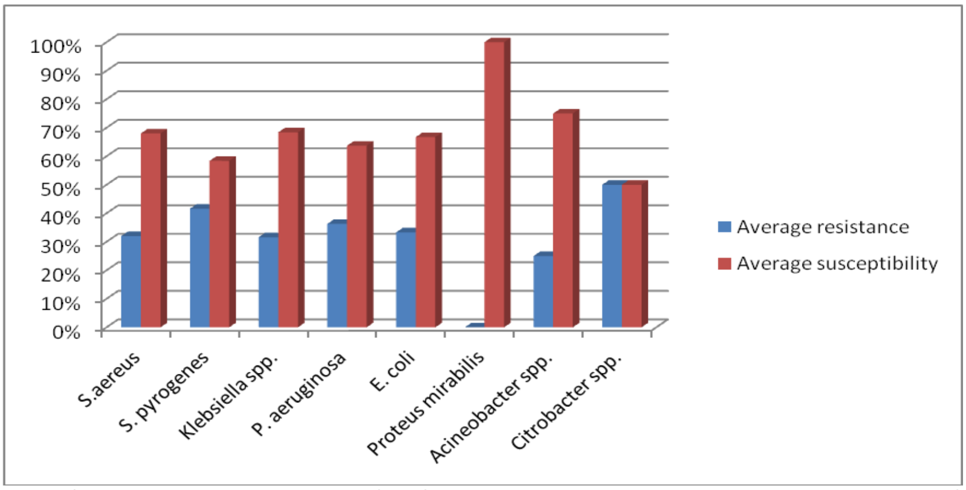

Figure 5: A graph of antimicrobial susceptibility profile of honey indicating average susceptibility and resistance of organisms to honey.

DISCUSSION

Bacterial contamination of wounds is a serious problem in the hospital as well as its resistance to antibiotics available for the treatment of wound infections[21, 22.].Our study demonstrated a high prevalence (89%) of pathogenic bacteria in wounds as previously reported in Nigeria[23,24] Multidrug resistant Gram-positive and Gram-negative bacteria organisms were isolated from wound samples screened.

Staphylococcus aureus and *Pseudomonas aeruginosa* were the most frequently isolated Gram-positive and Gram-negative organisms representing 23.2% and 22.5% respectively, followed by *Klebsiella oxytoca* 21.3%, *E. coli* 13.5%, *Proteus mirabilis* 12.4%, *Streptococcus spp.* 3.4%, *Acinetobacter spp.* 2.2% and *Citrobacter spp.* 1.1%. This is in harmony with previous study[25]. However, previous report presented *Staph. aureus* and *E. coli* as the most frequently isolated organisms from infected wounds[26]. These organisms are frequently found in the hospital environments and can increase the rate of wound infection and cross contamination among admitted patients[26,27].

There is a high level of antibiotic resistance among all the species isolated from wounds. This study revealed the emergence of pro-drug resistant (PDR) *Acinetobacter baumannii*. This is a threat to public health hence a need for newer or alternative antibiotics for the management of wound infection. All the bacteria isolates were resistance to Augmentin, Cefuroxime and Ampicillin. This is probably because of their frequent use as first line antibiotics for wound infections. This is in accordance with the reports by Sosina, 2014[25].

The average antimicrobial resistance among Gram-positive and Gram-negative organisms ranged between 33.3% to 91.7% and 36.9% to 100% respectively. Most Gram-positive isolates were highly resistance to tetracycline (TET) by 91.7% and erythromycin (ER) 83.3% but mostly susceptible to gentamicin (CN) by 66.7% and chloramphenicol (CHLOR) by 50% as it was similarly reported by Girma *et al*., 2013[27]. On the other hand, most Gram-negative organisms were highly resistant to augmentin (AUG), cefuroxime (CRX) and ampicillin (AMP) by 100% followed by ceftazidime (CAZ) 96.9%, ciprofloxacin (CPR) 75.4%, ofloxacin (OFL) 69.2% and gentamicin (GEN) 56.9%. However, they were mostly susceptible to Nitrofurantoin (NIT) by 62.1%.

The average antimicrobial resistance of Gram-positive and negative wound isolates against honey ranged between 0 to 50%. This is far lower than 33.3 to 100% when compared with antibiotics. Antimicrobial studies on honey showed greater susceptibility patterns for Gram-positive and Gram-negative wound isolates. Pro-drug resistant *Acinetobacter baumannii* were susceptible to honey at 100% and 50% concentrations but was resistant to all antibiotics used in this study. This calls for routine microbiological surveillance of wounds and a mandatory incorporation of honey into wound management regimen.

The antimicrobial activity of honey showed that undiluted (100% concentration) form was most effective as was previously reported by Teke and Ngienyikeh, 2016[12].

CONCLUSION

There is high prevalence of Gram-negative bacteria than Gram-positive counterparts in causing wound infections. All isolates from infected wound are multidrug resistant (MDR). There is emergence of pro-drug resistant (PDR) *Acinetobacter baumannii* among bacteria isolates of wound infection. This study confirms that honey possesses excellent antibacterial activity and may serve as a good alternative to curtail the further spreading of MDR and PDR isolates in management of infected wounds.

Recommendation

1. Future studies on this subject should involve isolation of anaerobic and fungi microorganisms responsible in causing wound infections.

2. The choice of antibiotics for treatment of wound infections should be based on the result obtained from microbial culture and sensitivity.
3. We advocate immediate withdrawal of augmentin, cefuroxime, ceftazidime and ampicillin as antibiotics of choice in the management of infected wounds and the inclusion of Nitrofurantoin and Gentamicin for prophylactic and empirical management of infected wounds.
4. Honey should be included as a topical agent in the management protocols of wound infections in hospitals.

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