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Antibiotic Resistance and the Prospects of Medicinal Plants in the Treatment of Salmonellosis

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1. Introduction

Salmonella enterica serotype typhi is the aetiological agent of typhoid fever, a multisystemic disease with protean manifestations and initial lesions in the bowel. Typhoid fever still remains a major public health problem in developing countries even in the twenty first century (Lin et al., 2000; Otegbayo et al., 2003). This was also the case in America and Europe three centuries ago, until measures for sanitary disposal and supply of potable water were put in place. Unacceptable morbidity and mortality are still recorded in developing countries in spite of availability of several drugs over the years for the treatment of typhoid fever. There is enough evidence to show that the prevalence of typhoid fever in any community is an index of communal hygiene and effectiveness of sanitary disposal. In Nigeria, as in other developing countries of the world, studies have estimated over 33 million cases and 500,000 deaths due to typhoid fever per year (Institute of Medicine, 1986). Otegbayo (2005) enumerated several factors responsible for the failure of public health measures to tame the tide of the continuing rise in the incidence, prevalence, morbidity and mortality of typhoid fever.

Salmonellosis is an infection with Salmonella bacteria, often restricted to the gastro-intestinal tract and is often a self limiting disease. Most individuals infected with *Salmonella typhimurium* experience mild gastrointestinal illness involving diarrhoea, chills, abdominal cramps, fever, head and body aches, nausea, and vomiting (Honish, 1999). Infections are usually self-limiting, and antimicrobial treatment is not recommended for uncomplicated illnesses (Aserkoff and Bennet, 1969; Gill and Hammer, 2001). However, extraintestinal infection can occur, particularly in very young, elderly, and immunocompromised patients (Angulo and Swerdlow, 1995; Thuluvath and McKendrick, 1998). In these cases, effective antimicrobial treatment is essential (Cruchaga et al., 2001). Every year, approximately 40,000 cases of salmonellosis are reported in the United States. The actual number of infections may be thirty or more times greater (CDC, 2006). In many parts of the world, such cases are either not documented or because many milder cases are not diagnosed or reported. Cases, however, of systemic disease due to *Salmonella typhimurium* and other salmonellae have been reported (Panhot and Agarwal, 1982; Varma et al., 2005). Salmonelloses have been

reported to be season dependent and occur more in the winter than summer and often referred to as gastroenteritis or diarrheoa. Likewise more cases of diarrhoea caused by enterobacteriacea especially *E. coli*, occurring more during wet season than dry season (Olowe et al., 2003). Children are the most likely to get salmonellosis, however the elderly, and the immunocompromised are the most likely to have severe infections. It is estimated that approximately 600 persons die each year with acute salmonellosis as reported by Centre for disease control (CDC, 2006).

2. Multidrug-resistant (MDR) strains of *Salmonella*

Multidrug-resistant (MDR) strains of *Salmonella* are now encountered frequently and the rates of multidrug-resistance have increased considerably in recent years (CDC, 2006). Even worse, some variants of *Salmonella* have developed multidrug-resistance as an integral part of the genetic material of the organism, and are therefore likely to retain their drug-resistant genes even when antimicrobial drugs are no longer used, a situation where other resistant strains would typically lose their resistance (CDC, 2006). Most of the strains of *Salmonella typhimurium* isolated in a study in western part on Nigeria were resistant to drugs like streptomycin, amoxicilin, tetracycline, ampicillin, kanamycin and chloramphenicol (Olowe et al., 2007). This data is alarming since the isolates were already showing high resistance to drugs that are meant as alternate therapy to salmonellosis treatment; especially isolates from blood were resistant to the commonly used antibiotics. Drug-resistant *Salmonella* emerged in response to antimicrobial usage in food animals, which has also contributed or resulted in major outbreaks of salmonellosis (Olowe et al., 2007). Selective pressure from the use of antimicrobials is a major driving force behind the emergence of resistance, but other factors also need to be taken into consideration. Four types of species namely *S. typhi* (55.5%) *S. paratyphi* A (48.1%), *S. paratyphi* B (25.9%) and *S. typhimurium* (22.2%) were isolated from food samples in Namakkal and the isolates showed multiple drug resistance, and 100 % resistant to Vancomycin, Novobiocin, Nitrofurantoin, Ciproflaxacin, and Methicillin (Jegadeeshkumar et al., 2010). Jegadeeshkumar et al. (2010) also observed increasing resistance for Amoxiclave (92.55 %) and Bacitracin (78.57 %). Akinyemi et al. (2000) reported that out of the total blood samples cultured, 101 (15.9%) isolates of *Salmonella* species were isolated of which 68 (67.3%) were *S. typhi*, 17 (16.8%) and 16 (15.8%) were *S. paratyphi A* and *S. arizonae* respectively. All the *S. typhi* and *S. paratyphi* isolates showed resistance to two or more of the 10 of 12 antibiotics tested particularly the 3-first-line antibiotics commonly used (chloramphenicol, ampicillin and cotrimoxazole) in the treatment of typhoid fever in Nigeria.

Since the discovery of antibiotics and their uses as chemotherapeutic agents, there was a belief in the medical fraternity that this would lead to the eradication of infectious diseases. However, diseases and disease agents that were once thought to have been controlled by antibiotics are returning in new forms resistant to antibiotic therapies (Levy and Marshall, 2004). Incidents of epidemics due to such drug resistant microorganisms are now a common global problem posing enormous public health concerns (Iwu et al., 1999). The global emergence of multi-drug resistant bacterial strains is increasingly limiting the effectiveness of current drugs and significantly causing treatment failure of infections (Hancock, 2005). Examples include methicillin-resistant staphylococci, pneumococci resistant to penicillin and macrolides, vancomycin-resistant enterococci as well as multidrug resistant gram-

negative organisms (Norrby et al., 2005). As resistance to old antibiotics spreads, the development of new antimicrobial agents has to be expedited if the problem is to be contained. However, the past record of rapid, widespread and emergence of resistance to newly introduced antimicrobial agents indicates that even new families of antimicrobial agents will have a short life expectancy (Coates et al., 2002). Confronted with a possible shortage of new antimicrobials, there is need to ensure a careful use of our available drugs. This has led to calls for controlled use of antibiotics through the reduction of dosage used per regime of treatment or by regulating prescriptions in areas such as animal husbandry and aquaculture (Hernandez, 2005). While, reduced use could lead to delayed resistance development, the emergence of resistant strains is from an evolutionary viewpoint inevitable. It becomes imperative therefore that alternative approaches are explored. Targeting and blocking resistance processes could be an attractive approach. The presence of efflux pumps and multidrug resistance (MDR) proteins in antibiotic resistant organisms contribute significantly to the intrinsic and acquired resistance in these pathogens. The discovery and development of new compounds that either block or circumvent resistance mechanisms could improve the containment, treatment, and eradication of these strains (Oluwatuyi et al., 2004).

3. Problems of antibiotic resistance

The origin of antibiotic resistance extends much further back in evolutionary terms and reflects the attack and counter-attack of complex microbial flora in order to establish ecological niches and survive. Early treatment failures with antibiotics did represent a significant clinical problem because other classes of agents, with different cellular targets, were available. The emergence of multiple resistances is causing major problems in the treatment options today. Several factors drove this situation in the 1970s and 1980s, including the introduction of extended-spectrum agents and advances in medical techniques such as organ transplantation and cancer chemotherapy. The net result has been a huge selective pressure in favour of multiply resistant species. Coupled with this, there has been a sharp decline in the introduction of agents acting on new cellular targets over the last 30 years compared with the 20-year period following World War II. Smith (2004) reported that the resistant organisms causing concern among Gram-positive organisms at present are methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci, glycopeptides intermediate sensitivity *S. aureus* (GISA), vancomycin-resistant *Enterococcus* (VRE) species and penicillin-resistant *Streptococcus pneumoniae*. Concerns among the Gram-negative organisms include multidrug-resistant *Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and *Acinetobacter baumannii* and members of the Enterobacteriaceae with extended-spectrum beta- lactamases.

When infections become resistant to first choice or first line antimicrobials, treatment has to be switched to second-or third-line drugs, which are nearly always expensive (Sibanda and Okoh, 2007). In many poor countries in developing nations, the high cost of such replacement drugs is not easy to come-by, with the result that some diseases can no longer be treated in areas where resistance to first-line drugs is widespread (WHO, 2002). The alarming challenges facing physicians and pharmacist now, is the need to develop alternative approaches in addition to the search for new antimicrobial compounds (Sibanda and Okoh, 2007). Plants might hold a promise for combating the problem of antibiotic resistance.

4. Mechanisms of antibiotic resistance in pathogenic bacteria

Resistance to antimicrobial agents typically occurs as a result of four main mechanisms namely enzymatic inactivation of the drug (Davies, 1994), alteration of target sites (Spratt, 1994), reduced cellular uptake (Smith, 2004) and extrusion by efflux (Nakaido, 1994). It has been reported that chemical modifications could be significant in antibiotic resistance, though exclusion from the cell of unaltered antibiotic represents the primary means in denying the antibiotic access to its targets and this is believed to enhance resistance even in cases where modification is the main mechanism (Li et al., 1994b).

4.1 Alteration of target site

Chemical modifications in the antibiotic target may result in reduced affinity of the antibiotic to its binding site (Lambert, 2005). These mechanisms have been reported to be employed by a number of pathogenic bacteria in over-powering the effect of antibiotics and are usually mediated by constitutive and inducible enzymes. Resistance to macrolides, lincosamide and streptogramin B antibiotics (MLSB resistance) in pathogenic *Streptococcus* species is a result of methylation of the N6 amino group of an adenine residue in 23S rRNA. This is presumed to cause conformational changes in the ribosome leading to reduced binding affinity of these antibiotics to their binding sites in the 50S ribosomal subunit (Seppala et al., 1998; Kataja et al., 1998). Beta-lactams antibiotics function by binding to and inhibiting the biosynthetic activity of Penicillin Binding Proteins (PBPs), thereby blocking cell wall synthesis.

4.2 Enzymatic inactivation

The production of hydrolytic enzymes and group transferases is a strategy employed by a number of pathogens in evading the effect of antibiotics (Wright, 2005). Genes that code for antibiotic degrading enzymes are often carried on plasmids and other mobile genetic elements. The resistance to-lactam antibiotics by both gram negative and gram positive bacteria has long been attributed to -lactamases (Frere, 1995). These enzymes confer significant antibiotic resistance to their bacterial hosts by hydrolysis of the amide bond of the four membered-lactam ring (Wilke et al., 2005). Resistance to aminoglycosides in gram-negative bacteria is most often mediated by a variety of enzymes that modify the antibiotic molecule by acetylation, adenylation or phosphorylation (Over et al., 2001).

4.3 Antibiotic efflux pump

It is now widely recognized that constitutive expression of efflux pump proteins encoded by house-keeping genes that are widespread in bacterial genomes are largely responsible for the phenomenon of intrinsic antibiotic resistance (Lomovskaya and Bostian, 2006). Several studies have shown that active efflux can be a mechanism of resistance for almost all antibiotics (Li et al., 1994a; Gill et al., 1999; Lin et al., 2002). The majority of the efflux systems in bacteria are non-drug-specific proteins that can recognize and pump out a broad range of chemically and structurally unrelated compounds from bacteria in an energy-dependent manner, without drug alteration or degradation (Kumar and Schweizer, 2005).

The consequence of this drug extrusion is that, it leads to a reduced intracellular concentration of the antimicrobial such that the bacterium can survive under conditions of elevated antimicrobial concentration (Marquez, 2005). The MIC of the drug against such organisms will be higher than predicted. Multi-drug resistance efflux pumps are ubiquitous proteins present in both gram-positive and gram-negative bacteria as either chromosomally encoded or plasmid encoded (Akama et al., 2005). Although, such proteins are present constitutively in bacteria, the continued presence of the substrate induces over-expression (Teran et al., 2003). This increased transcription is responsible for the acquired resistance. In gram negatives bacteria, the effect of the efflux pumps in combination with the reduced drug uptake due to the double membrane barrier is responsible for the high inherent and acquired antibiotic resistance often associated with this group of organisms (Lomovskaya and Bostian, 2006).

The NorA protein which is the best studied chromosomally encoded pump in pathogenic gram positive bacteria (Hooper, 2005) has been reported to be present in *S. epidermidis* but appears to be absent in *Enterococcus faecalis* or in gram-negative organisms, such as *E. coli* and *K. pneumoniae* (Kaatz et al., 1993). Over expression of the NorA gene in *S. aureus* confers resistance to chloramphenicol and hydrophilic fluoroquinolone antimicrobials (Hooper, 2005; Kaatz and Seo, 1995; Hooper, 2005 instead of Hooper, 2005; Kaatz and Seo, 1995). QacA is a member of the major facilitator super-family of transport proteins, which are involved in the uniport, symport, and antiport of a wide range of substances across the cell membrane (Mitchell et al., 1998). The QacA multidrug exporter from *S. aureus* mediates resistance to a wide array of monovalent or divalent cationic, lipophilic, antimicrobial compounds. QacA provides resistance to these various compounds via a proton motive force-dependent antiport mechanism (Brown and Skurray, 2001).

Baucheron et al. (2004) reported the resistance of *Salmonella enteric* serovar Typhimurium to fluororoquinolones, chloramphenicol-florfenicol and tetracycline is highly dependent on the presence of AcrAB-TolC efflux pump. *S. enterica* includes nontyphoidal Salmonella belonging to different serotypes on the basis of the flagellar and somatic antigens, and represents one of the most important food-borne pathogens causing gastroenteritis in humans (Neidhardt, 1996). Nontyphoidal *S. enterica* strains are easily passed from animals to humans and are thus classified as zoonotic pathogens. They can colonize or infect humans as well as a variety of domesticated and wild animals ranging from mammals to birds and reptiles. Most infections are related to ingestion of contaminated food products rather than person-to-person transmission or direct fecal-oral transmission (Mead et al., 1999). Several *S. enterica* isolates are characterized by the presence of host-adapted virulence plasmids encoding genes contributing to colonization and resistance to complement killing, such as the spvA, spvB and spvC (salmonella plasmid virulence) and the rck (resistance to complement killing) genes (Guiney et al., 1994).

In the last few years, Salmonella shows increasing antimicrobial resistance rates in isolates obtained from both food animals and humans. *S. enterica* strains belonging to different serotypes and showing multiple antibiotic resistance (to four or more antimicrobials) are now widespread in both developed and developing countries, most of these strains are zoonotic in origin, acquire their resistance in the food-animal host and cause human infections through the food chain (Threlfall, 2002). Salmonella infections have been associated with the ingestion of poultry, meat, milk and dairy products (Bean et al., 1996).

Most infections result in self-limiting diarrhea and do not require antimicrobial treatment. However, severe life-threatening bacteremias and other deep-seated infections do occur, particularly in children and immunocompromised hosts and in these cases an antimicrobial therapy is recommended (Blaser and Feldman, 1981). Good drugs for Salmonella infections include fluoroquinolones, ampicillin, trimethoprimsulfamethoxazole or third-generation cephalosporins. Rising rates of resistance to ampicillin and trimethoprimsulfamethoxazole have significantly reduced their efficacy and fluoroquinolones are not approved for the use in children. Consequently, extended-spectrum cephalosporins have become the current drugs of choice for the treatment for invasive infections in children (Hohmann, 2001). The emergence of Salmonella species that are resistant to extended-spectrum cephalosporins (Herikstad et al., 1997; Threlfall et al., 1997) is cause of worldwide concern.

4.4 Importance of plasmids in the dissemination of resistance in *S. enterica*

Since the aminoglycoside antibiotic apramycin was licensed for veterinary use in the 1980s, resistance to apramycin and the related antibiotic gentamicin, one the most frequently used aminoglycoside in human therapy (Sibanda and Okoh, 2007). In the United Kindom, during the period 1982-84, the incidence of resistance to apramycin in salmonellas increased from 0.1% in 1982 to 1.4% in 1984 (Wray et al., 1986). Resistance to both apramycin and gentamicin was detected in different Salmonella serotypes, as well in *Escherichia coli*. In particular, the incidence of *S. enterica* (S.) *typhimurium* definitive type 204c (DT204c) from calves showed a dramatically increase (Wray et al., 1986). In *S. typhimurium* DT204c the gentamicin resistance was specified by three types of plasmids of the I1 incompatibility group, which also conferred resistance to apramycin (Threlfall et al., 1986). Most of these plasmids produced the enzyme aminoglycoside 3-N-acetyltransferase IV and the resistance was transferable by conjugation in most of the strains examined. The increasing incidence of the gentamicin-resistant *S. typhimurium* DT204c was also observed in humans, providing the first evidence that the use of apramycin in animal husbandry gave rise to resistance to gentamicin, an antimicrobial used for human therapy (Threlfall et al., 1986).

In the 1990s, the increasing frequency of *E. coli* and Salmonella with plasmids conferring resistance to gentamicin and apramycin was reported in other European countries (Chaslus-Dancla et al., 1991; Pohl et al., 1993). Gentamicin- and apramycin- resistant strains were isolated from both humans and cattle in France and Belgium and six different types of replicons were identified (Pohl et al., 1993). During the 1990-1997 alarming reports pointed out the rapid development in several countries of resistance to β-lactam antibiotics in Salmonella (Threlfall et al., 1997). A survey conducted between 1987 and 1994 in France, demonstrated a dramatic increase (from 0 to 42.5%) in the prevalence of β-lactam resistance among Salmonella isolates. Several types of β-lactamases were found on plasmids belonging to different incompatibility groups Q, P, F and HI (Llanes et al., 1999).

Resistance to β-lactams in Gram-negative bacteria is mediated predominantly by two major types of β- lactamases: the chromosomally-encoded enzymes of the Amber class C (e.g. AmpC β-lactamase in *Citrobacter, Enterobacter, Serratia spp, Morganella morganii* and *Pseudomonas aeruginosa*) or by plasmid-encoded enzymes of the Amber class A, in species that do not produce AmpC β-lactamases, such as *E. coli, Salmonella spp*., and *Shigella spp*. (Bauernfeind et al., 1998a).

Extended-spectrum β-lactamase (ESBL), evolved from the blaTEM-1, blaTEM-2, and blaSHV-1 genes, extending resistance to new third-generation cephalosporins. During the last decade, infections caused by *S. enterica* carrying ESBLs have been reported, and most of the ESBL-producing strains were found to carry plasmids encoding the blaTEM- 1, and blaSHV-1 gene derivatives (Hammani et al., 1991; Morosini et al., 1995; Tassios et al., 1997; Villa et al., 2000; Mulvey et al., 2003).

In Southern Italy, during the period 1990 to 1998, several epidemiologically unrelated *S. enteriditis* isolates showing resistance to expanded-spectrum cephalosporins were recurrently isolated from ill patients. Most of these strains carried the blaSHV-12 gene located on conjugative plasmids (Villa et al., 2002a). Notably, this was the first case of acquisition of the blaSHV-12 gene by Salmonella in Italy and worldwide. However, SHV-12-encoding plasmids were previously encountered in *K. pneumoniae* isolated from hospitals throughout Italy (Laksai et al., 2000; Pagani et al., 2000). Therefore, it is plausible that SHV-12-encoding plasmids originated from nosocomial bacterial pathogens and were horizontally transmitted to *S. enteriditis* strains.

In 1999, the spread of a *S. typhimurium* clone resistant to third generation cephalosporins has been reported in Russia, Hungary and Greece. In this case non distinguishable institutional and community outbreak of *S. typhimurium* isolates harboured a transferable plasmid containing the blaCTX-M gene (Tassios et al., 1999). The relatedness of resistance plasmids harboured by strains of various origins can be demonstrated by incompatibility grouping, restriction fragmentation pattern analysis and identification of specific resistance determinants located within the plasmids. These analyses may allow a better understanding of how resistance plasmids propagate, helping to trace their evolution.

The *S. typhimurium* pSEM plasmid has a very similar restriction pattern to that of the *K. oxytoca* plasmid, pACM1. The pSEM plasmid was identified in 1997 in *S. typhimurium* strains isolated from children in Albania (Villa et al., 2000), while pACM1 was isolated from *K. oxytoca* strains responsible of a nosocomial outbreak in the USA (Preston et al., 1997; Preston et al., 1999). Both plasmids belonged to the same IncL/M group and conferred resistance to expanded-spectrum cephalosporins by the blaSHV-5 gene. Both plasmids carried a class 1 integron conferring aminoglycoside resistance by the aacA4, aacA1 and aadA1 resistance gene cassettes (Villa et al., 2000; Preston et al., 1997). Thus, these plasmids could be members of a family of broad-host-range replicons widely spreading among Gram-negative pathogens. Other plasmids of the IncL/M group showing similar restriction profiles, and carrying the blaSHV-5 gene and a class 1 integron, were previously described in several countries in Europe from clinical isolates of *P. aeruginosa* and *K. pneumoniae* (de Champs et al., 1991; Petit et al., 1990; de Champs et al., 1991; Prodinger et al., 1996; Preston et al., 1997 instaed of de Champs et al., 1991; Petit et al., 1990; Preston et al., 1997, Prodinger et al., 1996). The identification of a family of related plasmids has serious public health implications, since it demonstrates that broad-host-range plasmids carrying resistance to clinically relevant antibiotics can spread worldwide among bacteria responsible of both nosocomial and community-acquired infections. The fact that conserved plasmids can be identified in a wide variety of pathogens isolated in different countries, illustrates the important role of plasmids in the dissemination of antimicrobial resistance among Gram-negative bacteria.

Recently, a case of treatment failure due to ceftriaxone resistant *S. anatum* has been reported in Taiwan (Su et al., 2003). In this study, ceftriaxone-susceptible *S. anatum* was

initially isolated from the urine of a 70-year-old diabetic patient hospitalized for the treatment of a large pressure sore in the sacral area and urinary tract infection. The unexpected emergence of the resistance during the treatment with ceftriaxone led to systemic bacteraemia by *S. anatum* and to the fatal outcome in the patient. The emergence of the resistance has been linked to the *in vivo* acquisition of a resistance plasmid carrying the CTX-M3 β-lactamase by the susceptible *S. anatum* strain. In the same hospital this β-lactamase has been previously identified in clinical isolates of *E. coli, K. pneumoniae* and *Enterobacter cloacae*, suggesting that such bacteria may have acted as reservoirs of the resistance plasmid (Su et al., 2003).

4.5 Plasmid-mediated resistance to expanded-spectrum cephalosporins encoded by the CMY-2 AmpC β- lactamase

The ampC genes were regarded as exclusively chromosomal until 1989, when an AmpC-type β-lactamase was found for the first time on transmissible plasmids (Bauernfeind et al., 1998a). Plasmid-mediated AmpC β-lactamases belong to the homogeneous group of genes related to the chromosomal ampC gene of *Citrobacter freundii* (cmy-2, bil-1 and lat genes), the cmy-1, fox and mox family, or originate from the *Morganella morganii* AmpC β-lactamase (DHA-1) (Bauernfeind et al., 1998a). The latter was identified on a plasmid in *S. enteriditis* (Barnaud et al., 1998; Verdet et al., 2000). The first case of plasmid-mediated CMY-2 in Salmonella was reported on a conjugative plasmid of *S. senftenberg* recovered in 1994 from stool of an Algerian child (Koeck et al., 1997). Review of 1996 data from the National Antimicrobial Resistance Monitoring System (NARMS) in the United States identified only 1 (0.1%) Salmonella isolate among 1272 human Salmonella isolates showing expanded spectrum cephalosporin resistance (Dunne et al., 2000). However, in 1999, NARMS reported the emergence of domestically acquired broad-spectrum cephalosporin resistant Salmonella, most of them producing the CMY-2 AmpC β-lactamase (Dunne et al., 2000).

S. typhimurium strains carrying indistinguishable CMY-2-encoding plasmids were isolated in Nebraska from a patient and cattle during a local outbreak of salmonellosis, demonstrating that the Salmonella-resistant strain evolved primarily in livestock (Fey et al., 2000). Since 1998, *Salmonella* of human and animal origin were reported to show resistance to expanded-spectrum cephalosporins, in Iowa (Winokur et al., 2000; Winokur et al., 2001). Molecular studies demonstrate the emergence of plasmid encoded CMY-2 β-lactamase in most cephalosporin resistant isolates. During the 1998-1999 periods, nearly 16% of *E. coli* isolates and 5.1% of *Salmonella* isolates from clinically ill animals in Iowa produced CMY-2 (Winokur et al., 2000; Winokur et al., 2001).

Similar plasmids, carrying the cmy-2 gene were also reported in Salmonella isolated from animals in Illinois (Odeh et al., 2002). The spreading of the CMY-2-carrying plasmids in the USA was confirmed by molecular analysis of domestically acquired Salmonella strains of human origin isolated in nine different States, representing the 87% of the total expanded-spectrum cephalosporin resistant Salmonella collected by the Center for Disease Control and Prevention (CDC) during the 1996-1998 surveillance periods. The isolates were distinguishable by their chromosomal DNA patterns, thus demonstrating that they did not represent the epidemic spread of a clonal strain (Dunne et al., 2000).

4.6 The use of resistance modifying agents in combination with antibiotics to overcome resistance

The selection pressure exerted by the continued presence of bactericidal or bacteriostatic agents facilitates the emergence and dissemination of antibiotic resistance genes. Over generations, the genotypic makeup of bacterial populations is altered (Taylor et al., 2002). The clinical implications of this are that many infections become untreatable resulting in serious morbidity and mortality. Although the introduction of new compounds into clinical use has helped to curtail the spread of resistant pathogens, resistance to such new drugs, has developed in some cases. It has been observed by several studies that antibiotic combinations can have synergistic benefits and interactions between existing antibiotics (Bayer et al., 1980; Hallander et al., 1982; Hooton et al., 1984; Cottagnoud et al., 2000; instaed of Bayer et al., 1980; Hooton et al., 1984; Cottagnoud et al., 2000; Hallander et al., 1982.). Several current therapeutic regimes are based on synergistic interactions between antibiotics with different target sites. As new antimicrobial compounds are discovered, there is need to assess their potentials in combination therapies with old antibiotics that have been rendered ineffective by the development of resistant strains, even when such compounds are not directly evidently inhibitory. Taylor et al. (2002) suggested that the use of agents that do not kill pathogenic bacteria but modify them to produce a phenotype that is susceptible to the antibiotic could be an alternative approach to the treatment of infectious disease. Such agents could render the pathogen susceptible to a previously ineffective antibiotic, and because the modifying agent applies little or no direct selective pressure, this concept could slow down or prevent the emergence of resistant genotypes. The inhibition of resistance expression approach was successfully used in the production of Augmentin, a combination of amoxycillin and clavulanic acid (Reading and Cole, 1977). In this case, clavulanic acid is an inhibitor of class-A-lactamases which is coadministered with amoxicillin. The combination has been used clinically since the late 1970s (Neu et al., 1993). A similar approach can be used for target-modifying enzymes and for efflux systems. A number of *in vitro* studies have reported the use of plant extracts in combination with antibiotics, with significant reduction in the MICs of the antibiotics against some resistant strains (Al-hebshi et al., 2006; Darwish et al., 2002; Al-hebshi et al., 2006; Betoni et al., 2006 instead of Al-hebshi et al., 2006; Darwish et al., 2002; Betoni et al., 2006). The curative effect of plant extracts in this combination study has been variably referred to as resistance modifying/modulating activity (Gibbons, 2004). This ability of plant extracts to potentiate antibiotics has not been well explained. It is speculated that inhibition of drug efflux, and alternative mechanisms of action could be responsible for the synergistic interactions between plant extracts and antibiotics (Lewis and Ausubel, 2006; Zhao et al., 2001; Lewis and Ausubel, 2006; instead of Lewis and Ausubel, 2006; Zhao et al., 2001).

4.7 Efflux pump inhibition in combination with antibiotics as a strategy for overcoming resistance

The discovery and development of clinically useful Efflux Pump Inhibitors (EPIs) that decrease the effectiveness of efflux pumps represents a significant advance in the development of therapeutic regimes for the treatment of MDR-related conditions. This approach termed the EPI strategy (Lomovskaya and Bostian, 2006), is based on blocking the activity of the pumps, resulting in the accumulation of the antibiotic inside the bacterial cell, consequently increasing access to its target sites. In addition, this will lead to increased susceptibility of the bacterium, thus implying that the therapeutic effect of the drug is

achieved with low concentrations. Combining broad spectrum efflux pump inhibitors with current drugs that are pump substrates can recover clinically relevant activity of those compounds and thus may provide new dimensions to the ever increasing need for development of new antimicrobial agents. This approach will in addition lead to the preservation and improvement of the usefulness of old and cheap antibacterial agents. Ultimately this could reduce the appearance and spread of resistant mutants (Kaatz, 2002).

4.8 Role of Ethnopharmacology in the treatment of Salmonellosis

Herbal medicine is used globally and has a rapidly growing economic importance. In developing countries, traditional medicine is often the only accessible and affordable treatment available. In Africa, 80% of the population uses traditional medicine as the primary health care system (Fisher and Ward, 1994). Traditional medicine is also gaining more respect by national governments and health providers. Peru's national program in complementary medicine and the Pan American health organization recently compared complementary medicine in clinics and hospitals within the Peruvian social security system (Lima, 2000). Plants have been used in traditional medicine for several thousand years (Abu – Rabia, 2005). The knowledge of medicinal plants has been accumulated in the course of many centuries based on different medicinal system. During the last few decades there is an increasing interest in the study of medicinal plants and their traditional use in different parts of the world (Rossato et al., 1999). There are considerable economic benefits in the use of medicinal plants for the treatments of various diseases (Azaizeh, 2003). Due to less communication means, poverty, ignorance and unavailability of modern health facilities, most of the rural people are forced to practice traditional medicines for their common day ailments. Most of these people form the poorest link in the trade of medicinal plants (Khan, 2002). A vast knowledge of how to use the plants against different illness may be expected to have accumulated in areas were the use of plants is still of great importance (Diallo et al., 1999). In the developed countries, 25% of the medical drugs are based on plants and their derivatives (Principe, 1991). A group of World Health Organization experts, who met in Congo, Brazzaville in 1976, sought to define traditional African medicine as the sum total of practices, measures, ingredients and procedures of all kinds whether material or not, which from time immemorial has enabled the African to guard against diseases to alleviate his / her suffering and cure him / herself (Busia, 2005). Traditional medical knowledge of medicinal plants and their use by indigenous cultures are not only useful for conservation of community health care and biodiversity but also for community health care and drug development in the present and future (Pei, 2001).

A number of workers have evaluated the anti typhoidal activities of medicinal plants and some of them proved to be promising. For example: Aliero and Wara (2009) evaluated the efficacy of *Leptadenia hastata* (Pers.) Decne extracts against five selected bacterial species and two fungal species. Aqueous extract markedly inhibited the growth of *Salmonella paratyphi* and *Escherichia coli* and *Pseudomonas aeruginosa*. The result obtained in this study has provided a scientific support for the claimed ethnomedical uses of aqueous extracts of *L. hastata* in the treatment of bacterial diseases and suggest the potential of methanol extract as a source of antifungal agent. Evans et al. (2002) evaluated the efficacy of *Euphobia hirta*; *Citrus aurantifolia*, *Cassia occidentalis*, and *Cassia eucalyptus* claimed by the Nupes tribe of Nigeria to be effective in the treatment of typhoid fever. The result of *invitro* antimicrobial

analysis showed that, only *Cassia eucalyptus* showed inhibition of *Salmonella typhi* growth and concluded that the plant is efficacious and contains natural compounds that could be used in the treatment of typoid fever. Similarly, In Camerron, Nkuo-Akenji et al. (2001) evaluated the effects of herbal extracts derived from plants commonly prescribed by traditional practitioners for the treatment of typhoid fever against *Salmonella typhi*, *S. paratyphi* and *S. typhimurium* using formulations often prescribed by the traditional healers which includes; 1) Formulation A comprising *Cymbogogon citratus* leaves, *Carica papaya* leaves, and *Zea mays* silk. 2) Formulation B comprising *C. papaya* roots, *Mangifera indica* leaves, *Citrus limon* fruit and *C. citratus* leaves. 3) *C. papaya* leaves. 4) *Emilia coccinea* whole plant. 5) *Comelina bengalensis* leaves. 6) *Telfaria occidentalis* leaves. 7) *Gossypium arboreum* whole plant. The result obtained in this study, showed that Formulation A elicited inhibitory activity at a lower range of 0.02 to 0.06 mg/ml. Similarly, Formulation B elicited bacterial activity at the lowest range of 0.06 to 0.25mg/ml. *C. bengalensis* leaves on the other hand, showed the lowest activity with a concentration range of 0.132 to 2.0 mg/ml and 1 to 4 mg/ml in MIC and MBC assays respectively. The result demonstrated that *S. paratyphi* was most sensitive to the formulations (concentration range of 0.02 to 1 mg/ml in both MIC and MBC assays) while *S. typhimurium* was the least sensitive and concentrations of up to 4 mg/ml were required to be bactericidal.

Iroha et al. (2010) evaluated the anti *Salmonella typhi* activity of ethanol, hot and cold crude water extracts of *Vitex doniana* (root), *Cassia tora* (Leaf), *Alstonia boonei* (bark), *Stachytarpheta jamaicensis* (leaf), and *Carica papaya* (leaf) used as traditionally medicine in Ebonyi state, Nigeria. Ethanol extracts of *Vitex doniana* exhibited anti-typhoid activity against 9(90%) of the test organisms, *A. boonei* exhibited activity against 8(80%) of the test organisms, *C. papaya* against 2(20%), *C. tora* against 6(60%), and *S. jamaicensis* against 6(60%). Hot water extract of *Vitex doniana* showed anti-typhoid activity against 7(70%) of the test organisms, *A. boonei* against 9(90%), *C. papaya* against 1(10%), *C. tora* against 8(80%) and *S. jamaicensis* against 7(70%). Cold water extract of *V. doniana,* had anti-typhoid activity against 6(60%) of the test organisms, *A. boonei*, against 6(60%), *C. papaya* against 0(0%), *C. tora* against 6(60%) and *S. jamaicensis* against 4(40%). MIC of ethanol, hot and cold water extracts of *V. doniana*, *A. boonei, C. papaya, C. tora and S. jamaicensis,* fall within 0.4 -128, 0.8 -128, 64 -128, 32 – 128 and 32 – 128. MIC of hot water extracts were within 16 -128, 0.8 – 128, 128 -512, 0.8 – 512 and 0.8 – 128 while MIC of cold water extract are within 64 – 128, 64 – 512, 64 – 512, 64 – 512 and 128-512 respectively. The results of these findings showed that ethanol and hot water extracts of *V. doniana* and *A. boonei* had the best antityphoid activity.

The work of Oluduro and Omoboye (2010) investigated the antibacterial potency and synergistic effect of crude aqueous and methanolic extracts of nine plant parts against multi-drug resistant *S. typhi* tested against nine plant parts: unripe C*arica papaya* fruit, *Citrus aurantifoliia*, *Anana sativus*, *Citrus paradisi*, *Cymbopogon citratus*, *Cocos nucifera* leaves of *Carica papaya,* leaves of *Euphorbia heterophylla* and *Gossypium* spp. Both the aqueous and methanol extracts of each plant material and mixture showed appreciable antimicrobial activities on *S. typhi.* Antimicrobial activity increased with increasing concentration of the extracts. Synergistic activity of crude aqueous and crude methanolic extracts of the plant parts, in various combinations of two to nine against the test organism ranged from 10-33 mm zone of growth inhibition. The antibacterial efficacy of the mixture of extracts from plant parts increased considerably compared to the low activities recorded with the extract of

individual plant parts (P>0.05). Methanolic extracts of each plant material and mixture produced greater antimicrobial activity than the aqueous extracts at all concentrations. The minimum inhibitory concentration (MIC) of the individual plant parts ranged between 0.1 and 1.0 mg/ml in aqueous extracts and 0.01 and 0.1 mg/ml in methanol extracts while the MICs of the combined extracts ranged between 0.1 and 0.01 mg/ml in aqueous extracts and 0.01 and 0.0001 mg/ml in methanolic extracts. The combined or synergistic activity of the plant parts compared favourably with the standard antibiotics of choice for salmonella-infections therapy, and contained two or more phytochemicals responsible for their antimicrobial activities. There is the need therefore to develop effective combination of antimicrobial agents in purified form from higher plants and their parts for clinical trials. Frey and Meyers (2010) reported that *Achillea millefolium, Ipomoea pandurata, Hieracium pilosella*, and *Solidago canadensis* exhibited antimicrobial properties as expected, with particularly strong effectiveness against *S. typhimurium*. In addition, extracts from *Hesperis matronalis* and *Rosa multiflora* also exhibited effectiveness against this pathogen.

4.9 Plants as sources of new antimicrobials and resistance modifying agents

Plants have traditionally provided a source of hope for novel drug compounds, as plant herbal mixtures have made large contributions to human health and well-being (Iwu et al., 1999). Owing to their popular use as remedies for many infectious diseases, searches for substances with antimicrobial activity in plants are frequent (Shibata et al., 2005; Betoni et al., 2006). Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found *in vitro* to have antimicrobial properties (Cowan, 1999; Lewis and Ausubel, 2006). Examples of some of these compounds are shown in Table 1. Literature is awash with compounds that have been isolated from a variety of medicinal plants. Despite this abundant literature on the antimicrobial properties of plant extracts, none of the plant derived chemicals have successfully been exploited for clinical use as antibiotics (Gibbons, 2004). A significant part of the chemical diversity produced by plants is thought to protect plants against microbial pathogens. Gibbons (2004) reported that a number of plant compounds often classified as antimicrobial produce MIC greater than 1,000 µg/ml, which are of no relevance from a clinical perspective. Tegos et al. (2002) suggested that a vast majority of plant compounds showing little *in vitro* antibacterial activity are not antimicrobial but are regulatory compounds playing an indirect role in the plant defence against microbial infections. The observation that plant derived compounds are generally weak compared to bacterial or fungal produced antibiotics and that these compounds often show considerable activity against gram-positive bacteria than gram-negative species has been made by many (Nostro et al., 2000; Gibbons, 2004). This observations led Tegos et al. (2002) hypothesizing that; Plants produce compounds that can be effective antimicrobials if they find their way into the cell of the pathogen especially across the double membrane barrier of Gram negative bacteria. Production of efflux pump inhibitors by the plant would be one way to ensure delivery of the antimicrobial compound. This hypothesis has been supported by the findings of Stermitz et al. (2000 a,b), who observed that *Berberis* plants which produce the antimicrobial compound, berberine, also make the MDR inhibitors 5-methoxyhydnocarpin D (5-MHC-D) and pheophorbide A. The MDR inhibitors facilitated the penetration of berberine into a model gram-positive bacterium, *S. aureus*. In testing their hypothesis, Tegos et al. (2002), showed that two MDR inhibitors (INF271 and MC207110) dramatically increased the effectiveness of thirteen

putative plant antimicrobial compounds against gram-negative and gram positive bacteria including isolates known to express efflux pumps.

Class of compound	Examples	Plant sources	Reference
Coumarins and their derivatives	Asphodelin A 4'-*O*-D-glucoside Asphodelin A	*Asphodelus microcarpus*	El-Seedi (2007)
Simple phenols	Epicatechin	*Calophyllum brasiliense*	Pretto et al. (2004)
	Epigallocatechin Epigallocatechin gallate Epicatechin gallate	*Camellia sinensis*	Mabe et al. (1999) Hamilton-Miller (1995)
Flavonoids	Isocytisoside	*Aquilegia vulgaris* L.	Bylka et al. (2004)
	Eucalyptin	*Eucalyptus maculate*	Takahashi et al. (2004)
Flavones	Luteolin	*Senna petersiana*	Tshikalange et al. (2005)
	GB1(hydroxybiflavanonol)	*Garcinia kola*	Madubunyi (1995) Han et al. (2005)
Tannins	Ellagitannin	*Punica granatum*	Machado et al. (2002)
Alkaloids	Berberine	*Mahonia aquifolium*	Cernakova and Kostalova (2002)
Terpenes	Ferruginol, (Diterpene) Epipisiferol (Diterpene)	*Chamaecyparis lawsoniana*	Smith et al. (2007)
	1-Oxoferruginol	*Salvia viridis*	Ulubelen et al. (2000)

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Table 1. Examples of some plants with active antimicrobial derived compounds.

These studies have provided the bases for understanding the action of plant antimicrobials, namely that vast majority of such compounds are agents with weak or narrow-spectrum activities that act in synergy with intrinsically produced efflux pump inhibitors. There is

reason therefore to believe that, plants could be a source of compounds that can increase the sensitivity of bacterial cells to antibiotics. Such compounds could be useful particularly against antibiotic resistant strains of pathogenic bacteria. The rich chemical diversity in plants promises to be a potential source of antibiotic resistance modifying compounds and has yet to be adequately explored.

4.10 Resistance modifying activities of plants crude extracts: The basis for isolation of potentially useful compounds

If the isolation of resistance modifying compounds from plants is to be realistic, screening for such activities in crude extracts is the first step in identifying leads for isolation of such compounds, and some plants have provided good indications of these potentials for use in combination with antimicrobial therapy. Typical examples are as follows: Aqueous extracts of tea (*Camellia sinensis*) have been shown to reverse methicillin resistance in MRSA and also, to some extent, penicillin resistance in beta lactamase-producing *Staphylococcus aureus* (Stapleton et al., 2004). Forty to one hundred fold dilutions of tea extracts was able to reduce the MICs of high- level resistant MRSA (256 µg/ml) to less than 0.12 µg/ml for methicillin and penicillin (Yam et al., 1998; Stapleton et al., 2004). Aqueous crude khat (*Catha edulis*) extracts of Yemen showed varying antibacterial activities with a range of 5-20 mg/ml-1 against periodontal bacteria when tested in isolation. Addition of the extracts at a sub- MIC (5 mg/ml) resulted in a 2 to 4-folds potentiation of tetracycline against resistant strains *Streptococcus sanguis* TH-13, *Streptococcus oralis* SH-2, and *Fusobacterium nucleatum* (Al-hebshi et al., 2006). Betoni et al. (2006), observed synergistic interactions between extracts of guaco (*Mikania glomerata*), guava (*Psidium guajava*), clove (*Syzygium aromaticum*), garlic (*Allium sativum*), lemongrass (*Cymbopogon citratus*), ginger (*Zingiber officinale*), carqueja (*Baccharis trimera*), and mint (*Mentha pieria*) from Brazil and some antibiotics which represented inhibitors of protein synthesis, cell wall synthesis, nucleic acid synthesis and folic acid synthesis against *Staphylococcus aureus*. Darwish et al. (2002) reported that sub-inhibitory levels (200 µgml−1) of methanolic extracts of some Jordanian plants showed synergistic interactions in combination with chloramphenicol, gentamicin, erythromycin and penicillin G against resistant and sensitive *S. aureus*. The methanolic extract of *Punica granatum* (PGME) showed synergistic interactions with chloramphenicol, gentamicin, ampicillin, tetracycline, and oxacillin. The bactericidal activity of the combination of PGME (0.1×MIC) with ampicillin (0.5×MIC) by time-kill assays, reduced cell viability b 99.9 and 72.5% in MSSA and MRSA populations, respectively (Braga et al., 2005). The ethanol extracts of the Chinese plants, *Isatis tinctoria* and *Scutellaria baicalensis* in combination with ciprofloxacin had synergistic activities against antibiotic resistant *S. aureus* (Yang et al., 2005). The combinations of pencillin with ethanolic extracts of *Paederia scandens* and *Taraxacun monlicum* showed a strong bactericidal activity on two strains of *S. aureus* (Yang et al., 2005). When Ciprofloxacin was incorporated at sub-inhibitory concentrations (1/8MIC) to the crude chloroform extracts of *Jatropha elliptica* and the mixture assayed against NorA expressing *S. aureus*, the activity of the extract was enhanced. This suggests the presence of an inhibitor of the pump which could restore the activity of Ciprofloxacin (Marquez et al., 2005). In another study, Ahmad and Aqil (2006) observed that crude extracts of Indian medicinal plants, *Acorus calamus, Hemidesmus indicus, Holarrhena antidysenterica* and *Plumbago zeylanica* showed synergistic interactions with tetracycline and ciprofloxacin

against extended Spectrum beta-lactamase (ESBL), producing multidrug-resistant enteric bacteria with ciprofloxacin showing more synergy with the extracts than tetracycline.

4.11 Plant compounds as resistance modifying agents

Some isolated pure compounds of plant origin have been reported to have resistance modifying activities *in vitro*. Examples of some of the compounds are given in Table 2. This has prompted the search for such compounds from a variety of medicinal plants. Some of the compounds which have been observed to have direct antimicrobial activity have been

Compound	Plant source	Antibiotics potentiated	Reference
Ferruginol 5-Epipisiferol	*Chamaecyparis lawsoniana*	Oxacillin, Tetracycline, Norfloxacin Tetracycline	Smith et al. (2007)
2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylic acid diethyl ester	*Jatropha elliptica*	Ciprofloxacin, Norfloxacin, Pefloxacin, Acriflavine and Ethidium bromide	Marquez et al. (2005)
Carnosic acid carnosol	*Rosmarinus officinalis*	Erythromycin	Oluwatuyi et al. (2004)
Ethyl gallate	*Caesalpinia spinosa*	Bate-lactams	Shibata et al. (2005)
Methyl-1-_-acetoxy-7-_-14 _-dihydroxy-8,15-isopimaradien-18-oate Methyl-1-_-14-_-diacetoxy-7-_-hydroxy-8,15-isopimaradien-18-oate	*Lycopus europaeus*	Tetracycline and Erythromycin	Gibbons et al. (2003)
Epicatechin gallate Epigallocatechin gallate	*Camellia sinensis*	Norfloxacin Imipenem Panipenem beta-Lactams	Gibbons et al. (2004) Hu et al. (2002) Zhao et al. (2001)

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Table 2. Some antibiotic resistance modifying compounds from plants.

shown to be potentiating against the activity of antibiotics when used at low MIC levels. The antimicrobial properties of tea (*Camellia sinensis*) have been found to be a result of the presence of polyphenols (Yam et al., 1998; Stapleton et al., 2004; Si et al., 2006). Bioassay directed fractionation of the extracts revealed that epicatechin gallate (ECG), epigallocatechin gallate (EGCG), epicatechin (EC), and caffeine (CN) are the bioactive components. ECG and CG reduced MIC values for oxacillin from 256 and 512 to 1 and 4 mgl-1 against MRSA (Shibata et al., 2005). Ethyl gallate, a conginer of alkyl gallates purified from a dried pod of tara (*Caesalpinia spinosa*) native to South America, intensified lactam susceptibility in MRSA an MSSA strains (Shibata et al., 2005). The abietane diterpenes, (carnosic acid carnosol) isolated from the aerial parts of *Rosmarinus officinalis* by fractionation of its chloroform extract at 10 µgml-1, potentiated the activity of erythromycin (16 - 32 fold) against strains of *S. aureus* that express the two efflux proteins MsrA and TetK. Additionally, carnosic acid was shown to inhibit ethidium bromide efflux in a NorA expressing *S. aureus* strain (Oluwatuyi et al., 2004). A penta-substituted pyridine, 2, 6-dimethyl-4-phenylpyridine-3, 5-dicarboxylic acid diethyl ester and proparcine have been isolated from an ethanol extract of rhizome of *Jatropha elliptica* by bioassay guided fractionation. The pyridine at a concentration of 75 µgml-1 was shown to increase by 4-fold, the activity of ciprofloxacin and norfloxacin against NorA expressing *S. aureus* when tested at sub-inhibitory concentrations (Marquez et al., 2005). Smith et al. (2007) screened active compounds from the cones of *Chamaecyparis Lawsoniana* for resistance modifying activities and observed that Ferruginol and 5-Epipisiferol were effective in increasing the efficacy of tetracycline, norfloxacin, erythromycin and Oxacillin against resistant *S. aureus*. The majority of researches on the combinations between plant extracts and antibiotics have been focused on the identification and isolation of potential resistance modifiers from such natural sources which are considered to be positive results. However, it is likely that such combinations could produce antagonistic interactions that most studies have considered irrelevant and therefore ignored (Sibanda and Okoh, 2007).

5. Suggested solutions to challenges in management

There are still loopfuls of challenges in many developing countries for the management of typhoid fever. Otegbayo (2005) gave the following suggestions as solution for typhoid fever management. This include among others, the improvement in personal and communal hygiene, effective waste disposal system and provision of potable water. Effective treatment of index cases, health education both for the populace and physicians are other important measures. Determination of drug sensitivity patterns and aggressive policy will be quite helpful. The difficulty in diagnosis could also be overcome by making laboratory facilities such as culture media available. Parry et al. (2002) recently suggested the use of conjugate Vi vaccine as part of the Expanded Programme of Immunization. The cost-effectiveness of this latter measure may however be negative for resource – poor countries, where preventive measures by way of improved sanitation and provision of potable water would be more beneficial. Above all, resources should be made available, accessible and affordable to the common man; National Health Insurance appears to be the answer to this as well as economic empowerment of the people in emerging economies.

6. References

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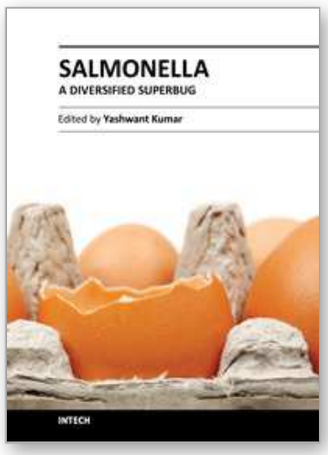

Salmonella - A Diversified Superbug
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Salmonella is an extremely diversified genus, infecting a range of hosts, and comprised of two species: enterica and bongori. This group is made up of 2579 serovars, making it versatile and fascinating for researchers drawing their attention towards different properties of this microorganism. Salmonella related diseases are a major problem in developed and developing countries resulting in economic losses, as well as problems of zoonoses and food borne illness. Moreover, the emergence of an ever increasing problem of antimicrobial resistance in salmonella makes it prudent to unveil different mechanisms involved. This book is the outcome of a collaboration between various researchers from all over the world. The recent advancements in the field of salmonella research are compiled and presented.

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