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Regulatory activity of nobiletin on MAPK/NF-κB signaling pathway in indomethacin-induced gastric damage

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Nobiletin (NOB) is an important flavonoid obtained from citrus fruits such as *Citrus depressa, Citrus reticulata, Citrus sinensis* and *Citrus limon*. Studies have demonstrated that effects are anti-inflammatory, antioxidant, immunomodulatory, anticancer, neuroprotective, anti-atherosclerosis, antiapoptotic, and antidiabetic. There are still limited studies on the efficacy of nobiletin on the pathways underlying gastric damage. Therefore, in the present study, we investigated both the effects of nobiletin on the mitogen-activated protein kinase (MAPK)/nuclear factor kappa B (NF-κB) signaling pathway, one of the pathways in indomethacin (IND)-induced inflammation and whether it has gastroprotective activity. NOB+IND and PAN+IND groups were treated with substances for 7 days (10 mg/kg NOB, 5 mg/kg PAN). On the 8th day, gastric damage model was created with a single dose of 100 mg/kg indomethacin. In indomethacin-induced gastric injury, nobiletin significantly decreased NF-κB-p65, MAPK levels and significantly increased prostaglandin E2 (PGE2) production in the stomach. In addition, nobiletin administration caused a decrease in interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and interleukin 1α (IL-1α) levels and an increase in interleukin 10 (IL-10) levels against indomethacin-induced inflammation. When the ulcerative areas were evaluated, it was found that ulcerative areas were significantly reduced in the nobiletin group compared to the indomethacin only group, and when the ulcer inhibition levels of nobiletin and pantoprazole administration were examined, both substances showed similar results. When these results were evaluated as a whole, it was determined that nobiletin had a candidate anti-inflammatory potential for the prevention of inflammation in the stomach and showed a strong gastroprotective effect.

Keywords: Gastric ulcer, Indomethacin, Cytokines, Inflammation pathways, Nobiletin

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with highly effective antipyretic, analgesic and anti-inflammatory activity. Side effects are reported to occur in approximately 30-60 % of patients receiving indomethacin at usual therapeutic doses, with the most common side effects occurring in the gastrointestinal tract. These undesirable effects include nausea, indigestion, heartburn, epigastric pain, anorexia, bloating, flatulence, gastroenteritis, rectal bleeding and proctitis, intestinal strictures, single or multiple ulcerations in the esophagus, stomach, duodenum, small or large intestine[1,2]. Indomethacin causes an increase in gastric acid secretion and may interfere with mucosal cell regeneration through inhibition of PGE2 synthesis, increase the production of free radicals and inflammatory cytokines, lead to the invasion of activated neutrophils and consequently induce gastrointestinal destruction[3]. Previous studies have shown that NF-κB and MAPK signaling pathways play an important role in regulating gastrointestinal damage by NSAIDs and actively participating in inflammation. Therefore, a growing body of research suggests that regulation of factors involved in the inflammatory response may play a key role in developing novel strategies for the prevention and treatment of gastric and intestinal ulcers[4,5].

In recent years, the increasing awareness of people's orientation towards a healthy life has increased the interest in alternative medicine and plants and their active ingredients, which have a wide range of bioactivity due to their low or no side effects. One of the important active substances obtained from citrus peel (*Citrus depressa*, *Citrus reticulata*, *Citrus sinensis* and *Citrus limon etc*.) is nobiletin[6]. Anti-inflammatory[7-9], antioxidant[10], antidiabetic[8], anticancer[11], immunomodulatory[9], and neuroprotective[10] are just a few of the properties of nobiletin. Numerous investigations have demonstrated that pretreatment with nobiletin can inhibit the activation of the NF-κB, MAPK, and Akt pathways, thereby exhibiting anti-inflammatory properties[12,13].

In light of this information, two main points were aimed in the present study. The first was to determine whether nobiletin has gastroprotective activity in indomethacin-induced gastric injury, and the second was to determine whether changes in the NF-κB/MAPK inflammation pathway, which is thought to be one of the underlying physiopathologic pathways underlying indomethacin-induced gastric injury, could

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serve as a stepping stone to establish new treatment strategies for further studies.

Materials and Methods

In this study, 32 male Sprague-Dawley rats were used. The rats were obtained from Erzincan Binali Yıldırım University Experimental Animals Research and Application Centre and housed in an environment with room temperature, standard 12 h light/dark cycle and adequate ventilation. They had *ad libitum* access to standard diet and water. Rats were divided into groups of 8 rats per group as follows, Group 1 - Control Group (C): DMSO was administered orally daily for 7 days; Group 2 - Indomethacin Group (IND): DMSO was administered orally daily for 7 days + 100 mg/kg single dose indomethacin was administered after the rats were fasted for 24 h; Group 3 - Nobiletin + Indomethacin Group (NOB+IND): 10 mg/kg dose of nobiletin was administered orally daily for 7 days + 100 mg/kg single dose of indomethacin was administered after the rats were fasted for 24 h; Group 4 Pantoprazole + Indomethacin Group (PAN+IND): 5 mg/kg pantoprazole (standard drug) orally daily for 7 days + 100 mg/kg single dose indomethacin after the rats were fasted for 24 h.

The study groups were administered substances for 7 days. The doses of the substances were designed with reference to previous studies[14-16]. DMSO was administered orally to the control and indomethacin groups during the same period in order to eliminate the stress difference between the control and indomethacin groups. At the end of the 7th day, the animals were fasted for 24 h and a single dose of 100 mg/kg indomethacin was administered orally. 24 h after indomethacin administration, the anaesthetized animals were euthanized by cervical dislocation and lung tissue samples were taken. The tissues were kept under appropriate storage conditions until analyzed (Fig. 1).

Biochemical markers were determined using commercial Elisa kits. Stomach tissues were homogenized according to the kit procedures. PGE2 (Bostonchem), MAPK (Btlab), NF-κB (p65-p105), IL-1α, IL-10 and TNF-α (Sunred), IL-6 (Elabscience) levels were determined in gastric tissue homogenates according to kit procedures. The damage index of gastric tissue samples was calculated with reference to the methods of Sabiu *et al.*[17] and Özbakiş-Dengiz *et al.*[18].

Statistical analysis

SPSS 27 statistical program was used for statistical evaluation of the data obtained from the analyses.

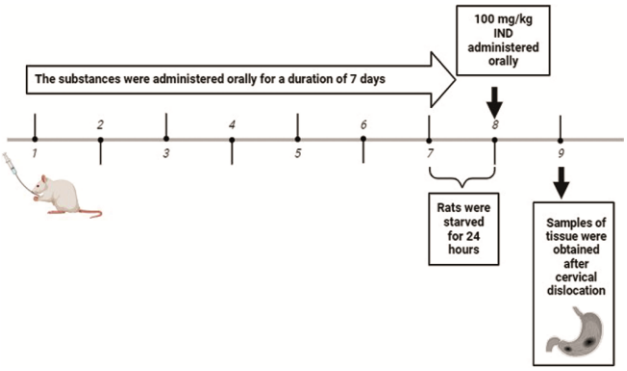

Fig. 1 — Summary of experimental procedure.

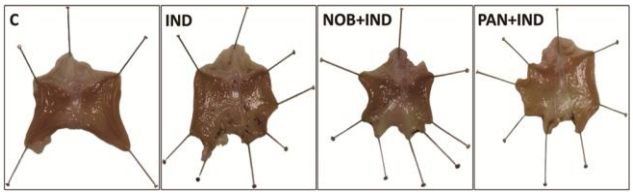

Fig. 2 — Macroscopic views of stomach tissues of control and experimental group animals.

One-way Anova and Tukey test were used for statistical evaluation of independent groups. All values were expressed as mean ± standard deviation (± SD) and differences with $P<0.05$ were considered significant.

Results and Discussion

Macroscopic examination of the gastric tissues revealed that the C group did not contain ulcerative areas and had a completely normal appearance. However, prominent ulcerative areas were observed in indomethacin-treated groups. Ulcerative areas increased by 4.12% in the IND group compared to the C group ($P<0.001$). The NOB+IND and PAN+IND groups still had ulcerative areas compared to the C group (1.29% and 1.27%, respectively), but these ulcerative areas were significantly reduced in both groups compared to the IND group ($P<0.001$). In addition, when the ulcer inhibition levels of nobiletin and pantoprazole administration were examined, it was determined that both substances showed similar results (68% and 69% inhibition, respectively) and were highly effective in preventing ulcer formation (Fig. 2 & 3). It was found that PGE2 levels of gastric tissues decreased in all indomethacin-treated groups at the level of $P<0.001$ compared to the C group, but when the IND group was compared with the NOB+IND and PAN+IND groups, these two groups showed an increase at the level of $P<0.01$ compared to the IND group. When NOB+IND and PAN+IND

groups were compared, there was no statistical difference between them. When NF-κB-p65 and MAPK levels were evaluated, there was an increase in the IND group compared to the C group (P<0.001), and significant decreases in the NOB+IND (P<0.001) and PAN+IND (P<0.01, P<0.001 respectively) groups compared to the IND group. There was no statistical significance between C, NOB+IND and PAN+IND groups in NF-κB-p65 levels, and no statistical significance between any groups in NF-κB-p105 levels. MAPK levels were found to be increased in NOB+IND group at P<0.01 level and PAN+IND group at P<0.05 level compared to C group (Fig. 4).

When pro-inflammatory cytokine levels were evaluated, it was determined that there was a significant increase in IL-1α, IL-6 and TNF-α levels in the IND group compared to the C group (P<0.001). There was a statistically significant decrease in IL-1α and TNF-α levels in NOB+IND and PAN+IND groups compared to the IND group (P<0.01). Compared to the IND group, IL-6 levels decreased in the PAN+IND group at P<0.001 and in the NOB+IND group at P<0.01. In addition, when the C group was compared with the NOB+IND and PAN+IND groups, significant increases in IL-1α (P<0.05) and TNF-α (P<0.01) levels were observed in these two groups. IL-6 levels increased in NOB+IND group at P<0.05 level, while there was no statistical significance between C and PAN+IND groups (Fig. 5). When NOB+IND and PAN+IND groups were compared, there was no statistical difference between IL-1α, IL-6 and TNF-α levels. When the anti-inflammatory IL-10 levels were evaluated, it was found that there was a decrease in all groups

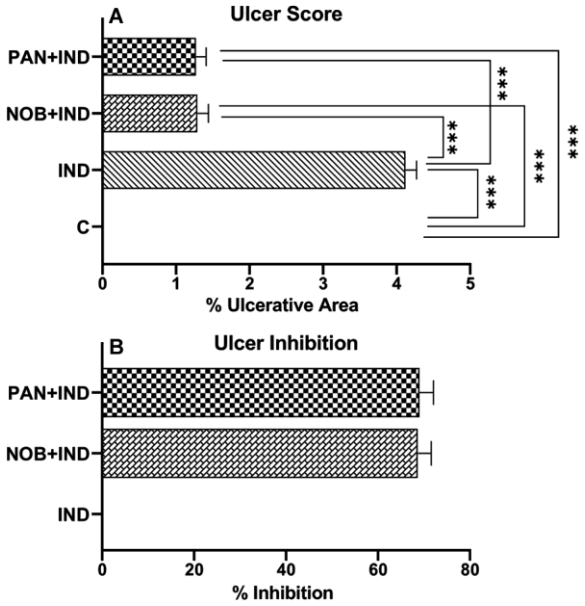

Fig. 3 — Ulcer scores and ulcer inhibition (%) of control and experimental groups. [***P<0.001]

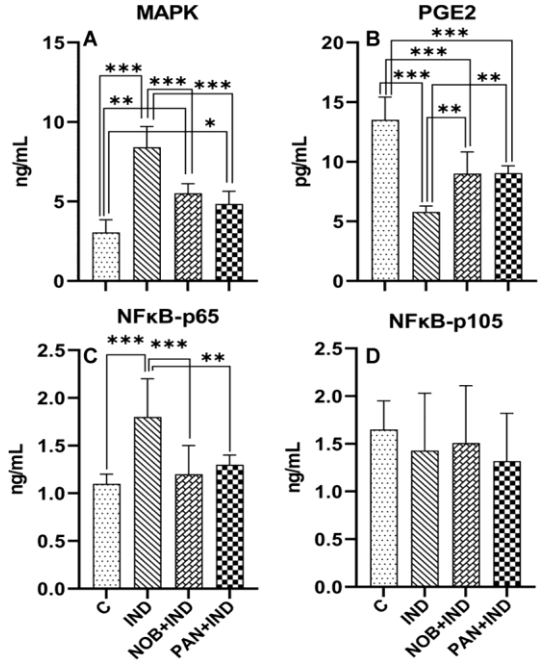

Fig. 4 — Stomach tissue MAPK, PGE2, NF-κB-p65, NF-κB-p105 levels. [*P <0.05 ** P <0.01 *** P <0.001]

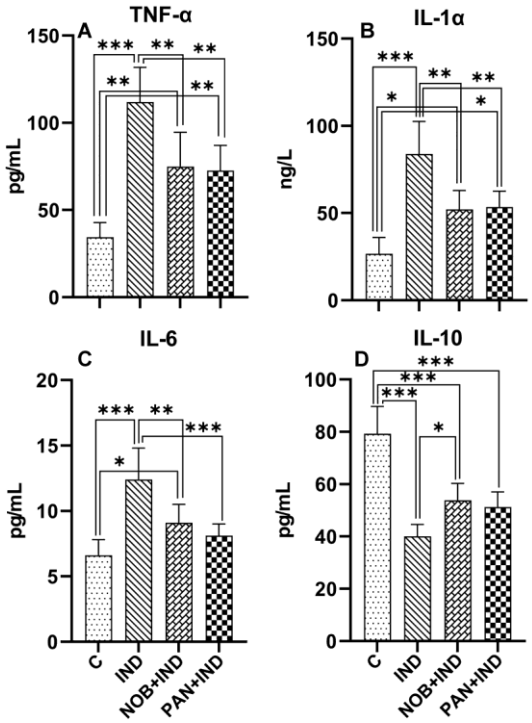

Fig. 5 — Stomach tissue TNF-α, IL1-α, IL-6, IL-10 levels. [*P <0.05 ** P <0.01 *** P <0.001]

administered indomethacin at the level of $P<0.001$ compared to the C group and an increase at the level of $P<0.05$ in the NOB+IND group compared to the IND group. There was no statistical difference between NOB+IND and PAN+IND groups and between IND and PAN+IND groups (Fig. 5).

Numerous studies have shown that indomethacin causes gastric mucosal damage, gastrointestinal bleeding, and the development of single or multiple ulcerations in the stomach, duodenum, small or large intestine[1,19-21]. Therefore, the indomethacin-induced gastric injury model is widely used to elucidate the pathogenesis of gastric injury and ulceration and to evaluate the gastroprotective effect of various drugs and natural products. It is known that gastrointestinal damage caused by indomethacin occurs as a result of inhibition of PGE2 synthesis, increase in gastric acid secretion, formation/aggravation of inflammation due to increased production of free radicals and inflammatory cytokines and development of disruptions in mucosal cell regeneration as a result of all these changes[22,23]. Numerous studies have revealed that the NF-κB/MAPK/cytokine pathway plays an extremely important role in inflammation[24-26]. In this study, we evaluated the activity of the NF-κB/MAPK/cytokine pathway, one of the important regulators of inflammation, which plays a very important role in indomethacin-induced gastric damage, and we observed that the damage was more severe in the IND group compared to the other groups. In addition, when the ulcer inhibition levels of nobiletin were examined, similar results were obtained with standard drug and pantoprazole (Fig. 2 & 3).

PGE2 is an important marker that plays a highly active role in maintaining the integrity of gastric mucosal defense and protecting the stomach from damage by increasing mucin production, improving blood flow and reducing gastric acid secretion. Decrease and/or inhibition of PGE2 expression is considered to be one of the mechanisms responsible for indomethacin-induced gastric damage[22,27]. In this study, PGE2 levels were found to be significantly decreased in the indomethacin-treated groups compared to the control group. However, PGE2 levels were significantly increased in the NOB and PAN (standard drug) groups compared to the IND group (Fig. 4). Aal-Aaboda *et al.*[22] attributed the gastroprotective property of zafirlukast in indomethacin-induced gastric ulcer to its anti-inflammatory and antioxidant activity as well as increased PGE2 levels. In another study, it was emphasized that oxidative stress and gastric inflammation should be suppressed and gastric PGE2 levels should be maintained in order to prevent the ulcerative effect of indomethacin[28].

It has been revealed that MAPKs and transcription factors such as NF-κB responsible for pro-inflammatory gene expression play an important role in the production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, which are effective in inflammation and are associated with the activation of inflammation signaling cascades[29-31]. In addition, indomethacin activates NF-κB and MAPKs by upregulating mucosal tumor necrosis factor-α and thus induces the release of various pro-inflammatory factors. Indeed, Ko *et al.*[32] demonstrated that in the indomethacin-induced gastropathy model, MAPK and NF-κB inflammation pathways were activated and that there was an increase in TNF-α, IL-1β, and IL-6 levels in both gastric tissue and serum samples. Gastritis caused by mucosal damage is associated with the inflammatory response in the gastric mucosa and if left untreated and/or uncontrolled, it may lead to further spread and aggravation of the damage. In this study, an increase in NF-κB-p65 and MAPK levels (Fig. 4) and a related increase in IL-6, TNF-α and IL-1α levels and a decrease in IL-10 levels were detected in the indomethacin-only group compared to the control group (Fig. 5). Keçeci *et al.*[33] also determined that there was an increase in pro-inflammatory cytokine levels and NF-κB levels in ethanol-induced gastric damage. Some flavonoids are known to be modulators of pro-inflammatory cytokine production[34]. In this study, in which the gastroprotective activity of NOB was also investigated, a significant decrease in NF-κB-p65, MAPK, IL-6, TNF-α and IL-1α levels and a significant increase in IL-10 levels were detected in the NOB-treated group compared to the indomethacin-only group. These results were similar to those of the PAN group treated with standard drug (except IL-10). It was reported that in rats with ethanol-induced gastric ulcers, ulcerative foci formed and IL-10 and PGE2 levels decreased; on the other hand, when petroleum ether extract from *Citrus sinensis* peels was applied as a protective and therapeutic measure, ulcerative areas decreased and IL-10 and PGE2 levels increased[35]. In another study in which gastric damage was induced by ethanol-hydrochloric acid, ethanol extract obtained from *Citrus reticulata* peels was similarly shown to be highly effective in preventing inflammation and ulcer formation

by reducing TNF-α, IL-1β and IL-6 levels[36]. We believe that the anti-inflammatory and antiulcer activity reported in these studies is due to nobiletin, one of the important flavonoid components of *Citrus sinensis* and *Citrus reticulata* plants. As a matter of fact, nobiletin was observed to have similar effects in this study. Corrado *et al.*[37] suggested that nobiletin neutralizes the effects of TNF-α on angiogenesis and invasiveness by reducing NF-κB expression. A different study found that nobiletin prevented the development of gastric cancer caused by *Helicobacter pylori* by inhibiting the production of mitogen-activated protein kinase molecules in gastric epithelial-1 cells, such as TNF-α and IL-6[38]. Another study reported that nobiletin has a candidate anti-inflammatory drug potential in lipopolysaccharide (LPS) induced neuroinflammation[39]. Rong *et al.*[40] suggested that nobiletin suppressed the inflammatory response in LPS-stimulated RAW264.7 cells by activating the IL-6/STAT3/FOXO3a pathway in macrophage cells. Liu *et al.*[41] showed that nobiletin inhibits the expression of pro-inflammatory cytokines against the development and progression of rheumatoid arthritis and may offer a safe and effective treatment thanks to its anti-inflammatory activity. Nobiletin has been reported to inhibit the increase in TNF-α, IL-1β and IL-6 activities and significantly increase IL-10, TGF-β and IFNγ expressions to attenuate the inflammatory response in the brain and spinal cord[9].

Conclusion

It is thought that raising gastric PGE2 levels and reducing the production of inflammatory markers are useful approaches for preventing and treating indomethacin-induced stomach damage. Nobiletin pretreatment increased PGE2 levels against indomethacin-induced gastric damage, decreased activation of the important inflammatory pathway MAPK/NF-κB pathway, decreased pro-inflammatory cytokines TNF-α, IL-6, and IL-1α levels, and increased anti-inflammatory IL-10 levels, according to the study's data. Furthermore, by demonstrating a typical medication-like action in inhibiting the development of stomach injury, nobiletin's gastroprotective activity was ascertained.

Author Contributions

GAU and HU Designed the study, conducted the experiments, carried out the analysis, performed literature reviews, writing and critical Reviews. TAÇ Designed the study, conducted the literature reviews and the critical reviews. EBÖ designed the study.

Ethical statement

The authors declare that all experimental procedures performed on experimental animals were carried out in accordance with national and international guidelines. Permission to perform these experimental studies was obtained from the local ethics committee for animal experiments of Erzincan Binali Yıldırım University (approval number: 2022/03-18).

Acknowledgment

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Conflict of interest

The authors declare no conflict of interest.

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