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Conceptual Drug Discovery and Societal Status may not be Sufficient to Combat Multidrug-Resistant Infections

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Abstract

The period between the 1940s and 1960s is commonly referred to as "the golden era of antibiotic discovery" saving million's life and good health. However, generation and spread of multi-drug resistant bacteria are highly claiming life. MDR, XDR and PDR infections are alarming as cautioned by CDC and WHO with ten million infections worldwide. ESBL and MBL beta-lactamases (blaOXA, blaNDM1), heterogeneous acetyl/phospho/adenyl-transferases (catB3, aacC1, strA/B, aphA4, ANT) and drug efflux proteins (MFS/RND/ABC) are very much abundant in plasmids and chromosomes of most Enterobacteriaceae infections. This has happened due to three main reasons: First, *mdr* genes are assembled into large conjugative plasmids allowing to transfer of *mdr* genes into household bacteria by conjugation and secondly, drug industries are reluctant to invest in new drug discovery due to drug void following astonishingly fast *mdr* gene creation like blaNDM-1 and Mcr-1, inactivating carbapenems and colistin drugs that used against superbug infections; lastly, a symbiotic relation has generated signals across the bio-film for quick generation of new *mdr* gene against the any new oral drug consumed repeatedly. We believe abuse of multi-doses antibiotic intake without vitamins and probiotics may cause many disorders like gastrointestinal disturbances, diabetes, neurological disorders and cancer, due to death of bio-film making gut bacteria that synthesize 20 vitamins and complex bio-molecules involved in >30,000 enzymatic reactions, known as human metabolosome. Symbiotic relation is so important that 16S rRNA and 70S ribosomal proteins of bacteria are mutated as also gyrA/B and porins to withstand adverse effects of antibiotics. Many drug binding proteins have also increase the drug MIC like TetM and PenA. Due to high cost of new antibiotics, gene medicines and cancer drugs, >100,000 household are plunged into poverty line each year due to inadequate medical insurance coverage in most Asian, African and Latin American countries. As population was reached 7000 million, we need social reforms and united research agenda to lower the cost of drug. Heterogeneous phyto-antibiotics will solve the problem based on ancient Hindu and Chinese civilization but land reform is must to get enough cultivation of medicinal plants.

Keywords: MDR genes; Antibiotic void; New antibiotics; Social reform; High cost; Toxic chemicals

Introduction

Spread of Multi Drug Resistance (MDR) genes into conjugative large plasmids as well as chromosome of the household gastrointestinal bacteria and acute pathogens send us alarm, causing a dead era of antibiotics [1-3]. Infections caused by MDR *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, *Bacillus anthrus*, *Mycobacterium tuberculosis* and *Niserria gonorrhoeae* are resistant to well-known antibiotics like ampicillin, amoxicillin-cavulinate, tetracycline, ciprofloxacin, azithromycin, gentamycin, sulfamethaxozole, trimethoprim, chloramphenicol, colistin, vancomycin, cefotaxime and imipenem [4-6]. Essentially, drug industries are in fear for their capital in the share markets as investors now knew about drug failures and patient's deaths due to toxicities of complex antibiotics. In recent estimates, the worldwide isolates of *Staphylococcus aureus* skin infections are highly resistant (40-60%) to oxacillin, ciprofloxacin, azithromycin but pretty sensitive to high cost drugs like linezolid, meropenem and vancomycin etc. However, *Enterobacter sp* and high amount of *Escherichia coli* are vancomycin resistant and *Mycobacterium bacilli* are now rifampicin resistant. East and South East of USA are great hit of XDR *S. aureus* outbreaks. In India >58,000 neonatal deaths due to multi-resistant infections have claimed in 2016. Sadly such infections have no barrier for developed nations as estimated death in Europe and America due to multi-resistance have estimated as >33,000 and >26,000. Worldwide MDR-TB death in 2016 was reported as 240,000. Which was astonishingly high [7]. We see, FDA has approved few new antibiotics (Delafloxacin, Zoliflodacin, Secnidazole, and Dalbavancin) between 2013-2017 which are just derivatives and will be inactivated by blaKPC-2, blaNDM-5, blaOXA58, AAC6'-1b-cr, aphA4 as well as *gyrAB* mutations, *vanA gene cluster* activation and *norA*, *macAB* and *mexAB/CD/EF* drug efflux genes over expression [8,9]. In 2008-2012 the scenario was very similar as new drug, Bedaquiline targeting ATP Synthase of *Mycobacterium tuberculosis* may be considered as only new antibiotic and other approved antibiotics in this period like Ceftaroline (cefalosporins, 2010), Gatifloxacin (fluoroquinolone, 2010), Televacin (lipoglycopeptides, 2009) could be inactivated by existing ESBL β-lactamases, 16S rRNA mutations or drug extrusion principles by mexAB, acrAB and macAB proteins. Study indicated that 200-300 prescriptions for macrolides (azithromycin, clrithromycin), 100-150 for cefotaxime-ceftriaxone, 60-120 for quinilones, 50-100 for tetracyclins and trimethoprim, 10-20 for ampicillin-amoxicillin whereas <1 prescription for carbapenems, glycylcyclines, chloramphenicols and polymyxins per 1000 populations in the United States of America [10-12]. In India the prescription of antibiotics are overwhelming even the fever is viral infection and gastrointestinal pain. In this mini-review I have addressed the sad social structure where microbes are smarter than us to overcome the toxic effects of thousand diversified antibiotics. This review is important as United Nations has predicted a calamity of manpower and wealth with 3% GDP loss as we approach 2030-2050 [13,14]

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Materials and Methods

Water from Ganga River was collected in the morning from Babu Ghat (Kolkata 700001) and Howrah Station area. About 100µl of water was spread onto 1.5% Luria Bartoni-agar plate containing different antibiotics at 5-50µg/ml [15]. MDR bacteria were selected in agar-plate containing ampicillin+ streptomycin+ chloramphenicol+ tetracycline or ciprofloxacin at 50, 50, 34, 20 µg/ml respectively. Antibiotics susceptibility test was conducted for determine the sensitivity of the A. *baumannii* to clinical common used antibiotics by Kirby-Bauer method. The results were determined by criteria from Clinical and Laboratory Standards Institute (CLSI). Plasmid DNA was isolated by Alkaline Lysis Method [16]. PCR amplification Amplification of mdr genes, were performed by PCR. The PCR reactions were initially denatured at 94°C for 5min, followed by 30 cycles of denaturation at 94°C for 45 s, and annealing at 52°C for 45s, with a final extension at 72°C for 7 min. The PCR products were separated by 1% agarose gel electrophoresis and visualized using ethidium bromide staining and UV light illumination [17]. DNA sequencing was performed by SciGenom Limited, Kerala, India [18]. Multalin protein sequence software was used to get the nature of conserved sequences among β-lactamases [19]. Sometime, diverged sequences are manually cut and paste into align position in MS word so that it is appeared both sequences have similarity. For retrieving any nucleotide, we type the same at the NCBI port (www.ncbi.nlm.nih.gov/nucleotide or Protein) and to BLAST search to type the accession number for protein or DNA into BLAST port [20]. Primers are presented in Table 1. PubMed search was performed for data analysis.

Result and Discussion

We have faced tremendous problem when we have wanted to genetic analyze of the *mdr* genes in multi-drug resistant bacteria isolated from Kolkata Ganga River water [16]. The diversities among the any class β-lactamases are so high (*blaTEM, blaCTX-M, blaOXA, blaCMY*) that 100 primers are necessary to locate the diversified *bla mdr* genes and almost 1000 primers for all mdr genes (*bla, aac, aad, aph, sul1, aar, mex, acr, ade* etc.) known today [21,22]. However, such work is practically impossible and all papers have published up till now on mdr genes are partial data and nature of the spread of hundred *mdr* genes on household pathogens has not been addressed for any MDR bacteria As multiple *mdr* genes are assembled in single plasmids and such "MDR islands" have moved into bacterial chromosomes, we checked many antibiotics on the isolated MDR bacteria and most penicillin and cephalosporins to some extent were no inhibitory at their 10xMIC [16-22]. Thus, inhibition of class A/D/C β-lactamases is an area of intense research [23,24]. With extensive sequence and structural variability among the β-lactamases, common drug discovery has been challenged. This is necessary as gradual discoveries of new penicillin derivatives like ampicillin, oxacillin, cefotaxime, imipenem has challenged by multidrug-resistant bacteria synthesizing new betalactamases like blaNDM-1 (for common drug structures see Figure 1). The first set (methylidene penems, penicillin sulfones) is derived from β-lactams, and the second (avibactam, phosphonates, boronic acids) are non-β-lactams [25]. From the structural diversities 9 (Figure 1) it is evident that there are too many *mdr* genes needed to inactivate them in vivo. In 1965, we got *amp* and *tet mdr* genes from the sequence data of plasmid pBR322 coding for penicillinase enzyme to inactivate benzyl penicillin and TET drug efflux protein to inactivate tetracycline [2]. Then we got *cat* gene and related aacC1 and aacA1 homologues to inactivate chloramphenicol and aminiglycosides and *strA/B* genes to inactivate streptomycin by phosphorylation [5,22]. *Sul1/2/3* genes gave resistant to sulfa-drugs and neo gene to kanamycin whereas *dhfr* gene promotes resistant to trimethoprim. After Tet drug efflux mechanism known, major breakthrough in the mechanism of multi-resistance disclosed in *Escherichia coli* acrA/B-TolC and *Pseudomonas aeruginosa* mexAB/CD/EF-OprM tripartite drug efflux genes giving acute resistant to acriflavin, ethidium bromide, azithromycin, imipenem and ciprofloxacin due to their capacity to kick out drug from bacterial cytoplasm by proton-mediated drug efflux [26]. In Figure 2 we presented few important *mdr* genes illustrating the impact of such deadly genes in multi-resistance and drug void. However, most horror anticipated when in 2009 blaNDM1 and in 2016 *mcr-1* genes were found in R as well as defective conjugative plasmids jeoparding the use of meropenem and colistin against multi-resistance. The gradual increase of plasmid size and wide spread integration into chromosome is so instrumental that any scientist is working in that field feel sick to write a review. Due to advancement of WGS technology, vast number of large plasmids and chromosomes has been available in the Gen Bank. *Acinetobacter sp. plasmid* (pNDM1-010045; accession no. CP028560, 190kb) has blaNDM1 (protein id. AVZ84373), sul2 (protein id. ANZ84383), aac3'-I (protein id. AVZ84355), *mph2'* (protein id. AVZ84457) and blaOXA-58 (protein id. AVZ84486) giving resistant to imipenem, cefotaxime, sulfamethoxazole, streptomycin and

Primers in Study			
Name	**Sequence of the primers**	**Tm**	**Size**
P27F	5'-AGA GTT TGA TCC GAA CGC T-3'	62°C	1.4kb
P1392R	5'-TAC GGC TAC CTT GTT ACG ACT TCA-3'	65°C	
cmrF	5'-TTC GTT AGT CTG CCG TTG CT-3'	56°C	323bp
cmrR	5'-ATC GCT GGC AAA CAG GGT TA-3'	57°C	
tem-sF1U	5'-ATGATGAGCACYTTTAAAGT-3' Y=C/T	56°C	312bp
tem-sR1U	5'-TCATTCAGYTCCGKTTCCCA-3'Y=C/T; K=G/T	58°C	
tetF	5'-CTT CGC TAC TTG GAG CCA CT-3'	57°C	910bp
tetR	5'-GCA GAC AAG GTA TAG GGC GG-3'	57°C	
OXA-1F	5'-CGCAAATGGCACCAGATTCA-3'	59°C	560bp
OXA-1R	5'-TCCTGTAAGTGCGGACACAA-3'	59°C	
OXA-2F	5'-CTACTCGCCTGCATCGACAT-3'	60°C	501bp
OXA-2R	5'-GCGAAGAATACGGAGCCAGT-3'	60°C	
OXA-48F	5'-TTATCGGAATGCCTGCGGTA-3'	57°C	627bp
OXA-48R	5'-CGACCCACCAGCCAATCTT-3	60°C	
acrAB-F	5'-ATG CTC TCA GGC AGC TTA GCC-3'	59°C	1kb
acrAB-R	5'-TGT CAC CAG CCA CTT ATC GCC-3'	59°C	

Table 1: Primers are presented in Study.

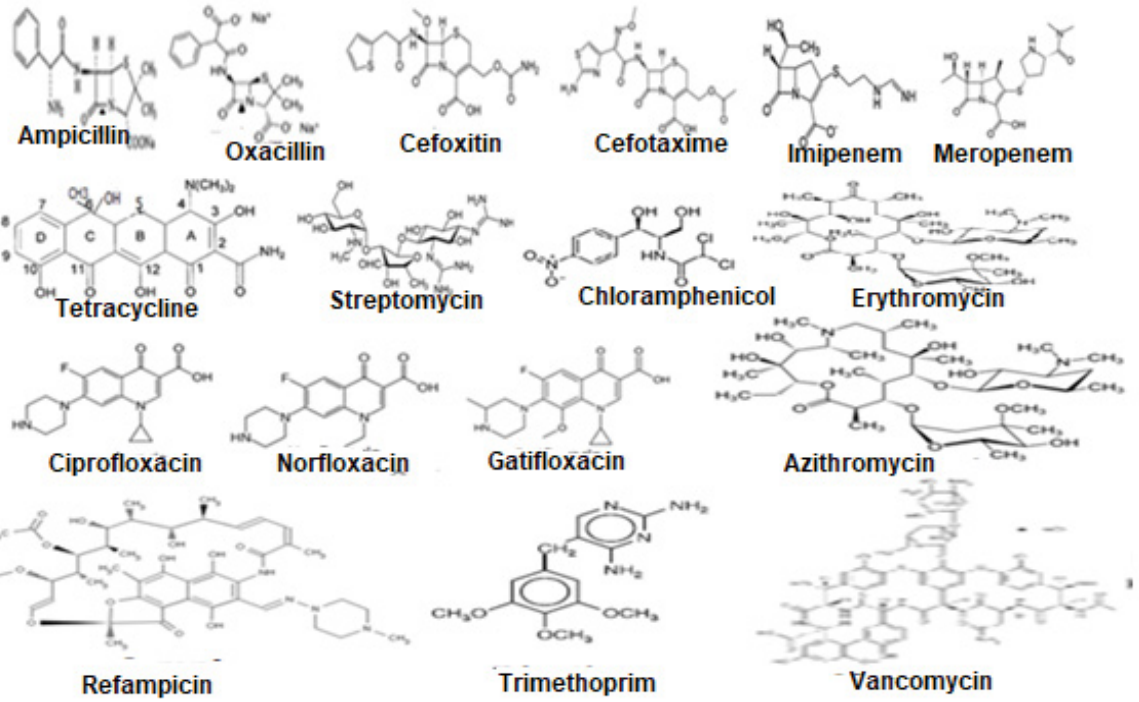

Figure 1: Structures of antibiotics that are useless now but widely used between 1940-1990 to cure bacterial infections.

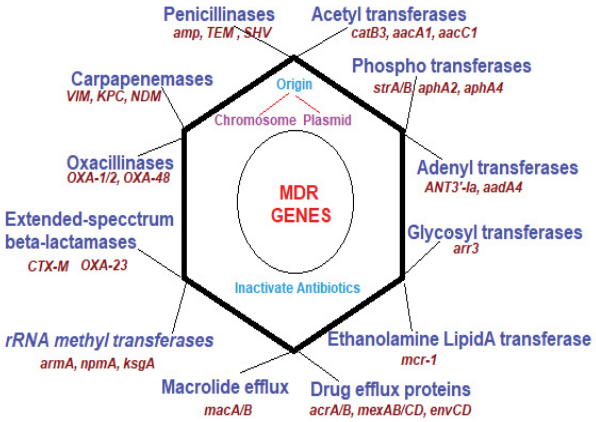

Figure 2: Different MDR genes that accumulated in plasmids and chromosome to inactivate antibiotics giving multi-resistance.

azithromycin (Hu et al., 2018). Similarly, *K. pneumoniae* plasmid pPMK1-NDM has three blaNDM1 genes at nt. 47947, 56535 and 65123 including blaOXA1 and blaCTX-M beta-lactamse isomers giving complete resistance to penicillin, cephalosporins and carbapenems. Such plasmid also has multiple *mdr* genes like catB3, aac6'-Ia and ANT but no acrA, mexAB/CD and macA/B drug trasporters. *Vibrio cholerae* strain 2012EL-2176 harbouring IncA/C2 plasmid containing *bla*CMY-2, *bla*CTX-M-2, *blaTEM-1, floR, aac(3)-IIa, strA/B, sul1/2, dfrA1, dfrA27, tetA, mphA, mdr*-genes and also resistant to ciprofloxacin due to mutation in *gyrA*(S83I)/*parC*(S85L). E. coli plasmid pWJ1 has numerous *mdr* genes like *aac6'-1b-cr, blaOXA1, cat, arr3 sul1, aph6'-1d, aph3'-IV, sul2, aad3"-Ia, aad3"-Ia* including drug transporters TetC, EamA and CmlA1. *Acinetobacter baumannii* plasmid (accession no. KU549175) has Zeta-toxin, Hemolysin but also drug phosphotransferase *mdr* gene, few metal resistant genes (*copA, cusA*). Similarly, *Bacillus anthrus* plasmid pX01 (accession no. CM002399) has toxin gene (protein id. AFL55645) and also in pBMB293 plasmid. *Mcr-1* gene gives colistin resistant as seen in *Escherichia coli* plasmids, pWJ1, pLV23529-MCR-3 and pKP37-BE (accession nos. KY924928, LT598652, KY964067). *Bacillus thuringiensis* plasmid pBMB293 (Accession no. CP007615) has no *mdr* gene but genes for enterotoxins (protein id. AIM34697) dipterans toxin (protein id. AIM34741) and proteins for new *mdr* gene creation like reverse transcriptase DNA polymerase β, DNA topoisomerase III and type II secretion system. Such plasmids also contribute in association of MDR plasmid in any bacteria, and without toxins and signalling growth regulatory genes, many *mdr* genes are likely harmless. Rats were injected with MDR bacteria stay good for at least 3 months. Genomic content of *mdr* genes also has astonishingly increased. *Klebsiella pneumoniae* strain NR5632 (accession no. CP025143) has MDR island between nt. 125952- nt. 158826 containing *mdr* genes like *blaCTX-M-15, dhfr, AAC3'-IIa, AAC6'-1b-cr, and blaOXA-1* followed by many drug efflux proteins like TetA, EamA, QnrB1, AcrAB, *mdt*D, and MATE. It has also tunicamycin resistant protein (protein id. AUD31966) and penicillin binding protein C (protein id. AUD33159) as well as enterohemolysin toxin protein (protein id. AUD33054). The transcriptional repressor and activators are predominant in many plasmids. As for example, TetR, ArsR, AraC, LysR, LacI, MurR, DeoR and ExuR have shown to regulate *mdr* genes. Similarly, *mdr* genes like *amp, tetC, strAB, catB3, accC1/A1, aphA4, mcr-1, arr, sul1, dhfr, acrAB, mexAB/EF, tetM, penA* are sequenced in many chromosomes of S. *aureus, E. coli, P. aeruginosa, K. pneumoniae, M. tuberculosis, N. gonorrhoeae, S. enterica, P. mirabilis and A. baumannii* (accession nos. CP024576, CP025266, CP020597 and CP018421). Astonishing increase of air particulate matters (PM1, PM2.5 and PM10; normal 50, 50, 100 μg/cubic metre respectively) concentrations in major cities of the world like New Delhi, Mumbai, New York, Riyadh, Xingtai, Zabol, Bamenda etc have tremendous

calamity to promote MDR bacteria contamination worldwide [27]. Recently, New Delhi PM10 was increased to >500 µg/cubic metre (PM2.5 index was 150-250 and it has increased to 362 in Kolkata on December 18, 2017 issuing "stay indoor" by WHO) and MDR infections were increased in those cities of India including Mumbai, Kanpur, Noida, Amritsar, Durgapur, Lucknow, and Kolkata assessed on 12th January, 2018). Such air particulate travel carrying MDR bacterial spores and may contaminate any place during rain. According to the 2016 EPI, more than 3.5 billion people – half of the world's population – are exposed to unsafe air quality which also includes 75% of India's population. When we detected the MDR bacteria in rain water, then obviously above discussion is important to authenticate that MDR infection will be maximum in India. Thus we see that 95% clinical bacteria are drug resistant and critical messages have generated between bacteria and intestinal cells to make more *mdr* genes in plasmids as well as *mdr* genes have moved into bacterial chromosome including many integrons, transposons and IS-elements. Such hypothesis got momentum from US Human Microbiome Project (HMP) and European Metagenomics of the Human Intestinal Tract (MetaHIT) where 300 *mdr* genes have been detected in normal human subjects [28-30]. We described in early reviews that 500-100 mutated isomers among each *blaTEM, blaCTX-M, blaOXA, MEX* and *AAC* genes [5,21,22]. One set primers will give no conclusive status of mdr gene. It is almost impossible to demonstrate the spread of 10-15 *mdr* genes by 100 PCR primers and thousands PCR reactions requiring costly dXTP and Taq DNA polymerase followed by costly DNA sequencing. Poor countries from Latin America, Africa and Asia will never be able to guide us how seriously hereditary DNA have changed in microbes due to insult of gut microbiota using antibiotics as well as urban pollution of river water from sewage of household as well as industries and agricultural land. The cost of new drugs are so high, every year 100 million people are plunged into poverty line losing house, land and gold jewellery. As the new drug is only work well for few months to get drug resistance, no drug company agrees to invest highly in antibiotic discovery. On the other hand, anti-cancer drugs, anti-diabetic drugs, anti-hypertensive drugs research have showed promise these days (Figure 3). Carbapepem drugs are now widely used to clear ESBL infections but VIM, KPC, GIS, and lastly NDM strains are increasing in clinical as well as environmental isolates [31-33]. Thus increased carbapenemase activities in recent isolates might be co-related to the huge increase in use carbapenem drugs in recent years and its molecular mechanisms remain elusive [34]. We conclude that symbiotic relation in the intestine for vitamin synthesis and high dose drug exposure creates superbugs that are almost untreatable and has created horror worldwide [35]. Now we use 200000 tons of antibiotics per year to remove infections and antibiotics void may cause tremendous calamity in coming decades with 2-4% reduced world GDP, a statement recently given by DGs of UN and WHO. Such hypothesis might be true as we drastically killed the gut microbiome with oral antibiotics and gut bacteria produce vitamins and nutrients for human metabolosome with 30,000 enzymatic reactions. Perhaps sequencing of millions of diverged *mdr* genes (*bla, tet, mex, aac, aph, mcr-1, sul1/2, dhfr, neo*) and target genes (*gyrAB, parC, penA, rpsL, rRNA*) in bacterial large MDR conjugative plasmids (100-500kb) and MDR chromosome (4000-5000kb) as well as isolation of 300 *mdr* genes in the Human Microbiome Project registered the calamity of 21st century science and civilization. In other words, *mdr* genes creation is to protect human and animal from extinct [32]. Hypothesis is unless toxin and virulence genes activated, *mdr* genes in bacteria are likely non-toxic to health. But such infections in the blood (sepsis) may cause death as first line drugs are unable to stop growth of bacteria that savage important nutrients and cause inflammation, convulsion and coma

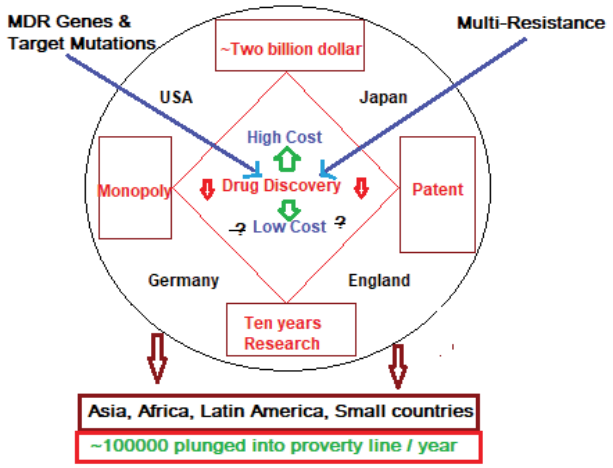

Figure 3: Higher cost and antibiotic void reduced new drug discovery but high cost of drugs increase poverty in poor nations.

[36]. How we can developed new technology to overcome deadly antibiotic void as we all like to get clear infections since 1940s by consuming antibiotics? I think most people are poor and cannot support the 100-1000 dollar antibiotics per dose as in cancer immune drug and anti-retroviral di-deoxy nucleotide analogues [37,38]. Only one direction is left to believe in ancient Hindu and Chinese civilization based on herbal medicine. Many modern widely used drugs targeted against cancer, malaria and fever like aspirin, vincristine, taxol, quinine, topotecan, epitope and artimisinin are of plant derived [39,40]. I strictly believe on Ayurvedic remedy as depicted in India's Sanskrit books like Charaka Samhita, Atharva Veda and China's book like Pen T'Sao. Similarly, The Iliad and The Odysseys of Greek and Talmud Hebrew Bible (200CE-500CE) and Holy Bible (1300BC) of Christian dogna have similar protocols for ayurvedic medicine. In the middle age, Simplicum Alimentorum Et Medicamentorum by Ibn baiter (1197) or in very recent Bengali books Chiranchib Banoushadhi (1976) by Shibkali Bhattacharcha (Ananda Press, Kolkata) are great in popularizing Ayurvedic concept. In my limit, Labanga and Derchini extracts are great to inhibit multidrug resistant infections [4]. Further, root and bark extract of *Suregada multiflora*, *Cassia fistula* and root of *Jatropha gossypiifolia* (it is very smaller tree than *Jatropha curcas*, oil tree) have great potential for new drug discovery against multidrug-resistant bacteria [5]. Cinnamon (*Cinnamomum zeylanicum*) and Aloe (*Aquilaria malaccensis*) were described in Bible (Proverbs 7:17) and castor oil (*Ricinus communis* L.) in chapter Jonah 4 and garlic (*Allium sativum*) in chapter Numbers 11:5. The above discussion is to imply our notion on forgotten old tradition to cure the diseases using herbal drugs as described in ancient Sanskrit books. As that time there is no concept of microorganism (µm bacteria as seen through microscope only after Anton von Leeuwenhoek discovered microscope in 1670s). Few decades we saw a madness of making most plant extracts to see antibacterial activities [41-44]. Interestingly an improved MDR-Cure organic phyto-extracts (*Cassia fistula, Suregada multiflora, Syzygium aromaticum, Cinnamomum zeynalicum,* etc) inhibits Kolkata superbugs and gives a hope for new drug development [16,17]. Many technologies like enzybiotics, phage therapy and gene medicines are under development other than herbal therapy as shown in Figure 4 [45-48]. Some important enzybiotics are Lysins, Autolysins and Lysozymes and are very good in combating MDR infections. However, multisteps dissemination and recombination among the interspecies Enterobacteriaceae populations will be threat due to increasing power

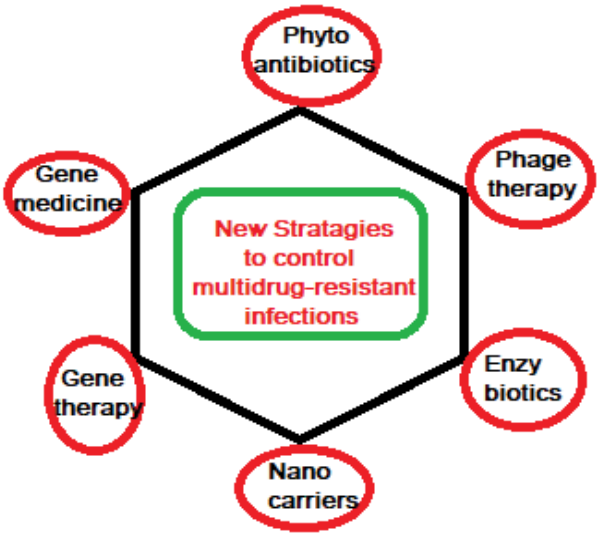

Figure 4: New directions to control superbugs, otherwise between 2030-2050 3% GDP loss worldwide.

of multi-resistance [9,49]. Virtual screening of small combinatorial libraries of peptides and organic molecules still remais main stream drug discovery programmes in the pharmaceutical industries as well academic research institutions as depicted in the Pubmed search [50-55]. But such complex chemicals are toxic and hard to deliver at the target organs due to insolubility. Nonotechnology like fullerenes,DNA and liposomes are great in delivering complex antibiotics as 10-100 nm nanocubes [56]. Metal nano-particles alone or in combination with bioactive plant extracts or antibiotic compounds have represented promising candidates in the drug delivery applications because of their dimensions, bio-applicability, biocompatibility and controlled drug release [57]. Most importantly such applications are cost effective and environmental compatible [58].

Conclusion

Civilization has created a tension among poor countrymen verses dominated rich countrymen for proper utility, education, health and social status. Scientific endeavor is great but mega industries are polluting the water resources creating huge genetic mutants among the microbes whose genomes as well as plasmids have been sequenced considerably. Best example is a Multidrug-resistant bacterium that has spread everywhere. Unresponsiveness to drugs has increased from bacteria to fungi, parasites and cancer cells. In my opinion, we generated excessive chemical contamination in air and water which are interchangeable in contact spreading mutation and rearrangement among the bacteria, fungi andparasites. Question remains how excessive pressure and toxicities have created genetic changes in human leading to widespread headache, obesity, diabetes, mental disorder and anxiety following weak immune system and infections spread. Rapid increase of hormones, heavy metals and pesticides contamination in foods and too much antibiotics, psychoactive drugs and steroids use are likely caused different types of cancer irrespective of age, sex and locality. Now we use 200000 tons of antibiotics per year to remove infections and antibiotics void may cause tremendous calamity in coming decades with 2-4% reduced world GDP, a statement recently given by DGs of UN and WHO. Such hypothesis might be true as we drastically killed the gut microbiome with oral antibiotics and gut bacteria produce vitamins and nutrients for human metabolosome with 30,000 enzymatic reactions. Perhaps sequencing of millions of diverged *mdr* genes (*bla, tet, mex, aac, aph, mcr-1, sul1/2, dhfr, neo*) and target genes (*gyrAB, parC, penA, rpsL, rRNA*) in bacterial large MDR conjugative plasmids (100-500kb) and MDR chromosome (4000-5000kb) as well as isolation of 300 *mdr* genes in the Human Microbiome Project registered the calamity of 21st century science and civilization. In other words, *mdr* genes creation is to protect human and animal from extinct. Hypothesis is unless toxin and virulence genes activated, *mdr* genes in bacteria are likely non-toxic to health. But such infections in the blood (sepsis) may cause death as first line drugs are unable to stop growth of bacteria that savage important nutrients and cause inflammation, convulsion and coma. In my opinion, due to lobby of drug industries and also lack of other alternative, we still use antibiotics. I and my neighbour have just used amoxicillin + cavulinate for cough and cold. I think that it may not be needed if we would wait for one week to get body's immune resistance against cold viruses. The only way to curb the current crisis of antimicrobial resistance will be to develop entirely novel strategies to fight these pathogens such as combining antimicrobial drugs with other agents that counteract and obstruct the antibiotic resistant mechanisms expressed by the pathogen. The United States is in the midst of a devastating opioid misuse epidemic leading to over 33,000 deaths per year from both prescription and illegal opioid.. Combinatorial chemistry, ultrahigh-throughput screening, next-generation sequencing, and genome mining to characterize novel antibiotic biosynthetic gene clusters may open unique opportunities for new antibiotic discovery against superbugs. But hidden toxicities are concern to human health. Indian NAP-AMR (The National Action Plan on Antimicrobial Resistance-2017-2021) has pinpointed five main areas to curve superbug horror: (i) improving awareness and understanding of AMR through effective education and surveillance, (ii) reducing infection by increasing preventive measures (iv) reducing the use of antimicrobials in health, food animals and agriculture (v) promoting for AMR research and drug innovations and (v) strengthening India's leadership on AMR and International collaboration. It is true Indian scientists and professors and engineers are not doing what they should do and anyway bye-selling is a good business. Politicians like to buy for countrymen as they get hidden royalties! If India has to grow, stop politics for ten years and the colleges, universities and research institutions must run by Indian Army or saints like Ramakrishna Mission. The debate remains but any day we may lose our democracy to USA or China dividing country again. The scenario is same in most small countries and underworld rackets are becoming powerful. Total human race is in danger as environment has crisis. Save plants and use as medicine. I hope human genome project should release data to demonstrate the new genes acquisition in 23 pair's human chromosomes. We search good castes to marry and cheap genetic counseling will be the basis of future marriage and job hunting. Such technology needs money and thus rich country will dominate the world creating superman but smarter country may not be behind. Sadly, FDA has approved very few drugs against MDR infections creating panic in the society as MDR bacterial spores are everywhere in water, air and belongings of the hospital and household.

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