Research Article

Comparative In Vitro Antifungal Analysis Of Selected Oral Anti-Diabetic Drugs Against Candida Species Commonly Encountered In Clinical Practice

Duha Hussain Abd-Alhadi [1]*, Hussam W. Al-Humadi[2]

[1]College of Medicine, University of Babylon, Hillah, Iraq; Email: med812.duha.hussien@student.uobabylon.edu.iq; ORCID: 0009-0005-1063-7392
[2]College of Pharmacy, University of Babylon, Hillah, Iraq; Email: alhumadi2010@gmail.com; phar.hussam.wahab@uobabylon.edu.iq; ORCID: 0000-0003-3691-0949
*Corresponding author: Duha Hussain Abd-Alhadi, College of Medicine, University of Babylon, Hillah, Iraq Tel.: +964-(0)7732503243 E-mail: med812.duha.hussien@student.uobabylon.edu.iq

ABSTRACT

Type 2 diabetes mellitus (T2DM) is associated with an increased susceptibility to opportunistic fungal infections, particularly those caused by Candida species. Recent pharmacological evidence suggests that certain oral antidiabetic drugs (OADs) may exhibit intrinsic antimicrobial activity beyond their glycemic control. This study aimed to evaluate and quantify the in vitro antifungal effects of five commonly prescribed OADs (metformin, pioglitazone, gliclazide, vildagliptin, and dapagliflozin) against two isolates of Candida albicans and Candida glabrata. Antifungal activity was initially assessed using a 96-well microdilution assay across clinically relevant concentrations (0.125–8.0 mg/L), with fungal growth quantified via relative optical density. Subsequently, a dynamic in vitro pharmacokinetic/pharmacodynamic model was employed to simulate human plasma clearance and drug exposure ($fAUC_{0\text{-}24}$). Key pharmacodynamic parameters, including half-maximal inhibitory concentration (IC_{50}), maximum effect (E_{max}), and Area Under the Curve (AUC), were estimated using a nonlinear sigmoidal E_{max} model. Metformin demonstrated the highest intrinsic antifungal efficacy, achieving E_{max} values of 72% for C. albicans (IC_{50}: 1.0 mg/L) and 68% for C. glabrata (IC_{50}: 2.0 mg/L). Pioglitazone and gliclazide exhibited moderate, clinically relevant fungistatic activity. Conversely, vildagliptin and dapagliflozin displayed the weakest effects, requiring high concentrations to achieve minimal inhibition. These findings highlight that specific OADs, particularly metformin and pioglitazone, possess intrinsic antifungal properties that may offer secondary clinical advantages in opportunistic fungal infections among immunocompromised patients with T2DM patients.

KEYWORDS: Oral anti-diabetic drugs; Antifungal Effects; metformin; PD parameters; In vitro Pharmacodynamic modeling.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global health challenge defined by chronic hyperglycemia, insulin resistance, and progressive beta-cell dysfunction. Beyond metabolic strain, the diabetic microenvironment compromises immunity and alters cytokine profiles, predisposing patients to severe, recurrent opportunistic fungal infections like candidiasis. This clinical reality highlights an urgent need for dual-action therapies that maintain glycemic control while providing supplementary antifungal benefits [1]. Oral anti-diabetic drugs (OADs)—comprising biguanides, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors form the cornerstone of T2DM care. Interestingly, the paradigm of drug repurposing has revealed that several OAD classes exhibit intrinsic antimicrobial capabilities independent of their glucose-lowering mechanisms, offering a viable strategy to mitigate the high incidence of Candida infections within this vulnerable population [2-11]. Metformin, the most widely prescribed biguanide, demonstrates distinct pleiotropic effects, including the capacity to restrict the proliferation of clinically significant yeasts. Mechanistically, it inhibits Candida albicans by regulating autophagy and exhibits synergistic potential that enhances conventional antifungals while boosting host macrophage-mediated clearance against non-albicans species like Candida glabrata [2,3]. Other OAD classes display similarly promising antimicrobial and immunomodulatory profiles. The TZD pioglitazone modulates inflammatory pathways via PPAR-γ activation and serves as an effective adjuvant in serious fungal infections like cryptococcosis. Meanwhile, second-generation sulfonylureas, such as gliclazide, act as dual-action agents by arresting C. albicans growth and suppressing candidalysin-mediated NLRP3 inflammasome activation to mitigate pathogen-induced inflammation and cellular damage [4-8]. The roles of newer OAD classes are more nuanced. DPP-4 inhibitors like vildagliptin reinforce host defenses indirectly by reducing oxidative stress and dampening hyperinflammatory responses. Conversely, SGLT2 inhibitors like dapagliflozin present a unique clinical paradox: despite in vitro evidence suggesting they may reduce microbial adhesion, their primary therapeutic mechanism promoting glucose excretion via glycosuria clinically predisposes patients to urogenital mycotic infections [9-13]. Despite these compelling individual insights, comprehensive in vitro analyses directly comparing antifungal efficacy across different OAD classes remain scarce [14]. Given the escalating threat of fungal infections in diabetic patients and the strategic value of exploring repurposed pharmacological therapies, this study systematically evaluates and compares the in vitro antifungal properties of metformin, pioglitazone, gliclazide, vildagliptin, and dapagliflozin against the prominent clinical pathogens C. albicans and C. glabrata.

2. METHODOLOGY

2.1. Fungal isolates and media: The current study utilized two fungal isolates (C. albicans ATCC-90028 and C.glabrata ATCC-90300), both incubated at 37°C in RPMI-1640 medium (Sigma-Aldrich, Germany). Suspensions were formulated by transferring 24 hours cultures into sterile normal saline. For the in vitro model, the final inoculum density was standardized to 2×10^4 CFU/ml utilizing a Neubour counting chamber.

2.2. OADs agents: Metformin (Glucophage; 1000 mg; Merck, Germany), pioglitazone (Pioxiga; 10 mg / tab; Pioneer, Iraq), gliclazid (Diamicron MR; 60 mg / tab; MIMS, Malaysia), vildagliptin (Galvus MR; 50 mg / tab; Novartis Pharma AG, Switzerland) and dapagliflozin (Forxiga; 10 mg; AstraZeneca, UK) were used in the experiments.

2.3. Drug preparation and susceptibility test:

2.3.1. Drug Preparation and Inoculation: OADs were initially dissolved in dimethyl sulfoxide (DMSO). The serial dilutions according to the simulated human free (unbound) maximum plasma concentrations (C_{max}) were prepared for metformin (1–5 mg/L) **[15]**, pioglitazone (1–3 mg/L) **[16]**, gliclazide (2–10 mg/L) **[17]**, vildagliptin (0.25–1.0 mg/L) **[18]**, and dapagliflozin (0.125–1.0 mg/L) **[19]**. The aliquots of two-fold serially diluted drugs (0.125 to 8.0 mg/L) as (100µl) were dispensed into 96-well flat-bottom microdilution plates. The wells were then inoculated with 2 x 10^4 CFU/ml of the respective fungal isolates suspended in normal sterile saline.

2.3.2. Incubation and Optical Density Measurement: Plates were incubated at 37°C for 24 hours. Fungal growth was quantified by measuring the relative optical density (ROD) at 600 nm utilizing a microplate reader (Mindray MR 96A, Korea). The recorded ROD values were used to determine the percentage of fungal growth inhibition.

2.3.3. Data and Statistical Analysis: The percentage of fungal growth inhibition (E) was analyzed using nonlinear regression software (GraphPad Prism 5.0, San Diego, CA, USA). Data were fitted to a variable-slope sigmoidal E_{max} model according to the following equation: $E = E_{max} \times C^n / C^n + IC_{50}^n$ In this model, E_{max} is the maximal growth inhibition, C represents the drug concentration, IC_{50} indicates the concentration yielding 50% inhibition, and n is the Hill slope. These parameters were derived by plotting the responses against the $\log_{10}$ of each drug concentration. Model reliability was verified by assessing the coefficient of determination (R^2) for each curve. The cumulative antifungal effect was evaluated across different exposures, the area under the curve (AUC) for the inhibition concentration relationship was also calculated.

2.4. In vitro pharmacokinetic/pharmacodynamic (PK/PD) Model Setup: A dynamic in vitro PK/PD model, driven by a peristaltic pump (Minipuls Evolution; Gilson Inc., France), was utilized for this study. The system comprised an external compartment (EC) consisting of a 500 ml beaker filled with RPMI-1640 medium, and an internal compartment (IC) represented by 5 ml dialysis tubes containing the fungal inoculum. The dialysis membrane tubes (cellulose, <50 kDa molecular weight cutoff, Float-A-Lyzer; Spectrum Europe BV, Breda, The Netherlands) permitted the free diffusion of antimicrobial agents while restricting the microorganisms to the IC. Drugs were introduced at IC_{50} for each OADs, and their elimination was simulated by continuously pumping fresh medium into the system. This dilution rate was specifically calibrated to mimic human plasma clearance, assuming a 24-hour half-life. Such a configuration allowed for dynamic, time-dependent fluctuations in drug concentration, accurately reflecting in vivo pharmacokinetics and establishing a robust platform for PD evaluation. Fungal growth inhibition within the IC_{50} was monitored over a 24-hour period. At predetermined intervals, 200 µl aliquots were extracted at multiple time points (0-24 hrs) and analyzed via spectrophotometry at 600 nm to ascertain ROD as PD parameter, was subsequently estimated via nonlinear regression analysis fitted to a variable-slope sigmoidal E_{max} model with a variable slope. E_{max} values were determined for each OADs.

3. RESULTS AND DISCUSSION

3.1. IC_{50} Values of the In Vitro Antifungal Activities of All Five OADs: The IC_{50} values provide critical insights into the relative potency of the evaluated OADs against specific fungal pathogens. Our data consistently suggest that the fungal isolate C. albicans exhibits a slightly greater sensitivity to these pharmacological agents compared to C. glabrata. Specifically, metformin demonstrated marked potency against both strains, achieving a low IC_{50} of 1.0 mg/L for C. albicans and 2.0 mg/L for C. glabrata. Pioglitazone also showed notable efficacy with an IC_{50} of 2.0 mg/L against C. albicans and 4.0 mg/L against C. glabrata. Gliclazide maintained a consistent IC_{50} of 4.0 mg/L across both species. This pharmacokinetic alignment suggests that the antimicrobial effects of these specific OADs are not merely artifactual observations restricted to high dose laboratory exposure, but rather represent a biologically plausible in vivo phenomenon. Such idiosyncratic capabilities mediating glycemic control while simultaneously exerting localized or systemic fungistatic effects underscore their potential secondary role in mitigating opportunistic infections frequently observed in immunocompromised diabetic patient populations **[2-7]**. Conversely, the inhibitory threshold for the remaining OADs was notably higher. Both vildagliptin and dapagliflozin required a substantially higher concentration of 8.0 mg/L to achieve 50% relative inhibition against both C. albicans and C. glabrata. Crucially, while these parameters reflect moderate in vitro antimicrobial activity, these specific IC_{50} values may exceed the standard physiological peak plasma concentrations attainable following typical oral administration of these specific OADs. Consequently, while the structural moieties of these inhibitors may interact with fungal survival pathways in a controlled laboratory setting, their direct utilization as independent antifungal agents in vivo is inherently limited by their pharmacokinetic profiles. Translating these specific in vitro concentrations into clinical practice would likely require supratherapeutic dosing, thereby elevating the risk of adverse pharmacological events and systemic toxicity without guaranteeing therapeutic antimicrobial success [8-11](Table 1).

3.2. E_{max} and AUC of the PD Modeling for In Vitro Antifungal Activities: PD modeling, assessing E_{max} and AUC, reveals that all five tested OADs possess measurable, albeit varying, in vitro antifungal activity. The coefficient of determination (R^2) for these concentration-dependent responses was highly reliable. As visualized in the sigmoidal dose-response curves, R^2 values ranged from 0.9736 to 0.9998 across all modeled curves, confirming a robust dose-dependent relationship for these agents (Table 1).

3.2.1. Metformin: Among the evaluated agents, metformin exhibited the most robust intrinsic antimicrobial profile. It achieved the highest maximal inhibition against both clinical isolates, recording a peak E_{max} of 72% for C. albicans and 68% for C. glabrata. This superior efficacy is further supported by substantial AUC values of 82.85% and 76.40%, respectively. The pronounced inhibitory effect of metformin aligns with established hypotheses suggesting its capacity to disrupt fundamental microbial processes, potentially through interference with respiratory chains and cellular energy metabolism [2,3,20]](Table 1)(Figure 1).
3.2.2. Pioglitazone and Gliclazide: Pioglitazone demonstrated the second-highest antifungal efficacy in the study, achieving an E_{max} of 65% (AUC 68.10%) against C. albicans and an E_{max} of 56% (AUC 52.95%) against C. glabrata. Gliclazide demonstrated moderate, yet clinically interesting, inhibitory profiles, achieving an E_{max} of 50% (AUC 51.90%) against C. albicans and an E_{max} of 45% (AUC 39.30%) against C. glabrata. The moderate antifungal activity of gliclazide may be partially attributed to its well-documented antioxidant properties and potential secondary interference with cell wall integrity. Such off-target pharmacological benefits underscore the value of exploring established medications for their inherent biochemical disruption of pathogenic structural components [4-7,21,22] (Table 1)(Figure 1).
3.2.3. Vildagliptin and Dapagliflozin: Both OADs exhibited distinct and restrained intrinsic efficacy across both strains. Vildagliptin recorded an E_{max} of 42% against C. albicans and 40% against C. glabrata. Dapagliflozin displayed the lowest overall activity, yielding an E_{max} of 40% against C. albicans and 38% against C. glabrata. These specific findings support the prevailing clinical theory that the increased incidence of genitourinary infections associated with SGLT2 inhibitors (like dapagliflozin) is primarily driven by induced glycosuria which creates a nutrient-rich environment favorable for microbial growth rather than an intrinsic pro-microbial property or direct mechanistic failure of the drug itself [8-10,23,24] (Table 1)(Figure 1).
3.3. Pharmacodynamic Modeling and Exposure–Response Relationships: The dynamic in vitro PK/PD model successfully simulated human pharmacokinetics and demonstrated a consistent relationship between drug exposure and antifungal activity across all OADs. Under drug-only conditions, increasing exposure was directly associated with improved pharmacodynamic responses. Metformin and pioglitazone produced the most significant upward shifts in exposure-response analysis, followed by gliclazide. The least pronounced effects were associated with vildagliptin and dapagliflozin. These findings emphasize the limitations of conventional static in vitro models, as they may underestimate true antimicrobial activity. In contrast, dynamic PK/PD models provide a more accurate prediction of in vivo drug performance [2-11, 20-24] (Figure 2 and Figure 3).

4. CONCLUSION

This study demonstrates that common OADs possess varying intrinsic antifungal activity against C. albicans and C. glabrata. Metformin and pioglitazone exhibit the highest potency, followed by gliclazide, while vildagliptin and dapagliflozin show the lowest. These secondary properties may reduce opportunistic infection severity in T2DM patients, though further in vivo research is required to confirm clinical efficacy.

AUTHOR CONTRIBUTIONS: Duha Hussain Abd-Alhadi contributed to study conceptualization, literature review, methodology development, data collection, experimental work, statistical analysis, data interpretation, manuscript drafting, and corresponding author responsibilities. Hussam W. Al-Humadi contributed to study supervision, project administration, methodology validation, data interpretation, critical revision of the manuscript, and final approval of the version submitted for publication. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT: None to declare.

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Table 1: The IC_{50}s (drug concentration corresponding to 50% of growth inhibition), E_{max} values (maximal fungal growth inhibition), Area Under Curve (AUC) and the coefficient of determination (R^2) values calculated for all five oral anti-diabetic drugs (metformin, pioglitazone, gliclazide, vildagliptin and dapagliflozin) against clinically relevant fungal pathogens (Candida albicans ATCC-90028 and Candida glabrata ATCC-90300)

Bacterial Isolates	Oral anti-diabetic drugs	Mean of IC_{50} (mg/l)	Mean of E_{max} (%)	AUC (%)	R^2 (≤1.0)
	Metformin	1.0	72	82.85	0.9960
	Pioglitazone	2.0	65	68.10	0.9971
	Gliclazide	4.0	50	51.90	0.9998

Candida albicans ATCC-90028	Vildagliptin	8.0	42	40.50	0.9979
	Dapagliflozin	8.0	40	34.05	0.9736
Candida glabrata ATCC-90300	Metformin	2.0	68	76.40	0.9945
	Pioglitazone	4.0	56	52.95	0.9965
	Gliclazide	4.0	45	39.30	0.9992
	Vildagliptin	8.0	40	34.20	0.9966
	Dapagliflozin	8.0	38	29.10	0.9995

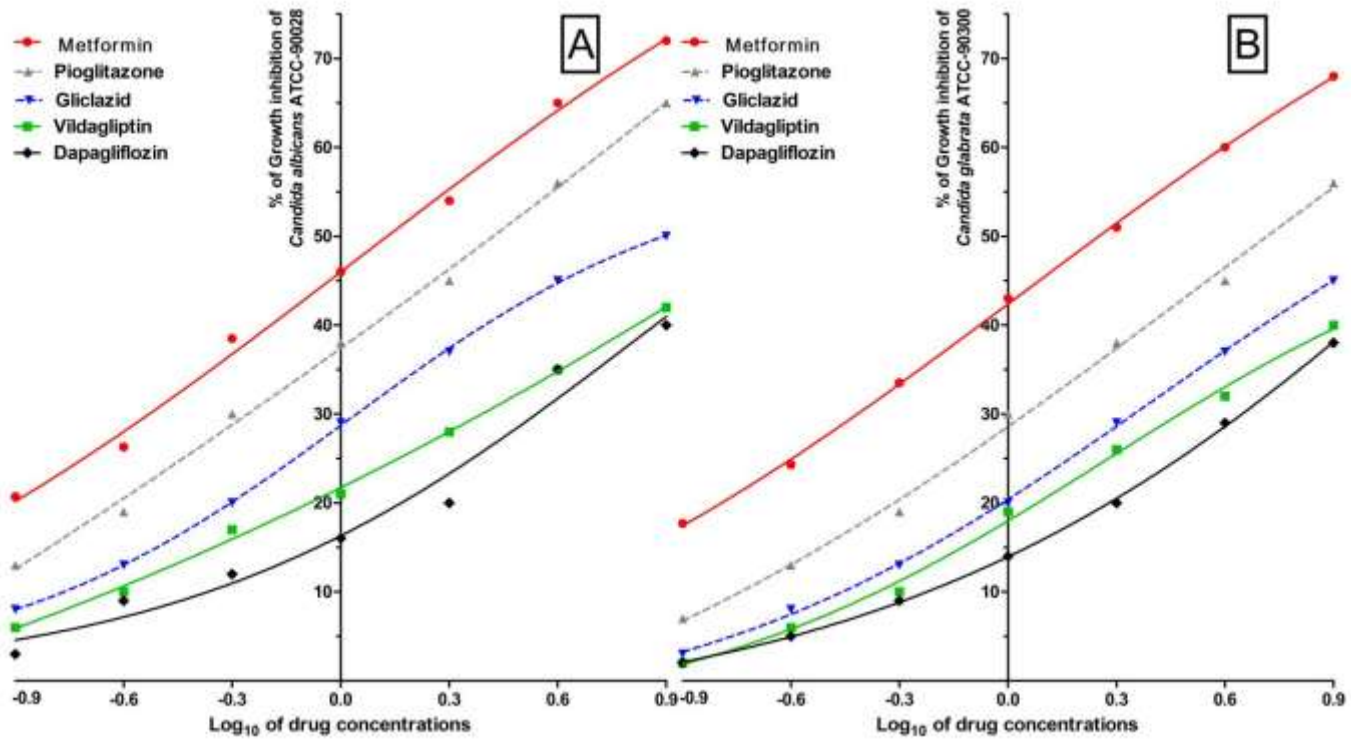

Figure 1: The anti-fungal activity of all five oral anti-diabetic drugs (metformin, pioglitazone, gliclazide, vildagliptin and dapagliflozin) against clinically relevant fungal pathogens (Candida albicans ATCC-90028 **[A]** and Candida glabrata ATCC-90300 **[B]**) by measuring E_{max} (maximal fungal growth inhibition) for serial concentrations of each drug (0.125-8.0 mg/L).

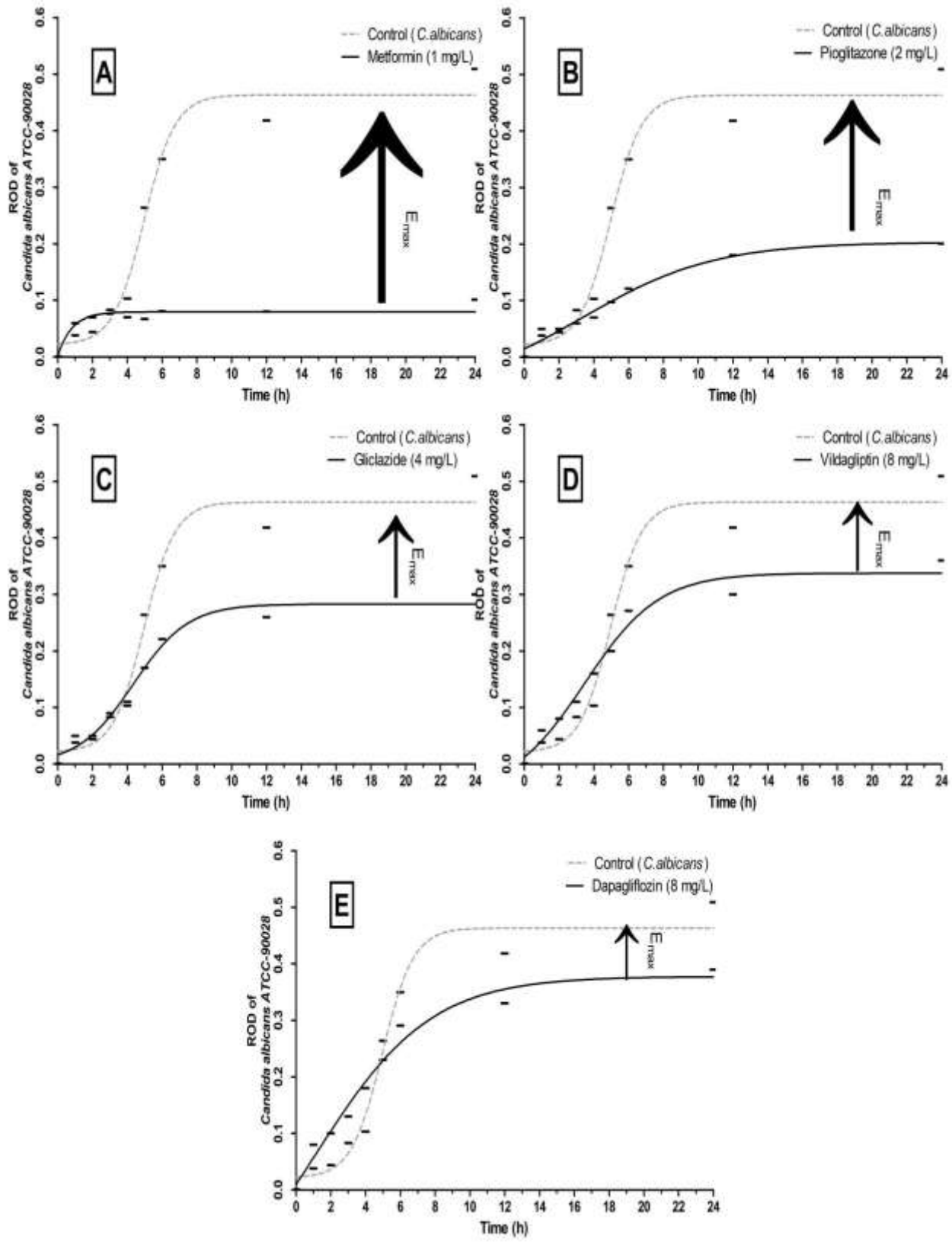

Figure 2: The anti-fungal activity of all five oral anti-diabetic drugs (metformin **[A]**, pioglitazone **[B]**, gliclazide **[C]**, vildagliptin **[D]** and dapagliflozin **[E]**) against Candida albicans ATCC-90028 by measuring E_{max} (maximal fungal growth inhibition) of IC_{50} (drug concentration corresponding to 50% of growth inhibition) for each drug.

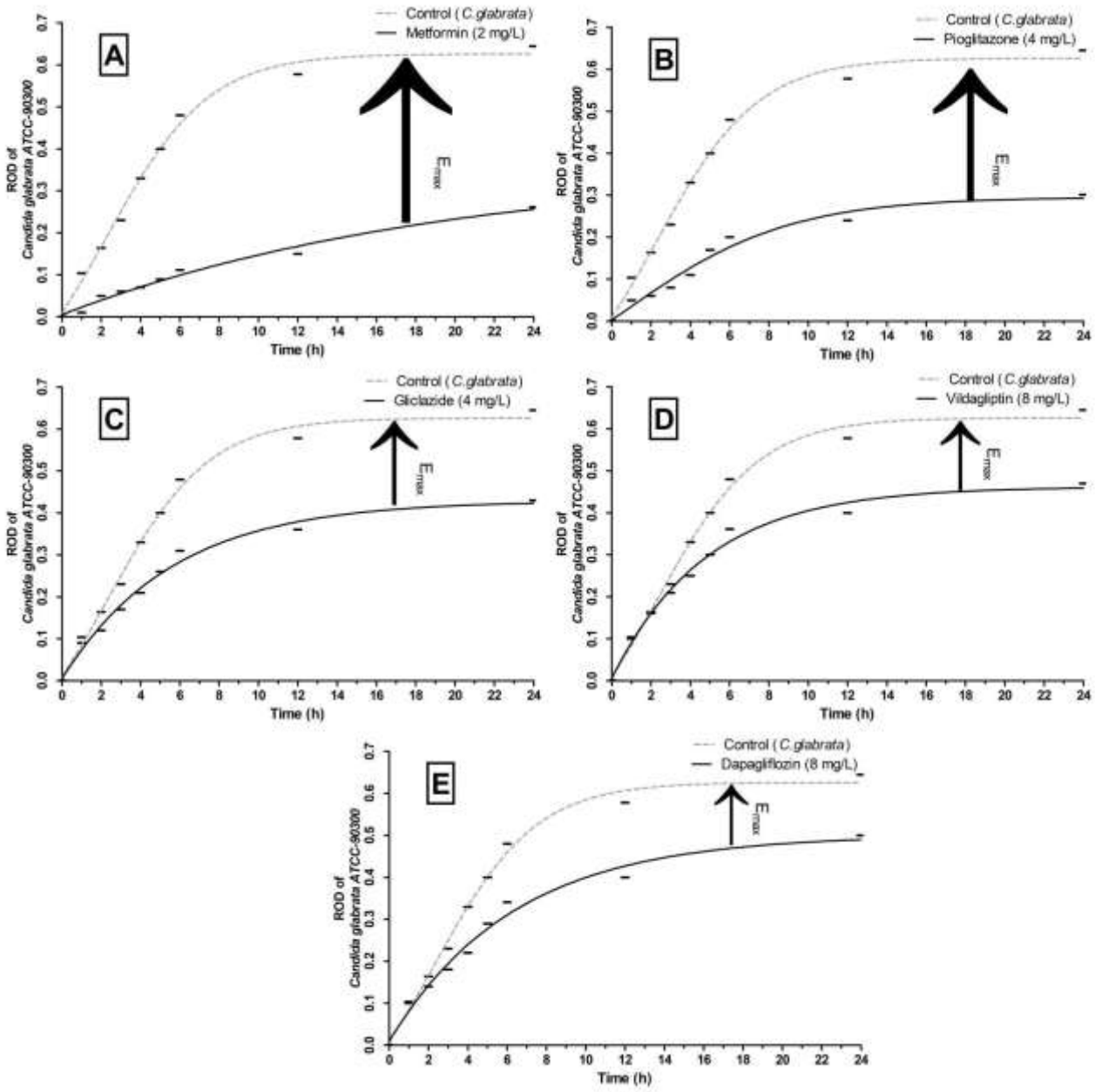

Figure 3: The anti-fungal activity of all five oral anti-diabetic drugs (metformin **[A]**, pioglitazone **[B]**, gliclazide **[C]**, vildagliptin **[D]** and dapagliflozin **[E]**) against Candida glabrata ATCC-90300 by measuring E_{max} (maximal fungal growth inhibition) of IC_{50} (drug concentration corresponding to 50% of growth inhibition) for each drug.