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REVIEW ARTICLE

Antimicrobial activity of selective serotonin reuptake inhibitors in bacteria and fungi: a systematic review

Atividade antimicrobiana de inibidores seletivos de recaptação de serotonina em bactérias e fungos: uma revisão sistemática

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Abstract

Objective: this systematic review aims to compile literature data on the antimicrobial action of Selective Serotonin Reuptake Inhibitors (SSRI). **Methods**: To this end, the articles in this review were searched in the PubMed database between the years 2010 to 2020, using terms found in MESH as descriptors. The PRISMA flow diagram was used to analyze the process flow of the research. Later, inclusion and exclusion criteria and eligibility for data extraction and statistical analysis were applied. **Results:** Thus, of 252 articles found, 13 were used for this systematic review. The period in which there were more publications was in 2016-2017. All articles demonstrated the antimicrobial activity of ISRS, such as sertraline, fluoxetine, and paroxetine, in addition to their synergistic activity with some antifungals and antibacterial. **Conclusion**: With this, it could be concluded that the repositioning of non-antibiotic drugs that have antimicrobial activity is a promising alternative for the scientific community and, in the future, in clinical practice

Keywords: Antibacterial; Antifungal; SSRI; Drug Repositioning; Antimicrobial and Nonantibiotic.

Resumo

Objetivo: compilar dados da literatura sobre a ação antimicrobiana dos Inibidores Seletivos de Recaptação de Serotonina (ISRS). **Métodos**: os artigos desta revisão foram pesquisados na base de dados PubMed, entre os anos de 2010 a 2020, utilizando, como descritores, termos encontrados no MESH. O fluxograma PRISMA foi utilizado para analisar o fluxo do processo da pesquisa. Posteriormente, foram aplicados os critérios de inclusão e exclusão e de elegibilidade para extração de dados e análise estatística. **Resultados**: dos 252 artigos encontrados, 13 foram utilizados para esta revisão sistemática. O período em que houve mais publicações foi em 2016-2017. Todos os artigos demonstraram a atividade antimicrobiana do ISRS, como sertralina, fluoxetina e paroxetina, além de sua atividade sinérgica com alguns antifúngicos e antibacterianos. **Conclusão**: o reposicionamento de medicamentos não antibióticos que possuam atividade antimicrobiana é uma alternativa promissora para a comunidade científica e, futuramente, na prática clínica.

Palavras-chave: Antibacteriano. Antifúngico; ISRS; Reposicionamento de Medicamentos; Antimicrobiano e Não Antibiótico.

INTRODUCTION

The clinical use of antimicrobials has brought innumerable advantages, considering that they have allowed the treatment of several infections, and made it possible to perform surgeries and transplants, besides being able to help in the treatment of other diseases, such as cancer. However, their incorrect use led to the appearance of bacteria and fungi resistant to antimicrobials[1,2]. This brings great concern worldwide since infectious diseases are strongly related to high morbidity and mortality rates[3,4].

In addition, a report made at the request of the UK government showed that if no new therapeutic strategies are discovered, by 2050 infections caused by resistant microorganisms will be responsible for the death of 10 million people[1,3,5]. Due to resistance, many drugs, currently available, are ineffective against certain infections, restricting the range of antimicrobials available for treatment[6,3].

In this context, in the case of resistance to antifungals, there is an increase in reports of species of Aspergillus and Candida, not albicans, such as Candida glabrata and C. auris, resistant to azolics, a worrying fact since these drugs are the only ones available today to treat invasive fungal infections[7,8,9,10]. In this sense, it is worth emphasizing that since 2006 no new class of antifungals was launched, due to the difficulties present in the production of these antimicrobials, once they need to have low or no toxicity, have selective action mechanism, be preferably fungicidal, besides presenting efficiency against resistant fungal species, among other characteristics[6,11,12].

On the other hand, bacterial resistance is also related to the low amount of new antibiotics being developed today, allied

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to the misuse of existing antibiotics and the various resistance mechanisms developed by the bacteria, which are easily transmitted between them through genetic material[13,14]. Moreover, new antibiotics take, on average, 10 to 15 years to be finally used in the treatment of human bacterial infections, which makes the pipeline of these antimicrobials unfavorable, allowing, to a certain extent, the increase in the number of multi-resistant bacteria. Thus, it is necessary to seek other means to obtain new antimicrobials[14].

In this context, the repositioning of drugs (RD) appears as an alternative for the development of new drugs[15]. This strategy consists in redirecting drugs already known in clinical practice to uses other than the original indication[16]. Safety in toxicity, exclusion of pre-clinical phases, and reduction of cost and study time are some of the advantages of RF in the development of new drugs to combat infections[17]. In addition, RD can rely on the use of bioinformatics techniques that allow tracking possible molecular interactions between the studied molecule and the target receptor[18].

In this scenario, a class of drugs known as Selective Serotonin Recaption Inhibitors (SSRI) has demonstrated antimicrobial activity, to which one of the main hypotheses is that they act on the efflux pumps, one of the main mechanisms of resistance to antimicrobials[17]. The traditional therapeutic use of the SSRI includes its mechanism of action in the CNS, acting through the blocking of the serotonin capture pump, which directly implies the availability of serotonin with the consequent increase in serotonergic activity[19].

Thus, taking into consideration the relevance of the study on RD and the need for new therapeutic options, a systematic review was conducted to assess the antifungal and antibacterial effect of SSRI in vitro through the analysis of selected articles in the scientific literature.

METHODOLOGY

Study design

A systematic literature review study was performed according to the research process flow diagram (http://www.prisma-statement.org/). The method used is characterized as reproducible and objective, aiming at finding answers to a certain scientific question and, through the data collected in the studies related to the question in focus, evaluating the results[20].

Research Strategy

The PubMed database was selected for the search of articles published in the period from 2010 to 2020. Initially, two groups of descriptors were separated from the analysis performed at MESH (Medical Subject Headings) for further advanced research on the PubMed platform. Below are the descriptors used for each group:

Grupo 1 - Fungus: #1 (Fungal OR Yeast) AND #2 (Serotonin Uptake Inhibitors OR Neurotransmitter Uptake Inhibitors OR Serotonin Agents) AND #3 (Antifungal Agents OR Therapeutic Fungicides OR Antifungal Antibiotic)

Grupo 2 - Bactérias: #1 (Bacteria OR Gram-Negative Bacteria OR Gram-Positive Bacteria OR Eubacteria) AND #2 (Serotonin Uptake Inhibitors OR Neurotransmitter Uptake Inhibitors OR Serotonin Agents OR Reuptake Inhibitors, Serotonin) AND #3 (Anti-Bacterial Agents OR Anti-Infective Agents OR Anti-Bacterial Compounds OR Antibiotic)

Selection of articles

Inclusion criteria

This review had the following criteria for inclusion: full articles; publication made in the last 10 years; English language and that had as objective to evaluate the antibacterial and/or antifungal activity in vitro of the SSRI.

Exclusion criteria

The following criteria were used to exclude articles from the review: studies that did not aim to evaluate the antibacterial and/or antifungal activity of SSRI; studies that exclusively evaluated the antibacterial and/or antifungal activity of other classes of drugs; articles in which the analysis was not performed through in vitro model; literature review; clinical trials; case reports and comments from editors.

Eligibility

The study was divided into two phases. In the first phase, three authors searched the PubMed database independently for descriptors from group 1 (fungi), and three other authors searched the same database independently for descriptors from group 2 (bacteria). Both groups selected the articles according to the established inclusion and exclusion criteria. Subsequently, the authors together evaluated which studies would be included in this review.

Next, the authors classified the quality of the articles through six classifications: a) representativeness of the microorganisms under study; b) coherence of the study; c) methodology and obtaining data; d) results and discussion; e) conclusion; f) relevance of the study. The items from "a" to "f" were classified as strong (1), moderate (2), or weak (3). The instrument used to perform this analysis consisted of an adaptation of the 'Effective Public Health Practice Project' (EPHPP) tool to evaluate of the study in vitro model.

Data Extraction

In the second phase, the articles included for review were read again for extraction of the following data: year of publication (subcategories: first period 2011-2012, second period 2013-

2014, third period 2015-2016, fourth period 2017-2018, and the fifth period 2019-2020), the title of the articles, names of the authors, intervention studied, results and conclusions.

Statistical analysis

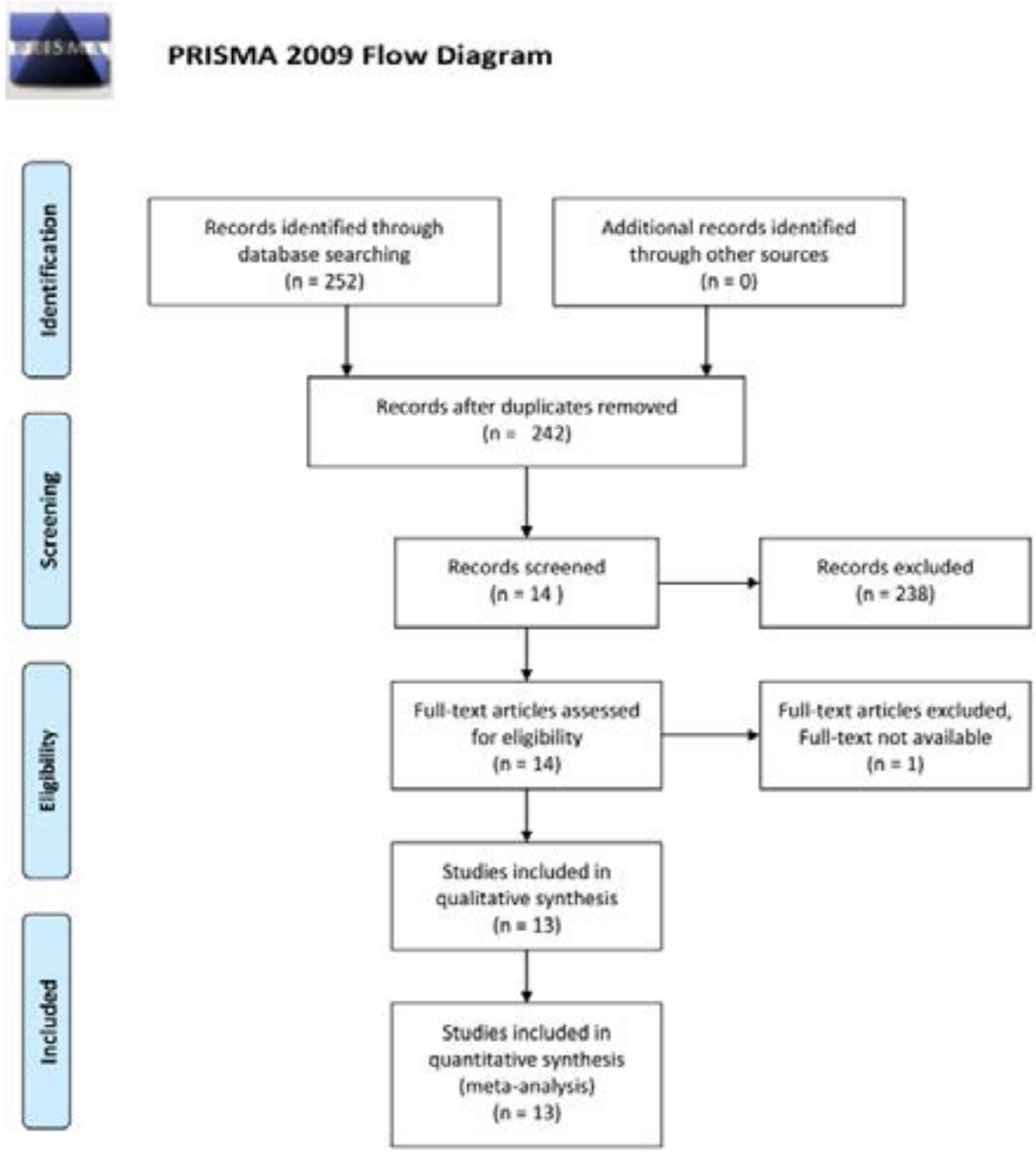
In the selected articles, the EPHPP tool was applied in which methodological criteria were proposed for a strong, moderate, and weak classification of the articles for the subsequent production of the heat map graphic. The data obtained in the analysis were plotted in the online statistical tool Morpheus® (https://software.broadinstitute.org/morpheus/), where heat maps were generated to identify the ligand-residue interaction and similarity profiles by the Pearson statistical test.

RESULTS

Included Studies

The Prisma flow diagram shows how the search for the articles was made (Figure 1). The search was performed in the PubMed database where 252 articles were found. The exclusion and inclusion criteria were applied, removing 238 articles that did not fit the criteria and, then, 14 potential articles were left. During the reading of the papers, it was observed that one of them did not have the complete text, which was withdrawn. Finally, after analysis, 13 articles were selected for this systematic review.

Figure 1. Representation of the search for articles by the Prisma flow diagram



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Qualitative Analysis

The period with the highest number of publications was 2016-2017 (Table 1). It was also seen that the largest number of articles that addressed the antimicrobial activity of ISRS was related to fungi, while the minority was to bacteria. The most commonly used drugs were sertraline, fluoxetine, and paroxetine, respectively.

After the complete reading of the articles, a table was prepared with the title of the work, author and year, the intervention studied, results, and recommendations/conclusions (Table 1). It was observed that the amount of articles that evaluated the antimicrobial activity in fungi is greater when compared to the bacteria. Moreover, the most cited microorganisms were Candida spp., Staphylococcus aureus, and Escherichia coli.

Table 1. Distribution of published studies from 2011 to 2020.

Periods	Absolute value (n)	Relative value (%)	Relative cumulative frequency (%)
2011 – 2012	1	8.0	8.0
2013 – 2014	0	0.0	8.0
2015 – 2016	5	38.0	46.0
2017 – 2018	4	31.0	77.0
2019 – 2020	3	23.0	100.0
Total	13	100.0	

Statistical evaluation of the study

The classification was based on the EPHPP tool in strong, moderate, and weak. In **chart 1** we can see that the most intense descriptors in the articles, in general, were sampling, conclusion, results, and discussion. In addition, we can also observe that the articles[3,27,39 45,46] were the ones that presented the best interaction strength. In **chart 2** there is a comparison between the articles and it was seen that the interaction force of the articles varied a lot.

In **figure 2**, taking into consideration the interaction force of the descriptors among themselves, we can observe that almost all the descriptors chosen to evaluate the articles presented determinant interaction force, except for "Data Collection/ Methodology".

Chart 1. Articles published in the databases according to authors, title and year of publication.

Authors	Title	Year
Gowri, M. et al.	Sertraline as a promising antifungal agent: inhibition of growth and biofilm of Candida auris with special focus on the mechanism of action in vitro	2020
Nobile, C. J. et al.	A selective serotonin reuptake inhibitor, a proton pump inhibitor, and two calcium channel blockers inhibit Candida albicans biofilms	2020
De Andrade Neto, J.B. et al.	A mechanistic approach to the in-vitro resistance modulating effects of fluoxetine against meticillin resistant Staphylococcus aureus strains	2019
De Sousa, A.K. et al.	New roles of fluoxetine in pharmacology: Antibacterial effect and modulation of antibiotic activity	2018
Oliveira, A. S. et al.	Anti-Candida activity of antidepressants sertraline and fluoxetine: effect upon pre-formed biofilms	2018
Costa, S. R. A. et al.	In vitro anti-Candida activity of selective serotonin reuptake inhibitors against fluconazole-resistant strains and their activity against biofilm-forming isolates	2017
Li, L. et al.	Insight into synergetic mechanisms of tetracycline and the selective serotonin reuptake inhibitor, sertraline, in a tetracycline-resistant strain of Escherichia coli	2017
Gu, W. et al.	The synergistic effect of Azoles and Fluoxetine against resistant Candida albicans strains is attributed to attenuating fungal virulence	2016
Cong, L. et al.	In Vitro Antifungal Activity of Sertraline and Synergistic Effects in Combination with Antifungal drugs against planktonic forms and biofilms of clinical Trichosporon asahii isolates	2016
Treviño-Rangel, R. J. et al.	Activity of sertraline against Cryptococcus neoformans: in vitro and in vivo assays	2016
Rossato, L. et al.	In vitro synergistic effects of chlorpromazine and sertraline in combination with amphotericin B against Cryptococcus neoformans var. grubii	2016
Ayaz, M. et al.	Sertraline enhances the activity of antimicrobial agents against pathogens of clinical relevance	2015
Bohnert, J. A. et al.	Efflux inhibition by selective serotonin reuptake inhibitors in Escherichia coli	2011

Chart 2. 13 articles selected for analysis, Fortaleza, Ceará, 2022

Title	Authors/Year	Studied Interventions	Results	Recommendations/ Conclusions
Sertraline as a promising antifungal agent: inhibition of growth and biofilm of Candida auris with special focus on the mechanism of action in vitro	Gowri M et al. (2020)	To investigate the antifungal effect and mechanism of action of sertraline against Candida auris and its effect on biofilm formation.	Sertraline inhibited the growth of C. auris and inhibited biofilm formation by 71% after treatment. Cellular damage caused by sertraline has also been observed. Molecular docking revealed that sertraline can bind to the sterol 14 alpha-demethylase that is involved in the ergosterol biosynthesis.	The results of this study suggest the antifungal potential of sertraline in the development of new drugs that are effective against infections by C. auris.
A selective serotonin reuptake inhibitor, a proton pump inhibitor, and two calcium channel blockers inhibit Candida albicans biofilms	Nobile CJ et al. (2020)	Perform two screenings of the pharmakon 1600 library containing 1600 compounds which were clinically tested and showed inhibitory activity against the formation of Candida albicans biofilm.	Among all tested drugs, selective serotonin reuptake inhibitors also showed antifungal effect against the formation of C. albicans biofilms.	Further studies are needed to evaluate the properties of these compounds against biofilm and to test derivatives of these compounds for antifungal activity.
A mechanistic approach to the in-vitro resistance modulating effects of fluoxetine against meticillin resistant Staphylococcus aureus strains	De Andrade Neto JB et al. (2019)	Verify the antibacterial effects of fluoxetine against strains of methicillin-resistant staphylococcus aureus (MRSA), elucidating the possible mechanisms involved in cytotoxic action using flow cytometry.	After 24 hours, the MRSA showed fluoxetine MICs equal to 64 µg/mL and 128 µg/mL, respectively. Cytometric analysis showed that treatment with fluoxetine caused changes in the integrity of plasma membranes and causes damage to DNA, which led to cell death, probably due to apoptosis.	The treatment of MRSA strains with the selective serotonin reuptake inhibitor, fluoxetine, promoted changes in the integrity of the plasma membrane and possibly acts on specific sites close to cellular DNA, leading to death by apoptosis. Therefore, due to its antimicrobial activity, fluoxetine can be used as an antibacterial agent in the treatment of MRSA infections.
New roles of fluoxetine in pharmacology: Antibacterial effect and modulation of antibiotic activity	De Sousa, AK et al. (2018)	To evaluate the in vitro antibacterial effect of fluoxetine and its antibiotic modulating activity against strains of standard and multi-resistant bacteria (S. aureus, E. coli and P. aeruginosa).	Fluoxetine MICs were 256 and 102 µg/mL against standard and resistant strains of S. aureus, respectively. The fluoxetine MIC against standard and resistant strains of P. aeruginosa was 161 µg/mL, and against E. coli the fluoxetine MIC was 102 µg/mL for standard and resistant strains, demonstrating that this drug has significant antibacterial activity. The association of fluoxetine with gentamicin and erythromycin in P. aeruginosa and E. coli showed synergistic effects, demonstrating that this drug can selectively modulate the activity of antibiotics for clinical use.	In conclusion, fluoxetine had a significant antibacterial effect and potential modulating activity of antibiotics against multi-resistant bacteria. Therefore, additional studies are needed to characterize the antimicrobial properties of this drug, as well as the clinical implications of its use in the treatment of infections by resistant microorganisms.

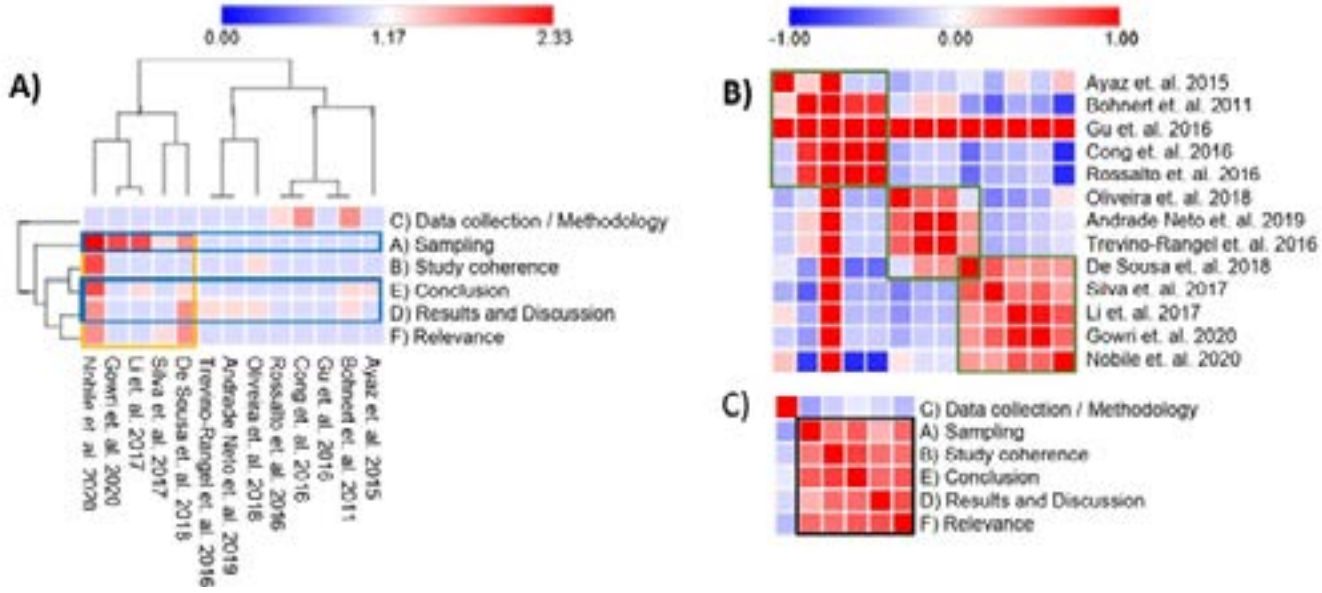
Title	Authors/Year	Studied Interventions	Results	Recommendations/ Conclusions
Anti-Candida activity of antidepressants sertraline and fluoxetine: effect upon pre-formed biofilms	Oliveira AS et al. (2018)	To determine the ability of two commonly used SSRIs, fluoxetine and sertraline, to impair the biofilm's metabolic viability and biofilm's biomass.	For both drugs, there was a dose-dependent reduction in biofilm metabolism and biomass. In high concentrations, fluoxetine was able to reduce biofilm metabolism by 96% (C. krusei) and biofilm biomass by 82% (C. glabrata), when compared to control. Under similar conditions, sertraline achieved an 88% reduction in biofilm biomass (C. glabrata) and 90% in biofilm metabolism (C. parapsilosis).	Further studies are needed to find out if the local administration is superior to the oral intake of mucocutaneous candidiasis and if the plasma has reached the values of both drugs, and may be beneficial in biofilms present in medical devices such as intravenous catheters.
In vitro anti-Candida activity of selective serotonin reuptake inhibitors against fluconazole-resistant strains and their activity against biofilm-forming isolates	Costa SRA et al. (2017)	To evaluate the antifungal effect of sertraline, fluoxetine and paroxetine against strains of Candida spp resistant to fluconazole. Evaluate the action of fluoxetine in biofilms and elucidate its mechanism of action.	SSRIs have antifungal activity against strains of Candida spp, with MIC ranging between 20 - 60 for fluoxetine, 10 - 20 for sertraline and 10 - 100.8 for paroxetine. The studied SSRIs cause damage to the membrane leading to an apoptotic process, in addition to fluoxetine reduces the formation of biofilms.	SSRIs have antifungal activity in vitro against strains of Candida spp. Fluoxetine showed activity against Candida spp. biofilm viability.
Insight into synergetic mechanisms of tetracycline and the selective serotonin reuptake inhibitor, sertraline, in a tetracycline-resistant strain of Escherichia coli	Li L et al. (2017)	To investigate the effect of combined exposure to sertraline and tetracycline to evaluate the properties of the sertraline auxiliary compound against resistance to tetracycline encoded by tetA in E. coli. In order to elucidate the mechanism behind the synergy observed between sertraline and tetracycline, the global transcriptomic response of a tetA-encoded tetracycline-resistant E. coli was further characterized	The fractional inhibitory concentration index for tetracycline and sertraline in E. coli APEC_O2 was 0.5. In the presence of ½ MIC of sertraline, E. coli APEC_O2 sensitivity to tetracycline can be restored according to clinical standards (from 64 to 4 mg/L). The RNA data suggest changes in respiration, which are likely to lower the intracellular pH and therefore the driving force of the proton, which provides the energy for the tetracycline efflux pump. Sertraline and tetracycline can induce a change from oxidation to E.coli fermentation, which further decreases the pH, resulting in cell death.	In vitro synergy between sertraline and tetracycline was observed, regardless of the inhibition of the AcrAB efflux pump (acr A and acr B). An intracellular acidification, a change from oxidation to fermentation and a decrease in PMF is suggested as the main cause of synergies between sertraline and tetracycline in E. coli APEC_O2.
The synergistic effect of Azoles and Fluoxetine against resistant Candida albicans strains is attributed to attenuating fungal virulence	Gu W et al. (2016)	Evaluate the synergistic effects of the selective serotonin reuptake inhibitor, fluoxetine, in combination with azoles against Candida albicans, both in vitro and in vivo and explored the underlying mechanism.	The combinations resulted in synergistic activity against strains of C. albicans, but the same effect was not found for strains of Candida non-albicans. For biofilms formed over 4, 8 and 12 hours, synergism was observed for the combination of fluconazole and fluoxetine. In addition, time-kill curves dynamically confirmed synergism. The results of the G. mellonella studies agreed with the in vitro analysis.	Fluoxetine showed synergism in combination with azoles against resistant C. albicans, both in vitro and in vivo. The results of this study encourage us to consider the future use of a combination of azole and fluoxetine against fungi, and animal models and further study of the mechanisms are more needed.

Title	Authors/Year	Studied Interventions	Results	Recommendations/ Conclusions
In Vitro Antifungal Activity of Sertraline and Synergistic Effects in Combination with Antifungal drugs against planktonic forms and biofilms of clinical Trichosporon asahii isolates	Cong L et al. (2016)	To study the in vitro activities of sertraline alone or combined with fluconazole, voriconazole, itraconazole, caspofungin and amphotericin B against planktonic forms and biofilms of 21 isolates from clinical patients with T. Asahii.	Sertraline alone exhibited antifungal effects against T. asahii planktonic cells (MICs, 4 ± 8 µg/ml) and T. asahii biofilms (SMICs, 16 ± 32 µg/ml). In addition, sertraline exhibited synergistic effects against T. asahii with amphotericin B, caspofungin and fluconazole (FICI 0.5)	The study suggests the therapeutic potential of sertraline against invasive T. asahii infection, mainly related to catheters, but more in vivo studies are needed to validate the findings.
Activity of sertraline against Cryptococcus neoformans: in vitro and in vivo assays	Treviño-Rangel RJ (2015)	To determine the antifungal effect of sertraline in vitro against strains of Cryptococcus spp.	It was observed that sertraline has an inhibitory effect on the growth of strains of Cryptococcus spp. with a MIC range ranging from 1-8 µg/mL.	The study provided clear evidence of the antifungal action of sertralines against the strains of Cryptococcus spp. However, clinical trials on the action of this compound in cryptococcal meningitis are needed.
In vitro synergistic effects of chlorpromazine and sertraline in combination with amphotericin B against Cryptococcus neoformans var. grubii	Rossato L et al. (2016)	Avaliar a ação antifúngica de agentes antipsicóticos como a clorpromazina e a sertralina isoladas e em combinação com anfotericina B em 30 cepas de isolados clínicos de Cryptococcus neoformas antes e depois da indução in vitro da capsula.	A interação entre anfotericina B e clorpromazina mostrou sinergismo em 50 a 67% das cepas antes ou depois da indução capsular. E a associação de anfotericina B com sertralina 60% de sinergismo em ambos os grupos.	Clorpromazina e sertralina inibem o crescimento in vitro de Cryptococcus neoformans. É necessário estudos in vivo com modelos de neurocriptococose para melhor entendimento da ação antifúngica desses compostos associados a anfotericina B.
Sertraline enhances the activity of antimicrobial agents against pathogens of clinical relevance	Ayaz M et al. (2015)	To evaluate the isolated antibacterial activity of sertraline against S. aureus, P. aeruginosa and E. coli, the antibacterial activity of sertraline associated with other antibiotics against S. aureus, P. aeruginosa and E. coli and the antifungal activity against A. Fumigatus and F. Solani; (MFC).	For S. aureus ATCC 6538, E. coli ATCC 8739 and P. aeruginosa ATCC 9027, the MICs of sertraline were 20, 40 and 60 µg/mL, respectively, while 55.5% of clinical isolates of S. aureus and 50% E. coli strains were inhibited at 20 and 60 µg / ml of sertraline, respectively. Among the fungi tested, 60% of A. niger and A. fumigatus were inhibited at 40 and 80µg/ml, respectively. The MFCs were 60 and 80 µg/mL for A. flavus and F. solani, respectively. The antibacterial activities of all antibiotics increased significantly ($p < 0.001$) with the addition of sertraline 100 µg/mL against all tested bacteria.	Sertraline has strong intrinsic antibacterial and antifungal activities. The combination study revealed that sertraline significantly increased the antimicrobial effect of antibiotics, and some previously resistant strains became susceptible. In addition, sertraline is very effective at higher concentrations, but neurological effects at higher concentrations should be studied. Additional derivation and use of bacteria containing efflux pumps with molecular characterization can provide more convincing results.

Title	Authors/Year	Studied Interventions	Results	Recommendations/ Conclusions
Efflux inhibition by selective serotonin reuptake inhibitors in Escherichia coli	Bohnert JA et al. (2011)	Possible antimicrobial and synergistic effects of selective serotonin reuptake inhibitors (SSRIs) in Escherichia coli strains that overexpress multi-drug efflux pumps.	Sertraline showed limited synergy with tetracycline, oxacillin, linezolid and clarithromycin, depending on the individual overexpressed pump and the use of medium. Sertraline, as the most potent SSRI in relation to the inhibition of bacterial growth, led to a rapid dose-dependent inhibition of Nile red efflux, in addition to increasing the expression of resistance genes: marA and acrB.	One possible explanation for the discrepancy between MIC and real-time efflux assays was that sertraline is a weak inducer of marA and acrB, thus reducing its initial antibacterial and sensitizing effects over time. The results indicate that sertraline may be useful as a model of an efflux pump inhibitor for short-term in vitro experiments in E. coli, but is unlikely to be clinically useful as a co-drug against Gram-negative bacteria.

Fonte: Autores (2022).

Figure 2. Heat map panel illustrating statistically regarding illustratings between the descriptors. (A) The relationship between descriptors (Y axis) and analyzed articles (X axis); (B) between analyzed articles and (C) between descriptors. In (A) graphic,the closer to 2.33 (red) the interaction force is more determinant and intense, the closer to 0 (blue) the interaction force is negligible. Clusters evidenced by yellow square. Best rated descriptor highlighted in blue squares. In B-C layouts, the closer to 1(red) the interaction force will be more determinant and intense, the closer to -1 (blue) the greater the distance and the interaction force will be negligible. Clusters highlighted by green and black squares ,respectively.



DISCUSSION

Studies on the antimicrobial activity of non-antibiotics have been increasingly common in the scientific community. This repositioning of drugs occurs due to the increase in the resistance of microorganisms to the antimicrobials already existing in the pharmaceutical industry[21].

In the present study, it was observed that the drugs that act as selective inhibitors of serotonin reuptake, much used as antidepressants, presented antibacterial and antifungal activity. Sertraline, fluoxetine, and paroxetine were the most cited, respectively.

E. coli has a high incidence of urinary tract infections[22] and has developed resistance factors to antimicrobials with the presence of ESBL and MDR strains[23,24]. This bacterial species has shown itself susceptible to the action of sertraline with a MIC of 60 µg/ml demonstrating strong activity against the growth of the colony[25]. Furthermore, it demonstrated inhibition characteristics of the efflux pumps as a possible mechanism of action against E. coli strains and a weak inducer of marA and acrB resistance genes[26].

Fluoxetine, used on large scale as an antidepressant, presented a MIC of 102 µg/ml against the standard strains and resistance of E. coli presenting a moderate activity when compared to sertraline[27]. However, in the literature, there is a description of the MIC of fluoxetine being 32 µg/ml[17]. It is also of great relevance to the action of sertraline in synergism with antibiotics which alone no longer had effects on resistant strains of E. coli, such as tetracycline[28].

The resistance of S. aureus strains and the clinical importance of this pathogen is widely discussed. Methicillin-resistant S. aureus (MRSA) strains are responsible for numerous cases of endocarditis, soft tissue infections, and osteoarticular infections[29]. This resistance has been reported since the 1960s, and new therapeutic alternatives have been studied[30].

The action of SSRI against the standard and resistant strains of S. aureus has proved to be more effective concerning gram-negatives. The MIC of sertraline against this microorganism was 20 µg/ml demonstrating a strong intrinsic antibacterial activity [25]. In strains (MRSA), fluoxetine has a MIC ranging from 64 to 256 µg/ml, and the antibacterial activity of this compound results from its entry into the cell with consequent bactericidal action[31]. This corroborates the literature on fluoxetine with a MIC of 255 µg/ml[32].

P. aeruginosa is responsible for numerous hospital and immunocompromised patient infections worldwide. Multi-resistant (MDR) and extensively resistant (XDR) strains are of concern, and one reason is the ability to transfer resistance genes to other strains[33].

Standard strains of P. aeruginosa are susceptible to the action of sertraline with a MIC of 60 µg/ml [25]. Moreover, there was an excellent synergistic activity of sertraline and fluoxetine with antibiotics used against this bacterium, because while the ISRS was added greater was the potentiation of the effect of the antibiotic [25, 27] which is ratified in the literature when it shows that polymyxin B had a synergistic effect with sertraline[34].

The literature reports that sertraline has antifungal activity, besides having the capacity to accumulate in the central nervous system, reaching values up to 40 times higher in this region compared to its blood levels, which makes it a drug with the potential to help in the treatment of cryptococcal meningitis[35, 36].

Thus, it was demonstrated that clinical isolates of Cryptococcus neoformans presented MIC ranging from 1 - 8 µg/ml to sertraline, with MIC 90 of 4 µg/ml [36], corroborating a study which obtained a value of MIC >10 µg/ml for a clinical strain of Cryptococcus spp., with MIC 90 of 6 µg/ml [37]. In addition, it is reported that sertraline showed a fungicidal effect and that there is a low probability of Cryptococcus spp. presenting intrinsic resistance to this drug[37].

It was demonstrated that the MIC value of sertraline in clinical isolates of C. neoformans before capsule induction varied from 16 - 64 µg/ml and the MIC of these strains after capsule induction varied from 8 - 32 µg/ml [35]. In this same study, it was reported that there was 60% synergism between sertraline and amphotericin B, both in the group of those fungi that had a capsule and those that did not. Furthermore, it was reported that sertraline also presented a significant synergistic effect with another drug, fluconazole[38,37].

Regarding the antifungal effect of ISRS on Candida spp., they reported that fluoxetine, sertraline, and paroxetine showed antifungal activity on clinical strains resistant to fluconazole of Candida albicans, C. tropicalis, C. parapsilosis and C. glabrata[39].

Thus, the MIC values for fluoxetine, sertraline and paroxetine varied from 20 - 160 µg/ml, 10 - 20 µg/ml and 10 - 100.8 µg/ml, respectively. These results were much lower than those obtained with the minimum fungicide concentration (MFC), in 48 hours, of 156 mg/L for fluoxetine and 500 mg/L for paroxetine[40]. Regarding sertraline, the results corroborate a study that obtained CBM, in 48 hours, ranging from 3 - 29 µg/ml for C. albicans, 14 - 29 µg/ml for C. glabrata and C. parapsilosis, and from 3-7 µg/ml for C. tropicalis[41].

In addition, fluoxetine was efficient against the biofilms of the tested Candida strains, the MIC value being 80 µg/ml for C. albicans, 40 µg/ml for C. parapsilosis, and 160 µg/ml for C. tropicalis and C. glabrata[39]. The authors also emphasized that the mechanism of action of the analyzed ISRS is due to their ability to cause damage to the fungal cell membrane, thus activating the signaling pathways of apoptosis and compromising the cellular viability in a dose-dependent manner, which culminates

in the death of the yeasts.

Regarding the antifungal activity of fluoxetine, it was seen that when combined with fluconazole, itraconazole, and voriconazole, fluoxetine significantly reduced the MIC of these azoles, presenting a synergistic effect against resistant clinical strains of C. albicans. Thus, the MIC of fluconazole was 256 µg/ml (fluconazole only) to 2 and 4 µg/ml (fluconazole + fluoxetine), of itraconazole was 4 µg/ml to 0.125 µg/ml and of voriconazole it was 4 µg/ml to 0.06 µg/ml[42].

The study also evaluated other resistant clinical species of Candida, such as C. krusei, C. tropicalis, and C. glabrata, but there was no synergistic effect for these strains. As for C. albicans biofilm, fluconazole and fluoxetine showed a synergistic effect in biofilms of up to 12 hours, but there was a gradual loss of this effect in mature biofilms of up to 24 hours[42].

On the other hand, when analyzing the antifungal activity of fluoxetine in clinical strains of Candida spp., they found MIC values ranging from 9.8 - 625 µg/ml. When analyzing the synergism between fluoxetine and fluconazole, the authors found synergism for strains of C. albicans, C. tropicalis, C. parapsilosis, and C. krusei, being observed a more significant synergism in the strains that presented resistance to fluconazole, which had a reduction of up to 64 times in the value of its MIC[43].

In another study, fluoxetine showed activity against Candida spp. biofilms, causing a reduction in metabolic activity and increasing biomass degradation. Regarding the metabolic activity analysis, C. krusei showed to be the most susceptible species to fluoxetine, with a MIC of 0.015 mg/mL, followed by C. albicans, with a MIC of 0.06mg/mL and the most resistant species was C. glabrata, presenting the highest MIC of 0.24 mg/mL[44].

Regarding fluoxetine in biomass analysis, C. krusei was also more susceptible, as it presented a reduction of more than 67% in the lowest concentration tested, which was 0.015 mg/mL. C. albicans and C. glabrata had a reduction of 63% and 82%, respectively, in the highest concentration tested, which was 3.9 mg/mL. The concentration of 0.15 mg/mL, considered the average of the planktonic MIC value of fluoxetine, also presented significant activity on the tested strains, being 38% the reduction of biomass of C. parapsilosis biofilm and 68% for C. krusei[44].

The antifungal sertraline activity in biofilms of Candida spp., also analyzed, reduced the metabolic activity of the biofilms, with variations in the MIC of 0.06 to 0.12 mg/mL, being observed with a greater metabolic compromise in the concentration of 3.9 mg/mL[44].

In the biomass analysis, with a concentration of 0.24 mg/mL, all the species tested presented 50% of biomass compromise. In the maximum concentration of 3.9 mg/mL, the percentage of involvement varied between 67% (C. albicans) and 88% (C. glabrata)[44]. It is worth mentioning that, in general, sertraline presented better results than fluoxetine in terms of biomass impairment of biofilm, possibly because it is more lipophilic, thus having an easier to penetrate the biofilm matrix and leading to its destruction[44,39].

In addition, paroxetine also showed antifungal activity against C. albicans biofilms, with a minimum inhibitory biofilm concentration (MBIC) value of 50 µM, a much lower value than the MIC of paroxetine in C. albicans planktonic cells, which was higher than 200 µM. Besides inhibiting the formation of C. albicans biofilm in isolation, this inhibition was also observed when paroxetine was combined with caspofungin antifungal[45].

Besides the Candida species mentioned throughout the text, one species that also deserves mention is Candida auris, an emerging pathogen, which has been standing out for presenting resistance to many available antifungals, besides causing severe systemic infections[46,47].

Thus, the antifungal activity of sertraline was analyzed against 3 clinical strains of C. auris, being the MIC value of 20 µg/ml for C. auris 70 and 40 µg/ml for C. auris 33 and C. auris IL. The sertraline showed fungicidal activity in 6 hours, after initial contact with the fungal cells, which shows a relationship of dependence of its activity with time[46].

It was also reported that sertraline was able to inhibit 71% of C. auris biofilm, having the ability to prevent fungal cells from adhering to a polystyrene surface or cellulose matrix. The mechanism of action of the sertraline in C. auris is not yet elucidated, but it is believed that there is no relation to damage to the fungal cell wall or with its direct connection to the ergosterol of the cell membrane. However, sertraline has been able to reduce the amount of ergosterol by binding to sterol 14 alpha demethylase[46].

Trichosporon asahii treatment is still a challenge, as this strain has shown low susceptibility to caspofungin and a limited in vitro effect of amphotericin B[48]. With this problem in mind, a promising agent is a sertraline. This showed strong fungicidal action with MIC ranging from 0.8 to 32 µg/ml and presented synergistic activity against planktonic cells of T. asahii with amphotericin B, caspofungin, and fluconazole. In addition, sertraline showed signs of a possible decrease in the toxicity of amphotericin B when administered together, however, further studies are still needed to ratify this information[49].

Thus, it is observed that all 13 articles used in our study showed that the selective serotonin reuptake inhibitors have a promising antifungal and antibacterial activity in several species and resistant strains. There was also a synergistic action between the SSRI and antifungal and antibacterial drugs which had reduced effect or no effect on some microorganisms and subsequently showed an improvement in their antimicrobial activity. Thus, the ISRS are promising alternative drugs for combating microbial infections.

CONCLUSION

The systematic review showed that the repositioning of non-antibiotic drugs that have antimicrobial activity is promising in the scientific community and, in the future, in clinical practice. Sertraline, fluoxetine, and paroxetine have antimicrobial action against fungi and bacteria with MIC ranging from strong to moderate. Thus, further in vitro studies are necessary to evaluate the activity of these drugs in other strains and synergism with other drugs, besides elucidating the possible mechanisms of action of these drugs. In vivo studies are also necessary to better evaluate the use of the SSRIs for antimicrobial purposes, and to ascertain their efficacy and safety in clinical practice.

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