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ANTIMICROBIAL RESISTANCE IN GRAM-NEGATIVE BACTERIA

"SALMONELLA"

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Abstract :Antimicrobial resistance (AMR) is the ability of bacteria to survive or proliferate in the presence of medications that are meant to kill or inhibit them. Antimicrobials are medications that treat infectious disorders caused by microorganisms such as bacteria, fungus, viruses, and protozoa parasites. Antimicrobial resistance is a major global issue to human and animal health that is growing in importance. It also affects the food safety, security, and economic well-being of millions of farming households. Antimicrobial resistance in zoonotic *Salmonella* has been linked to the overuse of antibiotics in food-producing animals in affluent countries. It is hoped that the use of Codes of Practice for the use of such agents, which were developed by the pharmaceutical industry in response to widespread international concern about the development of drug resistance in bacterial pathogens, will now result in a widespread reduction of drug-resistant *Salmonella* in food production animals and humans on a global scale. *Salmonella* is the most prevalent cause of food poisoning and a common bacterial infection of the intestines. When a patient has diarrhoea and a fever, a *Salmonella* infection, also known as salmonellosis, is the most likely cause. *Salmonella* typhoid strains (*Salmonella* enterica variants-*typhi* and *paratyphi*) easily pass through intestinal tissues, infect the body, and cause typhoid fever, one of the world's deadliest infectious diseases. Ceftriaxone, ciprofloxacin, and ampicillin are antimicrobials used to treat severe infections. The major goal of this study is to use bioinformatics methods to identify antimicrobial resistance genes found in *Salmonella* species so that we may learn about current research on antimicrobial medication classes used to treat infectious disorders. Antimicrobial Resistance Initiative is designed to help to fight the growing emergence and spread of pathogens resistant to antimicrobial drugs from a multidisciplinary approach through the institute's core activities: research, training, technical assistance and analysis. According to recently data antibiotics adjuvants will also play an important role in extending the shelf life of our existing antimicrobial therapeutic agents.

1. INTRODUCTION

1.1. Antimicrobial Resistance (AMR)

Antimicrobial Resistance refers to the microorganism like bacteria, viruses, and certain parasites) to inhibit antimicrobial agents (antibiotics, antivirals, and antimalarials) from its specified level of effectiveness against such microorganisms. In order to guide antimicrobial research, discoveries, and development of new antimicrobials, the World Health Organization (WHO) also released a list of antimicrobial-resistant microorganisms that required immediate attention. At the United Nations General Assembly in 2016, the enormity of AMR dangers got the highest level of political commitment from world leaders, and a democratic declaration on antimicrobials was made. Earlier inventions and manufacture of new drugs have contributed to the development of several new antimicrobial classes. These studies will look for empirical therapy and control techniques to combat AMR dangers. (Oloso et al., 2019). Antimicrobial resistance (AMR) is a global issue that has to be addressed. Microbes' ability to withstand the effects of antimicrobial medicines that were previously effective in treating infections caused by such pathogens is referred to as antimicrobial resistance(Frost et al., 2019). According to the Centers for Disease Control and Prevention (CDC), at least 2.8 million people died, resulting in over 35000 deaths. According to the Organisation for Economic Co-operation and Development (OECD), antimicrobial-resistant illnesses are expected to cause 2.4 million deaths in Europe, North America, and Australia over the next 30 years, costing up to US$3.5 billion in additional health care expenditures per year. As AMR becomes a global problem, both monetarily and in terms of public health, it is

critical to establish a preclinical tool for accurate AMR prediction. (Chowdhury et al., 2020). Antimicrobial drugs can have anti-inflammatory, anti-cancer, immunomodulatory, immunosuppressive, and other characteristics. Antimicrobials could therefore be utilised to treat malignancies, cardiovascular illnesses, autoimmune diseases, neurological diseases, chronic respiratory diseases, and other inflammatory diseases. Eukaryotic cells, such as those present in humans and animals, can also be regulated by antimicrobial drugs. Most antimicrobial agents have been a small number of habitats, including dirt, and a small number of taxonomic entities composed largely of actinomycetes. The entire chemical synthesis of antimicrobial drugs, developed by Paul Ehrlich over a century ago, was adapted as a fragment-based lead discovery technique in the late 1990s. Antimicrobials are becoming increasingly important in the treatment of non-infectious disorders, therefore preventing AMR is essential. At least for some antimicrobials, such as macrolides, it has been proven that ligands responsible for antibacterial and anti-inflammatory actions are different and can be adjusted individually. (Travis et al., 2018).

1.2. *Salmonella*:

Salmonella is a Gram-negative, rod-shaped, facultative anaerobe bacteria belonging to the Enterobacteriaceae family. This bacteria belongs to a huge genus with global public health implications, as it is the most common cause of foodborne infections, resulting in thousands of deaths globally. Eberth was the first to recognise *Salmonella* in the early nineteenth century, and Gaffky was the first to isolate the *Bacillus* responsible for human typhoid disease. Theobold Smith and Daniel Elmer Salmon then found and isolated *Salmonella* from the intestines of pigs ill with swine fever, also known as hog cholera, in 1885. Dr. Daniel Elmer Salmon, an American pathologist who collaborated with Smith, later called the bacterial strain *Salmonella*. AMR among foodborne pathogens such as *Salmonella* has been linked to a rise in (i) the number of human deaths, (ii) the length of hospital stays, and (iii) the high costs of treatment due to therapeutic failure in recent years (Jajere, 2019). *Salmonella* is a human pathogenic bacteria that is also a leading cause of death among food-borne illnesses, making it a global public health concern. The Sequence Read Archive (SRA) database on the National Biotechnology Information Center (NCBI) website was used to download 1077 *Salmonella* complete genome sequences. *Salmonella* is one of the 31 pathogens with a high propensity to cause intestinal or systemic disorders in humans among diarrheal and/or invasive pathogens such as bacteria, viruses, protozoa, helminths, and chemicals. The rapid spread of this infection in the presence of antibiotic resistant strains has been aided by the widespread transportation of food around the world, creating significant control issues in food safety and public health on a global scale. The antimicrobials used against pathogenic bacteria no longer effective and also the current development lack of novel antimicrobials to replace the first-generation drugs brings the urgency to preserve the efficacy of existing drugs through the judicious use of antimicrobials. It is necessary to use drugs that have been considered a reserve or last resort, and these antimicrobials are often overpriced and/or can cause severe side effects (Rodrigues et al., 2020).

Salmonella Enterica is a rod shaped , Gram negative, zoonotic pathogen of substantial concern to global health that is leading to the cause of morbidity and mortality in people worldwide. It can successfully colonize in animals, humans, plants and also found in the environment. It thrives in the intracellular niche, allowing it to develop intrinsic antimicrobial resistance and, in rare cases, persistent colonization. The phylogeny, clinical features and key molecular mechanisms driving the pathogenesis of salmonellosis are described here. Fever, abdominal pain, vomiting, and diarrheal are common symptoms of enteric salmonellosis, which is usually self-limiting. The pathogen can spread throughout the body in children under the age of five, the elderly, and immunocompromised adults, necessitating antibiotic treatment (Knodler & Elfenbein, 2019). *Salmonella* are classified into two groups based on their pathogenicity: typhoidal and non-typhoidal *salmonella* (NTS). Non-typhoidal *Salmonella* infections are normally self-limiting, whereas typhoidal *Salmonella* infections can result in systemic infections and serious complications (Wang et al., 2019). *Salmonella enterica* serovar *typhi* (*S. Typhi*) and *Salmonella enterica* subsp. *Enterica* serovar *Paratyphi* A, B, or C (*S. Paratyphi*) are human-host-restricted bacteria that cause systemic disease when food, water, or contact with an infected person is contaminated. Extended Spectrum Lactamase (ESBL)-producing *S. Typhi* and *S. paratyphi* A strains have recently appeared. AMR in typhoid *Salmonella* must be closely monitored for the best clinical outcomes. This information can be utilised to create a sentinel AMR monitoring system to track changing resistance patterns (Chattaway et al., 2021). Over 26 million persons are anticipated to test positive for *S. Typhi*/*Paratyphi* each year, with a large percentage of isolates resistant to several antimicrobials. The S. *Typhi* H58 haplotype is still dominant in many areas, making South and South east Asia significant hotspots for enteric fever. Fluoroquinolone resistance is common in Asia, owing to the widespread use of this antibiotic class. Because they were among the first antibiotics recommended by the World Health Organization for typhoid therapy, they are commonly referred to as first-line antimicrobials in the literature (Britto et al., 2018).

1.3 Antibiotics used for treating pathogenicity caused by *Salmonella* Species:

Antimicrobial agents, often known as antibiotics, are important medications derived from microorganisms that are used to prevent and treat bacterial infections. When Alexander Fleming developed penicillin in 1928, the role of antibiotics was established. Actinobacteria isolated from soil or water provide the majority (about 75 percent) of antibiotics currently in clinical use (Dahal & Chaudhary, 2018). Ceftriaxone, ciprofloxacin, and ampicillin are antimicrobials used to treat severe infections. Resistance to antimicrobial drugs has been linked to poor clinical results. In the United States, non-typhoidal *Salmonella* causes an estimated 1.2 million illnesses, 23,000 hospitalizations, and 450 fatalities each year. *Salmonella* infections have been related to a variety of foods, including meat, poultry, eggs, dairy, and fruit. Severe infections, such as bacteraemia and meningitis, are invasive diseases that require treatment. To treat severe non-typhoidal *Salmonella* infections, third-generation cephalosporins (e.g., ceftriaxone) and fluoroquinolones (e.g., ciprofloxacin) have been used empirically. Because fluoroquinolones are rarely given to children, third-generation cephalosporins are especially relevant. Infections that have been recognised as susceptible to ampicillin are still treatable. Infections with decreased susceptibility to ciprofloxacin have been linked to unfavourable clinical outcomes (e.g., increased rates of hospital admissions, bloodstream infections, invasive illness, and mortality), and treatment failures have been reported in infections with lower susceptibility (Medalla et al., 2017). Antibiotics are essential in the treatment of infectious diseases and they have significantly improved the quality of life while reducing mortality from bacterial infections. The selectivity of antibiotic drugs over invading germs

ensures that little harm is done to patients while ensuring maximum eradication of target microorganisms. *S. Typhi* and *S. Paratyphi* infections can cause major problems and require drugs such as cefixime, chloramphenicol, amoxicillin, trimethoprim/sulfamethoxazole (TMP-SMX), azithromycin, aztreonam, cefotaxime, or ceftriaxone to avoid death. If a condition such as delirium, loss of consciousness, light headedness, coma, or shock occurs, dexamethasone, a corticosteroid drug, may be given. *Salmonella* species develop resistance to first-line antibiotics and other therapies. *Salmonella* species' resistance to antimicrobial treatments is serotype specific, according to new studies. Antimicrobial resistance is on the rise among hazardous bacteria, including *salmonella*, due to a variety of factors, including the abuse of antibiotics in some countries due to easy access. Antibiotics used to boost livestock development and crop protection, as well as inadequate sanitation practises, have all contributed to antibiotic resistance (Gut et al., 2018). *Salmonella* germs are primarily found in animals in the United States, according to recent research. *Salmonella* strains that are resistant to antibiotics have become a global health issue. *Salmonella enterica* serotype *Typhimurium* definitive strain Type 104 (DT104) is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline, and has become a major source of human and animal sickness in Europe, particularly in the United Kingdom. According to the researchers, antimicrobial resistance mechanisms in these bacteria may have evolved as a result of plasmid exchange between *Salmonella enterica* serovar *Typhimurium* and E. coli or Shigella flexneri, as well as the transfer of mobile components from the nosocomial environment. Resistance to ceftriaxone, the preferred treatment for invasive *Salmonella*, is a public health concern because fluoroquinolones, which can also be used to treat this condition, are not permitted for use in children (Nami et al., 2015).

1.4 Genetic diversity of *Salmonella* species:

Carbapenemase-Producing Non-Typhoidal S.enterica: In Gram-negative bacteria, resistance to carbapenems is manifested by the formation of carbapenemase, extended-spectrum-lactamases (ESBLs) or AmpC-lactamases, and the loss of certain outer membrane porins. Despite the fact that carbapenem resistance is rare in NTS, both routes have been found. The majority of carbapenemases acquired belong to one of three-lactamase classes: Ambler class A, Ambler class B (zinc-dependent metallo-β-lactamases; MBLs), and Ambler class D (oxacillinases; OXAs). Within the in 58 integron, the five isolates carried the blaVIM-2 gene (together with the aacC7, aacC1, and aacA4 genes) on 30-kb IncW or untypeable plasmids. Antimicrobial therapy was severely limited by such isolates, which had taken a big stride toward pandrug resistance (Fernández et al., 2018). Each of these isolates tested positive for blaCMY, a gene associated with ceftriaxone and ceftiofur resistance in *Salmonella* bacteria. A single isolate tested positive for both blaCMY and blaTEM and was resistant to ceftriaxone. Resistance was most likely attributed to another member of the resistance gene class in cases where an associated resistance gene was not discovered (Lynne et al., 2008). Although deletions may be found in isolates from particular environments, the invA gene, which is involved in cellular invasion, appears to be present in all *Salmonella* isolates, as does *Salmonella* Pathogenicity Island 1 (SPI1). SPI-2 is found in all *Salmonella* lineages, however S. bongori lacks a portion of it. SPI-3 can be found in all lineages. The predicted SPI-4 and SPI-5 distributions have yet to be determined. Because some virulence factors are host-specific, variances in pathogenicity of *Salmonella* are a reflection of the variety of virulence factors and sensitivity of the host. Because virulence factors are plasmid encoded, they may be confined to a small number of strains (Fluit et al., 2005).

1.5 Mechanism responsible for antimicrobial resistance:

In recent years, AMR, particularly antibiotic resistance, has become a major public health concern. AMR, on the other hand, isn't a new phenomenon: bacteria have always been able to adapt, evolve, or gain antibiotic resistance mechanisms (Duval et al., 2019). Antimicrobial agents are divided into classes depending on their antimicrobial action mechanism, (i) compounds that inhibit cell wall formation (ii) agents that depolarize the cell membrane (iii) agents that inhibit protein synthesis (iv) agents that inhibit nucleic acid synthesis (v) agents that impair metabolic pathways in bacteria. There are four types of antimicrobial resistance mechanisms: (1) drug absorption limitation; (2) drug target modification; (3) drug inactivation; (4) active drug efflux. Gram-negative bacteria use all four major processes, but gram-positive bacteria are less likely to limit drug uptake (due to the absence of the LPS outer membrane) and lack the ability to use some drug efflux mechanisms. Gram-negative bacteria use different processes than gramm-positive bacteria due to differences in structure and other factors. (C Reygaert et al., 2018).

1.5.1 Intrinsic Resistance : Some bacterial genera have special structural/functional features that confer antibiotic resistance. These bacteria are generally untargeted by the antibiotic and hence are rendered useless. Example: Because *Mycoplasma* spp. lack a cell wall, they are resistant to β-lactam antibiotics and glycopeptides. Furthermore, an antibiotic cannot penetrate bacterial cells due to the presence of an outer membrane. It could also be due to the presence of an export system (such as the AcrAB-TolC system) or the ability of some bacterial species to manufacture antibiotic-inactivating enzymes (such as *E. coli's* AmpC-lactamase) (Abushaheen et al., 2020). The bacterium's inherent features resulted in intrinsic resistance. Glycopeptide resistance is displayed by gram-negative bacteria due to the impermeability of the outer membrane found in the cell envelope (Christaki et al., 2019).

1.5.2 Acquired Resistance : When a previously susceptible bacteria obtains a mechanism of resistance, either through mutation or the acquisition of new genetic material from an outside source, it is referred to as acquired resistance (horizontal gene transfer). Horizontal gene transfer can happen in three different ways. Transformation is a type of genetic recombination in which unbound bits of DNA from a dead bacterium are incorporated into the chromosome of a recipient bacterium. Only a few microorganisms can naturally change. A bacteriophage transfers genetic material from a donor to a recipient bacterium in the process of transduction. The most significant mechanism of horizontal gene transfer is conjugation. It entails the transmission of genetic material from one bacterial cell to another by direct physical contact (Christaki et al., 2019).

2. GLOBAL EMERGENCE OF ANTIMICROBIAL RESISTANCE: In 21st century the bacterial antimicrobial resistance has emerged as one of the foremost public health threats which usually occurs when changes in bacteria causes the drugs used to treat infections to become less effective. The burden of antimicrobial-resistant infections affects the

economy in developed and developing countries (Murray et al., 2022). More pathogenic organisms are resistant to one or more antibiotics. As a result, some common infections are very difficult to treat and in some cases almost impossible. Pneumonia, which was easily treatable after the introduction of penicillin, now requires more frequent secondary and tertiary antibiotics (Prestinaci et al., 2015). Despite the fact that the WHO and other groups and scholars have criticised these projections, the spread of AMR is an important issue that requires a global, coordinated response (Shankar et al., 2016). Human and animal health, the environment, trade, intellectual property, and innovation are all part of the global response to AMR. Today, an increasing number of entities, including national governments, international organisations, public–private partnerships, think tanks, academia, the pharmaceutical industry, and civil society, are expressing their worry about the issue. These international health actors communicate AMR in a variety of ways, implying differing values and remedies (Wernli et al., 2017). In addition, systematic efforts are yet to be made to assess antimicrobial drug usage styles, which could yield critical records to cope with AMR. These problems are in low-and middle-profits international locations, in which there's often insufficient surveillance, minimum laboratory ability, and restricted rights of entry to critical antimicrobials. In order to guide better surveillance of AMR and to promote the analytical use of antimicrobials around the arena, GBD (Global burden of disease) came into existence. GBD is an ongoing research program that provides similar estimates of deaths and disability that are arising from 328 disorder and injury causes, as well as from 84 risk elements, across age and intercourse groups, through the years and space or it offers an effective aid to apprehend the changing health challenges facing people across the world (Sun et al., 2019).

2.1 Current status of antimicrobial resistance: To reduce the burden of AMR, continuous surveillance for resistance clinical isolates in humans and animals, as well as the development of relevant policy intervention strategies in human and veterinary drug usage, are required. The Australian Centre for International Agricultural Research is now funding an AMR study to address several shortcomings in the region's AMR management. As a result, farmers, human patients, and the general public must be educated about AMR. Furthermore, AMR data are required for the development of effective AMR control techniques (Magiri et al., 2022). The plant-based antimicrobials have immense potential to combat bacterial, fungal, protozoal and viral diseases without any known side effects. Quinones, phenols, alkaloids, flavonoids, terpenoids, essential oil, tannins, lignans, glucosinolates, and other secondary metabolites are all thought to have antimicrobial activities in plants (Chandra et al., 2017). According to WHO there are seven common bacterial pathogens i.e, (*Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae, non-typhoidal Salmonella, Shigella spp. and Neisseria gonorrhoeae*) which contain worldwide data on Antimicrobial resistance (Zellweger et al., 2017). The current research state that in 2015 the Global Action Plan on antimicrobial resistance was developed and authorized by the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE). Approximately 37% of the retrieved documents were published in the last 5 years of the study period (2016–2020). Countries who agreed to follow the GAP were requested to create national plans to combat AMR using a one-health approach (Sweileh et al.,2021) .

2.2 Human health risk assessment in antimicrobial resistance: Risk measures include the severity and likelihood of human infections linked to foodborne AMR. They can be expressed in a variety of ways, including per-meal risk (e.g., probability of illness per serving), population or annual risk based on consumption (e.g., number of cases per year), and burden of illness estimates. To evaluate the public health risk associated with foodborne AMR, risk characterization combines the information from the hazard identification, exposure assessment, and hazard characterization phases. Not all cases of foodborne AMR are the same, and the health effects of different bacterial strains are known to differ significantly. For example, epidemiological data from 46,639 *Salmonella* infections in the United States from 1996 to 2006 revealed considerable differences between serovars in terms of case fatality rates, hospitalisation rates, and ability to produce invasive illness (Collineau et al., 2019). A recent review reported prevalence and distribution of genes giving resistance to tetracyclines, sulfonamides, quinolones, aminoglycosides, and macrolides in all of the habitats evaluated. Subinhibitory levels of antimicrobials, agrochemicals, and heavy metals prevalent in soil and water environments may provide the required circumstances for MGE carrying multiple antimicrobial, agrochemical, and heavy metal resistance genes to persist. The fundamental antimicrobials utilized as therapeutics in people and veterinary medication can be distinguished in surface waters. The primary significant flare-up happened on the Indian mainland, where water tests from various sources, including drinking water, have been defiled. The greater part of these antimicrobials are discharged in pee and stool, disturbing climate microbiomes. In this specific situation, the quick worldwide spread of the blaNDM quality is essential (Martins & Rabinowitz, 2020).

3. METHODOLOGY

Following is the flow chart showing steps for retrieval of different genes and protein structures of *Salmonella* involved in antimicrobial resistance (Figure 3.1).

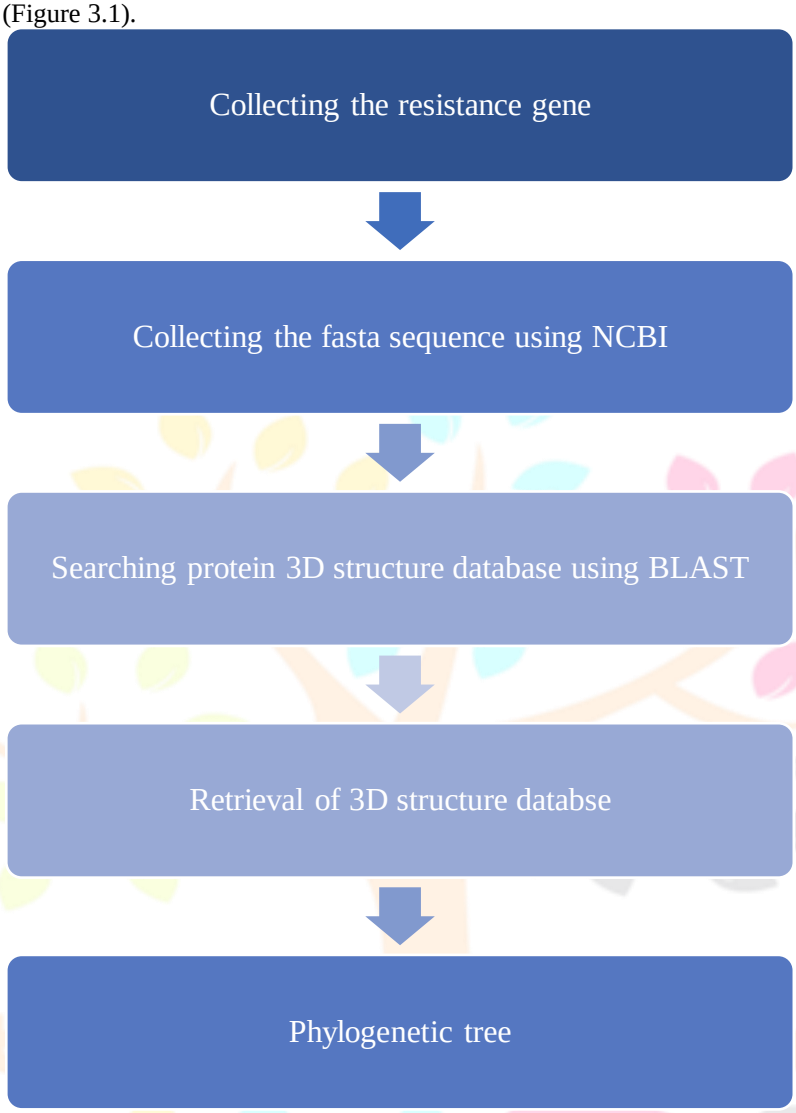


Fig. 3.1 Flowchart showing the steps of methodology.

3.1. Collecting genes responsible for Antimicrobial resistance from literature:

Table 1. Antimicrobial resistance gene detected in *Salmonella* species.

Sr. no.	Serovar Type	Resistance gene	Antimicrobial class	Gene Id	Length of gene
1.	*Salmonella enterica subsp. Typhimurium str. LT2*	*gyrA*	Quinolones Fluroquinolones	1253794	2713 bp
		parC		1254697	2274 bp
		parE		1254704	1893 bp
2.	*Salmonella Bongori*	*sulP*	Sulfonamides	66756721	1248 bp
3.	*Typhimurium*	*sul2*		39515199	816 bp
4.	*Salmonella enterica*	*sul3*		2829119	New entry
5.	*Salmonella sp. D76*	*dfrA1*	Trimethoprim	1028085797	157 aa
6.	*Salmonella enterica*	*dfrA12*		1028085799	165 aa
		dfrA14		1391852844	157 aa
		dfrA15		1028085865	157 aa
		dfrA16		1028085866	157 aa
7.	*Salmonella enterica*	*blaTEM-131*	β-lactams	1028110546	286 aa
		blaTEM-188		1028110607	286 aa
		blaTEM-108		1028110494	286 aa
		blaTEM-138		695269106	286 aa

		blaTEM-144		545323583	286 aa
8.	*Salmonella enterica*	*aadA1*	Aminoglycosides	1105502071	263 aa
9.	*Salmonella enterica subsp.Typhimurium*	*aadA*		1252782	796 bp
10.	*Salmonella enterica*	*floR*	Chloramphenicol	1028086745	404 aa

3.2. Collecting the FASTA sequence of genes using NCBI.

NCBI state as National Center for Biotechnology Information and is part of the united states National library of medicine which the branch of National Institute of Health. NCBI directed by David Lipman one of the original authors of BLAST sequence alignment program. It includes data about genes. In NCBI, there are various databases are available of various different organisms. In our project we accessed protein database for retrieval of gene sequence of *Salmonella* species. From literature, different genes were identified for the drug resistance against specific antibiotics. Those genes were identified and downloaded from NCBI in FASTA format. In present, we used NCBI for retrieval of Gene and protein sequence.

3.3 Searching protein 3D structure from Database using BLASTp.

BLAST define as Basic Local Alignment Search Tool. It finds the similarity between sequences. It compares the nucleotide or protein sequences and calculates the statistical significances of matches. BLAST can used to infer functional and evolutionary relationships between sequences as well as help identify members of gene families. BLAST was developed by David J. Lipman and William R. Pearson in 1985. BLAST is protein BLAST compares one or more protein query sequences to a subject protein sequence or a database of protein sequences. This is useful when trying to identify a protein. Starting with a sequence, identify the protein or gene and the source. To run software BLAST needs a query sequence to search for and against and a sequence to search against or a sequence database containing multiple sequence alignment. The BLAST web server hosted by NCBI allows anyone with a web browser to perform similarity searches against constantly updated databases of proteins and DNA that include most of the newly sequenced organisms. There are 2 sequences in BLAST (INPUT SEQUENCES and OUTPUT SEQUENCES). Input sequences (in FASTA or Genbank format), database to search and other optional parameters such as scoring matrix. BLAST output can be delivered in a variety of formats. These formats include HTML, plain text, and XML formatting. For NCBI's web-page, the default format for output is HTML. In present study we used BLASTp for searching the 3d structure of various genes of *salmonella* species.

3.4. Protein 3D structure retrieval from PDB database.

PDB stands for Protein Data Bank. It is the database used for three dimensional structural data of large biological molecules such as nucleic acids and proteins. The PDB is a key in areas of structural biology such as structural genomics. The data is typically obtained by X-ray crystallography, NMR, spectroscopy. In present study we used PDB for retrieve the 3D structure of various genes of *Salmonella* species.

3.5. Phylogenetic tree.

Phylogenetic tree is known as phylogeny and evolutionary tree is a branching diagram or tree showing the evolutionary relationships among various biological species or other entities based upon similarities and differences in their physical or genetic characteristics. CLUSTAL OMEGA is new multiple sequence alignment program that uses seeded guide tress and HMM profile techniques to generate alignments between three or more sequences. For the alignment of two sequences we enter the downloaded FASTA sequences so that this tool can align up to 4000 sequences or maximum file size of 4 MB. In this we did multiple sequence alignment of those genes that were showing multiple drug resistance.

4. RESULT AND DISCUSSION

4.1. Retrieval of desired Gene sequences of *Salmonella* sp. From NCBI:

>aadA [Salmonella enterica subsp. enterica serovar Typhimurium str. LT2]
MTLSIPPSIQCQTEAACRLITRVTGDTLRAIHLYGSAVAGGLKPNSDIDLLVTICQPLTEAQRATLMQEL
LALSSPPGASAEKRALEVTVVLYSQLVPWCFPPSREMQFGEWLREDICQGIYEPAQQDWDMVLLITQILE
TSIPLKGERAERLFTPAPAAQLLKALRYPLDLWQSTADVQGDEYHIVLTLARIWYTLSTGRFTSKDAAAD
WLLPQLPEDYAATLRAAQREYLGLEQQDWHILLPAVVRFVDFAKAHIPTQFT

>aadA1 [Salmonella enterica]
MREAVIAEVSTQLSEVVGVIERHLEPTLLAVHLYGSAVDGGLKPHSDIDLLVTVTVRLDETTRRALINDL
LETSASPGEREILRAVEVTIVVHDDIIPWRYPAKRELQFGEWQRNDILAGIFEPATIDIDLAILLTKARE
HSVALVGPAAEELFDPVPEQDLFEALNETLTLWNSPPDWAGDERNVVHTLSRIWYSAVTGRIAPKDVAAD
WAMERLPAQYQPVILEARQAYLGQEEDRLASRADQLEEFVHYVKGEITKVVGK

>beta-lactamase TEM-108 [Salmonella enterica]
MDPQHFRVALIPFFAAFCLPVFAHPETLVKVKDAEDQLGARVGYIELDLNSGKILESFRPEERFPMMSTF
KVLLCGAELSRVDAGQEQLGRRIHYSQNDLVEYSPVTEKHLTDGMTVRELCSAAITMSDNTAANLLLTTI
GGPKELTAFLHNMGDHVTRLDRWEPELNEAIPNDERDTTMPAAMATTLRKLLTSELLTLASRQQLIDWME
ADKVAGPLLRSALPAGWFIADKSGAGERGSRGIIAALGPDGKPSRIVVIYTTGSQATMDERSRQIAEIGA
SLIKHW

>beta-lactamase TEM-131 [Salmonella enterica]
MSIQHFRVALIPFFAAFCFPVFAHPETLVKVKDAEDQLGARVGYIELDLNSGKILESFRPEERFPMMSTF
KVLLCGAVLSRVDAGQEQLGRRIHYSQNDLVKYSPVTEKHLTDGMTVRELCSAAITMSDNTAANLLLTTI

GGPKELTAFLHNMGDHVTRLDSWEPELNEAIPNDERDTTTPAAMATTLRKLLTGELLTLASRQQLIDWME
ADKVAGPLLRSALPAGWFIADKSGTGERGSRGIIAALGPDGKPSRIVVIYTTGSQATMDERNRQIAEIGA
SLIKHW

> beta-lactamase TEM-138 [Salmonella enterica]
MSIQHFRVALIPFFAAFCLPVFAHPETLVKVKDAEDQLGARVGYIELDLNSGKILESFRPEERFPMMSTF
KVLLCGAVLSRVDAGQEQLGRRIHYSQNDLVKYSPVTEKHLTDGMTVRELCSAAITMSDNTAANLLLTTI
GGPKELTAFLHNMGDHVTRLDRWEPELNEAIPIDERDTTMPAAMATTLRKLLTGELLTLASRQQLIDWME
ADKVAGPLLRSALPAGWFIADKSGASERGSRGIIAALGPDGKPSRIVVIYTTGSQATMDERNRQIAEIGA
SLIKHW

>beta-lactamase TEM-144 [Salmonella enterica]
MSIQHFRVALIPFFAAFCLPVFAHPETLVKVKDAEDQLGARVGYIELDLNSGKILESFRPEERFPMMSTF
KVLLCGAVLSRVDAGQEQLGRRIHYSQNDLVEYSPVTEKHLTDGMTVRELCSAAITMSDNTAANLLLTTI
GGPKELTAFLHNMGDHVTRLDCWEPELNEAIPNDERDTTMPAAMATTLRKLLTGELLTLASRQQLIDWME
ADKVAGPLLRSALPAGWFIADKSGAGKRGSRGIIAALGPDGKPSRIVVIYTTGSQATMDERNRQIAEIGA
SLIKHW

>beta-lactamase TEM-188 [Salmonella enterica]
MSIQHFRVALIPFFAAFCFPVFAHPETLVKVKDAEDQLGARVGYIELDLNSGKILESFRPEERFPMMSTF
KVLLCGAVLSRVDAGQEQLGRRIHYSQNDLVEYSPVTEKHLTDGMTVRELCSAAITMSDNTAANLLLTTI
GGPKELTAFLHNMGDHVTRLDRWEPELNEAIPNDERDTTMPAAMATTLRKLLTGELLTLASRQQLIDWME
ADKVAGPLLRSALPAGWFIADKSGASKRGSRGIIAALGPDGKPSRIVVIYTTGSQATMDERNRQIAEIGA
SLIKHW

>trimethoprim-resistant dihydrofolate reductase DfrA1 [Salmonella sp. D76]
MKLSLMVAISKNGVIGNGPDIPWSAKGERLLFKAITYNQWLLVGRKTFESMGALPNRKYAVVTRSSFTSD
NENVLIFPSIKDALTNLKKITDHVIVSGGGEIYKSLIDQVDTLHISTIDIEPEGDVYFPEIPSNFRPVFT
QDFASNINYSYQIWQKG

>trimethoprim-resistant dihydrofolate reductase DfrA12 [Salmonella enterica]
MNSESVRIYLVAAMGANRVIGNGPNIPWKIPGEQKTFRRLTEGKVVVMGRKTFESIGKPLPNRHTLVISR
QANYRATGCVVVSTLSHAIALASELGNELYVAGGAEIYTLALPHAHGVFLSEVHQTFEGDAFFPMLNETE
FELVSTETIQAVIPYTHSVYARRNG

>trimethoprim-resistant dihydrofolate reductase DfrA14 [Salmonella enterica]
MKVSLIAAKAKNGVIGCGPDISWSAKGEQLLFKALTYNQWLLVGRKTFESMGALPNRKYAVVTRSGWTSN
DDNVVVFQSIEEAMDRLAEFTGHVIVSGGGEIYRETLPMASTLHLSTIDIEPEGDVFFPSIPNTFEVVFE
QHFTSNINYCYQIWKKG

>trimethoprim-resistant dihydrofolate reductase DfrA15 [Salmonella enterica]
MKLSLMAAISKNGVIGNGPDIPWSAKGEQLLFKAITYNQWLLVGRKTFESMGALPNRKYAVVTRSSFTSS
DENVLVFPSIDEALNHLKTITDHVIVSGGGEIYKSLIDKADTLHISTIDIEPEGDVYFPEIPGSFRPVFS
KDFVSNINYSYQIWQKG

>trimethoprim-resistant dihydrofolate reductase DfrA16 [Salmonella enterica]
MKLSLMAAKSKNGIIGNGPDIPWSAKGQQLLFRAIIYNQWLLVGRKTFESMGALPNRKYAVVTRSNFSTN
DEGVMVFSSIQDALINLEEITDHVIVSGGGEIYKSLISKVDTLHISTVDIERDGDIVFPEIPDTFKLVFE
QDFESNINYCYQIWQKS

>chloramphenicol/florfenicol efflux MFS transporter FloR [Salmonella enterica]
MTTTRPAWAYTLPAALLLMAPFDILASLAMDIYLPVVPAMPGILNTTPAMIQLTLSLYMVMLGVGQVIFG
PLSDRIGRRPILLAGATAFVIASLGAAWSPTAPAFVAFRLLQAVGASAMLVATFATVRDVYANRPEGVVI
YGLFSSMLAFVPALGPIAGALIGEFLGWQAIFITLAILAMLALLNAGFRWHETRPLDQVKTRRSVLPIFA
SPAFWVYTVGFSAGMGTFFVFFSTAPRVLIGQAEYSEIGFSFAFATVALVMIVTTRFAKSFVARWGIAGC
VARGMALLVCGAVLLGIGELYGSPSFLTFILPMWVVAVGIVFTVSVTANGALAEFDDIAGSAVAFYFCIQ
SLIVSIVGTLAVTLLNGDTAWPVICYATAMAVLVSLGLALLRSRDAATEKSPVV

>DNA gyrase subunit A [Salmonella enterica subsp. enterica serovar Typhimurium str. LT2]
MSDLAREITPVNIEEELKSSYLDYAMSVIVGRALPDVRDGLKPVHRRVLYAMNVLGNDWNKAYKKSARVV
GDVIGKYHPHGDSAVYDTIVRMAQPFSLRYMLVDGQGNFGSIDGDSAAAMRYTEIRLAKIAHELMADLEK
ETVDFVDNYDGTEKIPDVMPTKIPNLLVNGSSGIAVGMATNIPPHNLTEVINGCLAYIDNEDISIEGLME
HIPGPDFPTAAIINGRRGIEEAYRTGRGKVYIRARAEVEADAKTGRETIIVHEIPYQVNKARLIEKIAEL
VKDKRVEGISALRDESDKDGMRIVIEVKRDAVGEVVLNNLYSQTQLQVSFGINMVALHHGQPKIMNLKDI
ISAFVRHRREVVTRRTIFELRKARDRAHILEALAIALANIDPIIELIRRAPTPAEAKAALISRPWDLGNV
AAMLERAGDDAARPEWLEPEFGVRDGQYYLTEQQAQAILDLRLQKLTGLEHEKLLDEYKELLEQIAELLH
ILGSADRLMEVIREEMELIRDQFGDERRTEITANSADINIEDLISQEDVVVTLSHQGYVKYQPLTDYEAQ

RRGGKGKSAARIKEEDFIDRLLVANTHDTILCFSSRGRLYWMKVYQLPEASRGARGRPIVNLLPLEANER
ITAILPVREYEEGVNVFMATASGTVKKTALTEFSRPRSAGIIAVNLNDGDELIGVDLTSGSDEVMLFSAA
GKVVRFKEDAVRAMGRTATGVRGIKLAGDDKVVSLIIPRGEGAILTVTQNGYGKRTAADEYPTKSRATQG
VISIKVTERNGSVVGAVQVDDCDQIMMITDAGTLVRTRVSEISVVGRNTQGVILIRTAEDENVVGLQRVA
EPVDDEELDAIDGSVAEGDEDIAPEAESDDDVADDADE

>parC DNA topoisomerase IV, subunit A [Salmonella enterica subsp. enterica serovar Typhimurium str. LT2]
MSDMAERLALHEFTENAYLNYSMYVIMDRALPFIGDGLKPVQRRIVYAMSELGLNATAKFKKSARTVGDV
LGKYHPHGDSACYEAMVLMAQPFSYRYPLVDGQGNWGAPDDPKSFAAMRYTESRLSKYAELLLSELGQGT
ADWVPNFDGTMQEPKMLPARLPNILLNGTTGIAVGMATDIPPHNLREVAKAAITLIEQPKTTLDQLLDIV
QGPDYPTEAEIITPRAEIRKIYENGRGSVRMRAVWTKEDGAVVISALPHQVSGAKVLEQIAAQMRNKKLP
MVDDLRDESDHENPTRLVIVPRSNRVDMEQVMNHLFATTDLEKSYRINLNMIGLDGRPAVKNLLEILTEW
LAFRRDTVRRRLNYRLEKVLKRLHILEGLLVAFLNIDEVIEIIRSEDEPKPALMSRFGISETQAEAILEL
KLRHLAKLEEMKIRGEQDELEKERDQLQGILASERKMNTLLKKELQADADAYGDDRRSPLREREEAKAMS
EHDMLPSEPVTIVLSQMGWVRSAKGHDIDAPGLNYKAGDSFKAAVKGKSNQPVVFIDTTGRSYAIDPITL
PSARGQGEPLTGKLTLPPGATVEHMLMEGDDQKLLMASDAGYGFVCTFNDLVARNRAGKTLITLPENAHV
MPPLVIEDEHDMLLAITQAGRMLMFPVDSLPQLSKGKGNKIINIPSAEAAKGDDGLAHLYVLPPQSTLTI
HVGKRKIKLRPEELQKVVGERGRRGTLMRGLQRIDRIEIDSPHRVSHGDSEE

>parE DNA topoisomerase IV subunit B [Salmonella enterica subsp. enterica serovar Typhimurium str. LT2]
MTQTYNADAIEVLTGLEPVRRRPGMYTDTTRPNHLGQEVIDNSVDEALAGHAKRVDVILHADQSLEVIDD
GRGMPVDIHPEEGVPAVELILCRLHAGGKFSNKNYQFSGGLHGVGISVVNALSKRVEVTVRRDGQVYNIA
FENGEKVQDLQVVGTCGKRNTGTSVHFWPDESFFDSPRFSVSRLMHVLKAKAVLCPGVEITFKDEVNNSE
QRWCYQDGLNDYLGEAVNGLPTLPEKPFIGNFNGETEAVDWALLWLPEGGELLTESYVNLIPTMQGGTHV
NGLRQGLLDAMREFCEYRNILPRGVKLSAEDIWDRCAYVLSVKMQDPQFAGQTKERLSSRQCAAFVSGVV
KDAFSLWLNQNVQAAEQLAEMAIASAQRRLRAAKKVVRKKLTSGPALPGKLADCTAQDLNRTELFLVEGD
SAGGSAKQARDREYQAIMPLKGKILNTWEVSSDEVLASQEVHDISVAIGIDPDSDDLSQLRYGKICILAD
ADSDGLHIATLLCALFVRHFRALVKNGHVYVALPPLYRIDLGKEVYYALTEEEKAGVLEQLKRKKGKPNV
QRFKGLGEMNPMQLRETTLDPNTRRLVQLTISDEDDQRTNAMMDMLLAKKRSEDRRNWLQEKGDLADLDV

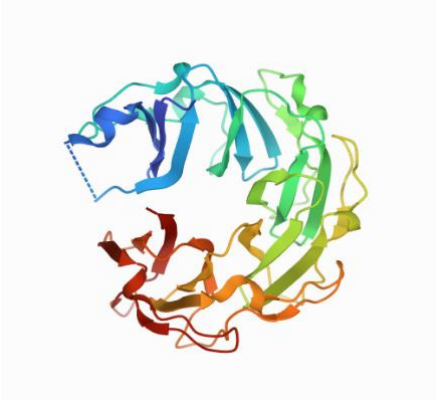
>SulP family inorganic anion transporter [Salmonella bongori]
MSVTSPPSTATMEYTVSHVVRSPRLLLRETLAGVITALALIPEVISFSVIAGVDPKVSLIASVVLCLAMS
VLGGRPAMVTAAAGSVALVIGPMVSQHGVQYILPAVVMAGVIQILFGVLGMARLMRFIPAAVMTGFVNAL
GILIFFAQVPHFWSKSPLIWGLFILTLLIVLWAPRVIKSIPAPLIAIVLLTMFTVTTGQLLPTVGDEGPM
NSSLPGLTLLSVPITWQTLAIIWPCALSIAFVGLMESLLTAKLVDDLTATPSNKKRESAGLGIANILAGF
YGGIAGCAMIGQTIVNVEMGKGRSRVSTLTAGVVLLLLVTALSEVMAKIPMTVLAGIMVIVAVKTFSWRS
LQPATLARLPVTETLVMLTTVAATVCTANLAIGVVAGVIAMLLLPRLARRKNAAATEAPSPAPEK

>sulfonamide-resistant dihydropteroate synthase Sul2 [Bacteria]
MNKSLIIFGIVNITSDSFSDGGRYLAPDAAIAQARKLMAEGADVIDLGPASSNPDAAPVSSDTEIARIAP
VLDALKADGIPVSLDSYQPATQAYALSRGVAYLNDIRGFPDAAFYPQLAKSSAKLVVMHSVQDGQADRRE
APAGDIMDHIAAFFDARIAALTGAGIKRNRLVLDPGMGFFLGAAPETSLSVLARFDELRLRFDLPVLLSV
SRKSFLRALTGRGPGDVGAATLAAELAAAAGGADFIRTHEPRPLRDGLAVLAALKETARIR

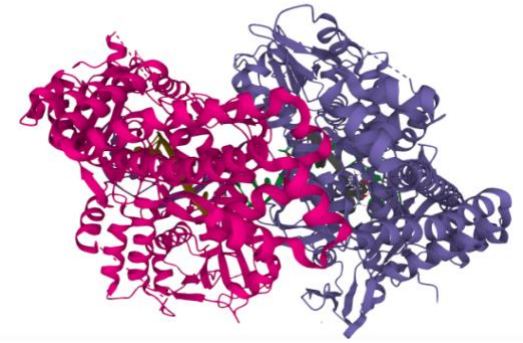
4.2 Retrieval of 3D structure from PDB.

The most identical structure from BLAST search was taken to retrieve structure from PDB.
The PDB ID of genes are as following [Figure 4.2]:

⇒ [5ZTJ] is the PDB ID of *gyrA* gene.
⇒ [7LHZ] is the PDB ID of *parC* gene.
⇒ [5ZXM] is the PDB ID of *parE* gene.
⇒ [5ECC] is the PDB ID of *dfrA1* gene.
⇒ [5ECC_] is the PDB ID of *dfrA15* gene.
⇒ [6B2N] is the PDB ID of *blaTEM-131* gene.
⇒ [1ERO] is the PDB ID of *blaTEM-108* gene.
⇒ [1HTZ] is the PDB ID of *blaTEM-138* gene.
⇒ [3CMZ] is the PDB ID of *blaTEM-144* gene.
⇒ [5G4A] is the PDB ID of *aadA1* gene.
⇒ [6FZB] is the PDB ID of *aadA* gene.

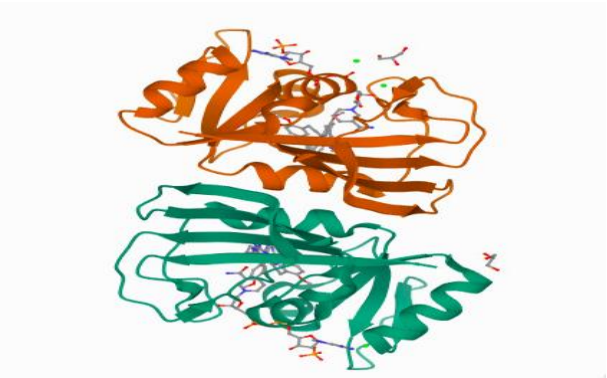


gyrA



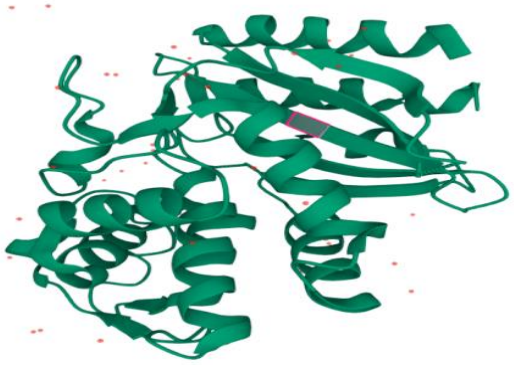
parC

parE



dfrA1

dfrA15



blaTEM-131

blaTEM-108

blaTEM-138

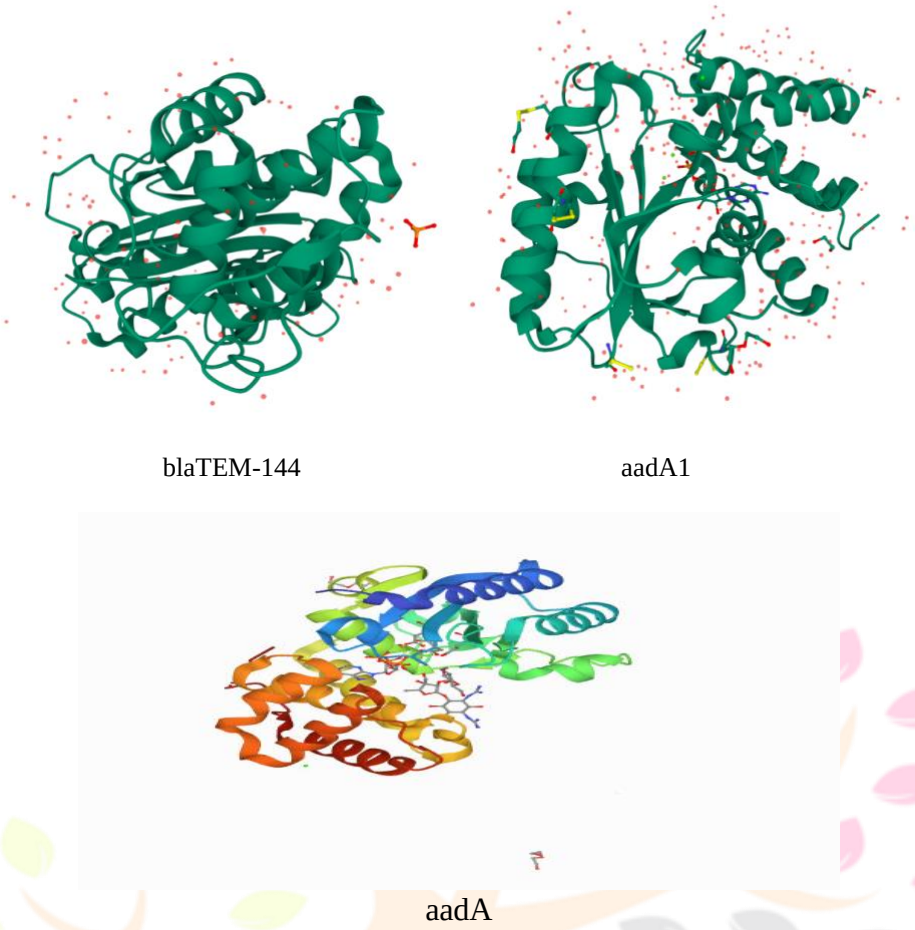


Fig 4.2 Retrieval of 3D structure from PDB database

4.3. Phylogenetic tree obtained from CLUSTAL OMEGA.

In a phylogenetic tree, every leaf node represents a species, each edge denotes a relationship between two neighbouring species and the length of an edge indicates the evolutionary distance among them. From Phylogenetic tree we can interpret that *SulP* gene are more similar to *blaTEM* gene. Whereas *FloR* gene doesn't showed any similarity among other genes. *ParE* gene is showing somewhat similarity towards *DfrA* genes. In present study, we used CLUSTAL OMEGA to obtain phylogenetic tree of various genes of *Salmonella* species [Figure 3.3].

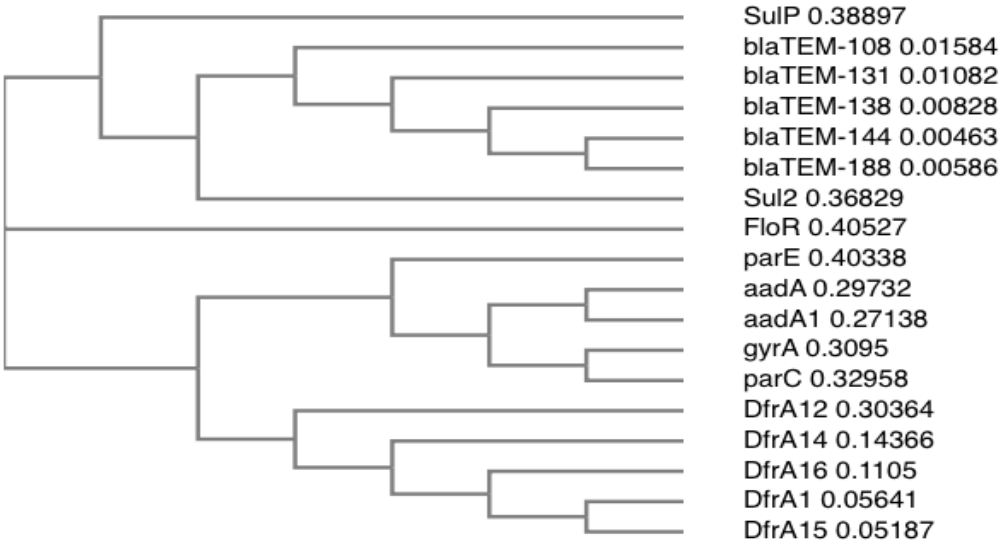


Fig 4.3. Phylogenetic tree obtained from Clustal Omega

4.4. Graphical representation of Microbial drug resistance of genes of *Salmonella* Species as described in Table 2 [Figure 4.4].

Gene *blaTEM*-131 shows maximum antimicrobial drug resistance when compared to all the other genes. *gyrA* and *parC* genes show same percentage of MDR. Genes *sulP*, *sul2*, *sul3* show approximately same value of MDR whereas gene *dfrA*1 shows minimum value throughout the genes.

Table 2 Microbial drug resistance of genes of *Salmonella* Species

GENE	CLASS	% MDR	References
gyrA	Quinolones	65	(Britto et al., 2018)
parC	Fluroquinolones	65	(Britto et al., 2018)
parE	Fluroquinoloes	11.1	(Deekshit et al., 2012)
sulP	Sulfonamides	24	(Britto et al., 2018)
sul2	Sulfonamides	24	(Britto et al., 2018)
sul3	Sulfonamides	24	(Britto et al., 2018)
dfrA1	trimethoprim	5.6	(Deekshit et al., 2012)
blaTEM-131	β-lactams	79.1	(Eguale et al., 2017)
aadA1	Aminoglycosides	20	(Deekshit et al., 2012)
floR	Chloramphenicol	50	(Deekshit et al., 2012)

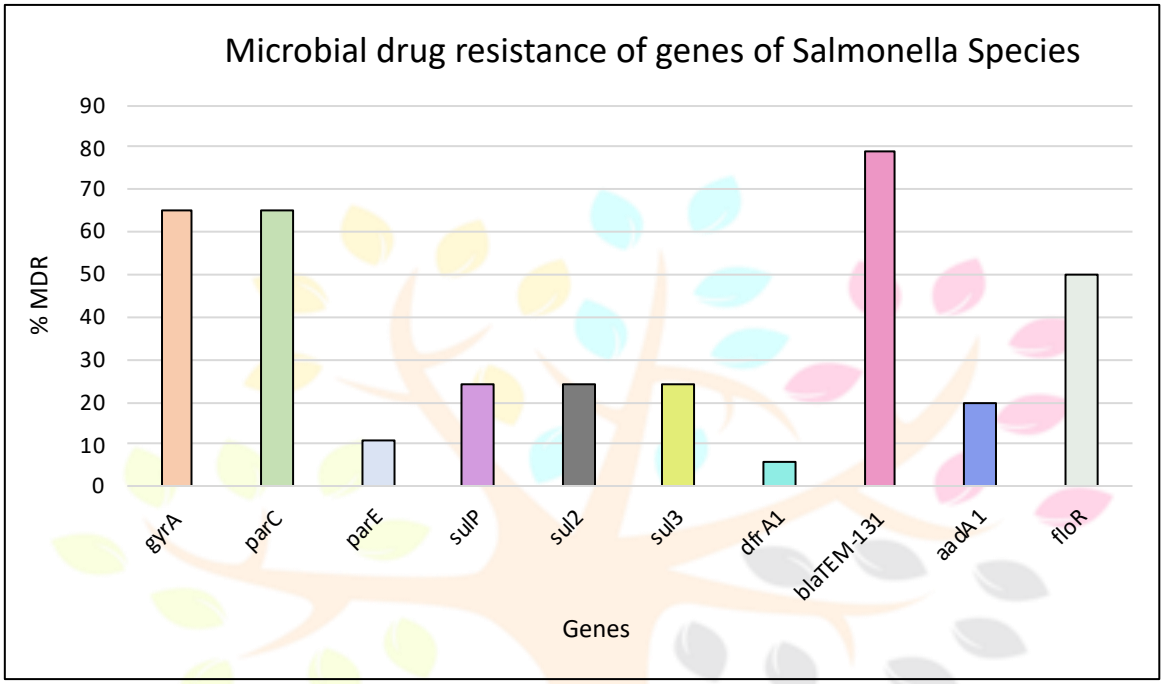


Fig 4.4 showing the MDR % of genes of *Salmonella* species

5. FUTURE PERSPECTIVES : The current emergency of antimicrobial resistance need more comprehensive risk assessment techniques. It need the development of novel strategies to fulfil the tasks, the integration of large amount of data is to be paramount (Pinilla-Redondo et al., 2018). In ongoing research there are number of new effective antibiotics against gram-negative bacteria has increased. In our knowledge there are eight new antibiotics and said to be that they are effective against ESBL(extended spectrum β-lactamase) and also effective against carbapenem-resistance (Terreni et al., 2021). The research of antimicrobial resistance has changed. As we know the antibiotics resistance genes (ARG) databases and analysis should be employed to understand the antimicrobial resistance at resistome level because they are now partially understood so, it is expected in future by these attempts we will improve our knowledge towards the ARG transmission and these strategies will help in antimicrobial resistance (Kim & Cha, 2021). Antibiotic resistance is becoming increasingly obvious as a major challenge to overcome in the near future. Due to the broad spectrum of antimicrobial activity given by these therapies, alternatives such as probiotics, prebiotics, phytobiotics, and others are being explored against drug-resistant infections (V. T. Nair et al., 2018). In future some innovative approaches are needed for the development of new antibiotics for the limit of antimicrobial resistance because as we know there are the shortage of new antibiotics. Oxazolidinones and cyclic lipopeptides there are only two novel classes of antibiotics from the past 30years and both these drugs target gram-positive bacteria in our knowledge there are very few effective drugs to treat multidrug resistant infections due to gram-negative bacteria which is said to be the main threat at present (Prestinaci et al., 2015).

6. CONCLUSION : Antimicrobial resistance may be an unavoidable outcome of evolution, but the mechanisms that ensure its persistence even in the absence of antibiotic selection pressure are yet unknown. Antibiotics used to treat illnesses in humans and pets were shown to be highly resistant to several isolated Salmonella strains in this investigation, raising the prospect that humans could become infected with multidrug-resistant Salmonella through contact with cats. Professionals must encourage appropriate antimicrobial stewardship in accordance with internationally accepted guidelines**.** Because the majority of the antimicrobials to which the Salmonella spp. were resistant in this investigation are on the WHO List of Essential Antimicrobials and are mentioned in the OIE Terrestrial Animal Health Code, a full assessment of AMR in humans in Nigeria is required. Salmonella spp. antimicrobial resistance is becoming more of a concern for food safety. Resistant Salmonella spp. are becoming more common in food in a variety of nations around the world, as this review has demonstrated. Because of the potential for rapid spread of resistance among bacteria, it's especially important to track antimicrobial susceptibility and resistance mechanisms in Salmonella spp. isolated from food, because new mechanisms of resistance found in animals could enter the food chain and be passed on to consumers. This alarming scenario highlights the

significance of cross-sector collaboration in order to track antimicrobial resistance and quickly identify trends that could impair the efficacy of therapeutic antibiotics.

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