

Anti-Bacterial Perspective of Non-Antibiotic Drugs [†]

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Abstract: Its scope is to provide a state of the art in pharmacological repositioning, envisioning the antibacterial activity of non-antibiotic drugs. The method of narrative literature review was adopted. The investigation took place during the months of January and February 2022 in electronic databases such as Medline, PubMed, VHL, MDPI. Studies in Portuguese, English and Spanish were included. The results reveal that several classes of drugs have antibiotic activity both in vitro and in vivo, such as the antihypertensive drug amlodipine, psychomodulators such as fluoxetine and thioridazine and anti-inflammatory drugs such as ibuprofen. However, not everyone has an elucidated hypothesis of the reason for such an effect. Some of the mechanisms pointed out by the consulted authors were damage to the cell wall, modification of the permeability of porin proteins, inhibition of sliding hairpins that act with DNA polymerase. A synergistic effect was also identified. In conclusion, the antibacterial potential of pharmacological redirection is promising, with emphasis on anti-inflammatory, psychotropic and cardiovascular intervention drugs. There is a need to deepen investigations on the mechanisms of action of the compounds already investigated, suggesting that research of phases II and III be developed, as well as investigations of other pharmacological classes little explored.

Keywords: pharmacological repositioning; antibiotics; drug development

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1. Introduction

The increase in bacterial infections has characterized a growing problem worldwide, since most of these infections are caused by microorganisms resistant to standard antibiotic therapy. This fact is responsible for the difficulty in instituting an adequate drug therapy, resulting in high rates of morbidity, hospitalizations and mortality of these patients [1].

This scenario has had a significant impact on the economy, given the high costs required by hospital occupation and the loss of a population that could be economically active. In addition, the search for new antibiotics that can combat such bacteria, with high effectiveness and low toxicity to humans, is growing, costly, difficult and takes a long time. This reality does not match the need for global public health [2–4].

The application of alternative methodologies for the production of antibacterial therapies rises, especially when it envisages achieving this objective in a cost space of time and with lower financial costs. The repositioning of medicines, for example, gains more prominence each year. Presented as a faster way to achieve results with lower expenses,

when compared to the traditional way of obtaining new drugs, this method shows interesting results in different areas of health [5].

Pharmacological repositioning acquires a wide scope of investigations in microbiology. Thus, highlighting the problem of the increase in infections by resistant bacteria and the scarcity of effective therapies, this study proposes the contemplation of a state of the art on the repositioning of drugs in bacteriology. In this context, its scope is to carry out a narrative review of the scientific literature, providing a basis for future investigations.

2. Materials and Methods

2.1. Characterization of the Research

It is configured as a theoretical study with a qualitative approach, of the exploratory descriptive type. Narrative review was used as a method, to conceive a relevant appreciation of the theme.

Therefore, a broad analysis of the scientific bibliography was carried out with the purpose of collecting the main information, focusing on the published and outstanding novelties in the selected literature. To start the investigation, a guiding question was elaborated to conduct the entire research process, using the PICO (Population/Interest/Context) strategy.

2.2. Conducting the Investigation

Thus, the question of the study was presented: “what does the scientific literature (P) present about antibacterial activity (I) arising from pharmacological repositioning (Co)?” Then, the bibliographic search began, during January and February 2022, in the databases intended for indexing journals and scientific articles.

We used as descriptors and search terms “pharmacological repositioning”; “antibiotic activity”, combined using the Boolean operator AND. A time interval was not determined, however, recent studies were prioritized. The selected works explicitly portrayed in their abstract or title that the text relates to the potential and activities of repositioned drugs against bacterial strains, multidrug-resistant or not.

2.3. Selection Criteria

Works published in the form of scientific articles were prioritized, and the languages used for the search were Portuguese, English and Spanish. After inclusion, articles that did not present the results of the research in full, duplicated, or that the body of the text did not match or answer the guiding question of the investigation were excluded from the sample. Then, the full reading of the selected works was conducted, highlighting the contributions that were relevant for contemplating the scope of this investigation.

2.4. Exposition of Findings and Synthesis of Information

After the individual study of each work, the construction of the state of the art began, aiming to answer the guiding research question. There was no need to resort to judges to carry out a qualitative treatment of the extracted data, due to the type of methodology chosen, as well as submission to the research ethics committee was not necessary, since the samples were obtained from data already published and available.

3. Results and Discussion

The speed and cost of the pharmacological repositioning process makes it an attractive method for several investigations in the microbiological area. 29 studies were used for the preparation of this research. It was observed that several classes of drugs have both *in vitro* and *in vivo* antibiotic activity, however not all of them have an elucidated hypothesis of the reason for such an effect. In addition to the antimicrobial response of non-antibiotic drugs, researchers also present interesting results regarding the synergistic effect, when combined with some standard treatment in infectious combat [6–11].

The group of cardiovascular drugs has promising investigations regarding drug re-direction. The antihypertensive drug amlodipine, a calcium channel blocker, acts by inhibiting the entry of calcium ions into vascular and cardiac muscle cells through long-lasting L-type channels. It is suggested that this molecule has potential against the bacteria *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhimurium*, *Bacillus cereus*, *Acinetobacter baumannii*, in an in vivo method and in tests with mice, as well as its synergistic effect with Imipenem, Streptomycin, Levofloxacin [12–16].

Table 1. Minimum inhibitory concentration of amlodipine in strains identified in the scientific literature.

Bacterial Strains	Minimum Inhibitory Concentration ($\mu\text{g}/\text{mL}^{-1}$)
<i>Staphylococcus aureus</i>	64–256
<i>Acinetobacter baumannii</i>	64–256
<i>Escherichia coli</i>	128
<i>Klebsiella pneumoniae</i>	128
<i>Salmonella typhimurium</i>	64
<i>Bacillus cereus</i>	128

Own author, 2021.

In an investigation carried out by Coelho et al. [17] reported antibiotic activity in multidrug-resistant clinical isolates, with a minimum inhibitory concentration between 32 and 512 $\mu\text{g}/\text{mL}$. In this study, its ability to cleave plasmid DNA was observed, suggesting that it acts through the hydrolytic mechanism. However, other studies suggest as possible mechanisms of action the inhibition of the efflux pump, and even action on macrophages, resulting in intracellular bacterial death without the microorganism being able to carry out mutations with the purpose of resistance [14,15].

Drugs used for the management of psychiatric disorders have received great attention in antimicrobial investigations of non-antibiotics. Fluoxetine, a selective serotonin reuptake inhibitor in neurons, has several data on its in vitro activity against different bacterial strains, such as *S. aureus*, *E. coli* and *P. aeruginosa* [18,19]. Studies propose as a hypothesis of this result the inhibition of efflux pump in bacteria [7,20]. From cytometric analysis, it was assumed that fluoxetine would be able to alter the integrity of the plasma membrane, as well as that of DNA, inducing apoptosis [21].

The antipsychotic and neuroleptic thioridazine has synergistic activity with β -lactams in methicillin-resistant *S. aureus* strains [22]. Chlorpromazine, also part of the phenothiazines, has interesting data regarding activity against mycobacteria [23]. Considering that *M. tuberculosis* has a tropism for macrophages, studies reveal an ability of these cells to concentrate chlorpromazine, its antimycobacterial activity is visualized both in vitro and, intracellularly, in mice [24–26]. The benzodiazepine bromperidol can act synergistically with spectinomycin, inhibiting the growth of *Mycobacterium smegmatis* and *M. tuberculosis* [9].

Table 2. Drugs, strains and concentrations of psychomodulators according to the literature consulted.

Drugs	Bacterial Strains	Concentrations That Showed Antibiotic Effect ($\mu\text{g}/\text{mL}$)
Fluoxetine	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>P. aeruginosa</i>	40–4000
Thioridazine	Methicillin-resistant <i>S. aureus</i> strains	128
Chlorpromazine	<i>Mycobacterium tuberculosis</i>	0.23–3.6
Bromperidol	<i>Mycobacterium smegmatis</i> , <i>M. tuberculosis</i>	50–60

Own author, 2021.

Considering the reassessment of non-antibiotic compounds to identify properties against bacteria, there is a leading role in investigations on non-steroidal anti-inflammatory drugs [11]. The antibacterial potential for both gram-positive and gram-negative strains is demonstrated in several works. Drugs such as ibuprofen, aspirin, diclofenac sodium, indomethacin showed activity against *S. aureus* (MIC = 0.05 – 0.16 mg/mL), *coagulase negative staphylococcus*, *E. coli* (MIC = 0.02 – 1.0 mg/mL), *P. aeruginosa* (MIC = 0.05 – 1.58 mg/mL), *Bacillus* spp. (MIC = 0.63 – 2.5 mg/mL), *Klebsiella* spp., *Proteus* spp., *Streptococcus* spp., *Enterococcus* spp. Considering bacterial resistance, methicillin-resistant *Staphylococcus aureus* showed sensitivity when in contact with ibuprofen and aspirin [27–30].

Some studies have deepened the investigations on these antibacterial mechanisms, being identified as some possible effects caused in microorganisms by this pharmacological class. Blocking bacterial adhesion and motility, by reducing the formation of fimbriae, adhesin, flagellin and flagellar motility [28,31]; inhibition of DNA synthesis from the inhibition of sliding hairpins [33]; modification of the permeability of porins and efflux pumps [33]; and increased oxidative stress and cell wall impairment [34].

4. Conclusions

In general, there is a great diversity of published studies on pharmacological repositioning, however, it is still necessary to deepen investigations on the mechanisms of action of these compounds against bacterial strains, and to evolve the research to phase II and III. Furthermore, it is recommended to investigate other drug classes that are not well explored, such as muscarinic receptor antagonists. The results observed in this review highlight the relevance that this strategy has, in the scientific community, as an alternative to the relevant health problem, which is the growing number of multidrug-resistant bacteria.

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Conflicts of Interest:

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