CASPASE IN PEPTIC ULCER

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Abstract

Peptic ulcer disease (PUD) is when gastric mucosa gets injured due to the increase of gastric acid and the pepsin enzyme. The common risk factors are the infection of Helicobacter pylori bacteria and the misused of NSAIDs. This review article aims to describe the role of caspase in PUD. Methods used are the selection of articles in PubMed. Caspase is a protease enzyme that plays an apoptotic and inflammatory reaction that can be activated when dimerized or cleaved. Caspase-3, caspase-6, caspase-7, caspase-8, and caspase-9 are divided into two subgroups for the apoptotic group. Caspase-1, caspase-4, and caspase-5 are part of the inflammation group. Some compounds can inhibit modulate it. Moreover, most of them work for being inhibitors to avoid PUD. Caspase-1 holds a high responsibility to activate other caspases.

Key words: caspase, helicobacter pylori, NSAIDs, peptic ulcer disease

Introduction

Gastrointestinal (GI) bleeding is a sign of digestive tract disorder that could be visible from the stool’s color darker than the standard color (black) because there is blood in the feces. However, sometimes it cannot be detected from the color of the feces.\textsuperscript{1} Many factors may cause GI bleeding, and one of them is peptic ulcer disease or PUD. This bleeding occurs due to injury to the mucosa because of increased gastric acid secretion and an abnormal amount of pepsin enzyme. Based on the location of the wound, peptic ulcer disease is divided into two types. If the wound forms on the gastric mucosa, it is called a gastric ulcer. If the wound occurs in the mucosa of the upper part of the duodenum, it is called a duodenal ulcer.\textsuperscript{2,3}

The peptic ulcer disease prevalence varies widely in each country in the world. Based on reports from 62 of 196 countries as of November 2016, the African region with a prevalence of 79.1%, the region with the highest prevalence among five other regions, namely Latin America and the Caribbean with a prevalence of 63.4%; North America
The prevalence in 2009-2018 in the United States stated that duodenal ulcer cases had a ratio of 10:1000 cases and gastric ulcer cases had a ratio of 35:1000 cases, with the trend of data being a decrease in cases of Helicobacter pylori infection.\textsuperscript{5} The prevalence in 2015 in five islands of Indonesia was 22.1%.\textsuperscript{6}

The condition that is often found in this case of PUD is Helicobacter pylori infection that lives attached to the gastric mucosa.\textsuperscript{2,7} The mechanism of Helicobacter pylori infection can occur because of the activation of caspase as a protease enzyme that induces programmed cell death, causing an increase in cytokine secretion so that the submucosal wall erodes and becomes inflamed.\textsuperscript{8,9}

This review article was created to understand caspases, the types of caspases that affect peptic ulcer disease, the pathophysiology of peptic ulcer disease, the role of each type of caspases in peptic ulcer disease, and the compounds that affect the action of the caspases.

\textbf{Method}

The method to gather the needed information in this article review is using PubMed as the search engine platform with ‘Caspase AND Peptic Ulcer’ as the keyword. The articles' criteria are related to the topic, published in the latest ten years, and the full version of the articles can be accessed for free.

\textbf{Caspase}

Cysteine aspartate protease, also known as caspase, is a protease enzyme that has a role in apoptosis and inflammation. Caspase in the body is in the form of procaspase, an inactive form. To become an active form, procaspases need to undergo a dimerization process and can also be separated.\textsuperscript{8}

\textbf{Type of caspase}

1. \textbf{Apoptotic caspases}

There are two types of apoptotic caspases: initiator caspases and executioner caspases. Initiator caspase (caspase-8 and caspase-9) activating the executioner caspases (caspase-3, caspase-6, and caspase-7). The caspases were previously in the form of procaspase monomers that underwent dimerization. After activation, initiator caspases can cleave executable caspases to be active. The cleavage between these large and small subunits forms two active sites into functional proteases. Once activated, the executable caspase can cleave and activate other executable caspases.\textsuperscript{8,10}

2. \textbf{Inflammatory caspases}

In the occurrence of inflammation, there is a role of caspase-1, caspase-4, and caspase-5, all in an inactive form as procaspases. To activate this kind of caspase needs to undergo dimerization, just like the caspase initiator.\textsuperscript{8,10}

3. \textbf{Pathophysiology of peptic ulcer disease}

PUD occurs because of an imbalance between the aggressive factors such as NSAIDs, H. pylori bacterial infection, acids, and pepsin, with protective factors, such as mucus, bicarbonate, epithelial renewal, and cellular restitution.\textsuperscript{11}
Figure 1. The left side is a healthy stomach, and the right side is a stomach that got a gastric ulcer and a duodenal ulcer. This image is cited from Peachpink with modifications.\(^\text{12}\)

For the cause of PUD, \textit{H. pylori} bacteria can produce urease which converts urea into an alkaline environment and survives in that environment (gastric mucosa). These bacterial enzymes, such as lipase and protease, reduce gastric mucosal levels. As a result, ammonia can be toxic to gastric epithelial cells. And then, attached bacteria can increase toxin intake to gastric epithelial cells. Gastric epithelial cells become inflamed by altering the inflammatory response or activating neutrophils that attach to phagocytic bacteria.\(^\text{11}\)

Consumption of NSAIDs at inappropriate doses and in the long term can also cause PUD due to NSAIDs' mechanism by inhibiting the production of COX-1 and COX-2 enzymes. So that the secretion of prostaglandins which protect the gastric mucosa is low, and the cytoprotective effect is weak. Thus, the gastric mucosa is exposed to acid, which can cause inflammation of the gastric mucosa.\(^\text{11,13}\) In addition, the acidic nature of NSAIDs causes a decrease in the hydrophobicity of the gastric mucosa lining.\(^\text{11}\)

\textbf{Role of caspase in peptic ulcer disease}

From all the articles about peptic ulcer disease and caspase, there are 4 of 12 caspase types that have roles in peptic ulcer disease there are Caspase-1 expresses IL-1\(\beta\) and IL-18, which leads to inflammation of gastric mucosa and leads to peptic ulcer disease, whereas caspase-3 was reported it could cleavage E-cadherin, the protein that encodes by CDH1 gene (tumor suppressor gene), then induced apoptosis gastric endothelial cells and led to gastric mucosa injury.\(^\text{14,15}\) Furthermore, caspase-4 and -8 induce the secretion of alarmins, endogenous chemotactic and immune-activating peptides in response to peptic ulcer and initiate the apoptotic executing caspase cascade.\(^\text{16}\)

\textbf{The compounds that affect caspase in peptic ulcer disease}

\textbf{Table 1. The Compounds That Affect Caspase in Peptic Ulcer Disease}

<table>
<thead>
<tr>
<th>Type of Caspase</th>
<th>The Compound</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspase-1</td>
<td>Ac-had-cmk(^\text{17})</td>
<td>Potent and irreversible caspase-1 inhibitor, reducing apoptosis(^\text{17}) inflammatory response and</td>
</tr>
<tr>
<td>Caspase-3</td>
<td>Z-devd-fmk(^\text{15})</td>
<td>Irreversible apoptosis(^\text{15}) caspase-3 inhibitor inhibited</td>
</tr>
</tbody>
</table>

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Several compounds have been reported in inhibiting caspases (Table 1); some of them are phytoconstituents, e.g., crocin (a carotenoid chemical compound that is found in the flowers crocus and gardenia), chrysin (a flavone found in honey, propolis, the passion flowers, *Passiflora caerulea*, and *Passiflora incarnata*), gallic acid (a phenolic acid found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants), walnut oligopeptide, mangiferin (a polyphenol compound isolated from the leaves and bark of *Mangifera indica*), wheat peptide-fucoidan, etc.

### Table 1. (Extension)

<table>
<thead>
<tr>
<th>Type of Caspase</th>
<th>The Compound</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspase-4</td>
<td>Z-vad-fmk</td>
<td>Caspase-4 inhibitor, irreversible bind to the catalytic site of caspase and reduce inflammatory response.</td>
</tr>
<tr>
<td>Caspase-8</td>
<td>Z-it-fmk</td>
<td>Potent caspase-8 inhibitor binding to the active sites. Suppressed RIPK1-dependent apoptosis.</td>
</tr>
<tr>
<td>Crocin</td>
<td>Caspase-3 inhibitor, reducing inflammatory response.</td>
<td></td>
</tr>
<tr>
<td>Chrysin</td>
<td>Caspase-3 modulators increase catalase activity, increase cell proliferation activity, and reduce apoptosis.</td>
<td></td>
</tr>
<tr>
<td>Gallic acid</td>
<td>Caspase-3 inhibitor down-regulated the immunohistochemical expression of caspase-3.</td>
<td></td>
</tr>
<tr>
<td>Walnut oligopeptide</td>
<td>Caspase-3 inhibitor.</td>
<td></td>
</tr>
<tr>
<td>Mangiferin</td>
<td>Caspase-3 inhibitor, modulation of oxidative stress, inflammation, and apoptosis via the Nrf2/HO-1, PPAR-γ/NF-κB signaling pathways.</td>
<td></td>
</tr>
<tr>
<td>Wheat peptides-fucoidan</td>
<td>Elevate PGE₂ and EGF to inhibit activated Caspase-3.</td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Potent caspase-3 inhibitor, downregulate inflammatory response, and TNF.</td>
<td></td>
</tr>
<tr>
<td>Zn(L)SCN</td>
<td>Caspase-3 inhibitor downregulates inflammatory response.</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 2. Chemical structure of Crocin](image-url)
However, by inhibiting caspases, these compounds could reduce inflammation and be an advantage for health due to their ability to regulate cell survival and death processes (apoptosis).

**Conclusion**

Of 12 caspases, four types that play a role in peptic ulcer disease are caspase-1, caspase-3, caspase-4, and caspase-8, with a different roles. Nine compounds can affect caspase-3, 1 compound for caspase-1, 1 compound for caspase-4, and 1 compound for caspase-8. This number can increase in the future because many conditions can be developed and become potential treatments for peptic ulcer disease.

**Conflict of interest**
The authors have no conflicts of interest regarding this investigation.
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