



***SYSTEMATIC LITERATURE REVIEW:***  
**PENGARUH PENGGUNAAN *PROTON PUMP***  
***INHIBITOR* JANGKA PANJANG TERHADAP**  
**IMUNITAS TRAKTUS GASTROINTESTINAL**

**SKRIPSI**

**Untuk Memenuhi Persyaratan**  
**Memperoleh Gelar Sarjana Kedokteran**



Oleh

**KEKE ANGGUN INDIRA YOSELA**

**21601101097**

**PROGRAM STUDI KEDOKTERAN**  
**FAKULTAS KEDOKTERAN**  
**UNIVERSITAS ISLAM MALANG**  
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## RINGKASAN

**Keke Anggun Indira Yosela**, Fakultas Kedokteran, Universitas Islam Malang, Januari 2021. Systematic Literature Review: Pengaruh Penggunaan Proton Pump Inhibitor Jangka Panjang Terhadap Imunitas Traktus Gastrointestinal. **Pembimbing I:** dr. H.R.M Hardadi Airlangga, Sp.PD. **Pembimbing II:** drg. Helmin Elyani, M.Kes.

**Pendahuluan :** Proton Pump Inhibitor (PPI) adalah kelompok obat yang digunakan untuk menurunkan kadar asam lambung sekaligus meredakan gejala yang disebabkan oleh peningkatan asam lambung secara patologis. Pada penggunaan PPI jangka panjang, dapat timbul sejumlah potensi efek samping, dikhawatirkan efek samping tersebut dapat mempengaruhi sistem kekebalan tubuh. Systematic literature review ini bertujuan untuk mengetahui pengaruh penggunaan PPI jangka panjang terhadap imunitas traktus gastrointestinal khususnya pada sel epitel, keasaman, kualitas mukus, mikrobiota traktus gastrointestinal, hingga efeknya pada neutrofil.

**Metode :** *Systematic Literature Review* mengenai pengaruh pemberian Proton Pump Inhibitor (PPI) jangka panjang terhadap sistem imunitas serta homeostasis traktus gastrointestinal yang dilakukan pencarian melalui database google scholar, pubmed central, dan sciencedirect dengan memasukkan kata kunci “Proton pump inhibitors” “Immunity dysfunction” “Disadvantages” “Side Effect” “Microflora” dan “GI Infection”. Jurnal dipilih sesuai kriteria inklusi yakni jurnal original article dengan rentang terbit tahun 2010-2020 dan dapat diakses full text.

**Hasil :** Sejumlah 13 jurnal terpilih sesuai kriteria inklusi. Didapatkan 2 jurnal tidak valid dan 11 jurnal valid, jurnal yang di dapat membahas mengenai keasaman, mukus, mikrobiota dan neutrofil. Jurnal yang didapat paling banyak membahas mengenai efek PPI terhadap keasaman serta mikrobiota gastrointestinal.

**Kesimpulan :** Pada Penggunaan Proton Pump Inhibitor (PPI) jangka panjang dapat mempengaruhi imunitas gastrointestinal khususnya pada keasaman dan mikrobiota GIT.

**Kata Kunci:** *Proton Pump Inhibitor, imunitas, traktus gastrointestinal*

## SUMMARY

**Keke Anggun Indira Yosela**, Faculty of Medicine, Islamic University of Malang, January 2021. Systematic Literature Review : The Effect Of Longterm Proton Pump Inhibitor (PPI) On Gastrointestinal Tract Immunity. **Supervisor I:** dr. H.R.M Hardadi Airlangga, Sp.PD. **Supervisor II:** drg. Helmin Elyani, M.Kes.

**Background:** : Proton Pump Inhibitors (PPIs) are a group of drugs used to reduce stomach acid levels and relieve symptoms caused by pathologically increased stomach acid. With long-term use of PPIs, there are a lot of potentially side effects, it is feared that these side effects can affect the immune system of GIT. This Systematic Literature Review aims to see and analyze the effect of long-term use of PPIs on gastrointestinal tract immunity, especially on epithelial cells, acidity, mucus quality, gastrointestinal tract microbiota, and their effect on neutrophils.

**Method:** Systematic Literature Review on the effect of long-term Proton Pump Inhibitor (PPI) on gastrointestinal tract, is searched through the google scholar, pubmed central, and science direct databases by entering the keywords: “Proton pump inhibitors” “Immunity dysfunction” “Disadvantages” “Side Effect” “Microflora” and “GI Infection”. Journals are selected according to the inclusion criteria, specifically the original journal articles with a range published in 2010-2020 and can be accessed in full text features.

**Result:** A total of 13 journals were selected according to the inclusion criteria. There were 2 invalid journals and 11 valid journals, journals that could discuss acidity, mucus, microbiota and neutrophils. The journals obtained mostly discuss the effect of PPIs on acidity and gastrointestinal microbiota.

**Conclusion:** Long-term use of Proton Pump Inhibitor (PPI) can affect gastrointestinal immunity, especially in pH and microbiota.

**Keywords:** *Proton Pump Inhibitor, immunity, gastrointestinal tract*

UNISMA

## BAB I PENDAHULUAN

### 1.1 Latar Belakang

*Proton Pump Inhibitor* (PPI) adalah kelompok obat yang digunakan untuk menurunkan kadar asam lambung sekaligus meredakan gejala yang disebabkan oleh peningkatan asam lambung. PPI biasa diresepkan oleh dokter umum di seluruh dunia serta menjadi obat yang menduduki peringkat teratas dalam peresepannya oleh *General Practitioner* (GP) dari tahun ke tahun (Oshima dan Miwa, 2015). Di Indonesia, 40-70% pasien yang dirawat inap di rumah sakit mendapatkan terapi obat PPI dan 2/3 diantaranya tidak memiliki indikasi yang tepat. Hal tersebut jelas akan menyebabkan dampak negatif bagi pasien mengingat beberapa efek samping yang dapat timbul dari penggunaan PPI (Mardhatillah, 2015).

PPI dapat mengobati penyakit gastroesophageal reflux, esofagitis erosif, tukak duodenum, dan kondisi hipersekresi HCl patologis dengan efektif. PPI memiliki efek samping jangka pendek yang minimal namun pada penggunaan jangka waktu panjang, dapat menimbulkan banyak efek samping (Vilcu *et al.*, 2018). Kinoshita *et al.*, (2018) menyebutkan bahwa efek samping jangka panjang PPI antara lain perubahan mikrobioma usus, infeksi patogen, pneumonia, polip fundus, kanker kolon, patah tulang pinggul akibat osteoporosis, nefritis interstisial akut, penyakit jantung, demensia, defisiensi zat besi serta mikronutrisi lainnya, hingga ensefalopati hepatikum (Kinoshita *et al.*, 2018). Efek samping tersebut lebih jelas terdokumentasi bagi populasi diatas usia 65 tahun. Hal tersebut disebabkan peningkatan prevalensi penyakit kronis yang lebih tinggi disertai

penurunan fungsi hati sebagai fungsi ekskresi PPI utama (Kristanto *et al.*, 2017). Selain masalah penyakit kronis, masalah lain dapat timbul pada berbagai populasi, khususnya lansia, terkait efek samping penggunaan PPI jangka panjang terhadap imunitas (Rodriguez *et al.*, 2013). Sedangkan, belum ada penelitian *Systematic Literature Review* yang membahas efek penggunaan PPI Jangka Panjang terhadap sistem imunitas.

Sistem imunitas alami (*innate*) dan adaptif saling bekerja sama dalam harmonisasi dalam membentuk kekebalan tubuh. Traktus Gastrointestinal (GIT) memiliki beberapa diferensiasi dalam fortifikasi imunitas dibandingkan sistem organ lainnya. Hal itu penting mengingat setiap hari, GIT dapat terinfeksi oleh sekitar 1 milyar bakteri (Heidelbaugh, Goldberg, dan Inadomi, 2009). Sistem imun tidak terlepas dari pengaruh efek samping PPI, khususnya pada penggunaan jangka panjang (Vilcu *et al.*, 2019). Kinoshita (2018) menjabarkan, penggunaan PPI lebih dari empat minggu sudah dapat menghasilkan gangguan terhadap sistem imunitas akibat efek supresi produksi HCl, terlebih jika penggunaannya diberikan dalam dosis tinggi (Kinoshita *et al.*, 2018). Semakin besar dosis yang diberikan maka akan semakin meningkatkan luaran maksimal hambatan produksi asam lambung (Shin dan Sachs, 2008).

Asam lambung merupakan suatu media pertahanan tubuh, apabila asam lambung menurun, baik akibat PPI ataupun penyebab lainnya, maka proses kinerja sistem kekebalan tubuh tidak akan maksimal khususnya pada traktus gastrointestinal. Asam lambung tergolong dalam sistem imun bawaan (Williams *et al.*, 2012). Sistem imun merupakan suatu bentuk pertahanan tubuh yang berfungsi untuk melindungi terhadap berbagai macam infeksi dengan cara mengidentifikasi

serta membunuh substansi patogen (Sudiono, 2014). Secara teori, sistem imun tubuh terbagi menjadi dua: bawaan (*innate*) serta adaptif (humoral) (Williams *et al.*, 2012). Apabila sistem kekebalan melemah, maka akan berakibat berkurangnya kemampuan untuk melindungi tubuh sehingga patogen dapat tumbuh dan berkembang (Siswanto *et al.*, 2013). Walau begitu, belum ada penelitian khususnya *Systematic Literature Review* yang menjelaskan efek penggunaan PPI jangka panjang terhadap sistem imunitas traktus gastrointestinal.

Berdasarkan pemaparan diatas, peneliti merasa perlu dilakukannya eksplorasi mendalam melalui *systematic literature review* tentang pengaruh PPI jangka panjang terhadap sistem imun traktus gastrointestinal.

## 1.2 Rumusan Masalah

Apakah pengaruh penggunaan *Proton Pump Inhibitor* (PPI) jangka panjang terhadap sistem imunitas traktus gastrointestinal ?

## 1.3 Tujuan Penelitian

Mengetahui pengaruh penggunaan *Proton Pump Inhibitor* (PPI) jangka panjang terhadap sistem imunitas traktus gastrointestinal.

## 1.4 Manfaat Penelitian

Penelitian ini sebagai *systematic literature review* yang diharapkan dapat memiliki manfaat berupa manfaat akademik maupun manfaat praktis.



#### 1.4.1 Manfaat Praktis

*Systematic literature review* ini diharapkan dapat menjadi dasar ilmiah serta landasan teori bahwa penggunaan *Proton Pump Inhibitor* (PPI) jangka panjang dapat mempengaruhi *sistem imun pada traktus gastrointestinal*.

#### 1.4.2 Manfaat Akademis

Diharapkan *Systematic literature review* ini dapat memberikan pengetahuan maupun informasi mengenai pengaruh penggunaan jangka panjang *Proton Pump Inhibitor* (PPI) terhadap sistem imunitas traktus gastrointestinal.



## BAB VII PENUTUP

### 7.1 Kesimpulan

Berdasarkan hasil penelitian dan pembahasan *Systematic Literature Review* tentang pengaruh penggunaan PPI jangka panjang terhadap Sistem Imunitas, maka dapat disimpulkan bahwa penggunaan *Proton Pump Inhibitor* (PPI) jangka panjang memiliki pengaruh terhadap imunitas Gastrointestinal.

### 7.2 Saran

Berdasarkan dari *Systematic Literature Review*, ini peneliti menyarankan untuk:

1. Melakukan penelitian lanjutan terhadap pengaruh penggunaan PPI jangka panjang terhadap beberapa unsur imunitas alami (*innate*) seperti sel epitel, neutrofil, serta kualitas mukus.
2. Melakukan penelitian lanjutan terhadap pengaruh penggunaan PPI jangka panjang terhadap imunitas adaptif berupa penelitian *in vivo*.
3. Melakukan penelitian pengaruh penggunaan PPI jangka panjang terhadap imunitas sistem organ lainnya dengan cara penelitian *in vivo*.
4. Memperbanyak serta memperbaharui literatur, baik berupa studi epidemiologi maupun *clinical trials*, mengenai data prevalensi penggunaan PPI di Indonesia dan efek sampingnya.

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