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COMMENTARY

# Anti-infective properties of proton pump inhibitors: perspectives

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**Abstract**
Infectious diseases are among the main causes of morbidity and mortality today. In facing this crisis, the development of new drug options and combat strategies is necessary. In this sense, drug repositioning or drug redirection has emerged for the faster identification of effective drugs. In this "Commentary," the anti-infective properties of the class of proton pump inhibitors (PPIs) are emphasized. Studies report activities against bacterial, fungal, parasitic, and viral agents. In addition, we have provided in a table a summary of the specific characteristics of PPIs and some of their anti-infective activities.

**Keywords** Anti-infective properties · Drug repurposing · Infectious diseases · Proton pump inhibitors

## Introduction

Infectious diseases are among the main causes of morbidity and mortality today. This problem is compounded by the current crisis of resistance to antibacterial, antifungal, antiparasitic, and antiviral drugs, which has become a public health issue not only in terms of limited treatment options but also because of its economic burden. In facing this crisis, studies that analyze the causes of resistance and its expansion, together with the development of new drug options and combat strategies, are necessary (Nolte 2014; Gil-Gil et al. 2019; Nathan 2020).

## Commentary

A promising alternative is drug repositioning. Repositioning, or also called redirection or repurposing, has been a trending topic in the literature and represents a new drug development strategy. This method consists of finding new uses for clinically approved drugs that already have a known chemical structure, toxicity, and safety profile. Thus, they can be redirected in the treatment of emerging diseases and pandemics, due to their speed of implementation, effectiveness, and lower costs when compared to the development of a new drug (Ashburn and Thor 2004; Serafin and Hörner 2018; Peyclit et al. 2019; Zhou et al. 2020).

Studies reporting the importance of drug repositioning for the treatment of infectious diseases are available, and among them we cite several classes, such as antidepressants (Bottega et al. 2020; da Rosa et al. 2020, 2021; Foletto et al. 2020, 2021; Machado et al. 2020; Serafin et al. 2020), antihypertensive (Hu et al. 2018), antihistamines (Bruer et al. 2019; El-Nakeeb et al. 2011), anti-inflammatory (Chan et al. 2017), alcohol-aversive agentes (Serafin et al. 2020), benzodiazepines (da Rosa et al. 2021), and statins (Rampelotto et al. 2018). In this commentary, the class of proton pump inhibitors (PPIs) is emphasized.

PPIs are known for their use in stomach acid–related disorders. Your representatives—dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, and tenatoprazole—are derived from the heterocyclic organic molecule benzimidazole and are first-line agents for the treatment of non-erosive reflux disease, peptic ulcer, Zollinger-Ellison syndrome, prevention of ulcers induced by non-steroidal anti-inflammatory drugs, eosinophilic esophagitis in pediatric patients, and eradication of

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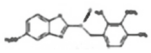
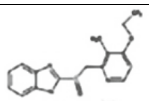
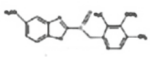
**Table 1** Summary of proton pump inhibitors and some of their anti-infective properties

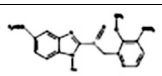
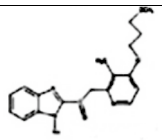
| Drug | Molecular structure | Chemical formula | Anti-infective activity (ies) | New indication | Type of study | Activity data | References |
|---|---|---|---|---|---|---|---|
| Esomeprazole |  | $C_{17}H_{19}N_3O_3S$ | Antibacterial | *Pseudomonas aeruginosa* | *In silico* | Virtually found as a LasR inhibitor - system that controls virulence genes | Sadiq et al. |
| Lansoprazole |  | $C_{16}H_{14}F_3N_3O_2S$ | Antibacterial | *Mycobacterium tuberculosis* | *In vivo* | Dose (µg/mL): 7.8411 and 9.761<br>Mentioned that hen it is administered intraperitoneally, significant amounts penetrate the tissue, being promising for further anti-tuberculosis tests | Mdanda et al.* |
| | | | | *Ureaplasma urealyticum* | *In vitro* | $IC_{50}$ (µM): 12.5-25.0 | Nagata et al. |
| | | | Antifungal | *Candida albicans* | *In vitro* | IC (µM): ≥200 | Biswas et al. |
| | | | | *Candida* spp. | *In vitro* | MFC (µg/mL): 128 | Siavoshi et al. |
| | | | Antiparasitic | *Trichomonas vaginalis*<br>*Giardia intestinalis*<br>*Entamoeba histolytica* | *In vitro* | $IC_{50}$ (µM): 0.1218<br>$IC_{50}$ (µM): 0.0731<br>$IC_{50}$ (µM): 0.3466 | Pérez-Villanueva et al. |
| | | | | *Plasmodium falciparum* | *In vitro* | $IC_{50}$ (µM): 9.3 | Riel et al. |
| | | | Antiviral | Rhinovirus | *In vitro* | Reduced supernatant titers and RNA of rhinovirus in tracheal epitelial cells with maximum effect with 10µM after 48h | Sasaki et al. |
| | | | | SARS-CoV-2 | *In silico* | Reported endolysosomal pH-mediated effect<br>pKa data:<br>Strongest acidic: 9.29<br>Strongest basic: 4.77 | Homolak et al. |
| Omeprazole |  | $C_{17}H_{19}N_3O_3S$ | Antibacterial | *Ureaplasma urealyticum* | *In vitro* | $IC_{50}$ (µM): 12500.00 | Nagata et al. |
| | | | | *Enterococcus faecalis* | *In vitro* | Bacterial growth curves (mg/L): 300<br>Time zero: 4 log CFU/mL<br>After 24h: less than 1 log CFU/mL | Jonkers et al. |
| | | | | *Staphylococcus aureus* | | Bacterial growth curves (mg/L): 300<br>Time zero: 4 log CFU/mL<br>After 24h: less than 1 log CFU/mL | |
| | | | | *Staphylococcus aureus* | *In vitro* | Strain SA-1199<br>MIC (µg/mL): 1 | Vidaillac et al.* |

*Helicobacter pylori* when in combination with antibacterials (Strand et al. 2017; Ward and Kearns 2013).

These drugs were clinically introduced over 25 years ago and have since proven to be invaluable, safe, and effective agents for the treatment of a variety of gastric acid–related disorders. Although adverse effects related to the use of PPIs have been reported, their clinical relevance is still unclear, as the evidence reported in these studies is based on retrospective observational studies. When compared to previous agents, this class demonstrates consistent patient tolerance, excellent safety, and generally superior acid-suppressing capacity. These are drugs widely used by the population, considering that omeprazole is among the 10 most prescribed in the USA (Perry et al. 2020; Strand et al. 2017).

PPIs have been continuously studied for presenting other activities, in addition to those already known and used commercially, and the most reported in the literature are the anti-infective ones. These properties are reported against different infectious agents: antibacterial activity, against *Pseudomonas aeruginosa* (Sadiq et al. 2020), *Mycobacterium*

**Table 1** (continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Strain SA-1199B (overexpressing NorA gene) MIC (μg/mL): 8 | |
| | | Antifungal | *Candida albicans* *Saccharomyces cerevisiae* | *In vitro* | IC (μM): ±860 IC (μM): 430 | Monk et al. |
| | | Antiparasitic | *Trichomonas vaginalis* *Giardia intestinalis* *Entamoeba histolytica* | *In vitro* | $IC_{50}$ (μM): 0.1216 $IC_{50}$ (μM): 0.0955 $IC_{50}$ (μM): 0.4922 | Pérez-Villanueva et al. |
| | | | *Plasmodium falciparum* | *In vitro* | $IC_{50}$ (μM): 27.1 | Riel et al. |
| | | | *Schistosoma mansoni* | *In vivo* | The number/liver section and diameter of hepatic granulomas in infected mice in all studied groups at 12 weeks post infection (m) Infected control: 0.00004310 ± 3.16 Omeprazole: 0.00004150 ± 8.90 | Ellakany et al. |
| | | | *Schistosoma mansoni* | *In vitro* | Dose effective (μg/mL): 25 after 120h | Almeida et al. |
| | | | *Giardia lamblia* | *In vitro* | Dose (μg/mL): 25. In combination with praziquantel it showed promising results because it increases the expression of the ATP1A2 gene, which increases the mortality of adult worms | Hernández-Ochoa et al.* |
| | | | *Tritrichomonas foetus* | *In vitro* | MLC (μg/mL): >80 | Kather et al. |
| | | | *Tritrichomonas foetus* | *In vitro* | $IC_{50}$ (μg/mL): 16 | Sutak et al. |
| | | Antiviral | SARS-CoV-2 | *In silico* | Reported endolysosomal pH-mediated effect pKa data: Strongest acidic: 9.35 Strongest basic: 4.16 | Homolak et al. |
| | | | SARS-CoV-2 | *In vitro* | Reported 8μM interfered viral formation | Aguila et al. |
| Pantoprazole |  $C_{16}H_{15}F_2N_3O_4S$ | Antiparasitic | *Trichomonas vaginalis* *Giardia intestinalis* *Entamoeba histolytica* | *In vitro* | $IC_{50}$ (μM): 0.0756 $IC_{50}$ (μM): 0.0157 $IC_{50}$ (μM): 0.0026 $IC_{50}$ (μM): 39 | Pérez-Villanueva et al. |
| | | | *Plasmodium falciparum* | *In vitro* | $IC_{50}$ (μM): 73.3 | Riel et al. |
| | | | *Plasmodium falciparum* | *In vitro* | $EC_{50}$ (μg/mL): 7.66 – 15.33 | Skinner-Adams et al. |
| Rabeprazole |  $C_{18}H_{21}N_3O_3S$ | Antiparasitic | *Trichomonas vaginalis* *Giardia intestinalis* *Entamoeba histolytica* | *In vitro* | $IC_{50}$ (μM): 0.1057 $IC_{50}$ (μM): 0.0181 $IC_{50}$ (μM): 0.0237 | Pérez-Villanueva et al. |
| | | | *Plasmodium falciparum* | *In vitro* | $IC_{50}$ (μM): 9.8 | Riel et al. |

*Structure similar to the drug indicated

Captions of abbreviations and acronyms that appear in the table: *CFU*, colony forming unit; *EC50*, half maximum effective concentration; *IC*, inhibitory concentration; *IC50*, half of the inhibitory concentration; *MFC*, minimum fungicidal concentration; *MIC*, minimum inhibitory concentration; *MLC*, minimum lethal concentration

SOURCE: elaborated by the author, 2021

*tuberculosis* (Mdanda et al. 2017), *Ureaplasma urealyticum* (Nagata et al. 1995), *Enterococcus faecalis* (Jonkers et al. 1996), and *Staphylococcus aureus* (Jonkers et al. 1996; Vidaillac et al. 2007); antifungal, against *Candida albicans* (Biswas et al. 2001; Monk et al. 1995), *Candida* spp. (Siavoshi et al. 2012), and *Saccharomyces cerevisiae* (Monk et al. 1995); antiparasitic, against *Trichomonas vaginalis* (Pérez-Villanueva et al. 2011), *Giardia intestinalis* (Pérez-Villanueva et al. 2011), *Entamoeba histolytica* (Pérez-Villanueva et al. 2011), *Plasmodium falciparum* (Riel et al. 2002; Skinner-Adams et al. 1997), *Schistosoma mansoni* (Almeida et al. 2015; Ellakany et al. 2019), *Giardia lamblia* (Hernández-Ochoa et al. 2017), and *Tritrichomonas foetus* (Sutak et al. 2004; Kather et al. 2007); antiviral, against SARS-CoV-2 (COVID-19) (Aguila and Cua 2020; Homolak and Kodvani 2020) and rhinovirus (Sasaki et al. 2005). In Table 1, we present a summary of the characteristics of PPIs and some of their anti-infective activities.

The activity of PPIs against COVID-19 is controversially reported. Some studies report that omeprazole would act positively against the virus, as previous studies had already reported that omeprazole was able to inhibit viral replication by interfering with the acidification of lysosomes. Drugs that affect the activity of vesicular acidification mechanisms neutralize endolysosomal compartments. A PPI can neutralize these compartments through inhibition of vacuolar-type H+-ATPase (V-ATPase). Furthermore, it is still presented that the class of PPIs could help not only in the treatment, but also in the prophylaxis against the virus (Aguila and Cua 2020; Homolak and Kodvani 2020; Shen et al. 2017; Tastemur and Ataseven 2020; Vuille-dit-Bille et al. 2015).

On the other hand, other studies report that patients taking PPIs are at increased risk for serious clinical outcomes of COVID-19. It was found that individuals who take drugs in this class twice a day are more likely to report a positive test for SARS-CoV-2, when compared to those who use a lower dose up to once a day. The mechanism of this worrisome clinical outcome would occur because PPIs would alter one of the main functions of the gastric juice, which is to inactivate ingested microorganisms, thus inhibiting infectious agents from reaching the intestine (Almario, Chey and Spiegel 2020; Charpiat et al. 2020; Lee et al. 2021).

## Conclusions

These considerations about the activities of PPIs against COVID-19 lead us to question what are the perspectives for the future use of PPIs as anti-infective agents?

Several drug classes that present significant adverse effects and control by medical prescription are used in studies with the objective of verifying the anti-infective activities. PPIs have a great advantage to be considered, since they are drugs that do not require a medical prescription to be marketed, have an excellent safety profile and ease of administration, and are among the most used drugs worldwide (Scarpignato et al. 2016). More studies are always welcome in clinical research to confirm the anti-infective potential of this class, but we can say that the therapeutic advantage will be great. Therapeutic activities are significantly reported in the literature, demonstrating the interest of researchers in this topic. Thus, the future perspectives for the use of anti-infective activities of PPIs are the best.

**Author contribution** T.F.R., V.S.F., M.B.S., A.B., and R.H.: the conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting and critical revision of the manuscript, and final approval of the version to be submitted.

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## Declarations

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

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**Conflict of interest** The authors declare no competing interests.

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