INTRODUCTION

The imbalance between aggressive and defensive factors determines the outcomes of gastric lesions under the exposure to noxious etiologies represented with either a relative increase in aggressive factors or a considerable decrease in protective factors (1-3). The gastric mucosa is continuously challenged by a variety of aggressive factors of both endogenous and exogenous irritants, including excess secretion of gastric acids and pepsin, ethanol, reactive oxygen species, non-steroidal anti-inflammatory drugs (NSAIDs), excess psychiatric stress, and Helicobacter pylori (H. pylori) infection (Fig. 1A). To protect the gastric mucosa from these aggressive factors, a complex defense system has evolved, which includes the production of surface mucus and bicarbonate, the regulation of gastric mucosal blood flow, the acceleration of epithelial regeneration, and the preservation of epithelial homeostasis (4-6), for which prostaglandin (PG), in particular PGE₂, enhances these protective mechanisms and is therefore believed to comprise a major gastric mucosal defensive factor (7-8). As much as PGs, heat shock proteins (HSPs) proved to be another key protective mechanism (9-10).

HSPs were first discovered in 1962 and described as a set of proteins whose expression was induced by heat shock and a variety of other stresses and HSPs are ubiquitous in expression, occurring in all organisms from bacteria and yeast to humans. HSPs come in various forms and are categorized into families on the basis of their molecular weights as summarized in Table 1. There is substantial evidence that HSPs play important physiological roles in normal conditions and pathological situations involving both systemic and cellular stress (Fig. 1B). Researchers have subsequently demonstrated that most HSPs have strong cytoprotective effects.
are involved in many regulatory pathways, and behave as molecular chaperones for preserving important cellular proteins (10, 11). Therefore, HSPs are crucial for the maintenance of gastric mucosal cell integrity during both normal cell growth and engaged
in several pathophysiological conditions (4-7). By controlling binding and release, HSPs function mainly as molecular chaperones, which participate in the folding and assembly of nascent and unfolding proteins and facilitate protein transport to sub-cellular compartments.

HSPs are classified into four major families according to their biological activities and apparent molecular weights; HSP90, HSP70, HSP60, and small HSPs including HSP27 and HSP10. While HSP60, HPS 70, and HSP90 are constitutively expressed, HSP70 and HSP27 are induced by various conditions, including heat, oxidative stress, or drug exposure (11-12). The type of HSP induced and its level of expression can determine the fate of a cell in response to stress or stimulus, by which HSPs may play a cytoprotective role in gastrointestinal tract. For instances, oral administration of geranylgeranylacetone (GGA), an anti-ulcer drug, rapidly induced HSP70 in rat gastric mucosal cells and the induced HSPs contributed to the suppression of inflammation accompanied with accelerated healing of ulcer induced by water immersion restraint stress (13). Animal studies have consistently demonstrated that though H. pylori infection delays gastric mucosal healing by disrupting the balance in cell apoptosis and proliferation, decreasing migration of epithelial cells, and decreasing blood flow and angiogenesis within the gastric mucosa (14-15), HSPs could reverse these limitation and inferiorities in mucosal healing. In this review, we are going to introduce the contributive roles of each HSP member in either gastric ulcer healing or regulating gastric inflammation according to HSP subtypes.

ROLE OF EACH HEAT SHOCK PROTEIN IN ATTENUATING GASTRIC INFLAMMATION AND FACILITATING ULCER HEALING

Heat shock protein 70 (HSP70)

1. HSP70 and biological action

70 kDa heat shock proteins assist a wide range of folding process, including the folding and assembly of newly synthesized proteins, refolding of misfolded and aggregated proteins, membrane translocation of organelar and secretory proteins, and control of the activity of regulatory proteins. Thus HSP70 have housekeeping functions in the cell in which they are built-in components of folding and signal transduction pathways, and quality control functions in which they proofread the structure of proteins and repair misfolded conformers. All of these activities appear to be based on the property of HSP70 to interact with hydrophobic peptide segments of proteins in an ATP-controlled fashion. The broad spectrum of cellular function of HSP70 proteins is achieved through the amplification and diversification of HSP70 genes in evolution, which has generated specialized HSP70 chaperones, co-chaperones which are selectively recruited by HSP70 chaperones to fulfill specific cellular functions and cooperation of HSP70s with other chaperone systems to broaden their activity spectrum. The role of HSP70 in the folding of non-native proteins can be divided into three related activities such as prevention of aggregation, promotion of folding to the native state, and stabilization and refolding of aggregated protein (16-17).

There are at least four distinct proteins in the HSP70 group presenting as HSP72, HSP73, HSP75 and HSP78, and since all of these proteins have several acronyms, they can be redundant and sometimes confusing. Since the evidence linking stress-induced HSP70 accumulation with tolerance to heat is common, they are well-known factor as stress tolerance or heat-inducible factor, by which attention has primarily been focused on the role of HSP70 as a chaperone and its potential ability to contribute to cellular repair processes in response to interventions such as heat, oxidative stress, activation of proteases, release of lysosomal and proteolytic enzymes, and alterations of the cytoskeleton structure. However, the phenomenon of acquired thermotolerance is transient in nature and depends primarily on the severity of the initial heat stress. In general, the greater the initial heat dose, the greater the magnitude and duration of thermo-tolerance. The expression of thermo-tolerance following heating will occur within several hours and last 3-5 days in duration.

In addition to heat shock and stress, the induction of HSP70 was associated with the diverse development of tolerance to a variety of stresses, including hypoxia (18-19), ischemia (20), acidosis (21), energy depletion (22), cytokines such as tumor necrosis factor-α (TNF-α) (23), and ultraviolet radiation (24) (Fig. 1B). Additional supporting evidence includes observations that have linked the kinetics of thermo-tolerance induction and decay with parallel changes in HSP70 induction and degradation (25-26). However, these studies have generally been correlated in nature, with no causal link established between induction of HSP70 and acquired thermo-tolerance. As noted, HSPs, also called molecular chaperones, play a crucial role in the folding of newly synthesized proteins and the refolding of denatured proteins (27, 28).

Some of the important house-keeping functions attributed to HSP70 include; import of proteins into cellular compartments; folding of proteins in the cytoplasm, endoplasmic reticulum and mitochondria; degradation of unstable proteins; dissolution of protein complexes; control of regulatory proteins; refolding of mis-folded proteins; and translocation of precursor proteins into mitochondria. Molecular chaperones are highly conserved proteins and are rapidly induced in cells in response to abrupt and advance change in their environment (29, 30). The cytosolic 70-kDa molecular chaperones, HSP70s, are present in cells as two different gene products, but are closely related to each other: a stress-inducible form HSP70, known as HSP72, and a constitutively expressed form HSP70, known as HSP72 or 70-kDa heat shock cognate protein (HSC70). HSP70s consist of two domains, NH2-terminal ATPase domain having a molecular mass of 45-kDa and COOH-terminal peptide-binding domain of 25-kDa (31, 32). The ATP-binding domain of HSP70s binds and releases peptide slowly by more stably (33, 34). Biding of ATP to the ATP-binding domain causes a conformational change, which in turn results in structural alterations in the COOH-terminal, thus leading to substrate release (35, 36).

HSP70 chaperone systems assist non-native intermediates to fold to the native state (‘folder’ activity). The mechanism by which HSP70 chaperones assist the folding of non-native substrates is still unclear. HSP70-dependent protein folding in vitro occurs typically on the time scale of minutes or longer. Substrates cycle between chaperone-bound and free states until the ensemble of molecules has reached the native state. There are at least two alternative modes of action. In the first mechanism HSP70s play a rather passive role. Through repetitive substrate binding and release cycles they keep the free concentration of the substrate sufficiently low to prevent aggregation, while allowing free molecules to fold to the native state (kinetic partitioning). In the second mechanism, the binding and release cycles induce local unfolding in the substrate, e.g. the untangling of a mis-folded β-sheet, which helps to overcome kinetic barriers for folding to the native state (‘local unfolding’) (37-40). The energy of ATP may be used to induce such conformation changes or alternatively to drive the ATPase cycle in the right direction.

2. HSP70 in H. pylori-induced gastritis

Helicobacter pylori (H. pylori) infection leads to significant inflammations in the gastric mucosa, which is closely associated with development of gastric cancer. H. pylori is recognized as an important cause of gastritis, peptic ulcer disease, and also associated with mucosa-associated lymphoid tissue (MALT)
lymphoma and gastric cancer. *H. pylori* have high urease activity that results in the production of ammonia and elicits oxidative burst of neutrophils. *H. pylori*-activated neutrophils reduce O₂⁻ to superoxide (O₂⁻), and dismutation of O₂⁻ yields more reactive radical of hydrogen peroxide (H₂O₂). Myeloperoxidase-catalyzed oxidation of chloride by H₂O₂ yields hypochlorous acid (HOCl), and the reaction of HOCl with ammonium (NH₄⁺) yields monochloramine (NH₂Cl), which is a stable, lipophilic oxidizing agent that readily penetrates the membranes of target cells and exhibits a greater cytotoxicity in gastric mucosal cells than did H₂O₂ or HOCl. In animal and human studies, several investigators have reported that NH₂Cl causes the gastric mucosal injury in vivo and in vitro. Since *H. pylori*-associated inflammation is characterized by severe infiltration of neutrophils and mononuclear cells.

**Table 2.** Down-regulated proteins after *H. pylori* infection.

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**Fig. 2.** HSPs after *H. pylori* infection (A) Changes of HSP70 expressions according to times after *H. pylori* infection. The expressions of HSP70 were significantly attenuated up to 2 hrs after *H. pylori* infection, after which the expression of HSP70 was cancelled. (B) 2-DE analysis of gastric mucosa after *H. pylori* infection. Non-transformed RGM-1 cells were co-cultured overnight in the presence or absence of *H. pylori*. Proteins extracted from the cells were used for 2-DE analysis. The 2D gel was visualized with 0.1% Coomassie.
Recent studies have demonstrated that mucosa levels of IL-1 inflammatory cytokines and resultant reactive oxygen free radicals in inflammatory cells is related to the robust productions of cells in the gastric mucosa, accumulation and activation of these inflammatory cells is related to the robust productions of inflammatory cytokines and resultant reactive oxygen free radicals. In addition to these damaging conditions after sustained infection of H. pylori, the cancellation of HSP70 might be the prominent event leading to perpetuation of gastric inflammation and epithelial cell damages. As shown in Fig. 2A & 2B, H. pylori triggered the disappearance of HSP70 in cells infected with H. pylori up to undetectable levels after 4 hrs. Fig. 2A is the western blot of HSP70 and Fig. 2B is the 2-DE display for proteome analysis. As for plausible explanation of cancellation of HSP70 related to H. pylori infection, the inhibition of the activation of HSF or decrease in the formation of HSF-HSE complex might be possible. Thus, since deregulation of HSP70 might be the prime cause of H. pylori-associated mucosal damage, the induction of HSP70 may constitute a novel therapeutic approach for the prevention and treatment of this condition (Table 2).

3. HSP70 in stress-induced gastritis

Considerable prospective evidence has been gathered along with studies that have found a synergic relationship between H. pylori infection and psychological stress on gastric ulcer formation. A study done immediately after the great Hanshin earthquake in Kobe, Japan at 1995 found that the recurrence rate of peptic ulcers in patients infected with H. pylori was much higher than that in patients in whom H. pylori has been eradicated, suggesting that H. pylori infection augmented the stress induced mucosal damages. In study performed under the hypothesis that impairment or stupid response of HSP induction might be responsible for these augmented mucosal damages, the significance of HSP induction was stressed. Simply the proteomes were compared between non-infected gastric cells and H. pylori-infected gastric cells to draw the proteomes differed between these groups as shown in Fig. 2B. MALDI-TOF mass spectroscopy identified the deranged status of HSPs (Table 2). In order to document the implication of HSP induction in H. pylori infection, HSP90, HSP70, HSP60, and HSP27. (B) RGM-1 cells were incubated in the absence or presence of 1mM GGA for 8hr prior to treatment with H. pylori for 0, 2, 4, 8, and 24 hrs. (C) Induction of iNOS mRNA by H. pylori infection. RGM-1 cells were co-cultured with H. pylori, after which RT-PCR was done for iNOS expression in different time points after H. pylori infection. (D) Attenuation of iNOS expression by exposure to heat shock. (E) Attenuation of iNOS expression by GGA treatment.
(WIRS) in the presence of *H. pylori* infection. Significant reductions in HSP 70, HSP 60, and HSP27 were all noted after applying WIRS (Fig. 4A), but supplementation of α-tocopherols could prevent the damages of WIRS-induced gastric mucosal injury through the preservation of HSP27 (Fig. 4B). Similar to our observation (43), Nagahashi *et al.* (44) published that ammonia aggravated stress-induced gastric mucosal injury, for which dominant cause was due to cancellation of cytoprotective HSP70.

4. HSP70 in alcoholic gastritis

Alcohol is one of major etiological factors for gastric mucosal injuries including gastritis, ulcer, which may progress to gastric ulcer. Pathophysiologically the alcohol-induced gastric mucosal damages can be mediated or modulated both directly and indirectly by various cellular molecules such as cyclooxygenase, lipoxygenase, cytokines, cytochrome P450 2E1, thromboxane and oxygen radical derived free radicals. Several publications that HSP70 inductions improved both short-term survival 2 fold and long-term survival 5-fold in mice challenged with ethanol and endotoxin in mice (45), HSP70 inductions protected rats against ethanol-induced gastric mucosal damages (46), and HSP70 inductions led to inactivation of MAPK in alcohol induced gastric injuries (47) all raised the possibility of the intervention of phytoceuticals as novel therapeutics for preventing alcohol-associated gastric damages.

5. HSP70 in other kinds of gastrointestinal injuries

Tomisato *et al.* (48) showed the evidence of adaptive cytoprotection through HSP70 induction in animal model experiment that pretreatment of ethanol, which induced HSP70, made cell resistance to indomethacin injury and Jin *et al.* (49) showed that HSP70 could play important role in gastric mucosal adaptation when the PGE2 level is suppressed by NSAID. Oyake *et al.* (50) added the data overexpression of HSP70 confers protection against monochloramine-induced gastric mucosal injury.

**HEAT SHOCK PROTEIN 27 (HSP27)**

**HSP27 and biological action**

HSP27 belong to the family of small stress proteins that are constitutively abundant and ubiquitously present. HSP27 regulates
apoptosis through its ability to interact with key components of the apoptotic-signaling pathways, particularly those involved in caspase activation (51-52). Changes in the intracellular redox balance and production of reactive oxygen species initiate the apoptotic cascade through changes in the mitochondria and release of pro-apoptotic factors. HSP27 can maintain both the redox homeostasis and mitochondrial stability in the cell. Increased expression of HSP27 during stress response correlates with the better survival from cytotoxic stress. Negatively it regulates the activation of procaspase-9 by sequestering cytosolic cytochrome c from α-1, after its release from mitochondria it prevents assembly of the apoptosome. HSP27 can block the release of cytochrome c from mitochondria in cells exposed to staurosporine, etoposide or cytchalasin D. it also mediates inhibition of procaspase-3 activation, most likely through its ability to prevent initiator caspases like caspase-9 from gaining access to the residues whose cleavage is essential for procaspase-3 activation. In addition, HSP27 maintains the actin network integrity and hence prevents translocation of pro-apoptotic factors like activated Bid onto the mitochondrial membrane.

HSP27 has been shown to increase the anti-oxidant defense of cells by decreasing reactive oxygen species, increasing the level of reduced glutathione, GSH (53), and neutralizing the toxic effects of oxidized proteins (54). This latter effect may occur more specifically in neuronal cells in which the protective effect of HSP27 does not depend on its interaction with cytochrome c and largely depends on the HSP27 phosphorylation status (55). The cytoprotective effect of the protein has also been related to its capacity to stabilize F-actin microfilaments during exposure to such stresses as hyperthermia (56), oxidants (57), and cytchalasin B (58).

**HSP27 in indomethacin-induced gastritis**

NSAIDs are the most commonly prescribed drugs worldwide, which attest to their efficacy as analgesic, antipyretic and anti-inflammatory agents as well as anticancer drugs. However, NSAID use also carries a risk of major gastroduodenal events, including symptomatic ulcers and their serious complications that can lead to fatal outcomes. The development of "coxib" (selective cyclooxygenase-2 inhibitors) offered similar efficacy with reduced toxicity, but the promise of gastroduodenal safety has only partially been fulfilled and is now dented with associated risks of cardiovascular or intestinal complications. Mechanistically all of these adverse outcomes with NSAID use are closely related to the impairment of integrity maintenance in the gastroduodenal mucosa (59). As one of solutions against NSAIDs-induced gastroduodenal damages, novel acid pump antagonist was invented named as revaprazane (Revanex®, Yuhan Pharma Co., Seoul) in Korea. Revaprazane exerted significant protection from 40 mg/kg indomethacin-induced gastric damages (60). Significant preservation of HSP27 was responsible for these protections (Fig. 5), imposing the novel finding that HSP27 is potentially engaged in the rescuing protection from NSAID injuries. Significant inhibition of HSP27 phosphorylation and perinuclear increment of HSP27 expression (61) with revaprazane treatment explained the clear cytoprotective role.

**HSP27 responsible for QOUH**

Quality of ulcer healing (QOUH) is defined as an "ideal ulcer healing" featuring with the fine granular ulcer scar, high level of functional restoration, and the resistance to ulcer recurrence (62). The better mechanism of QOUH is generally thought to be PG-dependent because exogenous PGs could reverse events involved in ulcer recurrence, inflammatory response, retarded ulcer healing, and defective angiogenesis. In clinic the considerable portion of patients suffered from recurrence or complication in spite of maintenance medication or even after complete resolution and the eradication of *H. pylori*, leaving the need to elucidate the core mechanisms defective in ulcer recurrence. We could identify that accelerated ulcer healing and resistance to ulcer recurrence could be achieved with additional prescription of gastroproteants, for which fundamental support was through the induction of HSPs. HSP27 induction might be one of major mechanisms imposing lower recurrence of gastric ulcer in addition to preservation of trefoil peptide, growth factors, and efficient remodeling activities (63).

**HEAT SHOCK PROTEIN 90 (HSP90)**

**HSP90 and biological action**

HSP90 is a molecular chaperone whose association is required for the stability and function of multiple mutated, chimeric and over-expressed signaling proteins that promote the growth and/or survival of cancer cells and their client proteins include mutated p53, Bcr-Abl, Raf-1, Akt, EbrB2 and hypoxia-inducible factor-1α (HIF-1α). That is, most of target proteins of HSP 90 are protein kinases or transcription factors which play important roles in cellular carcinogenesis. By the early 1990s, several groups reported the observation that HSP 90 was over-expressed in a wide variety of cancer cells and in virally transformed cells (64), in which cases HSP90 had been found in complex with the tyrosine kinase v-Src (65) and the serine/threonine kinase Raf-1 (66).
Although drugs targeting HSP90 remain to be identified, naturally occurring specific inhibitions of HSP90 have not only been identified, but also have also been amply documented to have antitumor activity in various preclinical models. Because of the chemoprotective activity of several proteins that are HSP90 clients, the combination of an HSP90 inhibitor with a standard chemotherapeutic agent could dramatically increase the in vivo efficacy of the therapeutic agent. One such compound, the bensoquinone ansamycin 17-allylamino geldanamycin (17-AAG), is clinical trial at worldwide. Bensoquinone ansamycins, in particular geldanamycin (GA), bound specifically to HSP90, inhibited the association of the chaperone with v-Src protein, and led to the eventual destabilization of the protein and as a result of these studies, it rapidly became clear that HSP90 might be a novel and very exciting target for cancer therapy. Although GA itself proved to be too hepatotoxic for clinical use, 17-AAG, a better tolerated derivative that also binds HSP90, has shown promising antitumor activity as well as predicted biological

![Fig. 6](image)

(A) Expression and modification of HSP90 in gastric mucosa epithelial cells during H. pylori infection. Human gastric epithelial AGS cells were co-cultured with H. pylori and the expressions of HSP90 were observed at 15 min, 30 min, 1 hr, 2 hrs, and 4 hrs after H. pylori infection. There was no apparent change in HSP90 expression on Western blot, but the pattern of HSP90 expression on 2-DE and Western blot was differently observed in this observation time. Significant phosphorylation reflected with acidic shifting of HSP90 just after H. pylori infection was noted and lasted up to 2 hrs. (B) AGS cells were incubated in the absence or presence of 1 mM GA for 16hr prior to treatment of H. pylori. Arrows indicated the acidic-shifted isoforms from basic spot, resulting from HSP90 phosphorylation. GA, a HSP90 inhibitor, treatment significantly blocked the H. pylori-induced phosphorylation of HSP90. (C) ELISA measurement of IL-8 and (D) RT-PCR for IL-8 C&D shows inhibitory effect of GA on H. pylori-induced IL-8 production, respectively.
activity, in preclinical models (67-69), and is now in phase I trial as a single agent. Preliminary data obtained from these trials demonstrate predicted biological activity achieved at drug concentrations below the maximally tolerated dose (69). The clinical benefit of 17AAG or other HSP90 inhibitors as single agents appears promising in certain defined settings. At the same time, exciting preclinical studies point to the probable wide-ranging use of such compounds when used in combination with standard agents.

One of the most HSP90-dependent client proteins is ErbB2 (HER-2/neu), whose over-expression in breast cancer antagonizes cytotoxicity of taxol. Munster et al. have shown that a combination of 17AAG and taxol was more cytotoxic than either agent alone (70). However, the Rb protein status of the cells was important. In cells that were Rb-negative, the simple combination of drugs was not important; however, in cells that were Rb-positive, exposure to 17-AAG before taxol administration enabled the cells to arrest in G1 phase of the cell cycle and become resistant to taxol-induced toxicity. This antagonism probably occurred because of the previously demonstrated ability of 17AAG to induce an Rb-dependent G1 arrest in a variety of tumor types. In contrast to taxol, the cytotoxicity produced by doxorubicin was also synergistically increased by 17-AAG but, in this case, order of drug addiction was not important, as doxorubicin toxicity is not cell-cycle dependent (71-72).

**HSP90 in H. pylori-gastritis**

Among the several kinds of cytokine induced in the gastric mucosa with the colonization of *H. pylori*, IL-8 is one of the major pro-inflammatory cytokines. IL-8 plays a crucial role in the initiation and maintenance of inflammatory response and recently has been identified to function as pro-angiogenic or carcinogenic factor based on the findings that gastric cancer cells in surgical specimens over-expressed IL-8 compared with corresponding normal mucosa and the IL-8 mRNA level directly correlated with the vascularities of the tumor (73-74). When *H. pylori* are co-cultured with gastric epithelial cells, IL-8 is one of the principal mediators of the inflammatory response to *H. pylori*, and recently has been identified as pro-oncogenic roles able to stimulate mitogenic activity, cell adhesion, metalloprotease activity, and angiogenesis. The over-expression of IL-8 mRNA or protein in the breast cancer was already reported to enhance one metastasis, presumably through increased adhesion and invasion ability (75). Human neutralizing antibodies of IL-8 inhibited metalloprotease-2 activity, invasion as well as angiogenesis and tumor necrosis factor-α induced IL-8 secretion increased in a colon cancer (76-77). All these results indicated that IL-8 has significant biological effects on the angiogenesis, carcinogenesis, and progression or metastasis of tumor. In the view of this knowledge, applications or agents that can inhibit the production of IL-8 are thought to be of therapeutic value in the treatment of *H. pylori*-induced gastric inflammation or carcinogenesis. We have documented that blockbuster of HSP90 modulates *H. pylori*-induced IL-8 productions through inactivation of transcriptional factors of AP-1 and NF-κB. *H. pylori* stimulated significant phosphorylation of HSP90 and the phosphorylation was diminished by administration of HSP90 inhibitor, GA (Fig. 6a & 6b). Treatment of GA completely inhibited *H. pylori*-induced IL-8 production (Fig. 6c), which was related to deactivation of ERK1/2 and NF-κB. Our publication provides important insights that HSP90 is involved as a crucial regulator in *H. pylori*-induced IL-8 production and its inhibitor could be potentially used for the inhibition of *H. pylori*-provoked inflammation.

**THERAPEUTICS PRESCRIBED FOR GASTRITIS OF WHICH ACTION IS PARTIALLY BASED ON HSP INDUCTION (FIG 7)**

**Geranylgeranylacetone**

GGA, an anti-ulcer agent, has the ability to induce 70k-Da HSP70 in various cell types including the gastric mucosa, intestine, liver, myocardium, retina, and central nervous system (78-81) and to protect cells from apoptotic insults. Oral administration of GA rapidly causes up-regulation of HSP70 expression in response to a variety of stresses, although this effect is weak under normal conditions. With extremely low toxicity of GGA, this compound has been widely used as an oral anti-ulcer drug. Even though the induction mechanism of HSP70 by GGA has not yet been well understood, Otaka et al. (82) documented that when the cells are exposed to many stress condition, the bound HSP70 to HSF-1 will be dissociated. The free HSF-1 will be able to bind to the HSE in the promoter region of HSP70 gene. In this state, GGA can bind to the C-terminal of HSP70 which is bound to the HSF-1 through same site of GGA binding resulting in dissociation of the HSP70 from HSF-1, after which HSF-1 will be activated and its trimerization would be occurred with increased synthesis of HSP70. GGA has the ability to protect various cells from apoptosis triggered by a wide range of stimuli, including ethanol, reactive oxygen species, proteasome inhibitors, and non-steroidal anti-inflammatory drugs and ischemia. It is worthwhile to note that all of these agents are potential inducers of endoplasmic reticulum stress. Although the cytoprotective effects of GGA have been ascribed to its ability to induce HSP70 and other endoplasmic reticulum chaperones induced by GGA could, at least in part, contribute to its cytoprotective action. In addition to the anti-apoptotic effect, some previous reports showed that GGA has the potential to induce apoptosis in malignant cells.

**Rebamipide**

Rebamipide, 2-(4-chlorobenzoylamino)-3-[2-(1H)-quinolinon-4-yl], is an efficient anti-ulcer agent, increasing endogenous PG and scavenging oxygen free radicals. An anti-ulcer effect of rebamipide was related inhibition of the production of reactive oxygen metabolites (ROM) by activated neutrophils. ROMs have been reported to be important in the pathogenesis of ischemia/reperfusion-, ethanol-, NSAIDs- or *H. pylori*-induced gastric mucosal injuries. We investigated the role of rebamipide in protecting against ROM-mediated cell damage in gastric mucosal cells, for which electron spin resonance and tracing of HSP was applied. As results, rebamipide exerted a significant protection on hypoxanthine-xanthin oxidase-induced gastric mucosal cell cytotoxicity through inhibition of lipid peroxidation of the cell membrane, direct hydroxyl radical scavenging activity, and significant induction of cellular cytoprotective protein such as HSP70 (83).

**Artemisia asiatica**

*Artemisia asiatica* extracts have been proven to possess anti-inflammatory, anti-oxidative, and cytoprotective actions and have been demonstrated effective protection from various models of gastric mucosal damages by NSAIDs, stress, *H. pylori* infection, and alcoholic gastritis. In addition, we could demonstrate that *Artemisia* extracts were quite efficient in either accelerating gastric ulcer healing or preventing ulcer recurrence, for which the preservation or induction of HSP70 or HSP27 played a critical role in achieving QOUH (qualified ulcer healing) through ideal remodeling of healed ulcer.
**Zinc compounds**

Zinc is an essential trace mineral required by many enzymes in different biological systems. Among zinc dependent enzymes, DNA and RNA polymerases are crucial during tissue repair, as they affect cell proliferation and protein synthesis. Therefore, zinc deficiency delays the process of wound healing in skin and halts restorative pathways in gastric ulcer healing. From extended points of view related to zinc in various gastroenterological disorders, zinc compounds conferred protection against radiation-induced cell damage and attenuated hepatic fibrosis in a mouse model of non-alcoholic steatohepatitis. Currently two kinds of zinc compounds are available clinically as tools for preventing NSAID toxicity or \textit{H. pylori}-induced damages; zinc carosine and zinc acexamate. Regarding HSP induction, these two zinc compounds protect GI epithelial cells from oxidative injury induced by hydrogen peroxide or NSAID administration relevant to HSP70 or HSP27 induction (84-86).

**Retinoid**

Retinoids are a class of compounds structurally related to vitamin A. The term "vitamin A" refers either to retinol and their synthetic analogues or to certain carotenoids, which are converted to retinol in the body as needed. Retinoids are integrally involved in cell growth and differentiation, after which retinoids are generally applied for differentiation therapy. Curiously the double-edged roles of retinoid related to HSP induction, they can impose significant levels of direct cytotoxic effect via labilization of lysosomal or plasma membrane, but can afford differentiation through HSP70 preservation (87).

**Phytoceuticals**

Phytoceuticals is a term for plant products that are active on biological systems. Phytoceuticals such as Korea red ginseng, green tea, red wine, flavonoids, broccoli sprouts, and garlic, are all known to inhibit \textit{H. pylori} colonization, decrease gastric inflammation, and even inhibit precancerous changes by inhibiting NF-xB DNA binding, inhibiting mutagenesis. Even though further unsolved issues are awaited before these phytoceuticals are accepted as a standard treatment for either \textit{H. pylori} infection or various forms of gastritis, common features of these phytoceuticals were very efficient in either preserving HSPs levels or inducing HSPs in the stomach (88-89).

**CONCLUSION**

Heat shock proteins (HSPs) are crucial for the maintenance of cell integrity during normal cell growth as well as during pathophysiological condition, especially under noxious stress. Recently, HSP, which functions mainly as the molecular chaperones, has been appeared to be involved in diverse biological activities such as rescuing from apoptosis, escape from carcinogenesis, protection from cytotoxic damages including NSAIDs or chemotherapeutics, stress, harmful infections, and acceleration of ulcer healing. Among infectious causes relevant to gastric diseases, \textit{H. pylori} infection unequivocally led to inflammation in the gastric mucosa, after which \textit{H. pylori} are known to be responsible for gastritis, gastric ulcers, duodenal ulcer disease, and even gastric cancer. In order to document the precise role of HSPs in \textit{H. pylori}-associated gastritis, two-dimensional electrophoresis (2-DE) with western blot was performed. The results all showed that \textit{H. pylori} infection on gastric mucosal cells significantly attenuated or cancelled the expression of HSP 70 and HSP 27 and stimulated phosphorylation of HSP 90. Therefore, the enrichment of HSPs or bioregulation of HSPs has been benefited in either the prevention of \textit{H. pylori}-induced gastric mucosal damages or contribution to accelerated or qualified ulcer healing. As the way of HSP enrichment, treatment of either non-cytotoxic heat or GGA preserved the expression of HSP 70 and HSP27 in spite of continued exposure to \textit{H. pylori}. In other study showing the contribution of HSP27 against NSAIDs-induced gastropathy,
novel acid pump antagonist, revaprazane, protected from indomethacin-induced gastropathy through maintaining the significant levels of HSP27. In addition to these advantages in ameliorating gastric inflammation, HSP imposed the QOUH as evidenced with accelerated gastric ulcer healing and resistance to ulcer recurrence. Taken together, the induction of these HSPs confers both cytoprotection and anti-inflammation in response to either H. pylori infection or NSAID administration. Several investigators including ours have published papers that HSPs were quite contributive in either acceleration of ulcer healing or prevention from recurrence, for which geranlygeranylacetone, rebamipide, Artemisia asiatica, zinc compounds, retinoids, and phytoceuticals were candidate of high rank possessing evidences that HSPs is partially or critically contributive action as evidenced from bench to bedside (77-89).

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