THE RESIDUAL ANTIBOBTIC IN MARKETABLE MILK IN KHARTOUM STATE; PLASMA& MILK CONCENTRATION OF GENTAMICIN IN GOATS& EWES

By

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DEDICATION

To my parents,

Brother and sisters

And to my husband

INTRODUCTION

1.1 Area of study

This study was conducted in Khartoum State. It lies between Latitude 15°:15 North and longitude 16°:45 East. It covers an area of about 20970 sq.km. The estimated population in (2002) was 5.35 million with annual growth rate 4.85%. It occupies semi arid climatic zone, the peak of rainful extend between July and September followed by winter and summer seasons respectively.

1.2 Livestock

No formal of livestock census took place; the following figures were only estimated as shown in table 1

Table (1)

Cattle	Sheep	Goats	Camel
203,600	224,000	617,000	5,4000

Ministry of animal resource report (2002)

1.3 Milk production in Khartoum State

Khartoum State is considered as one of most important Centers for milk and dairy products production, where methods of production are varing from traditional production system (TPS) and modern dairy farm production system (MDFPS).

1.3.3 Traditional production system

TPS is considered as the most common system now a days for milk production it includes:

(I) Back yard dairy unit

(II) Milk production unit around town& village (Dakkas)

(III) Small dairy units

1.3.3 Modern dairy form production system

M.D.F.P.S is very few in number. It produces pasteuralized milk and other dairy products. It consists of the following companies & dairy farms:

(I) Arab company for milk& dairy products

(II) Blue Nile company

(IV) Kafouri dairy farm

(V) KuKu dairy farm

(VI) Khartoum State company for milk production

The gap in milk production is covered through exportation of manufactured milk powder and dairy products (Mona & ElFaki, 2001).

Sudan has immense animal wealth which satisfies about 80% of local total milk need, (AOAD, 1992).

Estimated milk production in Khartoum State as 235 thousand metric tons.

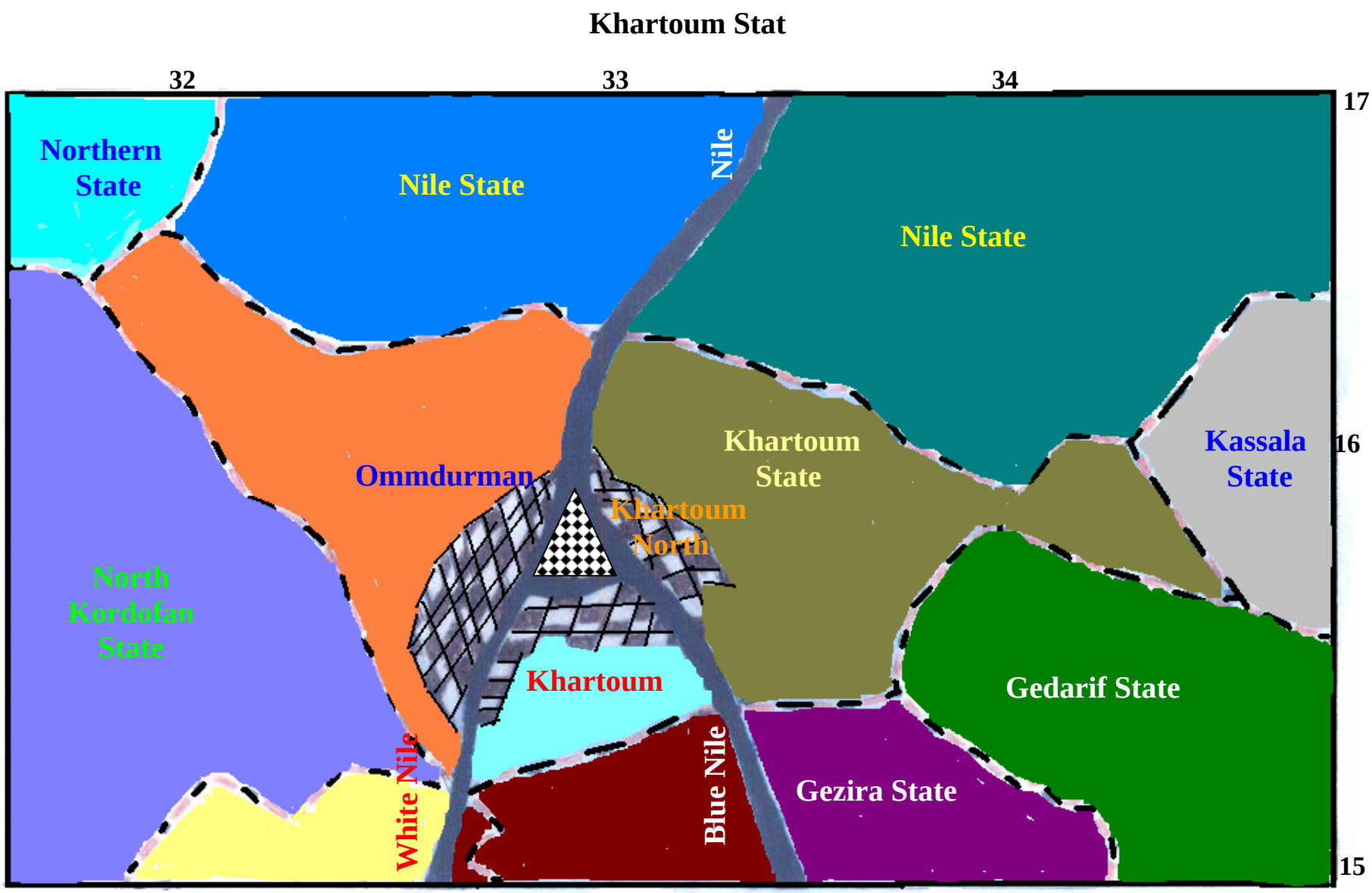


Fig. 1. Khartoum State Source: Ministry of Animal Resource, 2001)

CHAPTER ONE

LITERATURE REVIEW

1. Antibiotic

The term antibiotic means against life (antiagain, bios-life). This term was used for the first time by Vuillemin (1889).

Antibiotic and chemotherapy is used for drug of treatment of parasitic infections in which the parasites are destroyed or removed without injuring the host by convention, it includes therapy of cancer (Laurence and Bennet, 1995).

1.1 Definition of Antibiotic

In 1945 Waksman defined antibiotic as "chemical substances produced by microorganisms possessing the ability to kill or inhibit the growth of bacteria and microorganisms without harmful effect on the body of animal or man.

In 1960 Abraham and Newton made another definition of antibiotic "Natural compounds produced mainly by microorganisms, or antibiotics are compound, obtained by chemicals or microbiological modification of natural compounds".

Also Tyler.*et al* (1981) defined antibiotic as chemical substance produced by microorganisms that has the capacity in low concentration to inhibit selectively or even destroy bacteria and other micro-organisms through an antimetabolic mechanism .Singleton (1995) defined antibiotics as any microbial product which inhibits or kills certain

micro-organisms. Todar, (2000) defined antibiotics as low molecular weight, non-protien, molecules produced as secondary metabolites, mainly by microorganisms.

Newaz et *al* (2001) stated that, antibiotics are drugs, miracle drugs, that are extensively used for the treatment and prevention of infectious diseases in animals and human.

1.2 General classification of antibiotics and chemotherapeutic agents

1.2.1 Chemical classification

Chemical structure is the result of collaborative research program involving research group in Great Britain and the United States during the years 1943-1945. Martin (1991), Todar (2000) define the group based on structure. Each group has a structural component that defines the group Smith, (1966), Reilly (1977) classifications has been based on chemical structure and propuse of action as follows

1. Beta Lactams and other cell wall synthesis inhibitor (Gale, 1981) Penicillin and cephalosporin cause loss of viability and inhibits synthesis of the cell
2. Other cell wall inhibitor Bacitrein and vacomycin
3. Membrane active affecting permeability and lead to leakage of intracellular constituents e.g polymyxins
4. Agents inhibit microbial protein synthesis **(i)** macrolides these agents have large ring structure

and cause reversible inhibition of proteins synthesis (chloramphenicol tetracycline **(ii)** aminoglycossides composed of amino-sugar linked by glycosidic bonds to various bases. The agents bind to 30s ribosomal sub- unit and cause accumulation of protein synthetic intiation complexes.

5. DNA polymerase inhiitor (Rifampin) affect nucleic acid Metabolism DNA Gyrase inhibitor e.g Quinolones.

6. Folate antiagonists

(sulphonamide,trimethoprim)Antimetabolites which block specific step that are essential to micro-organsims.

1.2.2 functional classification

Alexander (1985) stated that antibacterial agents are classified into three groups based on their activities:

(i) Broad spectrum antibiotics: these effective against gram positive and gram negative (Ampenicillin and Tetracycline).

(ii) Narrow spectrum: mainly effective against gram positive (Penicillin and Macrolides).

(iii) Drugs active against aerobic gram –negative bacteria

1.3 Mode of action

Generally antibacterial agents can be divided into groups affecting the synthesis of:

1. Nucleic Acid
2. Protein.
3. The formation of the cell wall
4. Cell membrane

The detailed synthesis of protein in the bacterial cell is described by Garrod *et a*l (1973).

1.3.1 Antibacterial Action

A. Bacterio static antibiotics

Brander and Pugh (1977) mentioned that all antibiotics are bacteriostatic in suitable concentration and these produce stasis of bacterial growth in vitro; this means that Invivo, the bacteria are made susceptible to the body defence mechanisms: Sulphonamides, Tetracycline, Chloramphenicol and Erythromycin.

B. Bactericidal antibiotics

These produce actual death of the cell in vitro so when used clinically they should produce their therapeutic effect without the aid of body's defence mechanisms.

These antibi*otics include Penicillin, Streptomycin, Neomycin, Bactercin* and *Cephalosporins*

1.4 Types of Antibiotics

1.4.1 Penicillins

Is one of the most important antimicrobial agents. Although many other antimicrobial agents have been introduced since the discovery of Penicillin it is still widely used as a major antibiotic in as much as new derivatives of the basic nucleus are being introduced every year (Mandell and Sande, 1980).

Fleming in (1929) discovered Penicillin accidentally. He named it Penicillin after the organism that caused the bacteria to under go lysis on a culture contaminated with the mold belonging to the species *Penicillium notatum*.

Structure of Penicillins

Extensive chemical and physio chemical studies particularly with the aid of x-ray cry-stallography provided un equivocal of the fused B-Lactam thiazolidine structure of Penicillin. (Clarke *et al,* 1949).

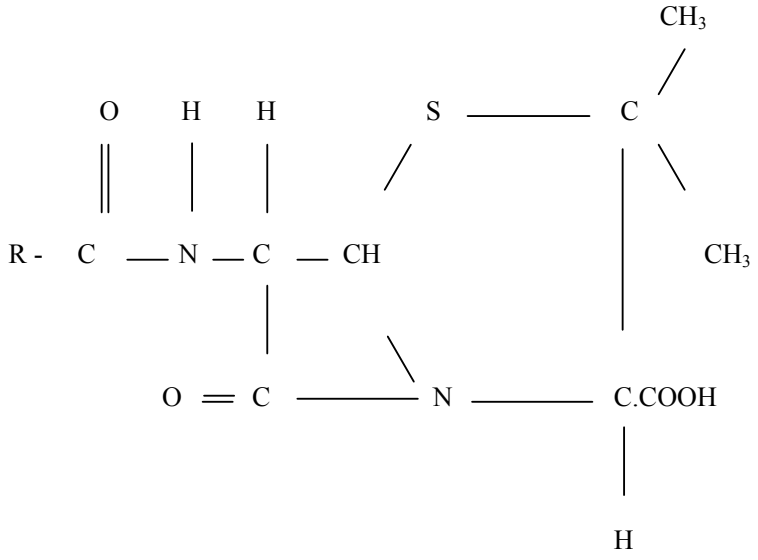


Fig. 2. Structure of Penicillin

Pharmacokinetics of Penicillin

Most absorption of Penicillin given orally takes place in the stomach and upper small Intestine. Once absorbed Penicillin are rapidly distributed through most tissues.

Some Penicillin are metabolized by Liver but the kidneys are primary organs for excretion of *penicillin.* Also they are excreted through the milk in small quantities.

Pharmacodynamic

Penicillin bind reversibly with enzymes called Penicillin-binding proteins (PBP) outside the bacterial *cytoplasmic* membrane.

Penicillin act by impairing the development of bacterial cell wall by interfering with transpeptidase enzymes responsible for the formation of the cross link between peptide-glycan strands.

These enzymes are involved in cell wall synthesis and cell division and when this binding occurs it increases the internal osmotic pressure and reptures the cell

Some bacteria produce beta-lactamase penicillinase which increases the bacteria's resistance by converting Penicillin to in active Penicillinic acid. Some Penicillins are more resistant to beta-Lactamase penicillinase hydrolysis and are referred to as beta-Lactamase penicillinase resistant.

Penicillins are divided into:

1. Narrow-spectrum B-lactamase sensitive Penicillins

active against many Gram positive and a limited number of gram negative, also susceptible to B-Lactamase hydrolysis. (Aiello & Mays, 1998). E.g phenoxymethyl Penicillin and phenethicillin.

2- Narrow –spectrum Resistant B-Lactamase

in this group Penicillins are not as active against many gram positive bacteria (Penicillin G) also all gram negative (Oxacillin, Cloxacillin)

3. Broad Spectrum B-Lactamase sensitive Penicillins

Against gram positive and gram negative e.g ampicillin and amoxicillin (Aiello & May, 1998).

4. Broad Spectrum- Resistant – B-Lactamase Penicillins

It is fully active Penicillins against a wide variety of resistant bacteria, withdrawal time varies from 10-30 days. Milk should be discarded for aperiod of 2 days for amoxicillin and 3 days for procaine Penicillin G.

1.4.2 Cephalosporins

In 1948 professor Giuseppe Brotzu hypothesized that the relative sterility of sea-water coast of Sardinia was due to substance produced by certain bacteria. These substances, he thought, inhibited the growth of other organisms.

In confirmation of his theory Brontzu isolated afungus, cephalosporium a cremorium, from sea water off the coast of Sardinia and found that it inhibited the growth of a variety of gram-positive and gram-negative bacteria.

Similar to Penicillin in various respects (Alexander, 1985).

Cephalosponins divided into 3 generations

First generation: quite active against gram positive and moderately against gram negative and not effective against an aerobes as Penicillins e.g Cephalothin, cephapiran

Second generation: Active against both gram positive and gram negative more over they are relatively resistant to B-Lactamase e.g cephachlor and cefoxin.

Third generation : They are moderately active against gram positive but active against a wide variety of gram negative bacteria they are usually highly resistant against B-Lactamase enzymes (Aiello & May, 1998).

1.4.3 Tetracyclines

They are broad spectrum antibiotics there are three naturally occurring members of this group:

Oxytetracycline, Chlortetracycline & Dimethyl chlortetracycline.

Pharmacokinetics

Tetracyclines distribute rapidly and extensively in the body and in some instances they penetrate into C.N.S. deposited irreversibly

in the growing bones and in dentin. Withdrawal time (5-28 days). Excretions via kidneys & Gastro-intestinal tract.

Pharmacodynamics

Act by binding reversibly to bacterial 30 s ribosmes and inhibit protein synthesis generally bacteriostatic but at high concentration they become bactericidal because the organisms seem to loose the Functional integrity of the Cytoplasm membrane. (Aiello & Mays, 1998).

1.4.4 Chloramphenicol

Is a relatively simple natural nitrobenzene derivative with a bitter taste.

Pharmacokinetics

Absorption occurs rapidly from the upper GI tract & maximum blood level occur in 1-3 hours. About 40-60% of it is in plasma is reversibly bound to albumin, the free fraction readily diffuses into almost all tissues including brain.

The principal route of excretion is Renal it cause irreversible a plastic anemia. Unlike other antibacterial agents, chloramphenicol under goes extensive hepatic metabolism withdrawal time 2 weeks.

Pharmacodynamic

It is highly effective and well tolerated broad-spectrum. Chloramphenicol inhibts protein synthesis by binding to 50s sub unit of 70s ribosome and impairing peptidyl transferase activity it is a

bacteriostatic but at high concentration my be bactericidal for some species (Aiello& Mays, 1998).

1.4.5 Quinolones

These are synthetic antibiotics (Renold, 1989)

Pharmacokinetics

By 1/V, 1/M, and S/C they penetrate all tissues well and quickly.

Some quinolones are eliminated un changed e.g (ofloxacin), some are partially metabolized e.g giprofloxacin and enrofloxacin and some are completely degraded. Metabolites are sometimes active.

Major excretion through Renal Route, Biliary (Cipprofloxacin and Nalidix acid). Quinolones appear in milk of lactating animals often at high concentrations that persist for sometime.

Pharmacodynamic

The quinolones act by inhibiting the enzyme DNA gyrase that is responsible for the super coiling of DNA so that the DNA can twist in a number of chromosomal domains and seal around an RNA core. When DNA-gyrase is inhibited by quinolones a reduction in the super coiling occurs with a consequent disruption of the spatial arrangement of DNA. Qunolones are usually bactericidal.

1.4.6 Sulfonamides

Derivatives of sulfanilamide

Pharmaco-kinetics

were absorbed from the gastrointestinal tract (Burtis and Ashwood, 1991).Once absorbed they were bound to protein mainly to albumin. About 60-90 percent of bounded protein was distributed to all tissues. The metabolism of sulphonamide was shown via N- acetylation. The product of metabolism had no antimicrobial effect.

Excretion by urine, Bile and Feaces

Pharmacodynamic

Sulfonamides are structural analogs of Paramino Benzoic Acid (PABA) and competitively inhibit on enzymatic step. (Dihydropterate synthetase) during which PABA is corporated into the synthesis of diyhdrofolic acid (Folic acid).

This result in suppression of protein synthesis impairment of metabolic processes and inhibition of growth and multiplication they are most effective in early stages of acute infections when organisms are multiplying (Aiello & May, 1998).

Trimethoprim is antibiotic which was used to complete the effect of sulfonamide. It was found to inhibit the reduction of dihydrofolic acid to tetrahydrofolic acid Brooks,(1995).

1.4.7 Macrolides Antibiotic

Have typical lactone ring in their structure (Tylosine &Erythromycin).

Pharmacokinetic

They become widely distributed in tissues and tend to be concentrated in the spleen, liver kidneys and particularly the lungs. They enter pleural and ascetic fluids but not the Cerebrospinal Fluid (C.S.F).

They concentrated in the biles and milk the concentration of macrolides in milk is several times greater than in plasma especially in mastitis (Aiello& May, 1998).

Pharmacodynamic

Interfere with protein synthesis by reversibly binding to the 50s sub unit of the ribosome they are bacteriostatic but at high concentration erythromycin is bactericidal (Aiello& Mays, 1998).

1.4.8 The polypeptide antibiotics

Polymyxin are polypeptide antibiotics produced by different strain of Bacillus polymxa including Bacitracin &Neomycin &polymyxin (Alexander, 1985).

Pharmacokinetic

Ziv (1981) stated that polymyxin are minimally absorbed from mucus surfaces and mammary glands. Peak Plasma levels are reached 2 hours after parentral administration. They under go renal elimination mostly as degradation.

Pharmacodynamic

They are bactericidal; they interact strongly with phospholipids in bacterial cell membranes and radically disrupt their permeability and function.

The polymyxins are more effective against gram negative than gram positive (Aiello & Mays, 1998).

Table (2): Kinetics of some antibiotics

ANTIBIOTIC	ACID/BASE	SERUM HALF-LIFE (HOURS)	ROUTE OF ADMINISTRATION
Penicillins			
Ampicillin	Either	1-2	Oral/i.m./i.v.
Benzylpenicillin	Acid	0.5-1	i.m./i.v.
Cephalosporins			
Cephalothin	Acid	0.5-1	i.m./i.v.
Cephaloridine	Acid	1-2	i.m./i.v.
Rifampicin	Base	2-3	oral
Macrolides			
Erythromycin	Base	1.5	Oral/i.m.
Tetracyelines			
Oxytetracycline	Base	10	Oral/im.
Tetracycline	Base	10	Oral/i.m.
Aminoglycosides			
Gentamicin	Base	2.5	i.m/i.v
Streptomycin	Base	2.4	oral/i.m./i.v

Table (3): Absorption pattern for various antibiotics

ANTIBIOTIC	ABSORPTION PATTERN
Penicillin	
Benzyl penicillin	Freely diffusible by intramuscular route. Not suitable for oral use (destroyed by gastric juices)
Ampicillin	Freely diffusible, partly absorbed when given orally.
Amoxicillin	Well absorbed when given orally.
Cephalosporins	
Cephalothin Cephaloridine Cephalexin	}Poorly absorbed; must be given intravenously or intramuscularly well absorbed when given orally.
Rifampicin	Well absorbed when given orally; enterohepatic recirculation maintains high blood level.
Macrolides	
Erythromycin	Variable absorption by the oral route; lactobionate salt gives effective intravenous injection.
Tylosin	Well absorbed when given orally.
Tetracyclines	
Oxytetarcycline Chlortetracycline	Absorption is incomplete by the oral route; low but continuous levels are obtained by the intramuscular route.
Aminoglycosides	
Gentamicin Streptomycin Neomycin	Not absorbed by oral route; good absorption when given by intramuscular route.

1.4.9 Aminoglycosides

Defined as a group of compounds, aminoglycosidesis bactericidal group and have abroad spectrum activity against G +ve & G-ve bacteria (Singelton, 1995). It includes Streptomycin, Neomycin-Framycetin, Gentamicin, Kanamycin and Tobramycin.

Pyatkin and Kuvoshein (1980), stated that Streptomycin was obtained from *streptomycesgriseus.*

Neomycin from *streptococcus Frachiae* (FAO, 1995).

Pharmacokinetics

Absorption after I/M injection site is rapid and nearly complete > 90% availability and peak blood levels are usually achieved within 30-90 minutes.

Absorption after intra-peritoneal administration can produce serious side effects. Intravenous injection can be intermittent or continuous however continuous infusions have high risk of toxicity (Aiello& Mays, 1998). Because of their polarity at physiologic PH, the aminoglycosides distribute into the extracellular fluid space with minimal penetration into most tissues except the kidneys and the endolymph of inner ear. Aminoglycosides are eliminated unchanged in the urine.

Pharmaco dynamic

They are more effective against rapidly multiplying organisms and they affect and ultimately destroy bacteria by several mechanisms.

They need a short contact with the bacteria to kill them. Their main site of action is the membrane associated bacterial ribosome through which interferes with protein synthesis by attachment to 30s Ribosome subunits causing misreading of messenger RNA (Alexander, 1985 & Aiello& Mays, 1998).

Toxicity of Aminoglycosides

Includes ototoxicity, neuromuscular blockage and nephrotoxicity.

Aminoglycosides Residues

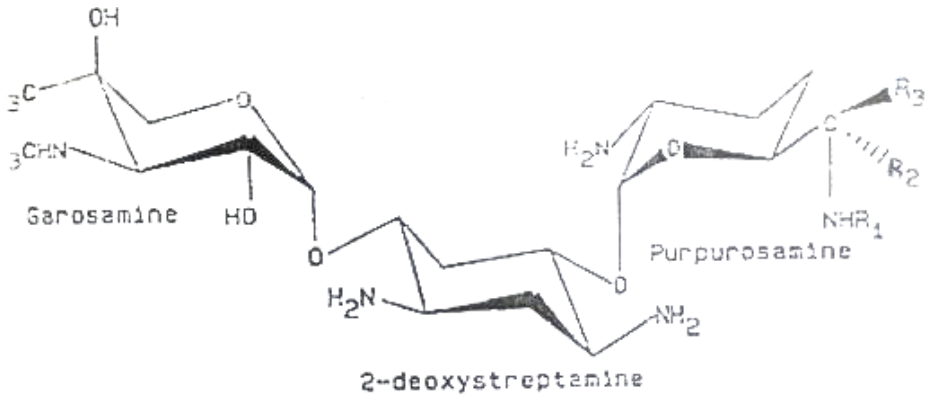
Gentamicin, kanamycin & Neomycin in cow milk was studied after intramamary administration by Moretain & Boisseau (1993). By cylinder plate method they suggested, that the sensitivity was 0.15 mg/ml Neomycin & Kanamycin and 0.05 mg/ml for Gentamicin. The mean elimination periods ranged between 4&13 milking periods the provisional maximum residue limits (MRLs) for Gentamicin, Neomycin & Kanamycin in milk and tissue (0.1-5 $mgkg^{-1}$) was detected by Haasnoot *et al* (1999).

Posyniak *et al* (2001) detected the gentamicin and neomycin residues in animal tissues by liquid chromatography method.

Limits of detection were 0.05 mg/kg & 0.10mg/kg for Gentamicin and Neomycin respectively. The residue of streptomycin & dihydrostreptomycin in meat developed by liquid chromatography electro spray mass spectromein (LC-ESI-MS) (Horie *et al,* 2002).

Gentamicin

It is a new basic pseudo-oligosaccharid antibiotic. It is discovered by (Brander & Pugh 1963). It is amixture drived from Micromonospora (WHO, 1995) purpurea. So the spelling ending in-micin is to indicate that the source is not streptomyces.gentamicin is an antibiotic administered to patients suffering from potentially life-threatening bacterial infections. It has a narrow therapeutic range and constant monitoring is necessary due to the fact that excess dosage can cause kidney and auditory nerve damage



Gentamicin Analog	R_1	R_2	R_3
C_1	Me	H	Me
C_{1A}	H	H	H
C_2	H	H	Me
C_{2A}	H	Me	H

Structure of gentamicin analogs C_1, C_{1a}, C_2 and C_{2a}.

Chemically, gentamicin is exceptionally stable, and is used extensively in animal husbandry. It can be stored at elevated temperatures for extended periods-of-time without loss of biological activity. Gentamicin occurs in four optically active analogs as figure 3 here.

Physical properties

It is a powder, white to buff in color readily soluble in water and heat stable.

Pharmacokinetic

Oral absorption is minimal and so for systemic use Gentamicin must be given by parenteral route.

It is absorbed very fast from the area of injection into serum since already one hour later the higher concentration with an average of 3.7 mg/ml has been reached (Baltimore ;Mary Land, 1970). Some thirty percent of the administrate dose of gentamicin is bound by serum proteins and released as drug is excreted. It excreted almost entirely by glomerular filtration high concentrations of the active form they are found in the urine. Fifty to one hundred percent of gentamicin injected can be recovered unchanged within 24 hours from urine of patient with normal renal function. Little antibiotic enters the cerebrospinal fluid, prostate and eye.

However concentrations of between one-half and one-third of serum levels are found in milk, bronchial secretion and other body fluids.

Toxicity

The main effect is ototoxicity with vestibular function being most often damage; there is also some kidney damage of high doses. A rare but serious side effect is respiratory paralysis due to neuromuscular blockage this can be treated by parenteral calcium or anticholinesterase agent such as neostigmine (Brander, *et al* 1985).

1.5 Metabolism and excretion of antibiotics

Drugs were removed from the body in unchanged form or converted to other substances. These conversions took place in the liver liver kidney, or intestinal epithelium. The kidney excreted the unchanged drugs or its metabolites. A constant proportion of drug was removed in a unit of time it is called exponential clearance. (Archimbault 1983).

Parke (1968) reported that on the whole system, these enzymes do not participate in the body's metabolism and are relatively un specific. A good antibiotic should be excreted in unchanged form. The drug was filtered in renal tubule by reabsorption of water. (Bird & Nayler, 1971).

1.6 Uses of antibiotics in food producing animals

1.6.1 Therapeutic uses

To control infection caused by bacteria and to get rid of disease causing on long-term health effects (Dixon, Tennant and Kay, 1993).

1.6.2 Prophylactic agent

To prevent out breaks of disease in particular circumstances (Dixon *et al*, 1993).

Antibiotic as growth promoters

Antibiotic was approved by FDA (1951) as feed additive for animals to aid growth. Antibiotics were mixed with feed at subtherapeutic concentrations to suppress the activity of some of natural bacteria in animal intestinal tract (Dixon *et al*, 1993).

1.7 Factors affecting drug residues

1. Hapke and Grahwit (1987) approved that the concentration of drug in animal tissues is directly correlated to the absorbed dose.
2. The route of drug administration, intramusular and subcutaneous injection causes high concentration and persistence of drug residue at the site of injection (Standers *et al*, 1988).
3. Sumano *et al* (1990) concluded that the drug clearance in healthy and diseased animals are not the same in diseased animals, residue can persist two or three times longer than in healthy animals.
4. Drug formulation affecting residues Baggot, (1992) stated that the only preparation of drugs are delayed in clearance after local intramuscular injection.

5. Baggot, (1992) also reported that different antibiotic types differ in their residues.
6. Katz & Brady (1993) stated that deposition is the reason for varying concentration in different tissues, high concentration must be expected in excretory organs.

2.1 Milk

Definition & Composition

Milk is defined as the lacteal secretion practically free from colostrum obtained by the complete milking of one or more healthy cows, which contains not less than 8¼% of milk solid non fat and less than 3¼% of milk fat.(United states department of Health, Education and Welfare, 1953).

Also Clarence *et al* (1982), A.Wahab and Mahmoud (1984) defined milk as normal secretion of the mammary glands. Another definition by Clarence (1982) stated that milk is essentially as an emulsion of fat in a watery solution of sugar and minerals salts (true solution and with protein in a colloidal suspension (dissolved phase). From the legal point of view, milk is defined as the normal, clear and fresh secretion obtained by complete milking of the udder of healthy cow or animal during the period following at least 72 hours after calving or until milk is colostrums-free whether such secretion has been processed or not (Harbar,1982 A.Wahab and Mahmoud,1984).

Temperate breeds are Kenna & Butana which are good milk producing animals (Bayoumi, 1954). Also Boyns (1947) discussed the potentialities of the Sudanese cattle as milk producers and reached to the conclusion that the Sudan possesses an excellent basis of cattle capable of rapid response to selection.

Chemical composition of milk from temperate breeds have an average milk composition as follow:

Water 87.3%, fat 3.7%, protein 3-5%, total Solid (T.S) 12.8%, lactose 4.8%, solid non fat (**SNF**)9.1%, Ash 0.65% (Webb *et al*, 1980; Clarence *et al*,1982).

The average composition of cow's milk would be as follows: water 87%, fat 3.5-3.7%, lactose 4.9%, protien3-5% and ash 0.7% (Kon, 1972).

2.1.1 Milk pasteurization

Pasteurization is typically associated with milk. There are two widely used methods to pasteurize milk :high temperature/short time (HTST), and ultra-high temperature (UHT).HTST is by far the most common method. Milk simply labeled "pasteurized" is usually treated with the HTST method, whereas milk labeled " ultra-pasteurized" must be treated with the UHT method. HTST involves holding the milk at a temperature of 161.5 degrees F for at least 15 seconds. UHT involves holding the milk at a temperature of 280 degrees F for at least two seconds.

HTST pasteurized milk typically has a refrigerated shelf life of two to three weeks, whereas ultra pasteurized milk can last much longer

when refrigerated, sometimes two to three months. When UHT pasteurization is combined with sterile handling and container technology, it can even be stored unrefrigerated for long periods of time.

In addition to be standard HTST and UHT pasteurization standards, there are other lesser-known pasteurization techniques. The first technique, called " batch pasteurization ", involves heating large batches of milk to a lower temperature, typically 155 degrees Fahrenheit. The other technique is called higher-heat/shorter time (HHST),and at lies somewhere between HTST and UHT in terms of time and temperature.

2.1.2 Sterilization

1. Destruction of spores and the effects on milk
2. Hydrostatic sterilizer
3. Horzontal sterilizer with rotary valve seal
4. UHT process with steam injection
5. UHT system with scraped surface heat exchangers.

2.1.3 Milk powder

Over view

Whole milk powder (WMP) is obtained removing water from pasteurized, homogenized whole milk through evaporation and spray drying processes. It possesses all the appealing qualities of milk and, in

its dry form, is an important ingredient in the manufacture of a remarkable range of food products.

WMP has a shelf life of about 6 months. Since the product contains a high level milk fat, deterioration in taste, caused by the tendency of fat to oxidize, can be prevented by introducing a nitrogen or carbon dioxide atmosphere or vacuum sealing at time of packaging. WMP should be kept in a cool, dry storage room and should not be exposed to direct sunlight or strong odours. The product should not come into contact with walls or floors.

Composition

Whole milk powder must contain not less than 95 percent milk solids and must not exceed 5 percent moisture. The milk fat content must be not less than 26 percent. Vitamins A and D may be added and the emulsifying agent lecithin may also be added in an amount not exceeding 0.5 percent.

Table (4) composition for whole milk powder

PRINCIPAL COMPONENTS	**PERCENTAGE RANGE**
Lactose	36.0-38.5%
Fat	26.0-28.5%
Protein	24.5-27.0%
Ash	5.5-6.5%
Moisture	2.0-4.5%

2.2 Residue detection methods

(Patal ,R. and Bond, D.1996)stated that many methods were used detect antimicrobial agents.

2.2.1 Biological Methods

Include microbial inhibition and enzyme-linked immuno sorbent assay (ELISA).

Bacterial growth inhibition methods

Was developed by Silver man& Kosikow (1952) bacterial growth inhibition methods were widely used as screening methods for detecting antibiotic residues. They had advantage of being relatively in expensive, rapid and permitted a large number of samples to be analyzed (Dixon *et al*, 1993). The major disadvantages of these methods are that they are not very specific for antibiotic identification, purposes are qualitative, have limited detection levels to many antibiotics and requires several hours before results are available (2.5-18hrs) (Suhren and Heeschen, 1996).

The four plates test was atypical bacterial inhibition test. In this method discs of tissue were placed on four agar plates inoculated with microorganism the plates were incubated under different conditions to allow inhibition of growth by a variety of antimicrobial drugs (Dixon *et al*, 1993). Apositive result was indicated by complete inhibition of growth on the surface of the medium in a zone not less than 2mm wide around the tissue disc.

1. Enzyme linked immunosorbent assay

Elisa was highly specific and easy to perform from simple extraction procedures and rapid reaction time (Patal ,R. and Bond, D.1996)

Results from ELISA were available in period less than one hour and large number of samples could be tested for antibiotic residues. However, wide ranges of ELISA tests were required to test for all possible antibiotics. ELISA could provide better identifications for antibiotic residues than microbial inhibition tests.

2.2.2 Chemical Methods

They include high performance liquid chromatography (HPLC) and mass spectroscopy these methods could differentiate between different antibiotics (Patal ,R. and Bond, D.1996)

HPLC is expensive, need different techniques to deal with different antibiotics, other chemical methods like thin layer chromatography (TLC) was also used, provide a solution to conduct simple& price techniques but they were limited by the complex extraction and clean up protocols.

High voltage electrophoresis bioautography was used for identification of sulphamethazine and penicillin in milk. They extracted the antibiotics using acteonitrite and thin layer, electrophresis using agar medium seeded with microorganism.

2.3. 1 Public Health Risks

1. The effect on the human gut microbial population, the emergency of resistant bacteria within animals and the transfer of antibiotic resistance genes to human pathogens (Garrod, 1964).
2. The use of antibiotic in humans will be rendered ineffective (Brander & Pugh, 1982 Weaver, 1992).
3. De paola (1995) reported that the presence of oxytetarcycline residue in feed may increase the bacterial resistance.
4. Penicillin Residues in milk triggered an allergic reaction, usually a rash (Dewdney, 1991). Allergy is characterized by a spectrum of reactions ranging from mild skin rashes to angio-oedema or life-threating anaphylaxis.
5. Reilly (1997) state that inappropriate use of antimicrobial might cause acquired drug resistance.
6. Packham and Broome (2001) stated that the inhibitory concentration of the antibiotics was in some instances below their detectable limits using either or both the bacillus stearothermophillus (Var calidolactic) disc assay and delvo sp.assay.
7. Residues of antibiotic may inhibit acid production by starter bacteria and significantly affect cheese making process leading to longer make time and disruption of cheese making

schedules. Also inhibit strain of streptococcus thermophillus used in yogurt manufacture.

8. Chloramphenicol and Diethystilbestrol induced carcinogenicity in number of vivo & Vitro test (Forty second report of export committee (1995). Also nitrofurans have been found to be animal carcinogen and mutagen in gentotoxin test (Voogd *et al*, 1979).

9. Aminoglycoside: cause acute tubular necrosis when used in high dose i.e. in a dose more than 35 Microgram per milliliter.

2.3.2. History of Antibiotic Residues in milk

In some countries the use of antibiotics in milk for improving keeping qualities has been suggested (Start well, 1977).

In Zimbabwe 73 samples of raw milk from 3 main dairy market board collection centres, were tested for the presence of microbial growth inhibitory substances. 4.4% of the samples were found to contain antibiotic residues (Chagonda and Ndiku wera, 1989) in Malaysia Salam *et al* (1991) examined 66 fresh milk samples from three small holder dairy farms for the presence of antibiotic residues.

In Lisbon 2248 samples of consumer milk were examined in 1981 to 1985. Six hundred and seventy four of them 30% contained inhibitory substances (Barbosa *et al* 1991). In Estonia, Paern and kind (1995) examined 47 raw milk, samples sold in Tartu for the presence of antibiotic residues, the residues were detected in 4(8-5%) row milk

samples. In Sudan Barakat (1995) used delvo test P for the detection of antibiotics residues in 80 milk samples, he found that 8.75% gave positive results.

Mustafa A. (2001) detected 100 milk samples & he got negative results in all of them.

Raga (2002) stated that the percentage of positive samples for total samples examined was 0.8% and for the samples taken directly from the udder, it was 4.0%.

2.3.4 Establishment of Safe Residue level

Current International agreements with the FAO/ WHO codex Alimentarius programme and Ec legislation established these levels on the bases of toxicology studies. In addition to conventional toxicological effects, immune system and pharmacological effects should be taken into account the latter also include specific effects of residue of Veterinary antibiotics on the human gut Flora (Boisseau, 1993 Mustafa, A. ,2002).

2.3.5 Maximum residue limits (MRLs)

The maximum concentration of marker residue (e.g. parent compound, metabolites. etc)resulting from the use of Veterinary drug expressed in parts per million (ppm) or parts billion (ppb) on a fresh weight bases that is legally permitted or recognized as acceptable in or on food.

AD amount of that can be ingested daily over a life time by a human being without appreciable toxicological health risk (Brynes-Sundlof, 1996).

ADI calculation

The ADI is determined by the observable effect level (NOEL) or the dosage level (mg/kg) at which no adverse effects are observed as established by animal bioassay toxicological studies.

$$\text{ADI (mg/kg/ day)} = \frac{\text{NOEL}}{\text{SF}}$$

SF: Safety Factor

Varies 100-1000 depending on the use of the drug in question and the amount and degree of toxicity data presented by the manufacturer.

2.4 10 points to prevent residues

1. Practice healthy herd management.
2. Establish a valid veterinarian/client/patient relationship.
3. Use only FDA-approved, over-the-counter or prescription drugs with veterinarian guidance.
4. Make sure all drugs you use have labels that comply with state and/or federal labeling requirements.
5. Store all drugs correctly.
6. Administer all drugs properly and identify all treated animals.
7. Maintain and use proper treatment records on all treated animals.

8. Use drug residue screening tests.
9. Implement employee/ family awareness of proper drug use to avoid marketing adulterated dairy products.
10. Complete the milk and dairy beef residue prevention protocol annually.

CHAPTER TWO

MATERIALS AND METHODS

1. Media

A. Nutrient Broth

The medium contained Bacto-beef extract, Bacto-peptone and was obtained in a dehydrated form. It was prepared according to manufacture's instruction by dissolving of the powder in 1000 ml of distilled water & sterilized by autoclaving at 15 Ib pressure for 15 minutes at 121c°.

C. Solid Media: Nutrient Agar

Contained heart infusion, tryptose and sodium chloride. It was prepared according to the manufacture's instructions by dissolving 40 gm of the medium into one litre of distilled water. It was distributed into 25 ml amounts in bottles & sterilized by autoclaving to 15 Ib pressure for 15 minutes at 121c°.

2. Sterilization

2.1 Sterilization of equipments

Glass-ware such as McCartney, Bijou and universal bottles were sterilized in the autoclave at 15 pounds pressure for 15 minutes at 121 c°. Petridishes, graduated pipettes, flasks, test-tubes and bottles were sterilized in the hot air oven at 160c°for 2 hours.

Instruments such as scissors, forceps, scapel & spatula were sterilized by flaming after dipping in spirit.

Sterilization of Culture Media & Solutions

Nutrient broth and nutrient gelatine sterilized in autoclave at 15 pounds pressure for 15 minutes at 121c°.

Collection of Samples

1. Milk samples were collected from milk markets or collection centres
    a. Omdurman locality: Alhigra, Lybia and Salha market.
    b. Khartoum locality: Alsajans, Alamarat and central market.
    c. Kh. North locality: Samrab, Shambat, Haj Yousif, AlGrafe and Kuku market.

Three hundred and twenty seven (327) milk samples were collected in Summer (April,May). Eighty eight (88) samples were collected in Winter (December, January).

2. one hundred and one Milk samples were collected from dairy farms. All these samples were collected in sterile screw-capped bottles, immediately closed to avoid contamination. Then packed in thermoflask transported to the lab. of dept. of Preventive Medicine and Public Health Faculty of Veterinary Science, university of Khartoum.
3. processed milk samples
    a. Twelve samples of milk powder.
    b. Eight samples of treated milk.

(B) Experimental design

- Blood samples were collected from healthy animals which were previously injected intramuscularly with therapeutic dose by Gentamicin 10%. Then plasma samples separated and were frozen for analysis by Microbiological method. Plasma samples were collected every hour from Group A (4 sheep, 4 goats) and Group B (4 sheep, 4 goats). This was done for the first 8 hours then every 12 hours for 3 days.
- Milk samples were collected from Group A every hour at the first 6 hours then every 12 hours for 3 days and milking was done once a day. groupB milk samples were collected every 3 hours and then empting the udder from milk also at the Same time.

2. Methods

The detection or measurement of residues of antibiotic is carried out using either bioassay or physicochemical methods.

Microbiological method is to measure the ability of the drug to inhibit the growth of standard bacteria which is selected for that purpose.

Biochemical assay is based on enzymatic. Reaction also HPLC. Technique can be applied.

A.Preparation of standard test organism culture

Bacillus subtilis (BGA) was seeded in nutrient broth. 100 ml of sterile nutrient broth prepared and distributed in ten test tubes.

In each test tube the standard bacteria (B.S) was inoculated with a sterile wire-loop and mixed well, then incubated at 37c° for over night.

B. Preparation of culture media

In every sterile Petri dish add one ml of B.S. Nutrient agar sterilized in autoclave was left to cool up to temp. 50°-55c°. 20 ml of this media was poured in the Petri dishes with 1 ml of standard organisms. Thoroughly mixed the content of each Petri dish was left for 10 minutes to solidify on a leveled surface bench. With a clean dry& sterile forceps pick up a sterile filter paper disc from the container, (paper susceptibility Disks without antibiotic). The filter paper disk was dipped into milk or plasma samples to be tested.

Immediately the disk was placed on agar surface nearly at the centre of the plate. The forceps was sterilized by flame.

This procedure was repeated for each type, of milk or plasma using separate disc. Other method was done by making wells in the solidifying agar by the tip of micropipette.

Then wells were filled with samples by micropipette 250 ml. plates were incubated at 35C° until growth visible within 18-24 hours. Zone of inhibition was noted around the discs that were dipped into

sample if the sample contain antibiotic; if not no zone appear. Measurement of the diameter zone to obtain concentration of drug in samples.

Determination of the Minimum Inhibition Concentration (MIC)

Standard curve

This was done by adding a known concentration of Gentamicin to known volumes of distilled water then mixed well and tested for sensitivity test. Tow papers were put on the surface of plate which had already been inoculated with Bacillus subtilus.

Control plate which contain distil water free of antibiotic and pyrogenic free was also made together with test plates the plates were incubated at 37c° overnight, zone of inhibition observed around the papers and measured by ruler. Then the mean values of inhibition zone for each concentration were obtained and log. Concentrations were also obtained, Then the standard curve was plotted (reference curve).

The minimum concentration of Gentamicin that caused inhibition was considered to be the minimum inhibitory MIC of Gentamicin 10%.

Testing for antibiotic Residues in plasma and milk

Milk or plasma which were suspected to contain antibiotics were taken by micropipette of 1 ml capacity equivalent to amount which saturated the filter paper of diameter (12-2 mm). If there was inhibition zone around the paper after incubation 18-24 hrs, was consider positive

and measured by ruler on the out side of the plate the diameters of growth inhibition zone were measured in millimeter to obtain concentration of drug in samples & to make monograph of the drug gentamicin 10%.

CHAPTER THREE

RESULTS

Recently venders have used antibiotics Penicillin's and others antibiotics to keep milk fresh for long periods. This affects human beings immunity especially children. These practices are strictly forbidden world-wide.

3. 1 Marketing milk samples

1. Milk venders (M.Vs) in summer
2. Milk venders (M.Vs) in winter.
3. Dairy farms (DFS).
4. Processed milk samples: milk powder and treated milk (M.P. &T.M).

All milk samples were tested for the presence of antibiotics. Their results were illustrated as follows:

25%, 79%, 18, 8%, and 0% see table (5) table (6), table (7) and table (8) for details.

Table (5) positive samples for the three localities of Khartoum State in summer

LOCALITY	NO OF SAMPLES	POSITIVE SAMPLES	PERCENTAGE
Omdurman	98	18	18.37%
Khartoum	126	44	34,92%
Khartoum.N	103	20	20%
Total	327	82	25%

Table (6) positive samples for the three localities of Khartoum State in winter

LOCALITY	NO OF SAMPLES	POSITIVE SAMPLES	PERCENTAGE
Omdurman	25	2	8%
Khartoum	33	3	9%
Khartoum.N	30	2	6%
Total	88	7	7.9%

Table (7) positive samples for the farms of the three localities

LOCALITY	NO OF SAMPLES	POSITIVE SAMPLES	PERCENTAGE
Omdurman	35	5	14.3%
Khartoum	33	6	18%
Khartoum.N	33	8	24%
Total	101	19	18.85

Table (8) result of antibiotic detection in samples of milk powder & treated milk

TYPES	NO. OF TYPES	NO. OF POSITIVE	PERCENTAGE
Milk powder	12	0	-
Treated milk	9	0	-

Figure (4), (5) and (6) show the results for summer, winter and farms for positive samples percentages respectively.

Figure (7) shows total positive percentage of M.Vs in summer-winter.

Figure (8) shows total positive percentage of summer M.Vs –famrs samples.

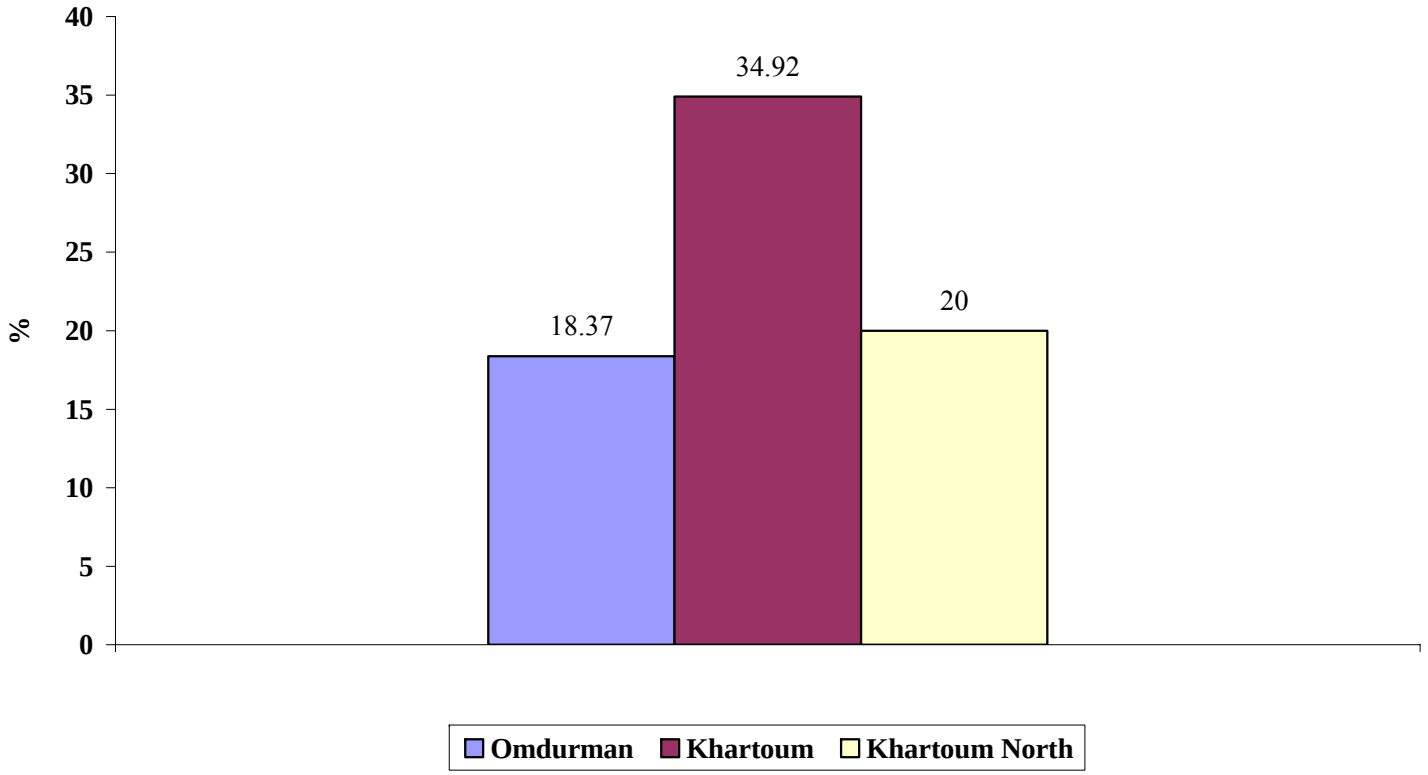


Fig. 4 Milk samples in summer season

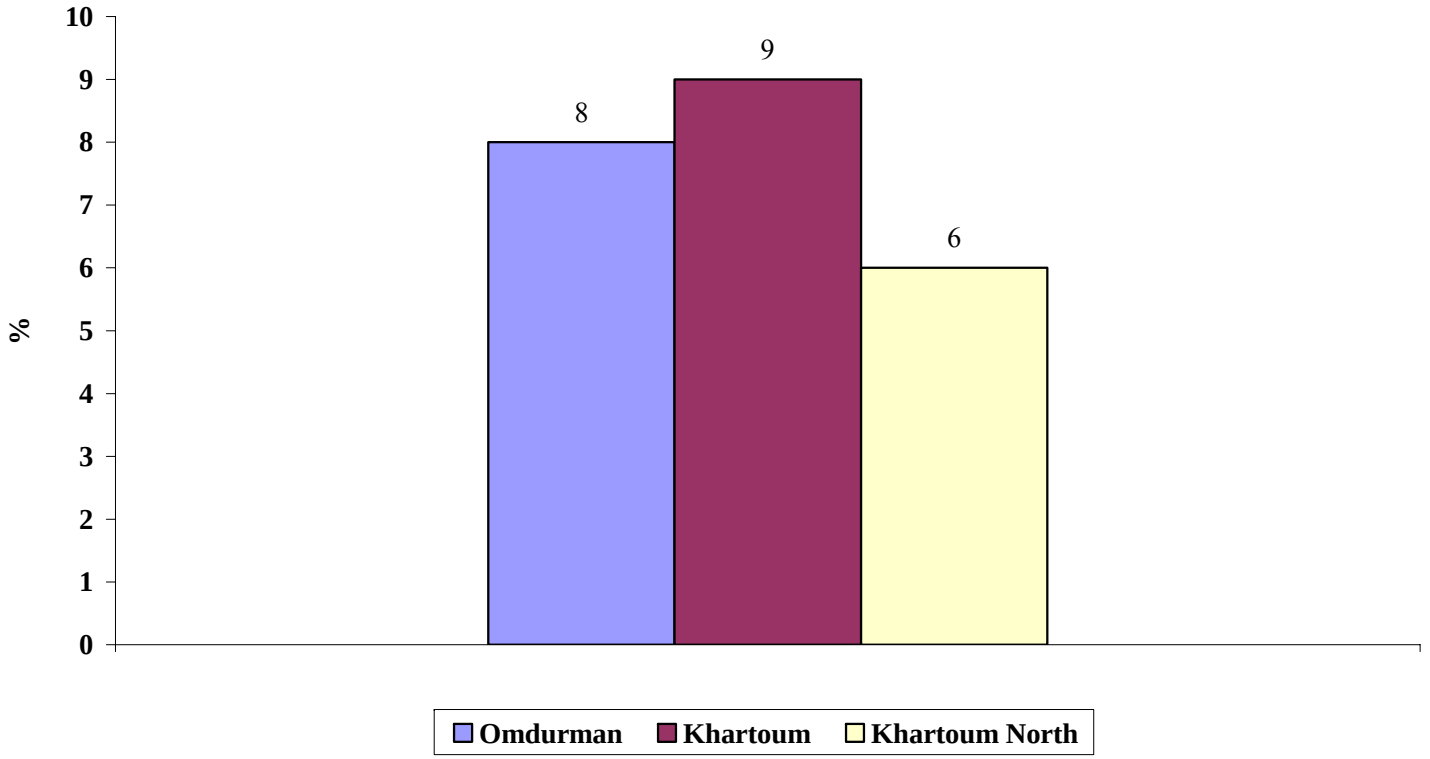


Fig. 5 Milk samples in winter season

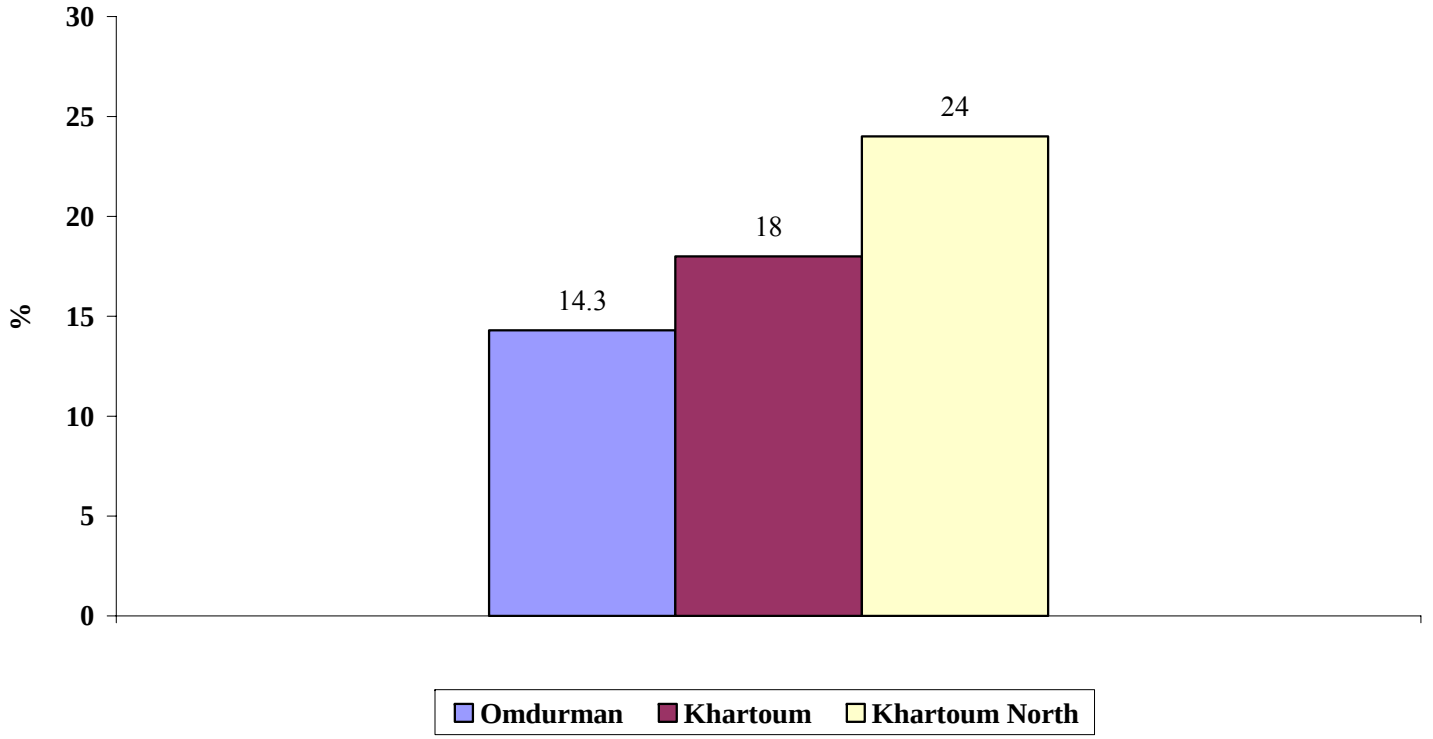


Fig. 6 Milk samples of farms

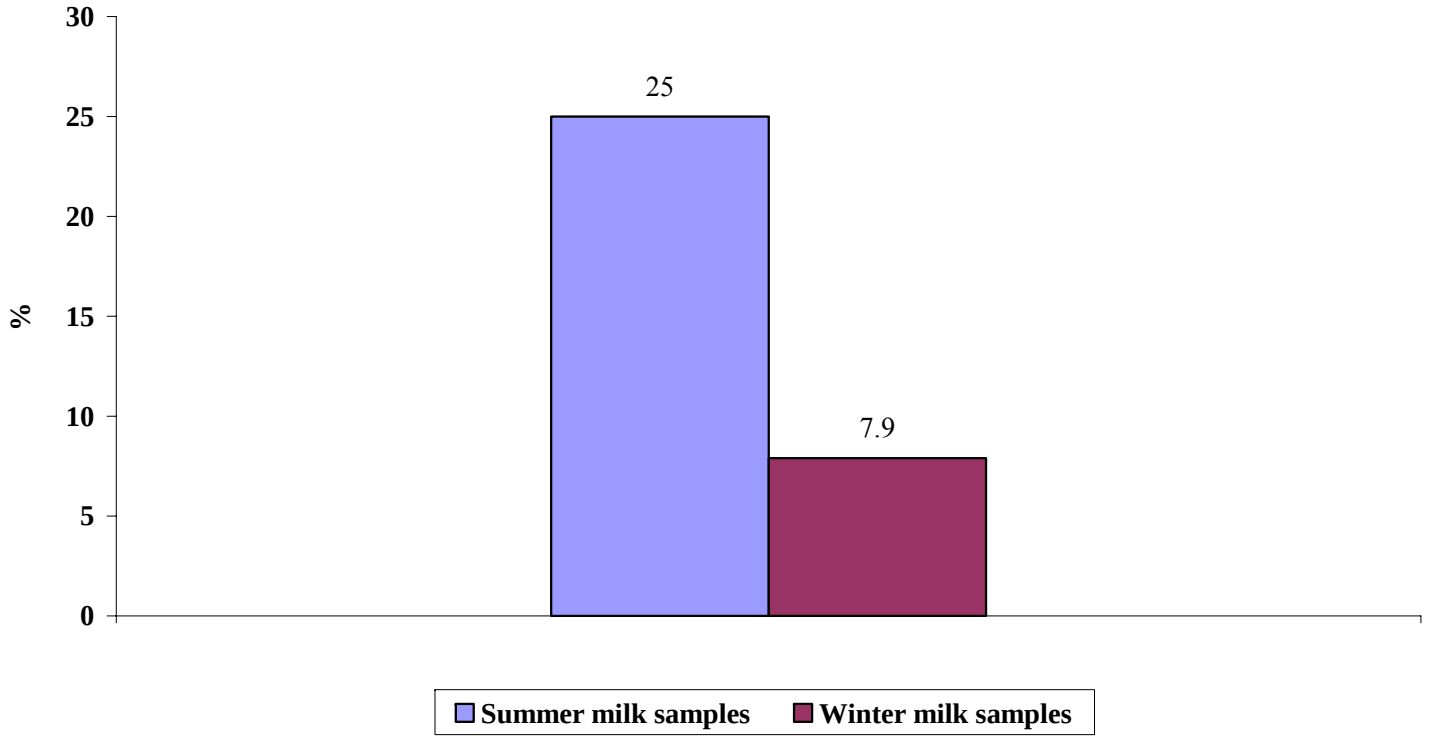


Fig. 7 Milk venders samples

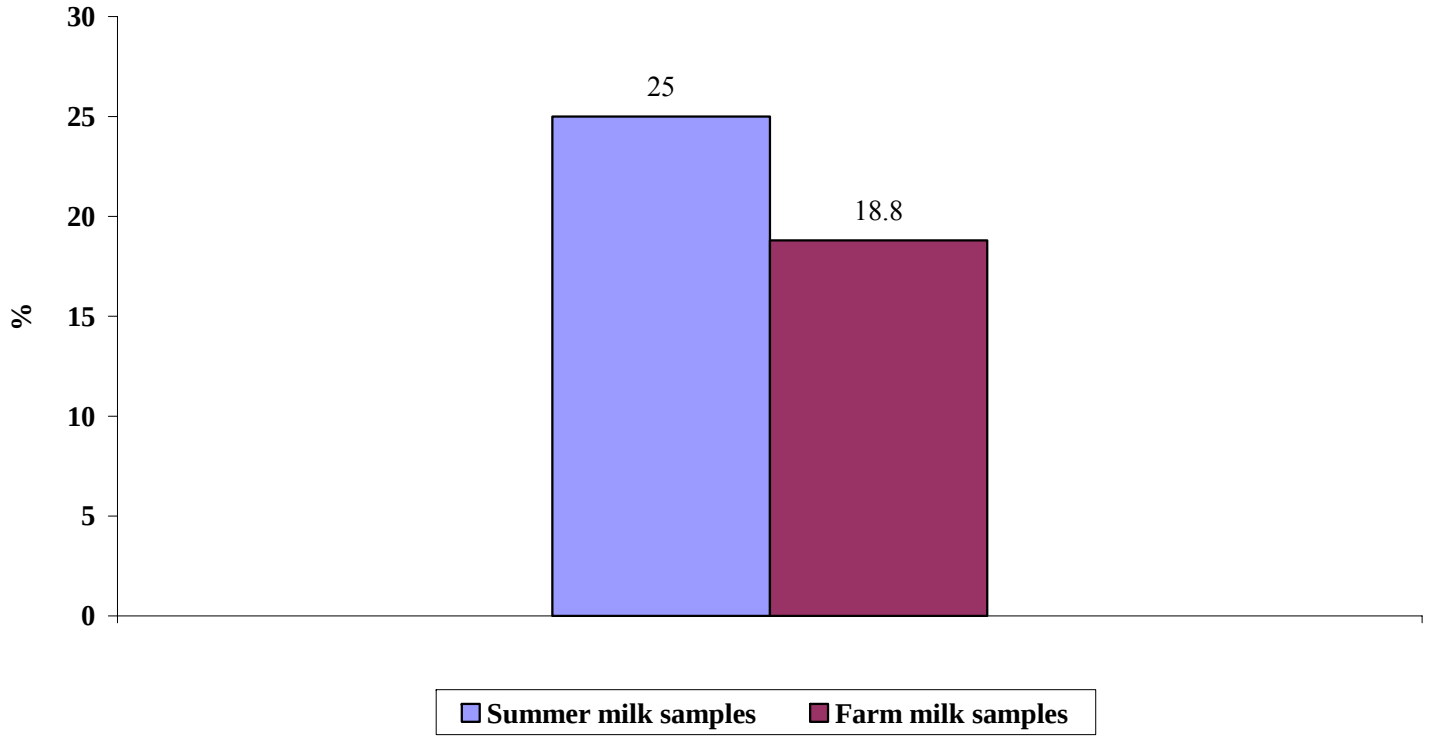


Fig. 8 Milk venders and farm samples

3.2 Experimental part

Diameter of zone of antibiotic inhibition were measured in mm the results of experiment of group A &group B were shown in table 9 and table 10.

Table (9) Diameter zone of inhibition of G(A) plasma samples following I/M injection of Gentamicin

HOURS	G1	G2	G3	G4	S1	S2	S3	S4
First	17	13	12	12	15	6	8	15
Second	15	15	13	12	14	9	11	13
Third	11	12	11	9	8	6	10	8
Fourth	6	6	7	6	7	6	6	7
Fifth	7	6	7	6	6	6	7	6
Sixth	0	0	0	0	6	0	0	0
Seventh	0	0	0	0	0	0	0	0
Other days	0	0	0	0	0	0	0	0

Table (10) Diameter zone of inhibition of G(B) plasma samples following I/M injection of Gentamicin

HOURS	G1	G2	G3	G4	S1	S2	S3	S4
First	14	16	16	16	17	17	14	**8**
Second	12	10	13	14	17	17	15	**6**
Third	14	10	12	12	16	15	15	**0**
Fourth	13	12	12	12	13	12	12	-
Fifth	12	10	11	9	9	10	11	-
Sixth	10	6	8	8	9	9	9	-
Seventh	7	0	6	6	6	6	6	-
Eighth	6	0	-	-	-	-	-	-
Second day	-	-	-	-	-	-	-	-

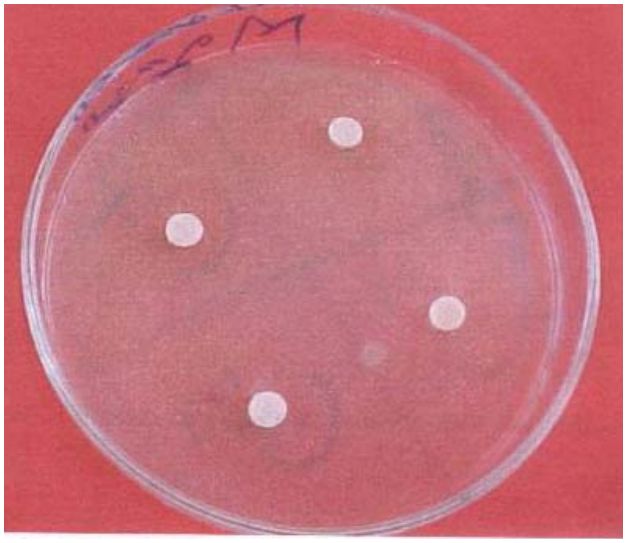
Also milk samples were collected from both GA&GB and were examined see table (11) for group A but No zones in GB.

Table (11) Diameter zone of inhibition of milk samples G(A)

HOURS	G1	G2	G3	G4	S1	S2	S3	S4
26 hours	6	6	-	6	7	6	6	6
29 hours	7	6	7	8	8	6	7	7
31 hours	6	6	6	6	6	7	8	6

Plate (1) shows zone of inhibition of milk samples GA at 29 hour after injection, plate (6) shows no zones for GB at 30 hours after injection.

Plate (2),(3),(4)and (5) show zone of inhibition of plasma samples at first hour of injection (group A) second hour (GA), first hour (GB) and second hour of (GB).



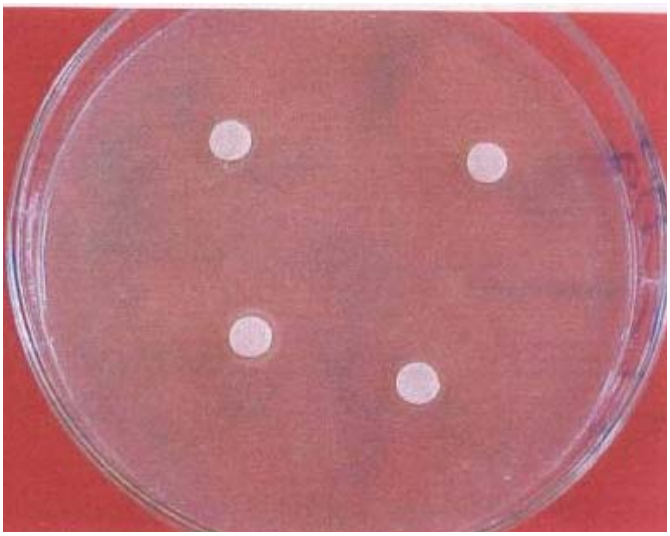


Plate 1: Inhibition tests for milk samples at 29 hrs

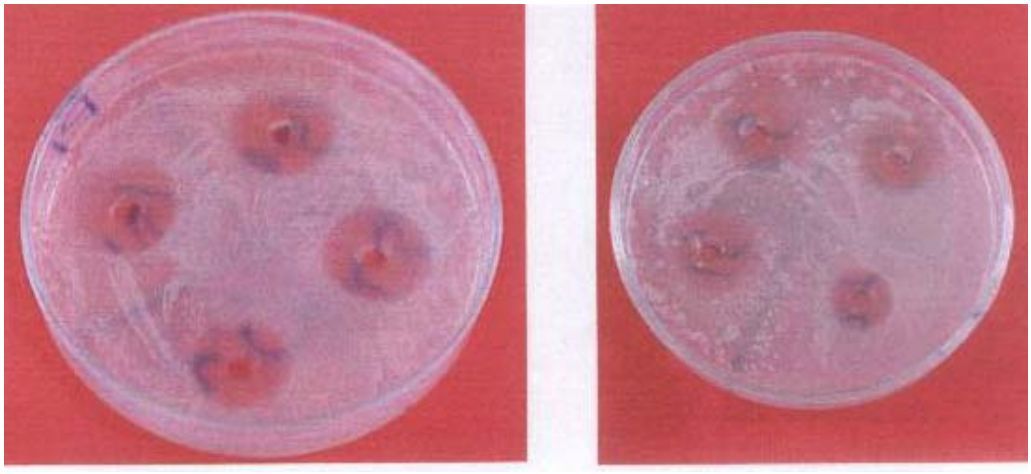


Plate 2: Plasma samples results at the first hrs of injection (GA)

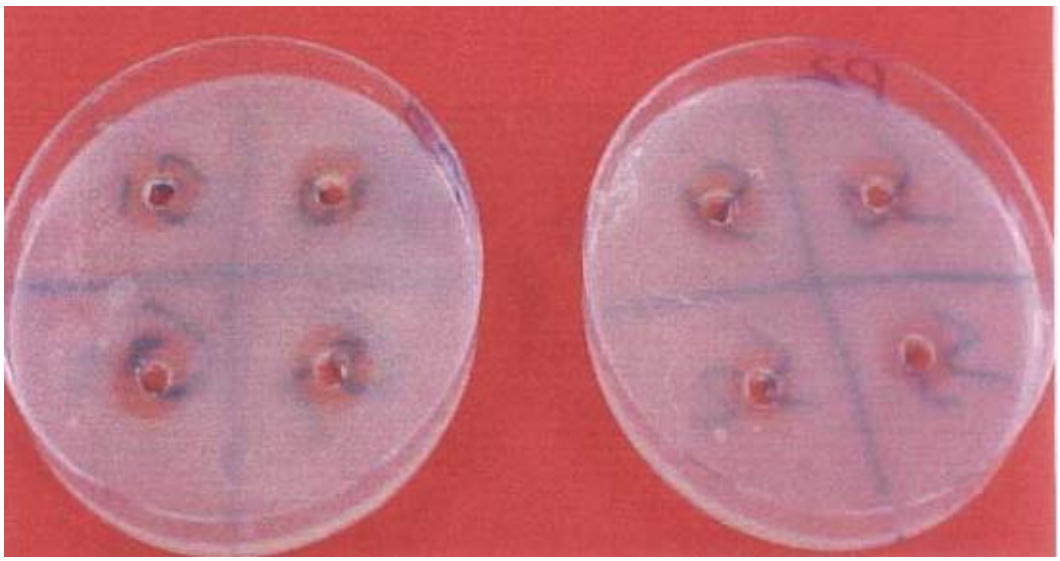
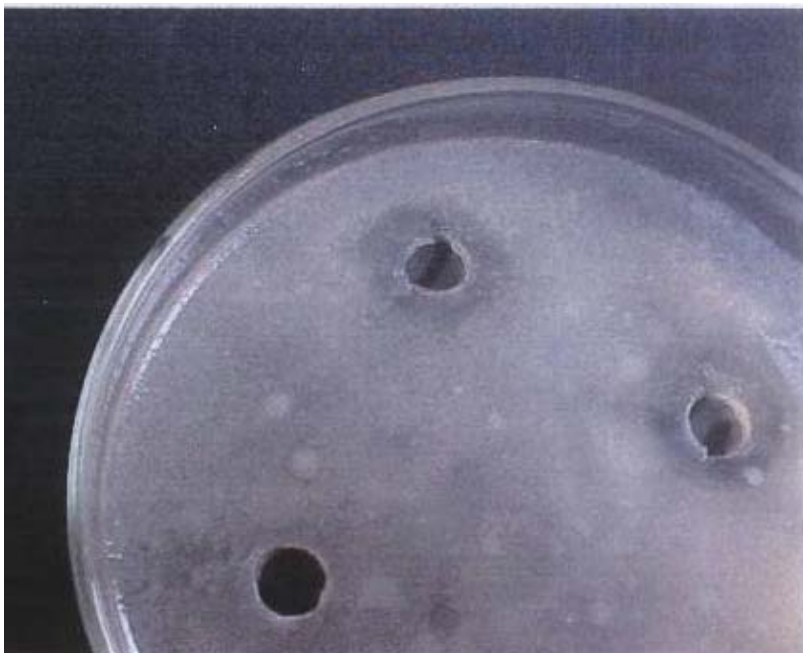


Plate 3: Plasma samples results at the second hrs of injection (GA)



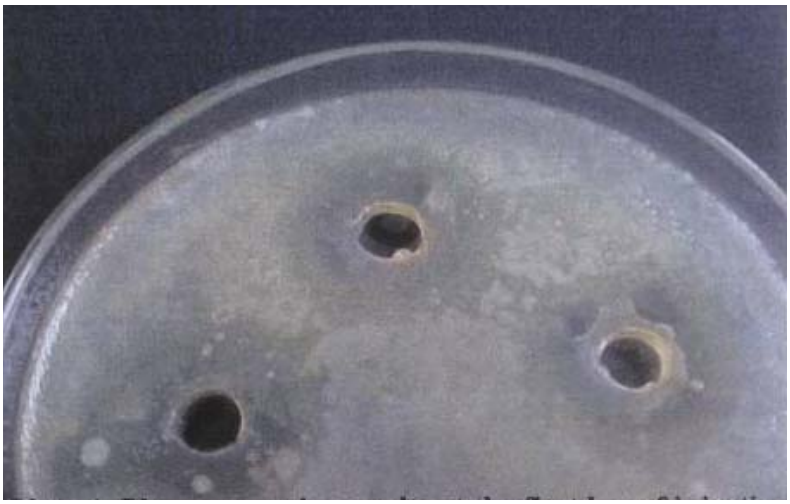


Plate 4: Plasma samples results at the first hrs of injection (GB)

Plate 5: Plasma samples results at the second hrs of injection (GB)

Plate 6: Results for milk samples at 30 hrs of injection (GB)

Table (12). Plasma concentrations of Gentamicin (group A).

Animals Hours	G_1	G_2	G_3	G_4	S_1	S_2	S_3	S_4	Mean
1st	1.29	0.27	0.15	0.15	0.62	0.037	0.03	0.62	0.396
2^{nd}	0.62	0.62	0.27	0.15	0.39	0.037	0.11	0.27	0.308
3^{rd}	0.11	0.15	0.11	0.037	0.03	0.018	0.074	0.03	0.070
4^{th}	0.018	0.018	0.024	0.018	0.024	0.018	0.018	0.024	0.020
5^{th}	0.024	0.018	0.024	0.018	0.018	0.018	0.24	0.018	0.047
6^{th}	0.018	0	0	0	0	0	0	0	0.002

Table 12-A: Descriptive statistic of plasma concentration of Gentamicin (group A)*

Time	Median	Mean	SD	95% CI
1st	0.210	0.396	0.431	0.285-0.877
2nd	0.270	0.308	0.221	0.146-0.450
3rd	0.056	0.070	0.049	0.032-0.099
4th	0.018	0.020	0.003	0.002-0.006
5th	0.018	0.047	0.079	0.052-0.159
6th	0.000	0.002	0.006	0.004-0.013

***: Eight animal were examined (4 goats and 4 ewes)**

SD: standard deviation

95% CI: 95% confidence intervals

Fig. 9: Mean plasma of Gentamicin in 4 goats and 4 ewes of group A

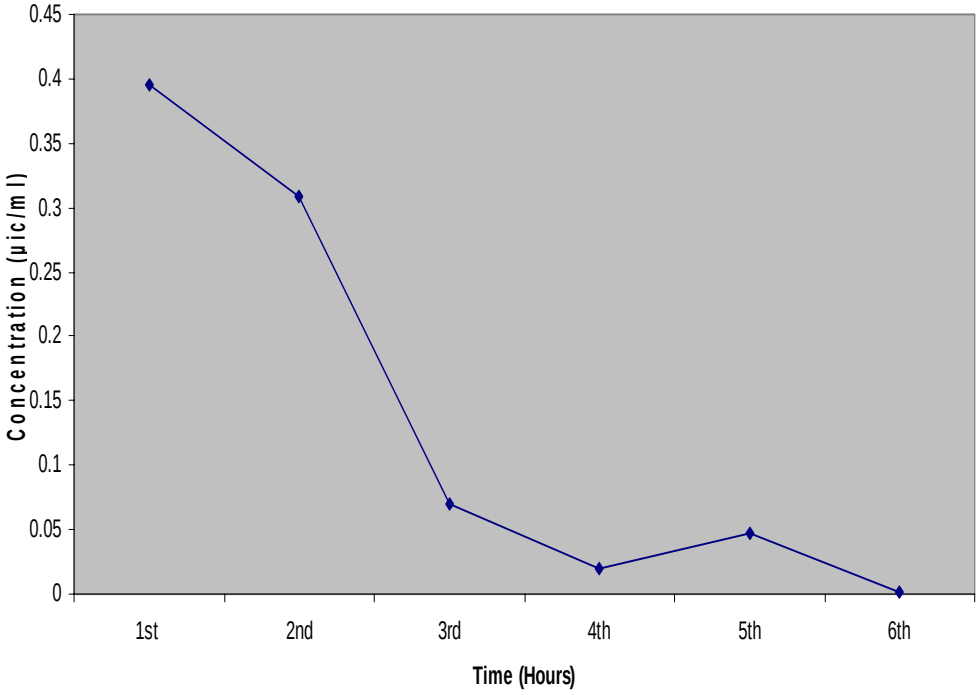


Table (13). Plasma concentrations of Gentamicin (group B).

Animals Hours	G_1	G_2	G_3	G_4	S_1	S_2	S_3	S_4	Mean
1st	0.39	1.01	1.01	1.01	1.29	1.29	0.039	0.03	0.758625
2nd	0.15	0.074	0.27	0.39	1.29	1.29	0.62	0.018	0.51275
3rd	0.39	0.074	0.15	0.15	1.01	0.62	0.62	0	0.37675
4th	0.27	0.15	0.15	0.15	0.27	0.15	0.15	0	0.16125
5th	0.15	0.074	0.11	0.037	0.037	0.074	0.11	0	0.074
6th	0.074	0.018	0.03	0.03	0.037	0.037	0.037	0	0.032875
7th	0.024	0	0.018	0.018	0.018	0.018	0.018	0	0.01425
8th	0.018	0	0	0	0	0	0	0	0.00225

Table 13-A: Descriptive statistic of plasma concentration of Gentamicin (group B)*

Time	Median	Mean	SD	95% CI
1st	1.010	0.759	0.526	0.285-0.877
2nd	0.330	0.513	0.516	0.341-1.050
3rd	0.270	0.377	0.350	0.231-0.712
4th	0.150	0.161	0.085	0.056-0.173
5th	0.074	0.074	0.049	0.032-0.099
6th	0.034	0.033	0.021	0.014-0.043
7th	0.018	0.014	0.009	0.006-0.018
8th	0.000	0.002	0.006	0.004-0.013

Fig. 10: Mean plasma of Gentamicin concentrations in 4 goats and 4 ewes of (group B)

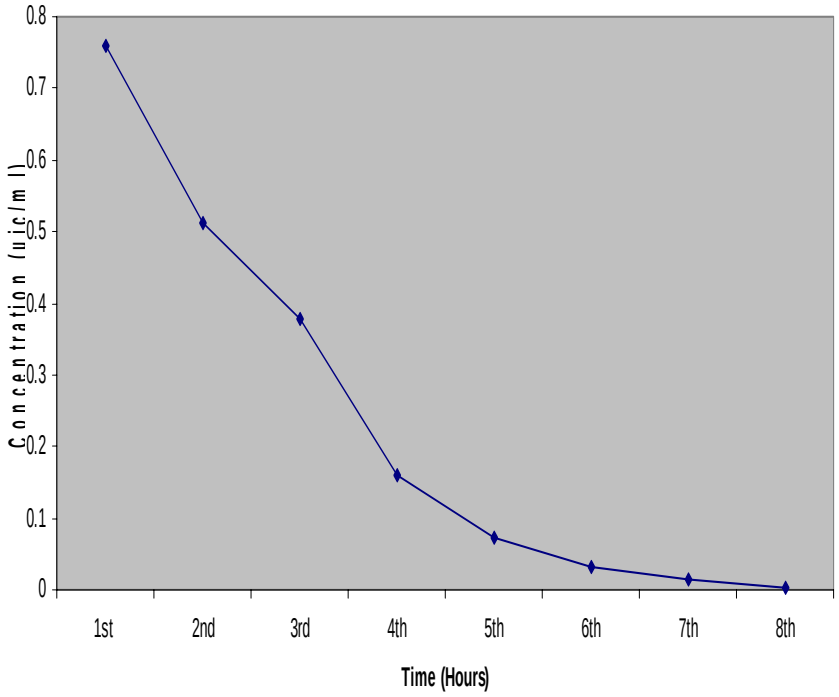
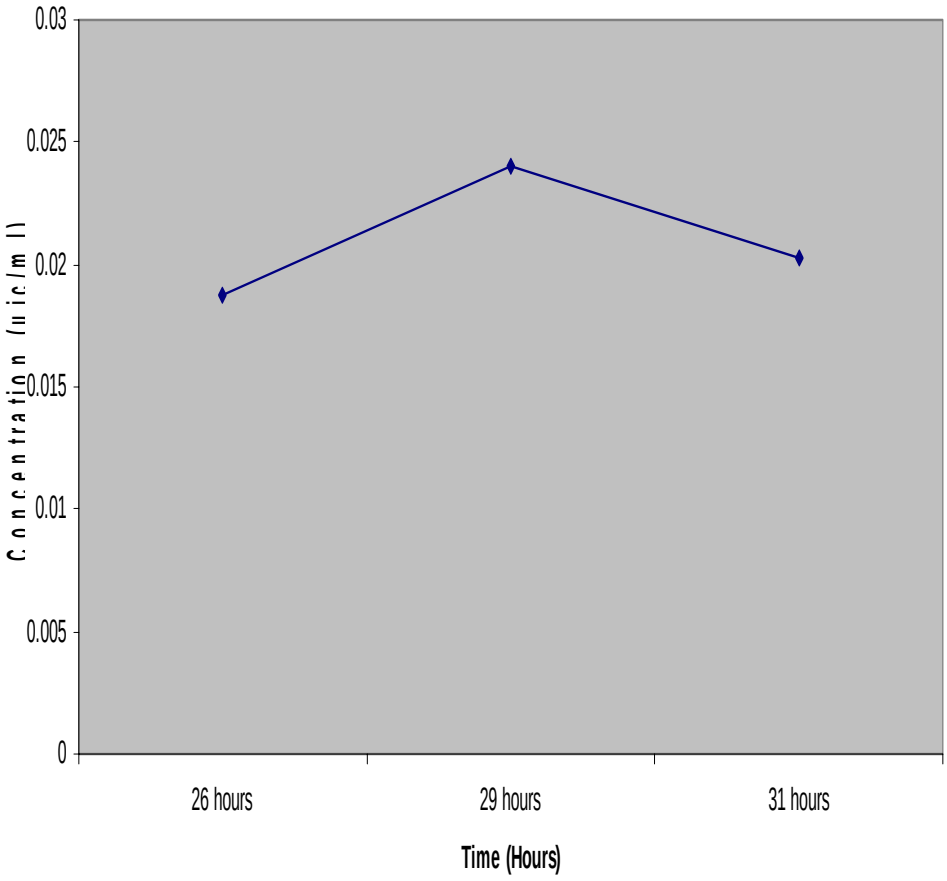


Table (14). Milk concentrations of Gentamicin (group A).

Animals / Hours	G_1	G_2	G_3	G_4	S_1	S_2	S_3	S_4	Mean
26hours	0.018	0.018	0.018	0.018	0.024	0.018	0.018	0.018	0.01875
29 hours	0.024	0.018	0.024	0.03	0.03	0.018	0.024	0.024	0.024
31 hours	0.018	0.018	0.018	0.018	0.018	0.024	0.03	0.018	0.02025

Fig 10: Mean milk of Gentamicin concentration in 4 goats and 4 ewes of group A



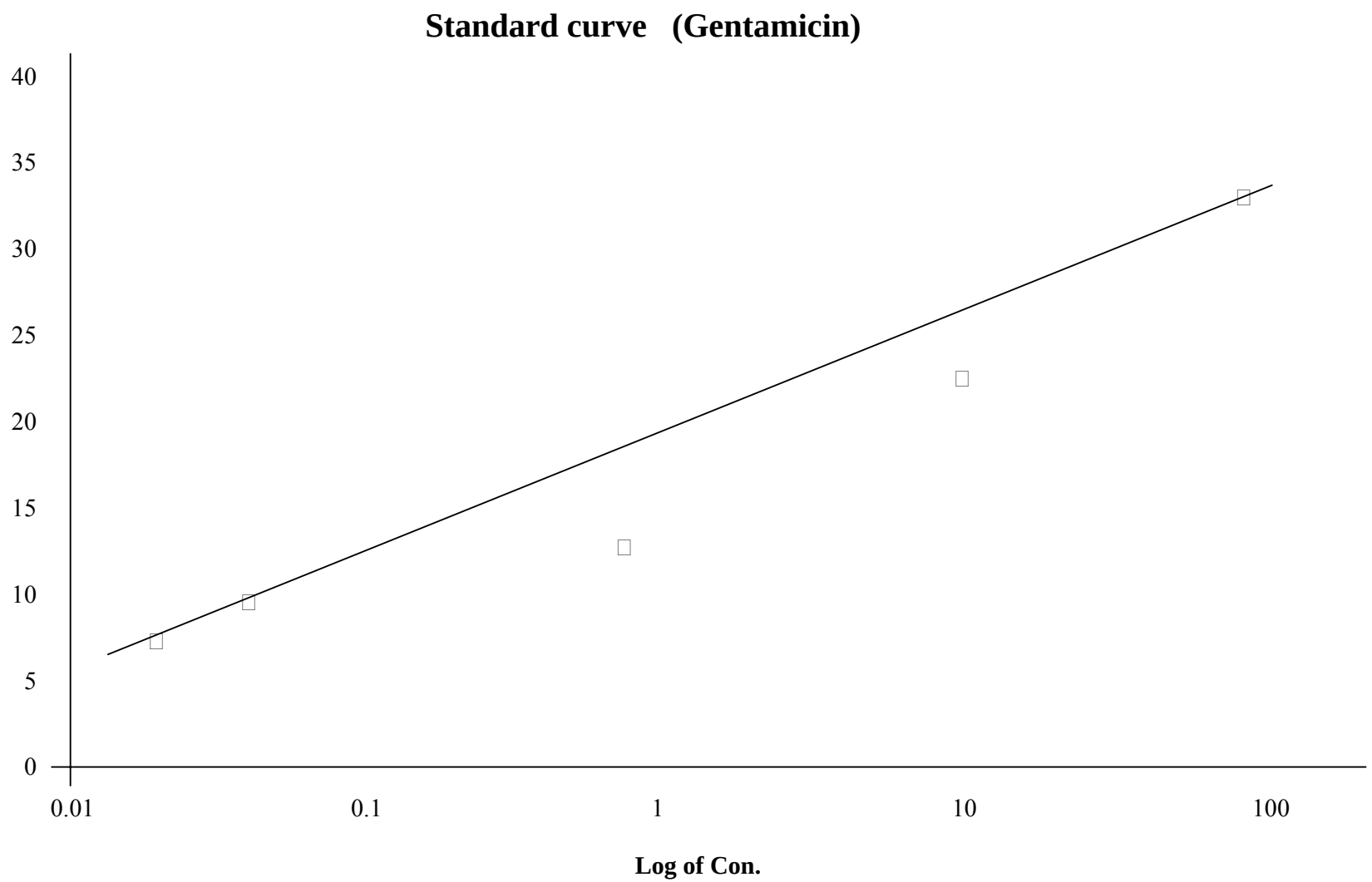


Fig. 12: Standard curve (Gentamicin)

The relationship between concentration of drug

and zone of inhibition

Correlation coefficient = 0.883 (Strong correlation)

Regres Con Zone

Source	SS	d.f.	MS	Number of obs = 8
Model	409.376912	1	409.376912	F(1, 6) = 21.17 Prob > F = 0.0037
Residual	116.040353	6	19.3400589	R-squared = 0.7791
Total	525.417265	7	75.0596093	Root MSE = 4.3977

Con	coef.	Std. Err	t	P > |t|	(95% Conf.	Interval
Zone	0.7397941	0.1607971	4.601	0.004	0.3463379	1.13325
Cons	-8.327963	3.428033	-2.429	0.051	16.71606	0.0601324

CHAPTER FOUR

DISCUSSION

4.1 Milk Samples

This survey was conducted in Khartoum State, number of markets and a number of farms have been visited to detect the residual antibiotics in milk in Khartoum, North Khartoum and Omdurman Localities.

Positive results detected were 35%, 20% and 18% in Khartoum locality, Kh. North and Omdurman localities respectively. The higher percentage in Kh. Locality may be due to facts that most of milk comes from Gezira State which is far away, so milk venders add antibiotics to preserve it. While in Kh. North and Omdurman , the lower percentage may be due to availability of consumers near milk production units.

Samples of collected milk in summer shows higher percentage (25%) to those which were collected in winter season (7.9%), which indicates effects of higher temperature on bacterial growth.

Also there were some milk samples collected directly from (101) farms to compare between MV's and farm's milk. Positive result were higher in MVs to those from farms. So residues of antibiotics in farm's milk due to treatment samples of treated milk and milk powder were tested positive result were (0%) this result may be due to methods of manufacturing.

4.2 Experimental Work

Gentamicin is one of the antibiotics that is used in animal treatment in Sudan. 16 animals have been injected to study pharmacokinetics of Gentamicin in plasma and milk. The animals were divided into two groups:

Group A (GA)(4 sheep and 4 goats) and group B (GB) (4 sheep and 4 goats).

4.2.1 GA

Plasma peak concentration of drug was detected at first hour and sometimes at second hour then it decreased gradually till it disappeared within 7-8 hours after injection.

Milk samples were taken every 4 hours during 35 hours from injection. Drug appeared at 20 hours from injection reach the peak amount of Gentamicin in milk at intervals from 29-31 hours.

The milking was done once a day.

4.2.2 GB

In GB we took samples and then emptied the udder every 3 hours this might have caused the disappearance of the drug.

CHAPTER FIVE

CONCLUSION & RECOMMENDATIONS

Antibiotics have been used on farms for almost half century to treat and control diseases and to improve animal productivity. Recently haphazard use of antibiotics and chemicals by venders has resulted in some health problems. Which may latter lead to severe loss in health especially in childrens and elders.

The following suggestions and recommendations were suggested for better control of milk production in dairy farms as well as in back yard system and milk venders.

5.1 Dairy farms

- Use pasteuralized methods, boiling and cooling to keep milk marketable.
- To encourage investment in production of milk using modern technological methods.
- Qualifying milk labs by modern devices such as HPLC to analize the added antibiotics and to discover froud milk if any.
- Addition of safe preservation agents H_2O_2 (Dirar,1967) & Nisin produced by bacteria Lacococcus lactis and Streptococcus lactis (Mona S.Awlan,2003) with a known efficient function.

5.2 Milk venders and Backyard systems

- Enforce strict regulation to forbid venders and farmers from adding antibiotics and chemicals to preserve milk.

- Big centre equipped with modern machines for collecting milk should be available.
- Applying of laws and regulations that concern with health.

More research in Gentamicin residues should be done

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الالبان ومنتجاتها وتحديات العولمه-المشاكل والحلول- سمنار ضبط الجوده في الصناعات الغذائيـه والروئ المستقبليه للالفيه الثالثه د. مني أحمد العجب- د.أحمد الفكـي جامعـة الـدول العربيه المنظمه العربيه للتنميه الزراعيه بالاشـتراك مـع جامعـة الـسودان للعلـوم والتكنولوجيا كلية الدراسات الزراعيه-الخرطوم اغسطس ٢٠٠٠.

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