Combined Extracts of *Artemisia* and Green Tea, Mitigated Alcoholic Gastritis Via Enhanced Heat-shock Protein 27

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**Background/Aims:** Several lines of evidence from epidemiologic and laboratory studies have shown that the consumption of *Artemisia* or green tea extracts (MPGT) is inversely associated with the risk of alcohol-induced damage and other chronic diseases. Supported by previous studies showing that the combined extract of *Artemisia* and green tea, MPGT, exerted significantly either anti-oxidative or anti-inflammatory actions against *Helicobacter pylori*-associated gastric diseases, it was hypothesized that MPGT can offer protection against alcoholic gastritis.

**Methods:** Ethanol was administered to induce gastric damage in Wistar rats, which had been pretreated with various doses of MPGT, to measure the rescuing action of a MPGT pretreatment against ethanol-induced gastric damage. In addition, the molecular mechanisms for the preventive effects were examined.

**Results:** The MPGT pretreatment (100, 300, and 500 mg/kg) alleviated the ethanol-induced gastric damage, which was evidenced by the significant decrease in calcium-dependent phospholipase A2, MAPKs, and NF-κB levels compared to ethanol alone. Furthermore, the MPGT pretreatment preserved 15-prostaglandin dehydrogenase, whereas cyclooxygenase-2 was decreased significantly. All of these biochemical changes led to the significant alleviation of alcohol-associated gastric mucosal damage. Ethanol significantly increased the TUNEL positivity in the stomach, but MPGT decreased the apoptotic index significantly, which was associated with significantly lower pathological scores of ethanol-induced mucosal ulcerations. The significant protective changes observed alcoholic gastritis with MPGT were related to the increased expression of cytoprotective genes, such as heat-shock protein (HSP)27, HSP60, and PDGF.

**Conclusions:** The efficient anti-inflammatory, anti-apoptotic, and regenerative actions of MPGT make it a potential nutrient phytoceutical to rescue the stomach from alcoholic gastritis. *(Korean J Gastroenterol 2018;71:132-142)*

**Key Words:** Ethanol; Gastric damages; *Artemisia* extracts; Green tea extracts; HSP27
INTRODUCTION

Alcohol intake is associated with a range of clinical damage, including psychiatric disease, chronic illness as well as cancer. Of these, gastric diseases include acute or chronic gastritis, peptic ulcer diseases, and gastric carcinoma. The common pathogenic mechanisms in these gastric damage include direct membrane damage, inflammation, erosion or ulcer formation, and mutagenesis. Mechanistically, ethanol-induced gastric damage is mediated by the generation of free radicals based on the finding that ethanol administration apparently elevates the lipid peroxide levels in the gastric mucosa and depletes the major antioxidant factors, including enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants, such reduced glutathione, and vitamins A, C, and E.1,2

Despite these studies, means of alleviating alcoholic gastritis are lacking because acid suppressants or some gastric mucosal protectants only provide partial protection from alcoholic gastritis; the only convincing way is to abstain from alcohol. This study showed that combined extracts of Artemisia and green tea extracts (MPGT) have a protective effect from several gastric irritant models, such as Helicobacter pylori (H. pylori)–associated gastritis, via anti-inflammation, antioxidant and cytoprotective action. MPGT extracts have been reported to have potential anti-inflammatory, antioxidative, and anti-mutagenic activities, especially targeted to various gastrointestinal diseases, including stress-related mucosal damage, inflammatory bowel diseases, and gastrointestinal cancers.3-6 In addition to gastrointestinal protection, Artemisia extracts alone have been used for circulatory disorders, such as dysmenorrhea, hematuria, hemorrhoids, and inflammation in the affected organs, and are also used to treat chronic conditions. Green tea extracts were reported to be possible cancer preventives in a long-term cohort study.7

The current study extends this investigation to determine if MPGT can prevent alcohol-induced gastric lesions in rats, whether their cytoprotective actions are dependent on the MPGT dose, and examine the underlying molecular mechanisms responsible for these protective actions.

SUBJECTS AND METHODS

1. Preparation of MPGT

The raw materials for the preparation of MPGT powder (Lot NO. SD-MPGT-001) were obtained from S&D Co., Ltd. (Cheongwon, Korea). The powders were prepared as follows: Artemisia capillaris (MP) was extracted with water for 8 hours at 95°C, and Camellia sinensis L (GT) was extracted with water for 4 hours at 80°C. The extracts were filtered and evaporated under vacuum (below 60°C). The concentrated extracts were added to ethanol and the precipitates were then dried. MPGT is a combination of the Artemisia and green tea extracts. Each powder was used separately in the test.8 The powders were dissolved in DMSO for the in vivo experiments by an oral gavage 6 hours before the ethanol treatment.

2. Other reagents used

All chemical reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA). The western blotting detection reagents were obtained from Bio-Rad Laboratories (Berkeley, CA, USA). The antibodies for cyclooxygenase-2 (COX-2), 15-hydroxyprostaglandin dehydrogenase (15-PGDH), p38, phosphor-p38, extracellular signal-regulated kinases (BAX), and heat-shock protein (HSP)70 were all obtained from Cell signaling Technology Inc. (Denver, CO, USA). Calcium-dependent phospholipase A2 (cPLA2), extracellular signal-regulated kinases (ERK1), phosphor-ERK, c-Jun N-terminal kinases (JNK), phosphor-JNK, HSP27, and β-actin were purchased from Santa Cruz Biotechnology (Dallas, TX, USA).

3. Ethanol–induced gastric damage in Wistar rats

1) Animal manipulation

All experiments were performed with five-weeks-old male Wistar rats (ORIENT, Seongnam, Korea), which were fed a sterilized commercial pellet diet (Biogenimics, Seoul, Korea) and sterile water ad libitum, and housed in an air-conditioned biohazard room at 24°C. After 1 week of adaptation, each animal was administered intragastrically with a pretreatment of MPGT for 6 hours, and a single dose of absolute ethanol (1 mL/200 g, BW), except for the control groups. Fig. 1 shows the experimental groups, all animal studies were carried out in accordance with the protocols approved by the Institutional Animal Care and Use Committee (IACUC) of CHA University.

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Fig. 1. MPGT pretreatment alleviated ethanol-induced gastric damage. (A) Experimental scheme. Five animal groups were set: Group 2 as the control and Groups 3, 4, and 5 pretreated with 100 mg/kg, 300 mg/kg, and 500 mg/kg MPGT. The rats were sacrificed after 1 hour of 100% ethanol. Representative pictures of the gross appearance of the rat stomach after alcohol ingestion in the absence or presence of 100, 300, and 500 mg/kg MPGT pretreatment. (B) Gross and microscopic photograph of ethanol-induced gastric mucosal lesions according to the group, ×40 magnification. (C, D) The scoring criteria are written in Methods. The mean score for the gross and pathologic lesion scores. The mean levels of the gross lesion index and mean scores of pathological evaluation are presented as the mean±SD from 8 rats/group. MPGT, extracts of artemisia and green tea; SD, standard deviation.

CHA Cancer Institute after IRB approval. Stomach tissues were isolated and subjected to further histology examination and Western blotting.

2) Gross lesion index
After sacrificing the animals, the isolated stomachs were cut open along the greater curvature and washed in ice-cold saline. To determine the degree of gross mucosal damage, the mucosal sides of the stomachs were photographed using a digital camera and a part of the mucosa was filled immediately with a 10% formalin solution. The gross damage to the gastric mucosa was assessed by three gastroenterologists,
Table 1. Determination of the Score in *H. pylori*-Induced Inflammation and Ulcers

| Scores | Inflammation | Gland |
|--------|--------------|-------|
| 0      | 0 μm         | 0     |
| 1      | 0-1,000 μm   | 1     |
| 2      | 1,001-2,000 μm | 2     |
| 3      | 2,001-3,000 μm | 3     |
| 4      | 3,001 μm     | 4     |

| Ulcers, erosion length×depth (in mucosa) | Ulcer or erosion up to 1 mm | Ulcer or erosion larger than 1 mm |
|------------------------------------------|-----------------------------|---------------------------------|
| 0.5                                      | n×2                         | n×3                             |

who were blinded to the treatments, using a gross ulcer index. In detail, these lesions scores were defied as follows: score 1, presence of edema, hyperemia, or single submucosal punctiform hemorrhage; score 2, presence of submucosal hemorrhagic lesions with small erosions; score 3, presence of deep ulcers with erosions and invasive lesions.

3) Histopathology and pathologic scores

For histopathology analysis, the stomach tissues were fixed in 10% neutralized buffered formalin, processed using the standard method, and embedded in paraffin. Sections, 4 μm in thickness, were then stained with hematoxylin and eosin. The glandular mucosa of corpus and antrum were examined histologically for the pathological changes in a *H. pylori* infection: inflammatory cell infiltration, erosive lesions, ulceration, dysplasia, adenoma formation, and adenocarcinoma. Table 1 presents the scoring system for the evaluation. Immunohistochemical staining with the proton-pump antibody was performed in all cases to determine the objective atrophy score.

4) Immunohistochemical staining

After the paraffin blocks were dewaxed and rehydrated with a graded series of alcohol, the tissue sections were heated in pressure jars filled with 10 mM citrate buffer in a microwave for 10 minutes. The slides were cooled in water for 15 minutes and washed in PBS. The slides were incubated overnight with the primary antibody. After incubation, a subsequent reaction was formed using a VECTOR kit (Vector laboratories, Burlingame, CA, USA). Finally, the slides were incubated with 3,3'-diaminobenzidine (Invitrogen LifeTechnologies, Carlsbad, CA, USA) and counterstained with hematoxylin and eosin (Sigma-Aldrich). Immunohistochemical staining was performed using the COX-2 antibody (Sigma-Aldrich), NF-κB, p50, and p65 (Santa Cruz, Santa Cruz, CA, USA).

5) Terminal deoxynucleotidyl transferase mediated dUTP nick–end labeling (TUNEL)

To detect apoptosis, the stomach tissues were stained with the TUNEL method using a Dead End TM Fluorometric TUNEL System (G3250#; Promega, Santa Cruz, CA, USA).

4. Western blot analysis

The extracted stomach tissues were washed twice with PBS and then lysed in ice-cold cell lysis buffer (Cell Signaling Technology, Denver, CO, USA) containing 1 mM phenylmethylsulfonyl fluoride (PMSF, Sigma-Aldrich, MO). After 20 minutes incubation, the samples were centrifuged at 10,000 g for 10 minutes. The supernatants were then collected. The proteins in the lysates were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes, which were then incubated with the primary antibodies, washed, incubated with peroxidase-conjugated secondary antibodies, rewashed, and then visualized using an enhanced chemiluminescence (ECL) system (Bio-Rad Laboratories).

5. Data analysis

The results are expressed as the mean±standard deviation. The data were analyzed by one-way ANOVA, and the statistical significance between the groups was determined using Duncan’s multiple range test. p-values<0.05 were considered significant.

RESULTS

1. Pretreatment of the MPGT, which is a combined extract of *Artemisia* capillaries and green tea, offered protection against ethanol–induced gastric damage

The administration of 1 mL of 100% ethanol to the fasting...
Fig. 2. Status of ethanol-induced gastric inflammation. (A) Mean score for inflammation according to group. (B) Changes in IL-8, phosphate ERK, phosphate JNK, and phosphate p38 mRNA and their protein expression. (C) Immunohistochemistry staining with the NF-κB p65 antibody, ×100 magnification, and the mean positivity according to the group. ERK, extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinases; mRNA, messenger RNA; SD, standard deviation.

The characteristic pathology of ethanol-induced gastritis was pyknosis and mucosal ulceration, mucosal hemorrhage, inflammatory cell infiltration, and submucosal edema. The gross and mean pathological score according to the group showed significant decreases in the mean pathological scores in Groups 4 and 5 (p<0.005, Fig. 1C and 1D).

2. MPGT decreased ethanol-induced gastric inflammation significantly via MAPK inactivation and NF-κB

As shown in Fig. 2A, the mean score for gastric inflammation was significantly higher in Group 2 than the other groups (p<0.001), but their mean scores were significantly lower in the Group pretreated with MPGT (p<0.05, Fig. 2A).
The expression of phosphorylated ERK, JNK and p38 were measured to determine the anti-inflammatory action of MPGT. As shown in Fig. 2B, ethanol administration increased the expression of phosphorylated ERK, JNK and p38 significantly, indicating that MAPK activation were implicated significantly in ethanol-induced gastric inflammation. On the other hand, the MPGT pretreatment inactivated all of these MAPKs, including ERK1/2, JNK, and p38. Next, the changes in the representative redox sensitive transcription factor, NF-kB with immunohistochemical staining with the NF-kB p65 antibody, were investigated (Fig. 2C). The ethanol-induced gastric mucosal damage was associated with NF-kB activation (p<0.01) but the MPGT pretreatment inactivated the NF-kB p65 activity in a dose dependent manner.

3. MPGT pretreatment led to significant attenuation of ethanol-induced gastric damage via the inhibition of cPLA2 and COX-2 and induction of 15-PGDH

One hour exposure to ethanol led to extensive mucosal damage as well as submucosal edema, whereas the MPGT pretreatment helped prevent the ethanol-induced gastric damage (Fig. 1B). The average score of the ethanol-induced gastric damage focusing on the mucosal and submucosal injuries, as shown in Fig. 3A, revealed the MPGT pretreatment...
김용석 등. Artemisia와 Green Tea 추출 복합물의 HSP27 발현 증가를 통한 알코올성 위염 억제 효과

Fig. 4. Status of an ethanol-induced gastric ulcer. (A) Mean score for ethanol-induced gastric ulcers. The arrow shows the significant denudation and exfoliation of gastric mucosa. (B) TUNEL staining for apoptotic cells. All images were obtained from the non-ulcerated mucosa of each group and significantly increased TUNEL positive cells were noted in Group 2 even in the non-ulcerated gastric mucosa. (C) Mean TUNEL positive (apoptotic index) according to the group. (D) Western blot for BAX expression. TUNEL, terminal deoxynucleotidyl transferase mediated dUTP nick-end labeling; SD, standard deviation.

4. MPGT mitigated ethanol-induced gastric ulcers via down-regulated apoptosis

When the degree of gastric ulceration was scored according to the group, as shown in Fig. 4A, the mean scores for gastric ulcers were significantly lower in Groups 4 and 5 than in Group 2 (p<0.05). Several studies have reported that ethanol induced gastric ulcers were based on gastric mucosal apoptosis. Therefore, TUNEL staining was performed to measure apoptosis according to the group. As shown in Fig. 4B, ethanol administration induced significant apoptosis in the ulcerative and unulcerated gastric mucosa (p<0.001, Fig. 4B). On the other hand, the MPGT pretreatment decreased the number of TUNEL positive cells significantly (p<0.05, Fig. 4B). Among the apoptosis executors, the level of BAX expression was measured. The expression of BAX was significantly higher in Group 2, whereas the expressions of all those were atte-
5. Increased expression of HSPs contributed to mitigation of ethanol-induced gastric damage by MPGT. As shown in Fig. 5A, the expression of HSP27 was significantly higher in the groups pretreated with MPGT, whereas there were no changes in HSP70. On repeated Hsp27 mRNA measurements, the MPGT pretreatment groups showed significantly higher Hsp27 and Hsp60 mRNA levels (Fig. 5B). In addition, pdgf mRNA was significantly higher in the MPGT pretreatment group, indicating that the molecular chaperone and growth factors were responsible for the protection from ethanol-induced gastric mucosal damage. Profound changes in HSP27 preservation in the group pretreated with MPGT accompanied by the additional preservation of PDGF can explain the effect of MPGT on alcoholic gastritis (Fig. 5C).

**DISCUSSION**

This study showed that combined extract of Artemisia and green tea, MPGT, offered protection from alcoholic gastritis as mediated by the MPGT treatment (p<0.01, Fig. 4C). The increased expression of HSPs contributed to mitigation of ethanol-induced gastric damage by MPGT. As observed in the gross lesion after the ethanol challenge, MPGT mitigated 100% of the ethanol-induced gastric damage, in which significantly less gastric inflammation, mucosal damage, and ulcerations were observed with the MPGT pretreatment. Although this should be proven further with a clinical trial, these findings suggest that MPGT natural product can be a reliable way of preventing alcoholic gastritis. Because alcoholic gastric damage is provoked by several mechanisms, the approach using natural extracts is attractive because of diverse concerted modes of rescuing actions. Alcohol intake causes gastric injury, such as gastritis, gastric ulcers, and gastric cancer, in which largely two main mechanisms are involved: direct effects, such as disruption of the mucosal cellular membrane; and indirect effects, such as oxidative stress, recruitment of leukocytes, secretion of cytokines including IL-1β, IL-8, IL-12, TNF-α, and activation of NF-κB.

Therefore, several interventions have been reported to reduce or prevent alcohol-associated gastric injury, such as the inhibitor of the alcohol-metabolizing enzyme, anti-inflammatory agents, and cytoprotective agents. Although reported to be effective, reliable agents or strategies are needed to reduce...
alcohol-associated injuries.

In dissecting the mechanisms implicated in the protection from alcoholic gastritis, the first mechanism stabilizing gastric epithelium is essential. This study focused on two regulations after alcohol administration: control of cPLA2 and COX-2, and the preservation of 15-PGDH. cPLA2 is an enzyme responsible for the hydrolysis of membrane phospholipids, such as phosphatidylcholine and with activation, cPLA2 cleaves phosphatidylcholine to yield free fatty acid and lysophosphatidylcholine. In the stomach, cPLA2 activation subsequent to CYP2E1 activation, lipid peroxidation, and intracellular Ca\(^{2+}\) release has been regarded as a direct mechanism of alcohol in the stomach and liver. Under this condition, Kang et al. reported that irissoidone and kakkalide can attenuate ethanol-induced gastric injury by inhibiting the infiltration of neutrophils accompanied by either inhibiting IL-8 secretion or inactivating NF-κB. 15-PGDH has tumor suppressive activity against gastric and colon cancer but has never been studied in alcoholic gastritis, despite being inferred to have some cytoprotective actions. In the current study, 15-PGDH was significantly lower in alcoholic gastritis. Together with the finding that COX-2 was significantly higher in alcoholic gastritis (Fig. 3C), the inhibition of COX-2 and the induction of 15-PGDH in the group pretreated with MPGT is one of the core actions in the protection.

As the next mechanism essential for rescuing from alcoholic gastritis, significant mitigation of alcohol-induced apoptosis was explored. As shown in Fig. 4, the MPGT pretreatment attenuated alcohol-induced apoptosis, of which accumulation has been associated with gastric erosion or ulcers. As an example of the connection between alcohol damage and apoptosis, miR-21 was recently identified as being responsible for ethanol-induced apoptosis in gastric cells, through which ghrelin was proven to offer protection against ethanol-induced apoptosis and crocin was proven to be protective against ethanol-induced gastric injury by antagonizing apoptosis. In the literature, many publications deal with the antagonizing effects of ethanol-induced apoptosis, but only for the mechanism results, not for clinical trials highlighting the need for concerted actions of cytoprotection against alcohol-induced gastric damage.

The third mechanism implicated in alleviating alcoholic gastritis is either potent anti-inflammatory or antioxidative action. As shown in Fig. 2, MPGT had significant anti-inflammatory activity through either MAPKs inactivation or NF-κB. Alcohol-induced gastric mucosal injury can be mediated by a range of cellular molecules, such as COX, lipoygenase, cytokines, and oxygen-derived free radicals, whereas polyphenols from green tea or Artemisia extract were reported to inhibit inflammation, scavenge excess free radicals, and stimulate the regeneration of damaged cells or tissues. In detail, under the hypothesis that green tea extracts may attenuate alcoholic gastritis, the gross pathology of alcohol-induced gastric damage and green tea extract pretreatment reduced gastric hemorrhage and mucoid cap formation dramatically in a dose-dependent manner. With green tea extracts, the COX-2 and iNOS levels were decreased significantly accompanied by the inhibition of NF-κB and the MAPK pathway. In addition, ethanol injury is associated with oxidative stress. The antioxidant effects of Oleumcinnamomi or Parkiaspeciosa extract or Pithecellobiumjiringa extract or Monollumaquadangular extracts exerted protection against ethanol-induced gastric damage. On the other hand, despite the many publications, the fact that only a few are available in clinics highlight the need for global and comprehensive actions after detailed clinical trials.

Together with these three mechanisms of MPGR against alcoholic gastritis, a cytoprotective and regenerative mechanism might be essential and must be used as an intervention in alcoholic gastritis. HSPs have core house-keeping functions in the cells, where they are built-in components of folding, protecting critical genes for survival, correcting abnormal signal transduction, and proofreading the structure of proteins and repair mis-folded conformers. A H. pylori infection or alcohol causes significant inflammation and oxidative stress to the gastric mucosa, proceeding to the development of either precancerous lesions, including chronic atrophic gastritis or gastric cancer, in addition to gastritis and peptic ulcers. Similarly, in the current study, the HSP70 levels were unchanged even after the green tea extract treatment, but the HSP27 levels were increased significantly by MPGT, indicating the intervention of HSPs as protective mechanisms. HSPs are generally considered to improve the cellular recovery by either refolding partially damaged functional proteins or increasing the delivery of precursor proteins to the important organelles, such as the mitochondria and endoplasmic reticulum, through which HSPs might complete the efficient mucosal defense mechanisms and achieve ulcer healing.
most likely protecting the key enzymes related to cytoprotection, conferring HSPs as a ‘hard worker’ for the stomach.27-29

Although not studied in the current study, acetaldehyde associated with alcoholic beverages has been classified as a Group 1, definite, carcinogen in humans.30 The cumulative cancer risk associated with increasing alcohol exposure has necessitated intervention studies, such as slow-release L-cysteine capsules31 or agents to reduce the mutagenic actions of alcohol.32 Although there is significant evidence, in the current study, ethanol exposure decreased the expression of 15-PGDH. Because 15-PGDH has been acknowledged as a Group 1, definite, carcinogen in humans.30 The cumulative associated with alcoholic beverages has been classified as a

tions of alcohol.32 Although there is significant evidence, in the current study, ethanol exposure decreased the expression of 15-PGDH. Because 15-PGDH has been acknowledged as a tumor suppressive enzyme in gastrointestinal cancer,33,34 the significant preservation of 15-PGDH with a MPGT pretreatment can provide the mechanistic advantage of reducing the alcohol-associated gastric cancer risk (Fig. 3C).

In conclusion, this study showed that a beverage or capsule containing MPGT can prevent alcohol-induced gastritis, in which MPGT extracts antagonized the damaging mechanisms of alcoholic gastritis via anti-inflammatory, anti-oxidative, and cytoprotective actions. Although not covered in detail in this study, the mucosal integrity is maintained by defense mechanisms, including pre-epithelial factors, such as the mucus and bicarbonate layer; epithelial factors, including mucus, phospholipids, prostaglandin, and heat shock proteins; increased cell renewal accomplished by the proliferation of progenitor cells regulated by growth factors, such as growth factors. In addition, the generation of prostaglandins and nitric oxide was operated efficiently by the MPGT pretreatment to resist alcoholic gastritis.

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