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ORIGINAL ARTICLE

# Antifungal and Antibiofilm Activities of Selective Serotonin Reuptake Inhibitors Alone and in Combination with Fluconazole

## Selektif Serotonin Geri Alım İnhibitörlerinin Tek Başına ve Flukonazol ile Kombinasyonlarının Antifungal ve Antibiyofilm Aktiviteleri

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## ABSTRACT

**Objectives:** *Candida* spp. are clinically important pathogens that cause difficulties for treatment by biofilm formation. Considering antifungal resistance rates and the limitations in the discovery of new antifungals, the antifungal and antibiofilm effects of various drugs used for different therapeutic purposes are becoming more important. The goal of our study was to determine the antifungal and antibiofilm effects of the selective serotonin reuptake inhibitors (SSRIs), namely sertraline (SRT), paroxetine (PRX), and fluoxetine (FLX) alone and in combination with fluconazole (FLC) against *Candida* spp.

**Materials and Methods:** Twenty *Candida* spp. strains isolated from clinical samples from Ege University Hospital were identified by the Dalmau method and matrix-assisted laser desorption ionization time of flight mass spectrometry. The minimum inhibitory concentrations (MICs) of the SSRIs and FLC were detected by broth microdilution method. Synergistic interactions between the SSRIs and FLC were investigated by checkerboard assay. The antibiofilm effects of the SSRIs were determined by spectrophotometric microplate method.

**Results:** Among the isolates, five different *Candida* spp. (*C. albicans, C. glabrata, C. krusei, C. tropicalis,* and *C.parapsilosis*) were identified. The MICs of the SSRIs ranged between 16-512 µg/mL. While SRT showed the highest antifungal effect, the antibiofilm efficacy of FLX was higher than that of the other agents. Moreover, FLX and PRX showed a synergistic effect with FLC in 13 and 19 isolates, respectively. Four isolates were strong biofilm producers while nine isolates were moderate biofilm producers. *C. parapsilosis* strains showed higher biofilm production than the other species. At MIC/2 concentration, FLX and SRT alone inhibited mature biofilms in six and five isolates, respectively, while PRX caused increases biofilm formation in seven isolates.

**Conclusion:** This study revealed that MIC/2 concentrations of SSRIs could have antifungal and antibiofilm effects. SRT and FLX alone or in combination with antifungals may possibly have therapeutic potential for combating fungal infections.

**Key words***: Candida* spp., fluconazole, EUCAST, synergistic effect, antibiofilm

## ÖZ

**Amaç:** Klinik açıdan önemli fungal patojenlerden olan *Candida* türleri, biyofilm üretme kapasiteleriyle tedavide zorluklara yol açmaktadır. Antifungal direnç oranları ve yeni antifungallerin keşfinin sınırlılığı göz önüne alındığında, farklı terapötik amaç için kullanılan çeşitli ilaç moleküllerinin antifungal ve antibiyofilm etkileri daha fazla önem kazanmaktadır. Çalışmamızın amacı, selektif serotonin geri alım inhibitörleri (SSRI) olan sertralin (SRT), paroksetin (PRX), fluoksetinin (FLX), tek başına ve flukonazol (FLC) ile kombine halde *Candida* türlerine karşı antifungal ve antibiyofilm etkilerinin belirlenmesidir.

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**Gereç ve Yöntemler:** Ege Üniversitesi Hastanesi'nde klinik örneklerden izole edilen 20 *Candida* spp. kökeni Dalmau metodu ve Matriks aracılı lazer dezorpsiyon/iyonizasyon uçuş zamanı kütle spektrometresi kullanılarak tanımlanmıştır. SSRI moleküllerin ve FLC'nin minimum inhibitör konsantrasyon (MIC) değerleri sıvı mikrodilüsyon yöntemiyle belirlenmiştir. FLC ve SSRI moleküllerin sinerjistik etkileşimleri dama tahtası metoduyla araştırılmıştır. SSRI'ların antibiyofilm etkinlikleri spektrofotometrik mikroplaka yöntemiyle değerlendirilmiştir.

**Bulgular:** Yirmi izolat arasında beş farklı *Candida* türü (*C. albicans, C. glabrata, C. krusei, C. tropicalis* ve *C. parapsilosis*) belirlenmiştir. SSRI'ların MIC değerlerinin 16-512 µg/mL aralığında değiştiği saptanmıştır. SRT'nin yüksek antifungal etkisi gözlenirken, FLX'in antibiyofilm etkinliğinin diğer ajanlardan daha yüksek olduğu belirlenmiştir. Ayrıca, FLX ve PRX'in FLC ile kombinasyonlarında sırasıyla on üç ve on izolat üzerinde sinerjistik etkisi görülmüştür. Dört izolatın güçlü, dokuz izolatın ise orta düzey biyofilm üreticisi olduğu saptanmıştır. *C. parapsilosis* suşlarının biyofilm üretim kapasitelerinin diğer türlerden daha yüksek olduğu gözlenmiştir. MIC/2 konsantrasyonda, tek başlarına FLX ve SRT sırasıyla altı ve beş izolatta olgun biyofilm üzerinde inhibe edici etki gösterirken, PRX'in yedi izolatın biyofilm oluşumunda artışa yol açtığı saptanmıştır.

**Sonuç:** Bu çalışma, SSRI'ların MIC/2 konsantrasyonlarda antifungal ve antibiyofilm etkinliklerinin olabileceğini göstermiştir. SRT ve FLX'in tek başına veya antifungal ajanlarla kombine kullanımının fungal enfeksiyonlarla mücadelede terapötik potansiyeli olabilir.

**Anahtar kelimeler:** *Candida* spp., flukonazol, EUCAST, sinerjistik etki, antibiyofilm

## INTRODUCTION

Fungal infections have received attention due to their higher prevalence and mortality rates in recent years.[1] Among the clinically important yeasts, *Candida* spp. are some of the most common opportunistic pathogens. Although species of this genus may live as members of the microbiota in healthy individuals, they may cause life-threatening infections in hospitalized and immunosuppressed patients.[2,3] One of the major reasons causing the increase in *Candida* infections is thought to be the greater use of medical devices such as catheters, cardiac pacemakers, or artificial hearts, which have suitable surfaces for biofilm formation.[4] A biofilm is a group of microbial cells embedded in extracellular polymeric substances, and recent studies have shown that these sessile cells in biofilms are much more resistant to both antimicrobials and host defense mechanisms compared to planktonic cells due to reduced penetration.[5]

The increased resistance rates to antifungals, the high biofilm production capacities, and the fact that certain *Candida* species are inherently resistant to some antifungals suggest that new antifungal molecules are needed for therapy. Because of the eukaryotic cell structures of fungal pathogens, antifungals should have selective mechanisms that target specific structures in microorganisms different from human cells. This situation makes it difficult to develop new antifungal agents. Consequently, it is becoming more and more beneficial to investigate the antifungal and antibiofilm activities of various molecules used for diverse therapeutic purposes.

Selective serotonin reuptake inhibitors (SSRIs) are used as antidepressants and as the first-line therapy for premenstrual syndrome. The antifungal activities of these agents were first discovered when three patients with chronic vulvovaginal candidiasis treated with sertraline (SRT) for premenstrual syndrome presented no symptoms of candidiasis during the treatment course.[6] Based on this knowledge, different studies have shown that these agents may have antifungal effects on yeast species. The main goal of the present study was to determine the antimicrobial activity and antibiofilm effects of SSRIs alone and in combination with fluconazole (FLC) against clinical *Candida* spp. isolates.

## MATERIALS AND METHODS

### *Fungal isolates and identification*

Twenty *Candida* spp. isolated from patients samples at Ege University Hospital, Mycology Laboratory of Medical Microbiology Department and *Candida parapsilosis* ATCC 22019 strain were examined. The yeast species were identified by the Dalmau method and matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI TOF-MS).

### *Agent solutions*

FLC (Sigma, USA), fluoxetine (FLX) (Abdi Ibrahim, Turkey), paroxetine (PRX) (ARIS, Turkey), and SRT (Sanovel, Turkey) were provided in powder form. The agents were dissolved with using sterile water and dimethyl sulfoxide to a final concentration of 4096 µg/mL. The stock solutions were stored at -80°C until use.

### *Determination of minimum inhibitory concentrations (MICs)*

MICs of the SSRIs and FLC were determined by broth microdilution method according to European Committee for Antimicrobial Susceptibility Testing (EUCAST) criteria.[7] Firstly, an appropriate volume of RPMI-1640 (Sigma, USA) supplemented with 2% glucose (Sigma, USA) was buffered with 0.165 M MOPS (Sigma, USA) at pH 7.0. Then the medium was added to 96-well U-bottom microplates. The agent solutions were added to the first well of the microplates and serially diluted. Fungal inoculums ($1x10^6$ cells) were added to the wells and the microplates were incubated at 37°C for 24 h. After incubation, the absorbance values were measured at 570 nm by spectrophotometric microplate reader (Varioskan Flash, Thermo Scientific, USA). The drug concentration that led to an approximately 50% reduction in growth relative to the drug-free well was accepted as the MIC. All experiments were performed in triplicate. The statistical analyses were performed using GraphPad Prism 5.03 (t-test).

### *Checkerboard assays*

Interaction types between the SSRI agents and FLC were determined using the checkerboard method in 96-well plates. The types of interaction between the SSRI agents and FLC were evaluated based on the fractional inhibitory index (FIX) and the fractional inhibitory concentration (FIC) values for each combination. The following formulae were used to calculate the

FIC index:

FIC of drug A: (MIC of drug A in combination) / (MIC of drug A alone)

FIC index (FIX): (FIC of drug A) + (FIC of drug B)

Synergistic, indifferent, and antagonist interactions were defined by FIX values of ‹0.5, 0.5 to 4, and ›4, respectively.[8]

*Biofilm formation and quantification*

Biofilm formation was also quantified by a modification of the crystal violet (CV) staining assay.[9] Briefly, 100 µL of standardized *Candida* spp. cell suspensions prepared in tryptic soy broth (TSB) medium (Oxoid, UK) ($1x10^6$ cells) were transferred into wells of sterile, flat-bottomed, polystyrene 96-well microplates. The microplates were incubated at 37°C for 24 h for biofilm production. Following incubation, the cell suspensions were aspirated and the wells were washed three times with sterile phosphate buffered saline (PBS) (Oxoid, UK) 200 µL per well in order to remove nonadherent cells. After each washing step, the microplates were air dried to remove the PBS. Afterwards, the remaining attached microorganisms were fixed with 200 µL of methanol for 15 min. The contents of the wells were poured off, the methanol was discarded, and the wells were air-dried. Then 200 µL of 0.02% CV solution was added to the wells for 20 min at room temperature. After 20 min, the CV solution was removed by washing with PBS and the microplates were dried. Each well was destained with 200 µL of 95% ethanol for 15 min. Biofilm formation was quantified by measuring the optical density (OD) at 570 nm using a microplate reader (Varioskan Flash, Thermo Scientific, USA). OD values of wells without inoculum were used as negative controls. *Enterococcus faecalis* ATCC 29212 was used as a positive control strain. The cut-off OD (ODc) was defined as three standard deviations above the mean OD of the negative controls. The biofilm production capacities of the isolates were evaluated as shown in Table 1. All tests were carried out in triplicate. The statistical analyses were performed using GraphPad Prism 5.03 (t-test).

*Antibiofilm effects of SSRIs*

The antibiofilm effects of the SSRI agents at sub-MICs (MIC/2, MIC/4) were investigated by CV staining assay. Biofilm formation was performed by adding standardized cell suspensions to the wells of the microplates and incubating them for 24 h at 37°C as described above. After biofilm formation, the medium in the wells was aspirated, and nonadherent cells were removed by thoroughly washing all wells three times with sterile PBS. The SSRI agent solutions at sub-MICs (MIC/2 and MIC/4) were prepared in TSB and added to the wells that contained preformed biofilm. After these agents were added to the wells, the microplates were incubated for a further 24 h at 37°C. Then the CV staining assay was performed. The antibiofilm effects of the agents were evaluated by measuring the OD of the wells at 570 nm using a microplate reader.

**Table 1. Categorizations of biofilm production capacities**

| | |
|---|---|
| OD ≤ ODc | **No biofilm production** |
| ODc ‹ OD ≤ (2×ODc) | **Weak biofilm producer** |
| (2×ODc) ‹ OD ≤ (4×ODc) | **Moderate biofilm producer** |
| (4×ODc) ‹OD | **Strong biofilm producer** |

OD: Optical density of the isolate, ODc: The mean OD of negative controls

*Statistical analysis*

All tests were carried out in triplicate. The ODc was defined as three standard deviations above the mean OD of the negative controls. The statistical analyses were performed using GraphPad Prism 5.03 (t-test) and $p<0.05$ was considered statistically significant.

## RESULTS

*Fungal isolates and identification*

The 20 clinical fungal isolates identified comprised six *C. albicans,* four *C. tropicalis,* four *C. krusei,* three *C. parapsilosis*, and three *C. glabrata* according to the Dalmau method and MALDITOF-MS.

*Minimum inhibitory concentrations of fluconazole and SSRIs*

Two isolates were resistant to FLC in addition to the inherently resistant *C. krusei* isolates. The MICs of SRT ranged from 16 µg/mL to 128 µg/mL by the broth microdilution method, while the MICs of PRX and FLX ranged from 64 µg/mL to 512 µg/mL. The MICs of all agents are shown in Table 2.

**Table 2. Minimum inhibitory concentrations of fluconazole and SSRIs**

| Isolate | FLC (µg/mL) | SRT (µg/mL) | PRX (µg/mL) | FLU (µg/mL) |
|---|---|---|---|---|
| *Candida glabrata* | 16 | 128 | 256 | 512 |
| *Candida glabrata* | 16 | 128 | 256 | 512 |
| *Candida glabrata* | 16 | 128 | 256 | 512 |
| *Candida albicans* | 0.25 | 128 | 256 | 512 |
| *Candida albicans* | 0.25 | 128 | 256 | 512 |
| *Candida albicans* | 0.25 | 128 | 256 | 256 |
| *Candida albicans* | 2 | 64 | 256 | 256 |
| *Candida albicans* | 1 | 64 | 256 | 256 |
| *Candida albicans* | 8 | 64 | 256 | 256 |
| *Candida tropicalis* | 1 | 32 | 128 | 128 |
| *Candida tropicalis* | 0.5 | 32 | 128 | 128 |
| *Candida tropicalis* | 4 | 32 | 128 | 256 |
| *Candida tropicalis* | 0.5 | 32 | 128 | 128 |
| *Candida krusei** | - | 64 | 64 | 128 |
| *Candida krusei** | - | 32 | 64 | 128 |
| *Candida krusei** | - | 32 | 64 | 64 |
| *Candida krusei** | - | 16 | 128 | 128 |
| *Candida parapsilosis* | 16 | 64 | 256 | 256 |
| *Candida parapsilosis* | 1 | 32 | 512 | 512 |
| *Candida parapsilosis* | 1 | 32 | 256 | 512 |
| *Candida parapsilosis ATCC 22019* | 2 | 128 | 256 | 512 |

*Intrinsically resistant to fluconazole, SSRIs: Selective serotonin reuptake inhibitors, SRT: Sertraline, PRX: Paroxetine, FLU: Fluoxetine, FLC: Fluconazole

*Checkerboard assay*

The interactions between the SSRI agents and FLC were examined by checkerboard assay. No antagonism was found between the agents tested. FLX showed a synergistic effect in the large number of isolates when it was compared to the other SSRIs. It was also determined that FLX is the only agent showing a synergistic interaction with FLC against five different *Candida* species. According to the checkerboard assay, SRT, FLX, and PRX were synergistic in six, thirteen, and ten isolates, respectively. The interaction types of the SSRI agents are shown in Table 3.

*Biofilm formation and quantification*

The biofilm quantification assays revealed that seven of the isolates have weak biofilm production capacity, nine isolates show moderate biofilm production, and four isolates have strong biofilm production capacity. The biofilm production capacities and the number of isolates are shown in Table 4.

*Antibiofilm effects of SSRIs*

In the presence of MIC/2 of FLX, biofilm formation decreased in six isolates, while it increased in two isolates. PRX and SRT, at MIC/2, inhibited biofilm in three and five isolates, respectively. The effects of sub-MIC of the SSRIs on mature biofilm formation in moderate and strong biofilm producer isolates are shown in Table 5.

**Table 4. Biofilm production capacities of the isolates**

| | Biofilm production capacity | | |
|---|---|---|---|
| *Candida* spp. | Weak | Moderate | Strong |
| *Candida albicans* (n=6) | 3 | 3 | - |
| *Candida parapsilosis* (n=3) | - | - | 3 |
| *Candida krusei* (n=4) | 2 | 2 | - |
| *Candida tropicalis* (n=4) | 1 | 2 | 1 |
| *Candida glabrata* (n=3) | 1 | 2 | - |

**Table 5. The effects of SSRIs on mature biofilm formation of the isolates**

| | Number of isolates | | | | | |
|---|---|---|---|---|---|---|
| Effects on mature biofilm | FLX (MIC/2) | FLX (MIC/4) | PRX (MIC/2) | PRX (MIC/4) | SRT (MIC/2) | SRT (MIC/4) |
| Decrease | 6 | 4 | 3 | - | 5 | 3 |
| Increase | 2 | 4 | 7 | 7 | 3 | 3 |
| No effect | 5 | 5 | 3 | 6 | 5 | 7 |

SSRIs: Selective serotonin reuptake inhibitors, FLX: Fluoxetine, PRX: Paroxetine, SRT: Sertraline, MIC: Minimum inhibitory concentration

**Table 3. Interaction types between SSRIs and fluconazole (FIX values)**

| | FLC + FLX | | FLC + SRT | | FLC + PRX | |
|---|---|---|---|---|---|---|
| Isolate | FIX | Profile | FIX | Profile | FIX | Profile |
| *Candida glabrata* | 0.5078 | I | 0.5156 | I | 0.2656 | S |
| *Candida glabrata* | 0.375 | S | 0.5156 | I | 0.2656 | S |
| *Candida glabrata* | 0.5 | S | 0.5156 | I | 0.2656 | S |
| *Candida albicans* | 0.375 | S | 0.625 | I | 0.75 | I |
| *Candida albicans* | 0.5 | S | 1.0313 | I | 0.75 | I |
| *Candida albicans* | 0.5 | S | 1.25 | I | 0.75 | I |
| *Candida albicans* | 0.2813 | S | 0.3125 | S | 0.1563 | S |
| *Candida albicans* | 0.1406 | S | 1.5 | I | 0.75 | I |
| *Candida albicans* | 1.0625 | I | 1 | I | 1 | I |
| *Candida tropicalis* | 0.5 | S | 1.5 | I | 0.75 | I |
| *Candida tropicalis* | 1.0625 | I | 2 | I | 1.5 | I |
| *Candida tropicalis* | 0.2656 | S | 0.375 | S | 0.5 | S |
| *Candida tropicalis* | 1.0625 | I | 2 | I | 1 | I |
| *Candida krusei** | 0.625 | I | 0.25 | S | 0.5 | S |
| *Candida krusei** | 0.5 | S | 0.5 | S | 0.375 | S |
| *Candida krusei** | 0.5 | S | 0.5 | S | 0.375 | S |
| *Candida krusei** | 0.2813 | S | 0.75 | I | 0.25 | S |
| *Candida parapsilosis* | 0.3125 | S | 0.25 | S | 0.2813 | S |
| *Candida parapsilosis* | 1.0078 | I | 1.125 | I | 1.0078 | I |
| *Candida parapsilosis* | 1.0156 | I | 1.25 | I | 1.0156 | I |
| *Candida parapsilosis ATCC 22019* | 0.5 | S | 0.2656 | S | 0.625 | I |

*Intrinsically resistant to fluconazole, SSRIs: Selective serotonin reuptake inhibitors, FLC: Fluconazole, FLX: Fluoxetine, PRX: Paroxetine, SRT: Sertraline, FIX: Fractional inhibitory index, S: Synergistic, I: Indifferent

## DISCUSSION

The significant increase in fungal infections over the past decade has increased the need for new antifungal agents and reliable and reproducible susceptibility testing methods.[10] There are two reference *in vitro* antifungal susceptibility testing methods for *Candida* spp. These reference methods have been developed by two scientific organizations, namely the Clinical and Laboratory Standards Institute and the EUCAST. Despite the differences such as in terms of media, plate types, and measurement methods between these methods, it was determined in several studies that these two methods give results consistent with each other.[10] Although the EUCAST method requires more material and equipment, it has the significant advantage of producing results after a 24-h incubation. Moreover, the measurement of absorbance by the automated device in the EUCAST method, instead of visual inspection, will be the major factor that reduces the error rate. Considering these reasons, we first investigated the *in vitro* activity of SSRIs and FLC by broth microdilution method according to EUCAST. The agent concentration that led to approximately 50% inhibition of growth relative to the controls, which was determined spectrophotometrically, was accepted as the MIC value (Table 2).

SRT was the prominent molecule with a lower MIC range (16-128 mg/mL) compared to FLX and PRX. According to the literature, SRT is generally more effective than the others, which is consistent with our study. In a study conducted on *Candida* spp., it was determined that SRT has antifungal effects on *Candida* species and it was also reported that SRT inhibits *Candida* virulence factors.[6] The inhibitory effects of SRT on different yeasts species, such as *Cryptococcus* isolates, are also shown by research.[11]

There are studies showing that FLX had antibiofilm activity at previously reported MIC values and even at sub-MIC values in the literature.[12] Oliveira et al.[12] reported that FLX was able to reduce biofilm metabolism at high concentrations by 96% (*C. krusei*) and biofilm biomass by 82% (*C. glabrata*), when compared to the control. They also detected that SRT achieved a reduction of 88% in biofilm biomass (*C. glabrata*) and 90% in biofilm metabolism (*C. parapsilosis*) under similar conditions. According to our results, FLX, at sub-MIC concentrations, showed an antibiofilm effect in six isolates, while SRT showed an antibiofilm effect in five isolates. It was also interesting that FLX's MIC ranges were lower on *C. krusei* isolates compared to other *Candida* species.

Unlike SRT and FLX, the number of studies about the antifungal effects of PRX is very limited in the literature. However, the results of a study conducted by Costa Silva et al.[13] and our data showed that PRX has antifungal activity at high concentrations. In parallel to this finding, the MICs of PRX were higher than those of FLX and PRX in our study. Considering our results on the antibiofilm effects of PRX, it was noteworthy that PRX, at MIC/2 levels, caused an increase in biofilm formation of seven isolates.

Even though it is not fully understood how SSRI agents provide their antifungal activities, the point of interest is that their antifungal activity is independent of the species and resistance properties of the *Candida* isolates. In a study investigating this situation, it was reported that the lethal effect of the agents is related to the induction of apoptosis due to damage to the plasma and mitochondrial membranes. It is thought that this condition may be related to genetic variation rather than factors such as species and resistance patterns.[13] Although antifungal activities of SSRIs have been shown in many studies in the literature, it is necessary to know more about the pharmacokinetics of these molecules, which are usually taken orally in clinical practice. The optimum concentrations that will be reached for these agents in several infection sites should be investigated in new studies. Considering the plasma drug concentration of SSRIs, it appears that the doses required for *Candida* inhibition are above the commonly used doses of these drugs.[14,15] On the other hand, it should be kept in mind that the commonly used dosage regimens and pharmacokinetic data of these drugs are regulated for oral therapeutic use. Undoubtedly, more research is needed to evaluate using different forms such as topical formulations of SSRIs as an antimicrobial agent.

A correlation between biofilm formation and antimicrobial resistance profiles was already shown in different studies and so the antibiofilm activities of drug molecules that have various known therapeutic effects are also gaining importance.[16,17] Therefore, we also analyzed the antibiofilm effects of SSRI molecules against mature biofilm of *Candida* isolates. Several different methods and devices could be used for the detection of biofilm formation such as the CV staining assay, light and fluorescence microscopy, bioluminescence, Congo red agar, and Christensen methods. The CV staining assay was used in our study, especially because more sensitive, specific, and quantitative results can be obtained by this method.[18,19] It has been demonstrated with the results of many studies that all *Candida* species could have biofilm forming ability.[20] In parallel with these data, the isolates in the present study identified as different *Candida* species showed moderate and strong biofilm production capacity (Table 4). It is thought that *C. parapsilosis* has the highest biofilm production capacity among non-*albicans* *Candida* species when considering the results of both previous reports and our study.[20,21]

## CONCLUSION

It is understood that SSRI agents show *in vitro* antifungal and antibiofilm activity against *Candida albicans, C. tropicalis, C. parapsilosis*, and *C. glabrata* strains at different concentration levels, based on our findings and other studies in the literature. In addition to the antifungal activity of SSRIs, it was also detected that these agents in combination with FLC could have a synergistic effect against *Candida* spp. The effects of SSRIs on mature biofilms were investigated in the present study and it was found that SRT and FLX molecules could have antibiofilm effects against *Candida* species. Given all these results and studies, it is thought that these agents could have potential as adjuvant therapeutic agents. Research that will be conducted on the antibiofilm activities of SSRIs can be beneficial for the development of new antifungal and antibiofilm

drug combinations and understanding the mechanisms of their antifungal effects.

*Conflicts of interest: No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.*

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