Nrf2 activator (DMF) Ameliorated Oxidative Stress and Inflammation During H. Pylori Infection

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***Abstract*— Introduction: Peptic ulcer disease is an illness that caused by an infection or long-term usage of stomach irritants such as medicines might cause it. H. Pylori cause gastric cell damage and may be death through generation of oxidative stress and an inflammation within the mucosal layer. It should be checked in all patients with peptic ulcers.**

Methods: The information on the protective effect of pharmacological Nrf2 activator, e.g. DMF, in the treatment of peptic ulcer was obtained from Electronic databases accessed included Google Scholar, PubMed, Web of Science, and Scopus.

Results: H. pylori cause damage to gastric cell via ROS generation and enhance inflammatory cytokines. Nrf2 is a transcription factor that induce anti-oxidative stress enzymes and inhibit NF-κB, thereby, pharmacological activation of Nrf2 could reduce the effect of the pathogen and may be prevent damage or cell death.

Conclusion: DMF is a Nrf2 activator can be use in clinical trial to H. pylori induce gastric cells damage.

***Index Terms*: DMF, H. pylori, Nrf2 activators, NF-κB, and ROS.**

I. INTRODUCTION

In the current period, peptic ulcer disease is one of the most frequent chronic gastrointestinal disorders. It is now a prevalent global health concern that affects a vast number of people all over the world (1). Peptic ulcer disease (PUD) is a multifactorial and complicated condition characterized by stomach and duodenal ulcers. A peptic ulcer is a breach in the mucosa lining the stomach or proximal intestine that extends through the muscularis mucosae that arises in areas exposed to acid and pepsin. Peptic ulcer disease is a chronic, recurring condition characterized by poor wound healing. NSAIDs (nonsteroidal anti-inflammatory medications) are commonly used to treat pain, fever, inflammation, and rheumatic disease. Chronic use of these medications can result in a variety of gastrointestinal side effects, including gastric erosions, gastric or duodenal ulcers, and serious consequences include gastrointestinal hemorrhage and perforation. Induced by NSAIDs such as aspirin and indomethacin (2, 3). Stress plays an important role in pathophysiology of gastroduodenal ulceration due to reduced mucus production and enhanced acid secretion (4).

Other factor lead to ulceration is Smoking via impair healing and increase rate of ulcer recurrence. Cigarette smoking also increases the chance of getting an ulcer (5). Caffeine boosts stomach acid output, which can worsen an ulcer. Though there is no evidence of a link between alcohol use and peptic ulcers, ulcers are common in patients who have liver cirrhosis, a disease connected to high alcohol consumption. The amount of salt consumed in the diet was linked to the development of stomach ulcers (6). Helicobacter pylori, a gram-negative rod, is one of the most common causes of gastritis and the subsequent development of gastric and duodenal ulcers. H. pylori causes gastroduodenal diseases, which are associated with neutrophil, lymphocyte, monocyte, and plasma cell infiltration of the gastric mucosa (7). High oxidative stress induced with H. pylori infection is a significant factor. The production of pro-inflammatory cytokines, particularly interleukine-8, is made through a process (IL-8). IL-8 activated neutrophils, basophils, and T cells, attracting cells to the infection site. This promotes oxidative stress-induced stomach injury by generating high levels of ROS at the mucosa (8).

A. Reactive Oxygen Species

In the presence of chloride ions, myeloperoxidase causes production of the strong oxidant in neutrophils. Excessive ROS generation causes oxidative stress in the stomach mucosa, potentially causing damage to cellular components such as polyunsaturated fatty acids, proteins, and DNA. (9). When the energy was decrease in gastric cells caused by H. pylori decreases the rate of intracellular GSH re-generation. These findings suggest that decreased GSH levels after H. pylori colonization (10). lower GSH levels in the stomach mucosa may be linked to gastric carcinogenesis due to increase oxidation of DNA (11). Figure (1). As a result, medicinal drugs that suppress or scavenge ROS could be useful in the treatment of H. pylori-related stomach mucosal.

B. Gastric Inflammation

H. pylori leads to significant increases in steady-state mRNA levels and cell surface expression of ICAM-1 (12). H. pylori protein that promotes neutrophil adherence to endothelial

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cells through the H. pylori neutrophil-activating protein (HP-NAP). HP-NAP activates neutrophil NADPH oxidase by binding to a particular receptor that is connected to a pertussin toxin-sensitive trimetric G protein (13). H. pylori infection activates NF-kB and causes translocation, as well as elevated IL-8 levels, all of which are consistent with NF-kB upregulation. NF-kB activation can also control cellular growth responses, such as apoptosis. H. pylori can also emit TNF-a, therefore NF-kB activation by H. pylori is a possibility (14). The production of ROS such as O, H2O2, and OH, as well as peroxidation of membrane phospholipids such as malondialdehyde (MDA), can induce cellular harm by disrupting membrane phospholipids and mitochondrial respiration, resulting in DNA damage and malfunction. Furthermore, ROS can activate other mediators including inflammatory factors such as tumor necrosis factor (TNF-), myocytes chemoattractant protein-1 (MCP-1), IL-1, IL-6, and others (15, 16). Figure (1)

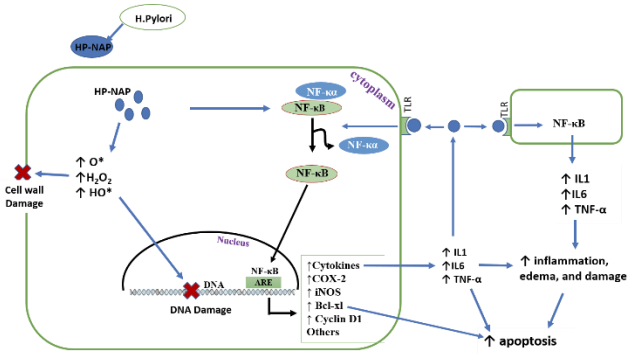

Fig. 1. A schematic diagram showing the pathogenesis Helicobacter pylori via enhance ROS generation and NF-kB of the mucosal cell.

C. *Pharmacological treatment*

pharmacological therapy of PU is still evolving, with the goal of focusing on relief of pain, healing of ulcer, and prevention it recurrent. However, many of the pharmaceutical treatments for PU are designed to either counteract hostile influences or stimulate mucosal defense. Such medications are available. Antacids, histamine H2-receptor antagonists, and other drugs (Table 1) are used to inhibit or neutralize stomach acid secretion.

Table 1: the drugs commonly used in management of PU.

Drug		M. A.	A. E.	R.
Proton Pump Inhibitors (PPIs)	Omeprazole Lansoprazole Rabeprazole	H+/K+-ATPase Inhibitor	Diarrhea N&V Constipation Flatulence B12 deficiency ↓ bone Ca	(17)
H_2-Blockers	Cimetidine Famotidine Ranitidine	Histamine H2R Blocker	CNS depresses ↓ platelet coun.	(18)
Anti-acids	Al- OH Mg-OH	↑gastric pH	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance	(19)
Cytoprotective Agents	Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Constipation Back pain Diarrhea Abdominal pain Headache Constipation	(20)

D. *Herbal products*

plant-derived items utilized in traditional around in the entire globe for the treatment of a wide range of maladies and diseases since ancient times. In the management and treatment of PU, herbal medicine is increasingly becoming a viable alternative to commercially available synthetic medicines (21). Strategies used by medicinal plants and their constituents for cytoprotectant are shown in figure 2. Some of the plants and their phytoconstituents showing antiulcer activity and their mechanism of cytoprotectant are tabulated in Table 2.

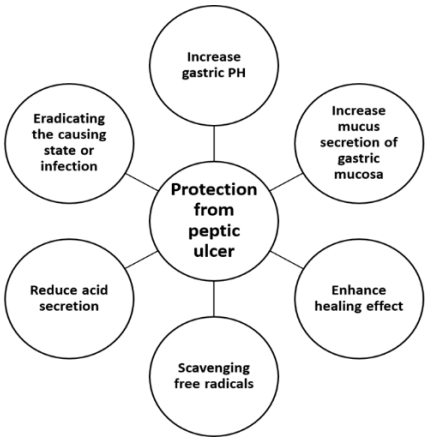

Fig. 2. Strategies used by medicinal plants and their constituents for cytoprotectant.

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***Table 2**: medicinal plants and their mechanism of gastroprotectant.*

Botanical name	Family	Plant extract used	Mechanism of Gastroprotection	Reference
Jasminum grandiflorm	Oleaceae	70% ethanolic extract of leaves	Antisecretory, antioxidant, promote gastric healing, cytoprotective	(22)
Ocimum sanctum	Labiatae	ethanolic extract of leaves	Antisecretory, increase mucus production, cytoprotective	(23)
Utleria salicifolia	Periplocaceae	50% ethanolic extract of rhizome	Antioxidant, increase mucus production, cytoprotective	(24)
Amomum subulatum	Zingiberaceae	Methanolic extract of fruit	Increase mucus production, cytoprotective	(25)
Rhizophora mangle	rhizophoraceae	Aqueous extract of bark	Antioxidant, cytoprotective	(26)
Aegle marmelos	Rutacae	Methanolic extract of fruit	Antioxidant, anti-inflammatory, promote gastric healing, cytoprotective	(27)
Calophyllum brasiliense	Calophyllaceae	Hexane extract of stem bark	Antisecretory, increase mucus production, cytoprotetive	(28)
Anacardium occidentale	Anacardiaceae	70% ethanolic extract of leaves	Cytoprotective	(29)
Centella asiatica	Apiaceae	Aqueous extract of leaves	Antioxidant, cytoprotective	(1)
Nerium indicum	Apocynaceae	Methanolic extract of leaves	Antisecretory, cytoprotective	(30)

Nrf2

Nrf2 is a member of the CNC family termed erythroid-cell-derived-protein with CNC-homology (ECH), and it is divided into seven domains named Nrf2–ECH-homology (Neh) domains Neh-1 to Neh-7. Those cysteine residues can be changed in stressful situations, causing Nrf2 to be released from DLG motif side and remain attached to the ETGE motif side, allowing Nrf2 to translocate to the nucleus (31). Nrf2 forms a dimerization complex with the masculo-apo-neurotic-fibro sarcoma (Maf) protein in the nucleus, which has facilitated Nrf2's binding to anti-response elements (AREs) within regulatory regions to activate a wide range of enzymes. These enzymes include NQO-1, SOD1, and HO-1, which work through oxidation-reduction reactions, nucleophile attack mechanisms, toxic metabolite efflux transporters, and thiol-containing compounds to maintain reduced conditions (32). The most prominent signaling that activates cellular defense systems against oxidative stress and electrophiles is the transcription factor Nrf2 (31). Keap1 forms a cytoplasmic complex with Nrf2 under non-stress conditions, involving the Kelch domain of Keap1 and the ETGE and DLG motifs on Nrf-2's Neh-2 domain (15). In stressful conditions, the Keap1 molecule, can be changed, causing Nrf2 to be released from the DLG motif side and remain connected to the ETGE motif side, allowing Nrf2 to translocate to the nucleus (33). Figure (3)

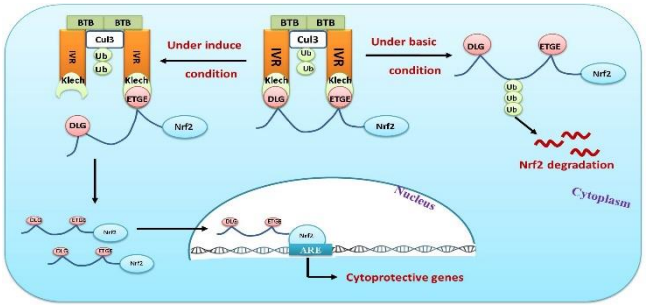

Fig. 3. Nrf2 activation mechanism (15).

II. AIM

Nrf2 activators have a role in the treatment peptic ulcer with H. Pylori positive patients.

III. DATA COLLECTIONS

The information on the protective effect of pharmacological Nrf2 activator, e.g. DMF, in the treatment of peptic ulcer was obtained from published peer-reviewed articles. Electronic databases accessed included Google Scholar, PubMed, Web of Science, and Scopus. All the articles obtained were reviewed to get the needed information on the activator used for the protective effect against H-pylori induce peptic ulcers.

IV. RESULTS

A. Anti-oxidant role of Nrf2

NQO1, HO-1, SODs, Grx1, and Trx1 are among the anti-oxidant enzymes and proteins produced when Nrf2 is activated. Oxygen free radicals were removed by SODs through converted it to H_2O_2; however, GSH systems were eliminated the latter (34). By acting as an electron donor for the reduction of peroxides, glutathione (GSH) detoxifies ROS such as superoxide and hydroxyl radicals. GSH synthesis is under the control of two enzymes which are γ-glutamylcysteine ligase and glutathione synthetase(35). NQO1 catalyzes the reduction and detoxification of quinones, as well as acting as an oxygen scavenger (36). Figure 4

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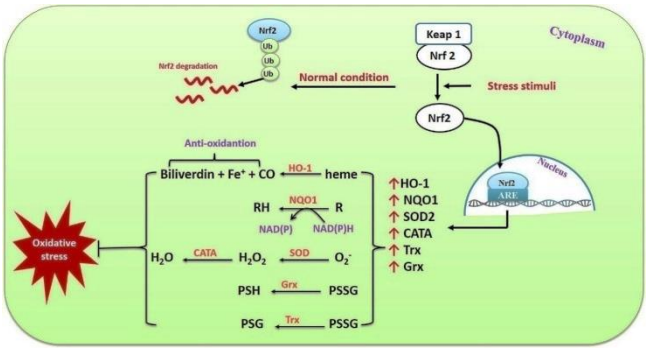

Fig. 4. mechanism of NRF2activation antioxidant enzymes.

B. Anti-Inflammatory role of Nrf2

Inflammatory cells produce cytokines and chemokines in response to oxidative stress (37). The first and only inflammatory pathway triggered by oxidative stress and excessive cytokines and chemokines is NF-kB. This overproduction stimulates ICAM-1 synthesis in leukocytes and vascular endothelium, as well as its ligand integrin, which leads to leukocyte migration into subendothelial tissues (38). Nrf2 inhibits NF-kB activity by ubiquitinating IKK and inducing gene transcription (39). On another hand, The anti-oxidant genes are activated, which inhibit the of inflammatory markers production including TNF-α, IL-6, MCP-1, and MIP2, as well as the reduce level of VCAM-1, adhesion molecules and selectins (40). Figure (5)

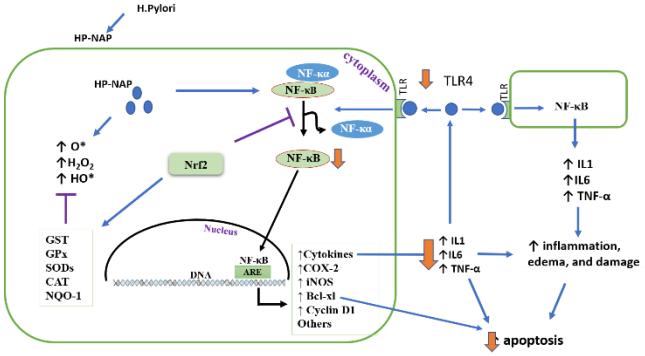

Fig. 5. mechanism of Nrf2 induce anti-inflammatory substances and suppress of proinflammatory one

C. Dimethyl Fumarate (DMF)

DMF is an anti-oxidant and anti-inflammatory drug that activates the Nrf2 pathway while inhibiting the NF-B pathway. In addition to the glutathione system being modulated and the cellular response to O.S (41). Nrf2 interacts to Keap1 in the absence of DMF, causing it to be ubiquitinated. DMF disturbs the Keap1-Nrf2 complex at cysteine residues, causing Nrf2 to be free and translocated to the nucleus. Additionally, it inhibits the nuclear factor kappa-B pathway by binding to and activating the IKK at Cys-179. This binding prevents NF-kB from being released from its cytoplasmic complex (NF-B-IB), hence suppressing downstream pro-inflammatory signaling pathways (15).

We hypothesize that DMF is an important medicine that can minimize H. Pylori pathogenesis by reducing oxidative stress and inflammation, causing gastric ulcers by triggering anti-oxidant enzymes, inhibiting the NF-B pathway, and inhibiting both apoptotic proteins and TLR gene expression.

CONCLUSION

H. Pylori infection is the most important factor that effect on gastric cell integrity due to its toxic products such as ROS that destroy the cell wall and DNA as well as induction of inflammatory processes via enhance expression of NF-kB. DMF, Nrf2 activator, has potential role in ameliorated oxidative stress via enhance induction of anti-oxidant genes and also inhibit activation of NF-kB induce inflammatory mediators. So, we concluded that DMF play a role in protection of gastric cells against H. Pylori infection.

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