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Control and Treatment of Superbug: A Review

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ABSTRACT

Superbugs are used to act against the resistance of multiple drugs. Around the world, there is an increase in several death of people because several microorganisms cannot be treated with an available antibiotic. Hospitals are the source of most serious infections like MRSA and VRS which have been gotten a start. Superbug infection increasingly affected the human community for the inappropriate use of antibiotics. To overcome this problem one type of way is repurposing the use of drugs. This method is less harmful and can't need to wait a long time for coming new drugs to treat these microorganisms. If the control and treatment of superbug scant be done, we face the risk of conducting surgery, because patients have a high chance to infect by superbugs. Repurposing is a cost-effective method. Here we found superbugs like *S. aureus*, *Pseudomonas aeruginosa*is treated by a non-antimicrobial agent such as Simvastatin, metformin, Flucytosine, Celecoxib.

INTRODUCTION:

In the 21st century, the occurrence of antibiotic resistance becomes global due to the inappropriate use of antibiotics. Microorganisms within the body develop their defence mechanism against the antibiotic. This further leads to a rise in mortality. Antibiotics are generally used to kill the pathogen but in recent times misuses associated with it may be found [1, 2].Antibiotic resistance may be found a great threat to the public health system [3]. Waksman and Woodruff formerly defined an Antibiotic as a clinical substance produced by a microorganism and may eventually destroy them [4]. Antibiotics used in recent times for normal fever or coughing in many cases. In recent times patient demographics indicate that antibiotic resistance is a very dangerous problem to treat multi-drug resistance bacteria which are generally called superbug and this inhibits the patient's quick recovery. Antibiotics are not only used for therapeutic purposes but also use in agriculture and animal husbandry.

Resistance is such type of clinical phenomenon where previously effective antibiotic shows no possible effect at the time because in the human body the target pathogen has developed a defence against this antibiotic [6]. Superbugs are the microorganisms such as bacteria that improve their defence mechanism against the commonly used antibiotic [7].

The resistance of antibiotics must be natural or acquired. An example of natural resistance in gram-negative bacteria is -"unaffected by penicillin" and for gram-positive bacteria- "unaffected by streptomycin". The development of resistance may be by mutation or by gene transfer [8].

Factors contributing to antibiotic misuse are (A) For health professionals–(1)Inadequate diagnosis (2) Incorrect drug selection (3) Unsuitable use of a broad-spectrum antibiotic (4)) An inappropriate dose of antibiotics. (B) For patients – (1) Self-medication (II) Poor adherence (III)Incomplete course of the prescribed drug.(IV) Skipping a dose of antibiotic (V) Not taking antibiotics at regular intervals [9].

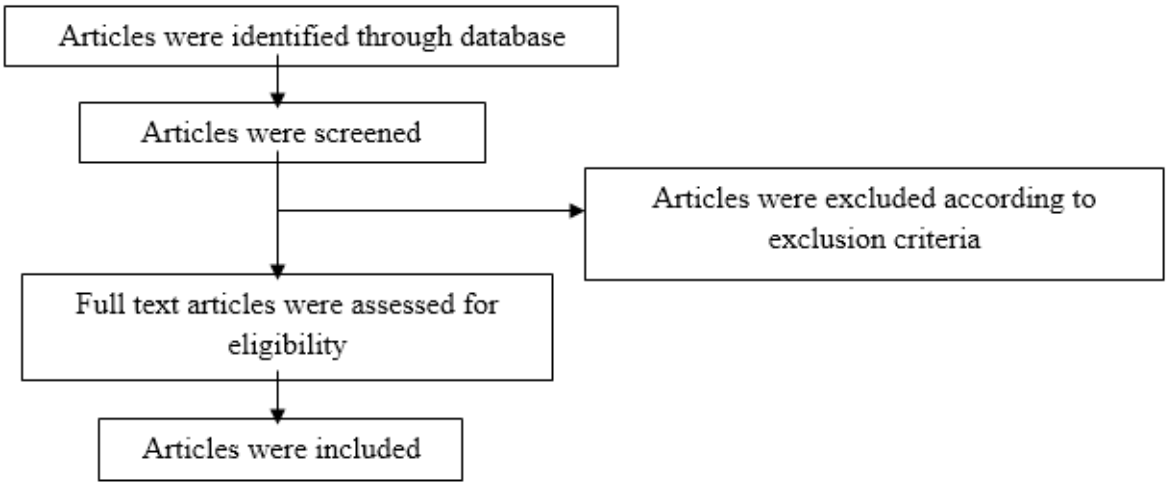
If this problem is skipped, in the future recovery from disease become tough and we also face a problem for surgical purpose, which is the greatest threat in the public health system.

Repurposing is an effective method to reduce time, cost, the risk associated with traditional antibiotic innovation. Discovering a new drug molecule which adverse effects are with unpredictable adverse effect become easy and time-effective. Repurposing the use of the conventional drug also overcome cross-resistance. So non-antimicrobial agents such as

Simvastatin, metformin, Flucytosine, Celecoxib are used to treat multidrug-resistant bacteria such as superbugs like *S. aureus*, *Pseudomonas aeruginosa*. The adverse effects of these drugs are known to a health professional and it also cost-effective [10].The Aim and objective of this study are to find that which non-antimicrobial drug recently used to treat the superbug infected disease and overcome the antibiotic resistance.

METHODOLOGY

To complete this article and gaining knowledge, searching is done in Science direct, Pubmed database and PMC database, and also WHO database.



The research papers were published in the English language.

Inclusion Criteria and Exclusion criteria:

Inclusion criteria may be defined as those characteristics, the prospective subjects must have these if they are to be included in the study. Exclusion criteria are those characteristics that disqualify prospective subjects from including the subjects in the study. The drugs must be used as non-antimicrobial agents conventionally. No other conventional antibiotic was excluded from this study. Only synthetic drugs were included in this study. Review articles, notes were excluded from this study.

Table No. 1: the conventional use and repurposing use of the non-antimicrobial drug

Name of Drug	The conventional use of Drug	Repurposing use of Drug	Reference
Simvastatin	Anti hyperlipidaemic drug	Topical antibacterial Agents act against *Staphylococcus aureus* that helps in the treatmentof skin infections and diseases.	[10]
Metformin	Anti Diabetic Drug	Quorum sensing inhibitor in *Pseudomonas aeruginosa*	[11]
Flucytosine	Anti mycotic Drug	Suppression of *Pseudomonas aeruginosa* pathogenicity	[12]
Celecoxib	Anti-inflammatory drug	Topical antibacterial agent.	[13]
Auranofin	Antirheumatic drug	Antibacterial activity against *Staphylococcus aureus*	[14]
Niclosamide	Anthelminthic agent	Use against *Helicobacter pylori and also used as a* negative surface charge on *A. baumannii* and *K. pneumonia*	[15-16]
Ganite	Hypocalcaemia and Hypocalcaemia for malignancy	Gallium nitrate disrupted *Acinetobacter baumanni* biofilm formation.	[16]

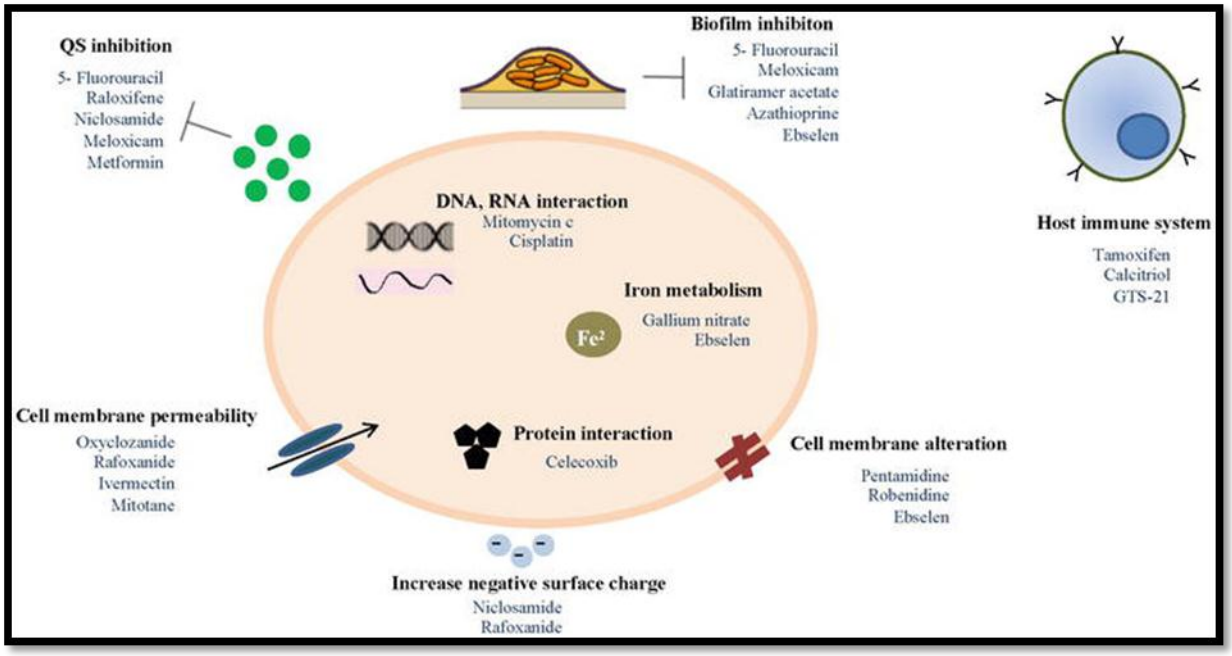


Figure No. 1: Mechanism of action of repurposing use of the non-anti-microbial agent

1.Simvastatin

Simvastatin, an antihyperlipidemic drug, and potential topical antibacterial agent. The broad-spectrum antibacterial activity of simvastatin against significant gram-positive including MRSA and gram-negative pathogens. The biosynthetic pathways of bacteria and the cellular process (selective interference of bacterial protein synthesis) inhibited by simvastatin. The selective interference of bacterial protein synthesis reduces the cure of infected skin wounds [10].

2.Metformin

Repurposing of metformin as quorum sensing inhibitor of *Pseudomonas aeruginosa* showed the effect on the cell wall of the bacteria. Metformin significantly reduced the production of violacein pigment. It inhibits the quorum sensitizing which regulates the virulence of bacteria [11].

3.Flucytosine

Repurposing the antimycotic drug flucytosine used for suppression of *Pseudomonas aeruginosa* pathogenicity. The antimycotic agent flucytosine inhibits the expression of iron–starvation sigma factor PvdS, thereby repressing the production of major *Pseudomonas aeruginosa* virulence factors, namely exotoxin A, pyoverdine, Prp Lprotease[12].

4.Celecoxib

Repurposing celecoxib as a topical antibacterial agent reported in several studies including the primary antimicrobial mechanism of action of celecoxib was the dose-dependent inhibition of RNA, DNA, and protein synthesis [13].

5.Auranofin

Repurposing auranofin for the treatment of cutaneous staphylococcal infection is included in several studies. Auranofin is generally used as an anti rheumatoid drug, but recently this is used as an antibacterial agent. It acts against S. aureus. It is an oral gold-containing chemical salt. This molecule helps to down regulate protein synthesis. Treatment of auranofin by topical route mayreduce the production of inflammatory cytokines like Tumour necrosis factor-α (TNFα), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) to a great extent in infected skin lesions [14]. The mode of action of auranofin against S. Aureus has been decoded by using the macromolecular biosynthesis assay which evidenced that auranofin acts by inhibiting the DNA replication and protein synthesis, downregulating the toxin production (In vivo).

6.Niclosamide

Repurposing of the anthelminthic drug niclosamide used to combat *Helicobacter pylori*in a dose of 0.25 µg /ml. Helicobacter pylorus is a Gram-negative, helically shaped enterococci that are present in the gastrointestinal and cause high immune- compromisation and leads to form high rates of infection. In the present time, it cannot treat by vancomycin because it resists this drug. A dose of 1-8 µg/mL Niclosamide can cross the GI tract & inhibit the growth of the multiple numbers of the Enterococcus faecium [15]. Increase of the negative surface charge of *A. baumannii* and *K. Pneumonia*[16].

7.Ganite

Acinetobacter baumanni forms Biofilm in human serum .16 µM inhibits the growth of the *Acinetobacter baumanni* and reduces the biofilm formation. 64 µM granite disrupted A .baumannii biofilm in human serum [16].The ion gallium [Ga(III)], a ferric iron [Fe(III)] mimetic, has been shown to inhibit the growth of many bacterial species by interfering with iron-dependent metabolic pathways. Therefore, gallium drugs have gained a special interest

in the fight against MDR-GNB infections[16]. Gallium nitrate inhibits colistin or carbapenem-resistant bacteria [17].

SUMMARY

The primary advantage of drug repurposing is increasing the bioavailability and other safety profiles that have already been conducted and can skip preclinical research for toxicological studies that already are measured. This method helps to discover the new pathways of an old drug to inhibit or reduce the current disease. But in the case of minimal inhibitory concentration (MIC), the drug cannot work by this method. This review showed the non-antimicrobial agent used to control the superbug[18]. But the combination therapy of two or more drugs increases successful drug repurposing[19]. By producing a synergistic effect it helps to decrease the microbial function. The combination therapy may not only include the synthetic drug this also applicable for natural compounds such as eugenol present in much essential oil, combined with colistin kill the *E.coli*[20].

In the conclusion, this review has been shown the last line of antibiotic resistance against superbugs, repurposing, which is a safe process and less or no side effect with fulfilling the demand for antibiotics and treating the multiple drug-resistant bacteria. Repurposing use is also cost-effective. This process also shows that the medicinal values of conventional drugs or non-antimicrobial agents are higher and also fewer side effects. So, Celecoxib, Simvastatin, Flucytosine, Metformin are safely used as an antibiotic to overcome antibiotic resistance and control superbug. So, to decrease the high demand for antibiotic use, we can easily recover from antibiotic resistance in the future.

FUTURE ASPECTS

The non-antibiotic drugs that showed antimicrobial activity serve as an untapped reservoir for a new antibiotic that leads to the identification of new targets which will give guidance about the future development of improved antimicrobial agents. The scarcity of available options is particularly disadvantageous for the treatment of multi-drug resistant (MDR) bacterial infections. Nowadays, bacterial infections constitute a global threat due to a constant increase of resistance against antibiotics; in fact, recent projections indicate that no new development of antibacterial by the year 2050 will be the reason for 10 million deaths per year due to in tractable bacterial diseases[21].Some molecules that failed to reach approval due to low efficacy in clinical trials could be revived as antimicrobials drug repurposing will certainly

benefit from pre-clinical research to characterize the mechanisms of action in bacteria. Toremifene (in S. aureus), azacitidin (in S. pneumoniae), raloxifene inhibited pyocyanin production in P. Aeruginosa. Besides this, it shows a reduction of virulence in an in vivo model of Caenorhabditis elegans[22]. So, many anticancer drugs maybe use as antimicrobial agents in the future and overcome antibiotic resistance.

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