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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 inflammation group. Some compounds can inhibit modulateit. 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 faeces.[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.[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

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with 37.1%; Asia 54.7%; Europe 47%; and Oceania 24.4%.[4] 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.[5]The prevalence in 2015 in five islands of Indonesia was 22.1%.[6]

The condition that is often found in this case of PUD is *Helicobacter pylori* infection that lives attached to the gastric mucosa.[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.[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.

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.

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.[8]

Type of caspase

1. **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.[8,10]

2. **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.[8,10]

3. **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.[11]

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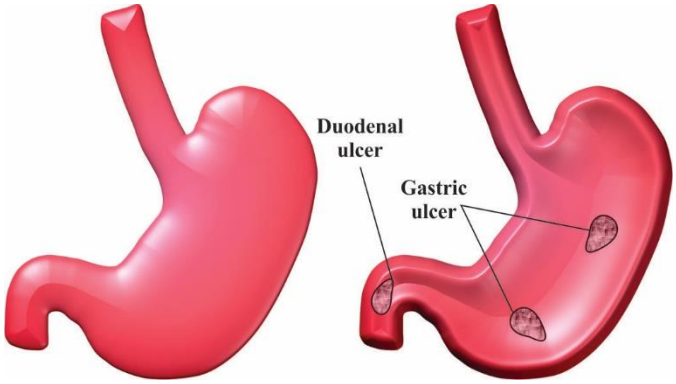

Figure 1. The left side is a healthy stomach, and the right side is a stomach that got a gastric ulcer and a duodenal ulcer. This image is cited from Peachpink with modifications.[12]

For the cause of PUD, *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.[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.[11,13] In addition, the acidic nature of NSAIDs causes a decrease in the hydrophobicity of the gastric mucosa lining.[11]

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-1β 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.[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.[16]

The compounds that affect caspase in peptic ulcer disease

Table 1. The Compounds That Affect Caspase in Peptic Ulcer Disease

Type of Caspase	The Compound	Information
Caspase-1	Ac-had-cmk[17]	Potent and irreversible caspase-1 inhibitor, reducing inflammatory response and apoptosis[17]
Caspase-3	Z-devd-fmk[15]	Irreversible caspase-3 inhibitor inhibited apoptosis[15]

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Table 1. (Extension)

Type of Caspase	The Compound	Information
	Crocin[18]	Caspase-3 inhibitor, reducing inflammatory response.[18]
	Chrysin[19]	Caspase-3 modulators increase catalase activity, increase cell proliferation activity, and reduce apoptosis.[19]
	Gallic acid[20]	Caspase-3 inhibitor down-regulated the immunohistochemical expression of caspase-3.[20]
	Walnut oligopeptide[21]	Caspase-3 inhibitor. [21]
	Mangiferin[22]	Caspase-3 inhibitor, modulation of oxidative stress, inflammation, and apoptosis via the Nrf2/HO-1, PPAR-γ/NF-κB signaling pathways.[22]
	Wheat peptides-fucoidan[23]	Elevate PGE_2 and EGF to inhibit activated Caspase-3.[23]
	Irbesartan[24]	Potent caspase-3 inhibitor, downregulate inflammatory response, and TNF.[24]
	Zn(L)SCN[25]	Caspase-3 inhibitor downregulates inflammatory response.[25]
Caspase-4	Z-vad-fmk[26]	Caspase-4 inhibitor, irreversible bind to the catalytic site of caspase and reduce inflammatory response.[26]
Caspase-8	Z-it-fmk[16]	Potent caspase-8 inhibitor binding to the active sites. Suppressed RIPK1-dependent apoptosis. [16]

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.

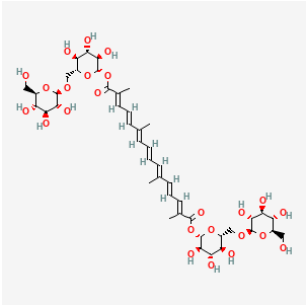

Figure 2. Chemical structure of Crocin[27]

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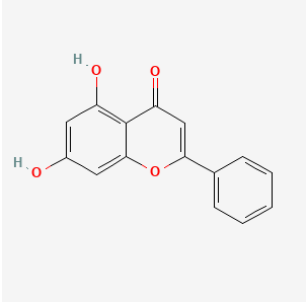

Figure 3. Chemical structure of Chrysin[28]

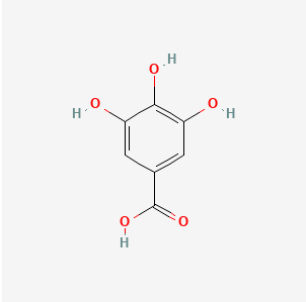

Figure 4. Chemical structure of Gallic Acid[29]

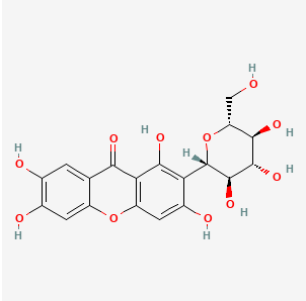

Figure 5. Chemical structure of Mangiferin[30]

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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References

1. DiGregorio AM, Alvey H. Gastrointestinal bleeding - StatPearls - NCBI Bookshelf. StatPearls. 2022.
2. DeVault KR, Talley NJ. Peptic Ulcer Disease. In: Wallace MB, Aqel BA, Lindor KD, editors. Practical Gastroenterology and hepatology board review toolkit. John Wiley & Sons; 2016.
3. Malik TF, Gnanapandithan K, Singh K. Peptic ulcer disease - StatPearls - NCBI Bookshelf. 2021.
4. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017;153(2):420–9.
5. Sonnenberg A, Turner KO, Genta RM. Low prevalence of helicobacter pylori-positive peptic ulcers in private outpatient endoscopy centers in the united states. Am J Gastroenterol. 2020;115(2):244–50.
6. Syam AF, Miftahussurur M, Makmun D, Nusi IA, Zain LH, Zulkhairi, et al. Risk factors and prevalence of Helicobacter pylori in five largest islands of Indonesia: A preliminary study. PLoS One. 2015;10(11).
7. Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician. 2007;76(7):1–8.
8. McIlwain DR, Berger T, Mak TW. Caspase functions in cell death and disease. Cold Spring Harb Perspect Biol. 2015;7(4).
9. Sari LM. Apoptosis: Mekanisme molekuler kematian sel. Cakradonya Dent J. 2018;10(2):65–70.
10. Julien O, Wells JA. Caspases and their substrates. Cell Death Differ. 2017;24:1380–9.
11. DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V. Peptic Ulcer disease and related disorders. in: pharmactherapy: a pathhophysiologgic approach. 11th ed. New York: McGraw Hill; 2020. p. 1434–9.
12. Peachpink. Stomach health empty - free image on pixabay. 2021.
13. Darini M. Peptic ulcer disease and non-steroidal anti - inflammatory drugs. Aust Prescr. 2017;40(3):91–3.
14. Sun Q, Scott MJ. Caspase-1 as a multifunctional inflammatory mediator: noncytokine maturation roles. J Leukoc Biol. 2016;100:967–961.
15. Yang Y, Du J, Liu F, Wang X, Li X, Li Y. Role of caspase-3/E-cadherin in helicobacter pylori-induced apoptosis of gastric epithelial cells. Oncotarget. 2017;8(35):59204–16.
16. Lin WC, Tsai HF, Liao HJ, Tang CH, Wu YY, Hsu PI, et al. Helicobacter pylori sensitizes TNF-related apoptosisinducing ligand (TRAIL)-mediated apoptosis in human gastric epithelial cells through regulation of FLIP. Cell Death Dis. 2014 Mar;5(3):e1109–e1109.
17. Li G, Zhu L, Cao Z, Wang J, Zhou F, Wang X, et al. Cellular physiology and biochemistry cellular physiology and biochemistry a new participant in the pathogenesis of alcoholic gastritis: pyroptosis cellular physiology and biochemistry cellular physiology and biochemistry. Cell Physiol Biochem. 2018;49:406–18.
18. Ghafarzadeh S, Hobbenaghi R, Tamaddonfard E, Farshid AA, Imani M. Crocin

exerts improving effects on indomethacin-induced small intestinal ulcer by antioxidant, anti-inflammatory and anti-apoptotic mechanisms. Vet Res Forum. 2019 Sep;10(4):277–84.

19. Fagundes FL, Piffer G de M, Périco LL, Rodrigues VP, Hiruma-Lima CA, Dos Santos R de C. Chrysin modulates genes related to inflammation, tissue remodeling, and cell proliferation in the gastric ulcer healing. Int J Mol Sci. 2020 Feb;21(3).
20. Zhou D, Yang Q, Tian T, Chang Y, Li Y, Duan LR, et al. Gastroprotective effect of gallic acid against ethanol-induced gastric ulcer in rats: Involvement of the Nrf2/HO-1 signaling and anti-apoptosis role. Biomed Pharmacother. 2020 Jun;126.
21. Liu R, Hao Y-T, Zhu N, Liu X-R, Kang J-W, Mao R-X, et al. The gastroprotective effect of small molecule oligopeptides isolated from walnut (Juglans regia L.) against ethanol-induced gastric mucosal injury in rats. Nutrients. 2020;12:1--20.
22. Mahmoud-Awny M, Attia AS, Abd-Ellah MF, Salah El-Abhar H. Mangiferin mitigates gastric ulcer in ischemia/ reperfused rats: involvement of PPAR-γ, NF-κB and Nrf2/HO-1 signaling pathways. PLoS One. 2015;10(7):1–14.
23. Kan J, Hood M, Burns C, Scholten J, Chuang J, Tian F, et al. A novel combination of wheat peptides and fucoidan attenuates ethanol-induced gastric mucosal damage through anti-oxidant, anti-inflammatory, and pro-survival mechanisms.
24. Shahin NN, Abdelkader NF, Safar MM. A novel role of irbesartan in gastroprotection against indomethacin-induced gastric injury in rats: targeting DDAH/ ADMA and EGFR/ERK signaling OPEN. Sci REpoRTS |. 2018;8:4280.
25. Salama SM, Suleiman Gwaram N, Alrashdi AS, Khalifa SAM, Abdulla MA, Ali HM, et al. A zinc morpholine complex prevents hcl/ethanol-induced gastric ulcers in a Rat Model OPEN. Nat Publ Gr. 2016;
26. Douglas D, Mcnamara S, Smith LAJ, O'neill EM, Creagh Z, Zaslona E, et al. Caspase-4: A therapeutic target for peptic ulcer disease. ImmunoHorizons. 2020;4(10):627–33.
27. National Center for Biotechnology Information. Crocin | C44H64O24 - PubChem. PubChem. Published 2022. Accessed July 25, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/5281233
28. National Center for Biotechnology Information. Chrysin | C15H10O4 - PubChem. PubChem. Published 2022. Accessed July 25, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/5281607
29. Information NC for B. Gallic acid | C7H6O5 - PubChem. PubChem. Published 2022. Accessed July 25, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/370
30. National Center for Biotechnology Information. Mangiferin | C19H18O11 - PubChem. PubChem. Published 2022. Accessed July 25, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/5281647

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