Araştırma Makalesi – Original Article

Peripheral Analgesic Effect and Possible Mechanisms of Ferulic Acid*

Ferulik Asitin Periferik Analjezik Etkisi ve Olası Mekanizmaları

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ABSTRACT

Ferulic acid is a bioactive phenolic compound that is found intensely in plants used in traditional medicine such as *Ferula assa-foetida L.*. The analgesic effect of various medicinal plants has been associated with its constituent, ferulic acid. However, there are limited number of studies about mechanism of its analgesic action. The aim of this study was to evaluate the contribution of NO/cGMP/PKG/K_{ATP} pathway in peripheral analgesic effect of ferulic acid by acetic acid-induced (0.6 % acetic acid, *i.p.*) writhing test in mice. For this purpose, following the determination of the analgesic effect of ferulic acid at the doses of 20, 40, 80 and 160 mg/kg (*p.o.*), NO precursor 100 mg/kg L-arginine (*i.p.*), nitric oxide synthase inhibitor 30 mg/kg L-NAME (*i.p.*), guanylate cyclase inhibitor 20 mg/kg methylene blue (*i.p.*) and K_{ATP} channel blocker 10 mg/kg glibenclamide (*i.p.*) were administered separately prior to ferulic acid treatment at the dose effective for clarifying the mechanism of action. Reduction in the number of writhes was evaluated as peripheral analgesic activity. Ferulic acid significantly decreased the number of writhes at the doses of 40, 80 and 160 mg/kg. 80 mg/kg ferulic acid and 100 mg/kg acetyl salicylic acid demonstrated similar efficacy. L-arginine and methylene blue relatively reversed the reduction in the number of writhes caused by ferulic acid at 80 mg/kg, whereas L-NAME did not. Glibenclamide pre-treatment significantly inhibited analgesic effect induced by ferulic acid. The results of the study indicate that ferulic acid has peripheral analgesic activity and it is mediated predominantly by activation of K_{ATP} channels and partially by cGMP. In conclusion, findings of this study demonstrate that ferulic acid may provide an advantage in K_{ATP} channel-targeted management of pain.

Keywords: Ferulic acid, Nitric oxide, Guanylate cyclase, KATP channels, Pain

ÖZ

Ferulik asit, *Ferula assa-foetida L.*. gibi geleneksel tıpta kullanılan bitkilerin içerisinde yoğun olarak yer alan biyoaktif bir fenolik bileşiktir. Çeşitli tıbbi bitkilerin analjezik etkileri içerdiği ferulik asit ile ilişkilendirilmektedir. Fakat, analjezik etkinin mekanizmasına ilişkin çalışmalar sınırlı sayıdadır. Bu çalışmada farelerde % 0.6 asetik asit, *i.p.*, injeksiyonu ile indüklenen kıvranma testinde ferulik asitin periferal analjezik etkisine NO/sGMP/PKG/K_{ATP} yolağının katılımının araştırılması amaçlandı. Bu amaçla ferulik asitin 20, 40, 80 ve 160 mg/kg (*p.o.*) dozlarda oluşturduğu analjezik etkinin belirlenmesini takiben, etki mekanizmasının aydınlatılması için etkili bulunan dozda uygulanan ferulik asit öncesi ayrı ayrı, NO prekürsörü 100 mg/kg L-arjinin (*i.p.*), nitrik oksit sentaz inhibitörü 30 mg/kg L-NAME (*i.p.*), guanilat siklaz inhibitörü 20 mg/kg metilen mavisi (*i.p.*) ve K_{ATP} kanal blokörü 10 mg/kg glibenklamid (*i.p.*) kullanıldı. Kıvranma sayısındaki azalma analjezik aktivite olarak değerlendirildi. 40, 80 ve 160 mg/kg dozlarda ferulik asitin kıvranma sayılarını anlamlı olarak azalttığı gözlendi. 80 mg/kg ferulik asit ve 100 mg/kg asetil salisilik asitin birbirine yakın seviyelerde etkinlik gösterdiği belirlendi. 80 mg/kg ferulik asitin neden olduğu kıvranma sayısındaki azalmayı; L-arjinin ve metilen mavisinin göreceli olarak geri çevirdiği, L-NAME'nin ise geri çeviremediği gözlendi. Glibenklamid ön-uygulaması ise ferulik asit ile indüklenen bu azalmayı anlamlı bir şekilde önledi. Çalışma bulguları ferulik asitin periferal analjezik etkinliğe sahip olduğunu ve bu etkinliğe sGMP'nin kısmen fakat K_{ATP} kanalları aktivasyonunun daha baskın olarak katılımının olduğunu göstermektedir. Sonuç olarak, bu çalışma ferulik asitin ağrının K_{ATP} kanalları hedefli tedavisinde avantaj sağlayabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Ferulik asit, Nitrik oksit, Guanilat siklaz, K_{ATP} kanalları, Ağrı

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INTRODUCTION

Pain acts as an alarm system in order to keep the body from potential tissue damage and may as well affect one's life negatively by hindering one from engaging in daily activities. Thus, pain which once was considered as a 'warning', now became a case requiring treatment.[1] Current analgesics continue to attract notice due to safety concerns and the potential risks that have sprung up recently despite their widespread use.[2] Even though a multitude of pharmaceutical products such as nonsteroidal anti-inflammatory drugs, opioids, tricyclic antidepressants and anticonvulsants on the market for pain treatment, many patients turn to herbal remedies because of the side effects and tolerability problems of existing drugs.[3]

Herbal remedies are in great demand in pain treatment due to their efficacy and safety.[4] Even though synthetic drugs have a significant share in the pharmaceutical industry, drugs made from natural active substances and compounds make up almost 50 % of the drugs currently used.[5] In recent years, ferulic acid draws attention as it is a bioactive molecule found naturally in plants. Ferulic acid [(E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid)] was first isolated from Ferula *assa-foetida L. Ferula assa-foetida* has been used as a spice and traditionally as a treatment of different diseases for centuries, such as asthma, epilepsy, stomachache, flatulence, intestinal parasites, weak digestion and influenza.[6] Conformably, it has been shown to exhibit analgesic effect and the effect was attributed to high concentration of ferulic acid in the plant.[7] Ferulic acid, which is also present in many medicinal plants that are used in traditional medicine for various health problems such as lavender oil and grapevine[8,9], is known to be one of the major compounds in foods that are widely consumed such as rice, wheat, oat, pineapple, beans, coffee beans, artichoke, peanuts and nuts.[10,11] Ferulic acid is known to have anti-inflammatory, antimicrobial, antidiabetic, anticancer and neuroprotective activities besides analgesic activity with low toxicity.[12] Most biological activity of ferulic acid is associated with its antioxidant properties.[13] It is a free radical scavenger, but also an inhibitor of enzymes that catalyze free radical generation and an enhancer of scavenger enzyme activity.[12]

Revealing the activity and effect profiles of pure forms of bioactive molecules that are thought to be responsible for the effect in plants is highly important in terms of drug development studies and rational drug use. Experimental studies have claimed that ferulic acid has an analgesic effect on pain induced by various pathways in different experimental models.[14-16] However, existing data regarding the antinociceptive mechanism of action of ferulic acid is limited.

Analgesia is a complex process involving many neurochemicals at central and peripheral pathways.[17,18] Efficacy and safety problems with current analgesics lead researchers to develop drugs targeting other systems that play a role in the pain control process. In this context, one of the salient pathways is the L-arginine/NO (nitric oxide)-cGMP (cyclic guanosine monophosphate)/ATP sensitive K^+ (K_{ATP}) channel pathway. L-arginine/NO-cGMP/ K_{ATP} channel pathway acts as an analgesic pathway through NO formation that results in phosphorylation of K_{ATP} channels by the activation of PKG (protein kinase G).[19] It is also known that this pathway mediates the mechanism of action of various analgesic drugs such as diclofenac, rofecoxib, ketorolac and morphine.[20] The aim of this study is to evaluate the peripheral analgesic efficacy of the ferulic acid administered at different doses by the acetic acid-induced writhing test in mice and to investigate the contribution of the NO/cGMP/PKG/K_{ATP} channel pathway to the antinociceptive activity.

MATERIAL AND METHOD

Chemicals

Trans-ferulic acid, L-arginine, L-NAME (N(G)-Nitro-L-arginine methyl ester), glibenclamide, acetic acid, acetylsalicylic acid (ASA) and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Methylene blue was purchased from Merck, Darmstadt, Germany.

Experimental Animals

Adult CD-1 male mice were used to perform the experiments. Animals were kept in well-ventilated rooms which are set to 12-hour light/dark cycle at 22 ± 1 ºC temperature and were fed with standard pellet and tap water. Experimental procedure was prepared in accordance with the ethical principles of Helsinki

Declaration and was approved by Anadolu University Local Ethics Committee, Eskisehir, Turkey (Approval Number:2018-06).

Experimental Groups

Fifteen experimental groups were formed separately. Equal volume of vehicle [control group, 2 % DMSO], 20, 40, 80, 160 mg/kg ferulic acid and 100 mg/kg acetyl salicylic acid (ASA) as a reference drug were orally (*p.o.*) administered separately to analyze the peripheral analgesic effect.

As it was determined that the analgesic effect of ferulic acid was significant at the dose of 80 mg/kg, the contribution of L-arginine/NO-cGMP/ K_{ATP} channel pathway to the analgesic effect was investigated in 80 mg/kg ferulic acid groups. NO synthase (NOS) inhibitor 30 mg/kg L-NAME and NO precursor 100 mg/kg L-arginine were injected 20 minutes prior, a guanylate cyclase (GC) inhibitor 20 mg/kg methylene blue and a K_{ATP} channel blocker 10 mg/kg glibenclamide were injected 15 minutes prior to vehicle and 80 mg/kg ferulic acid administration. One group was injected with 100 mg/kg L-arginine 20 minutes prior to 30 mg/kg L-NAME injection. All pre-treatments were performed intraperitoneally (*i.p.*). The writhing test procedure was performed 30 minutes after ASA administration, 20 minutes after L-NAME administration in the L-arginine+L-NAME treated group, and 40 minutes after the vehicle or ferulic acid administration in all other groups.

Experimental Method

Acetic Acid-Induced Writhing Test

Writhing behavior formed in animals following acetic-acid (*i.p.*) administration is characterized by the contraction of abdominal muscles, stretching of the back legs backward and friction of abdomen. Mice were injected with 0.6 % acetic acid (*i.p.*) solution. After 5-minute waiting period, number of writhes was counted for 10 minutes.[21]

Statistical Analysis

Data analysis was performed by using one-way analysis of variance (ANOVA) followed by Tukey's HSD multiple comparison test. All statistical analysis results were calculated using GraphPad Prism ver 5.0. package software. Analysis results were stated as mean ± standard error of mean (S.E.M) and the statistical significance was considered to begin at $p<0.05$.

RESULTS

Acetic Acid-Induced Writhing Test

In ***Figure 1***, the number of writhes in acetic acid-induced writhing test are shown for groups treated with 20, 40, 80, 160 mg/kg (*p.o.*) ferulic acid and 100 mg/kg ASA (*p.o.*). 40, 80, 160 mg/kg ferulic acid and 100 mg/kg ASA treatments decreased the number of writhes significantly ($p<0.05$, $p<0.001$, $p<0.01$ and $p<0.001$, respectively) compared to the control group. Inhibition percentages of 20, 40, 80, 160 mg/kg (*p.o.*) ferulic acid and 100 mg/kg ASA treatments on the number of writhes are shown in ***Table 1***.

Contribution of L-arginine/NO Pathway to the Analgesic Effect of Ferulic Acid

The alteration in the peripheral analgesic effect of 80 mg/kg ferulic acid with pre-treatment of NO precursor L-arginine at the dose of 100 mg/kg (i.p.) and NOS inhibitor L-NAME at the dose of 30 mg/kg (i.p.) is demonstrated in **Figure 2**. L-arginine did not affect the number of writhes in the acetic acid-induced writhing test when administered alone, whereas it partially reversed the significant decrease induced by L-NAME or ferulic acid. Treatment with L-NAME alone significantly ($p<0.001$) decreased the number of writhes. Pre-treatment with L-NAME following ferulic acid administration had no significant effect on the responses induced by ferulic acid alone.

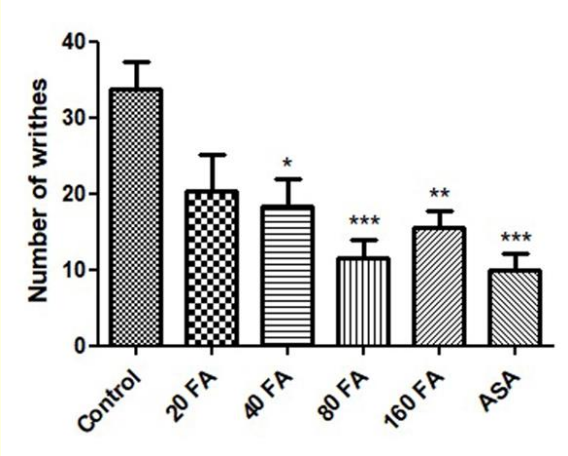

Fig. 1. The analgesic effect of ferulic acid at the doses of 20, 40, 80, 160 mg/kg and ASA at the dose of 100 mg/kg.
FA; Ferulic acid, ASA; Acetyl salicylic acid. *p<0.05, **p<0.01, ***p<0.001; significant differences based on the control group. One-way analysis of variance (ANOVA) followed by Tukey's HSD multiple comparison test was performed. Values expressed as mean ± S.E.M. (n = 8).

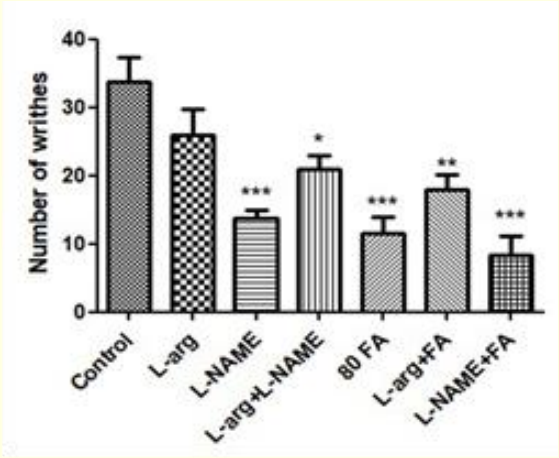

Fig. 2. The effect of 100 mg/kg L-arginine and 30 mg/kg L-NAME pre-treatment on the analgesia induced by 80 mg/kg ferulic acid in the acetic acid-induced writhing test.
FA; Ferulic acid, L-arg; L-arginine, L-NAME; N(ω)-nitro-L-arginine methyl ester. *p<0.05, **p<0.01, ***p<0.001; significant differences based on the control group. One-way analysis of variance (ANOVA) followed by Tukey's HSD multiple comparison test was performed. Values expressed as mean ± S.E.M. (n = 8).

Table 1. Inhibition % of ferulic acid or ASA on the number of writhes induced by acetic acid.

Treatments	20 FA	40 FA	80 FA	160 FA	ASA
Inhibition %	39.93 %	45.86 %	65.89 %	44.91 %	70.34 %

FA; Ferulic Acid, ASA; acetylsalicylic acid. Inhibition % = [(the number of writhes of control group- the number of writhes of treatment group) / the number of writhes of control group] x 100.[22]

Contribution of cGMP Pathway to the Analgesic Effect of Ferulic Acid

The alteration in the peripheral analgesic effect of 80 mg/kg ferulic acid with pre-treatment of GC inhibitor methylene blue at the dose of 20 mg/kg (*i.p.*) is demonstrated in ***Figure 3***. Methylene blue alone or with ferulic acid caused an insignificant reduction on the number of writhes.

Contribution of K_{ATP} Channel Pathway to the Analgesic Effect of Ferulic Acid

The alteration in the peripheral analgesic effect of 80 mg/kg (*i.p.*) ferulic acid with pre-treatment of K_{ATP} channel blocker glibenclamide at the dose of 10 mg/kg (*i.p.*) is demonstrated in ***Figure 4***. Glibenclamide did not affect the number of writhes in the acetic acid-induced writhing test when administered alone. Glibenclamide pre-treatment followed by ferulic acid significantly (p<0.05) reversed the decrease in the number of writhes induced by ferulic acid.

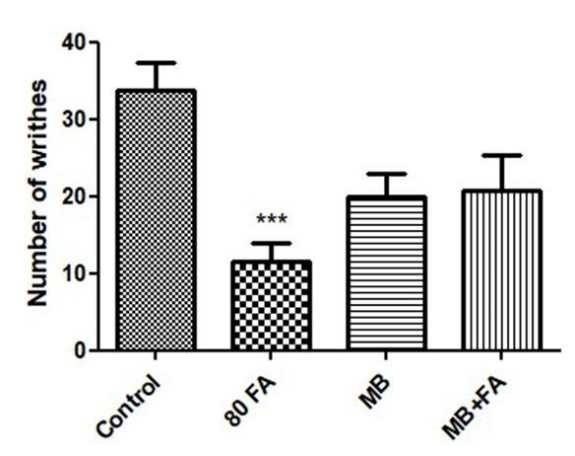

Fig. 3. The effect of 20 mg/kg methylene blue pre-treatment on the analgesia induced by 80 mg/kg ferulic acid in the acetic acid-induced writhing test.
FA; Ferulic acid, MB; Methylene blue. ***p<0.001; significant differences based on the control group. One-way analysis of variance (ANOVA) followed by Tukey's HSD multiple comparison test was performed. Values expressed as mean ± S.E.M. (n = 8).

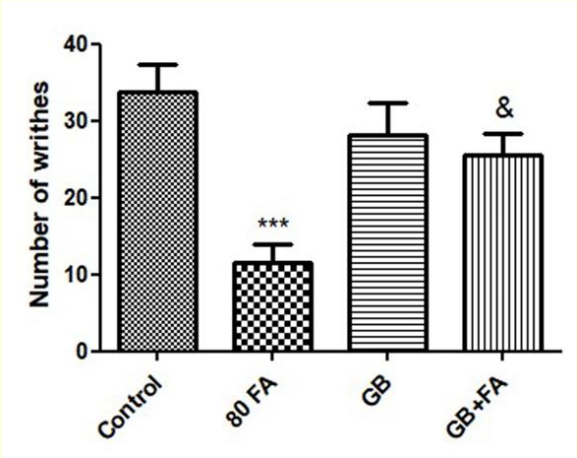

Fig. 4. The effect of 10 mg/kg glibenclamide pre-treatment on the analgesia induced by 80 mg/kg ferulic acid in the acetic acid-induced writhing test.
FA; Ferulic acid, GB; Glibenclamide. ***p<0.001; significant differences based on the control group, $^{\&}p$<0.05; significant differences based on 80 mg/kg ferulic acid. One-way analysis of variance (ANOVA) followed by Tukey's HSD multiple comparison test was performed. Values expressed as mean ± S.E.M. (n = 8).

DISCUSSION

In this study, it was aimed to investigate the mechanism of analgesic action of ferulic acid which is a major bioactive compound found in many medicinal plants and traditionally used for its anti-inflammatory, antimicrobial, anticancer, antidiabetic and neuroprotective activities.[13] Acetic acid-induced writhing test, which is used to evaluate the antinociceptive and anti-inflammatory features of potential analgesic agents in visceral pain, was used to evaluate the peripheral analgesic effect of ferulic acid and the contribution of NO/cGMP/PKG/K_{ATP} pathway to this effect in mice.[23] Writhing test is a chemical procedure which is used to arouse peripheral pain in mice with the injection of irritant substances such as acetic acid. The writhing behavior is characterized by contractions in abdominal muscles and backward extension of back extremities and rubbing of the stomach on the floor.[24] These symptoms are regarded as signals of pain. Test substance is considered to have peripheral analgesic effect when it caused a reduction in these symptoms.[25] In this study, it is seen that the acetic acid-induced writhing behavior was significantly reduced by ferulic acid at the doses of 40, 80, and 160 mg/kg. Ferulic acid at the dose of 80 mg/kg entailed significant inhibition in abdominal contractions caused by acetic acid by decreasing the number of writhes in mice at the rate of 65.89 %. This inhibition is close to the 70.34 % inhibition rate achieved by 100 mg/kg ASA administration. Increase in number of writhes at 160 mg/kg compared to 80 mg/kg ferulic acid can be explained with hormesis or U-shaped dosage. Namely the increase in dosage may reduce the pharmacological effect that can be achieved with lower or intermediate doses.[26] In summary, it is demonstrated that ferulic acid induces peripheral analgesia. This outcome coincides with the results of similar studies conducted.[14-16] The effect of plants that are used for their analgesic effect in traditional medicine may be, therefore, originating from ferulic acid. For instance, blueberries (Vaccinium corymbosum), which were shown to exhibit analgesic effect[27], were reported to contain 66.5-68.3% of ferulic acid.[28] However, there are limited number of studies conducted on the peripheral analgesic effect mechanism of ferulic acid. For instance, it was stated in a study conducted with CCI model of neuropathic pain that ferulic acid administration decreases thermal hyperalgesia and mechanical allodynia through descending monoaminergic system via β_2-adrenoceptors and 5-HT_{1A} receptors.[29] Whereas in a study conducted on the reserpine-induced pain in mice, it was stated that ferulic acid reduced thermal hyperalgesia and mechanical allodynia by decreasing noradrenaline, serotonin and dopamine levels in the frontal cortex and hippocampus.[30] However, as mentioned before, pain and its management are complex processes where multiple chemicals are involved.

Hence, it is of great importance that pharmacological effects are tested with methods based on different mechanisms and that mechanistic studies are performed with the agonist/antagonists of relevant systems. Consequently, the fact that ferulic acid was active in this test model can lead to the conclusion that it may have peripheral analgesic effect for it reduced the amount of nociceptive substances or the activities of nociceptors stimulated by these substances that are induced by acetic acid-injection. It is also possible to consider that ferulic acid possesses its analgesic activity via antioxidant mechanisms since the studies revealed the crosstalk between antioxidant and anti-inflammatory activities and the test method used in this study evaluated also anti-inflammatory activity which is usually associated with analgesia due to increase in nociceptor sensitivity by pro-inflammatory mediators.[31,32] However, this study focuses on a more specific pathway that stands out recently in pain management.

On the other hand, the contribution of L-arginine/NO/cGMP/K_{ATP} pathway to the analgesic effect of ferulic acid was investigated. It is known that the agents stimulating L-arginine/NO/cGMP/K_{ATP} pathway blocked nociception via the opening of K_{ATP} channels.[33] In this study, L-arginine and L-NAME was used in order to illuminate the role of L-arginine-NO pathway. L-arginine is a basic semi-essential amino acid and a precursor in NO production. It was stated that L-arginine administration causes nociceptive or inflammatory responses stimulated by hyperalgesia and bradykinin, substance P and dextran.[34] However, NO produced by L-arginine has the feature of inducing or reducing pain depending on the level of nociceptive system (peripheral, central), targeted tissue, animal pain model and concentration.[35] L-NAME, on the other hand, is a non-selective inhibitor of NOS isoforms and its administration reduces the production of NO.[20] In our study it was observed that compared with the control group, pre-administration of L-arginine did not change the nociception generated from acetic acid, whereas L-NAME reduced nociception significantly. The standalone antinociceptive effect of L-NAME supports that NO is one of the mediators that have a role in the acetic acid induced nociception. Analgesic effect of ferulic acid was not reversed with L-NAME pre-treatment. Also, when they administered separately alone, they displayed similar efficacies. At the same time, L-arginine partially reversed the antinociceptive activity induced by both L-NAME and ferulic acid. It is thought that the alleviation in the analgesic effect of ferulic acid in presence of L-arginine is associated with the increased algesia via NO release induced by L-arginine since L-NAME did not antagonized ferulic acid analgesia. Thereby, these results are not sufficient to suggest that L-arginine/NO pathway may be effective in peripheral antinociceptive effect of ferulic acid.

Methylene blue was used to determine the involvement of cGMP in analgesic effect of ferulic acid. Methylene blue is a specific GC inhibitor which indirectly inhibits cGMP production.[36] It is known that cGMP can be activated with carbon monoxide and hydroxyl besides NO.[37,38] In this study, it was observed that methylene blue administration not significantly but remarkably decreases the writhing behavior induced by the administration of acetic acid in our experimental conditions. It is known that cGMP mediated intracellular modulation may reveal both hyperalgesic and antinociceptive effects.[38] Additionally, methylene blue administration followed by ferulic acid could not significantly reverse the peripheral analgesic effect of ferulic acid however it caused the loss of analgesia induced by ferulic acid. According to these data, it was considered that cGMP partially mediates the antinociceptive effect of ferulic acid. It is reported that cGMP can induce analgesia by opening K^+ channels through phosphorylation, indirectly inhibiting TRPV1 activity, decreasing the activity of sodium channels and/or altering the Ca^{+2} channel dynamics.[39-41]

In this study, the role of K_{ATP} channel in the antinociceptive effect of ferulic acid was also investigated by glibenclamide pre-treatment. Glibenclamide specifically blocks K_{ATP} channels and do not affect other types of K^+ channels such as calcium activated or voltage-gated K^+ channels. It was observed that pre-administration of glibenclamide significantly reversed the antinociceptive effect of ferulic acid. Thereby, it was concluded that the opening of K_{ATP} channels takes part in the peripheral antinociceptive effect of ferulic acid. The opening of K_{ATP} channels results in the decrease of membrane excitability by causing repolarization and/or hyperpolarization in the cell membrane which leads to analgesia.[42] It is known that these channels are activated by G-protein coupled receptors such as noradrenergic, opioid, adenosinergic, serotonergic, and muscarinic receptors.[43-47] At this point, attention can be drawn to studies where it is shown that some of these systems contribute to the analgesia induced by ferulic acid. For instance, central

antinociceptive mechanism of action of ferulic acid was investigated in a study performed in our laboratory and it was shown that supraspinal/spinal noradrenergic, opioidergic, and spinal cholinergic systems are involved in the analgesic effect.[15] In another study it was stated that delta-opioid receptors and 5-HT_{1A} receptors may be mediating the analgesic effect of ferulic acid in neuropathic pain.[29] According to these data, it may be considered that the effect of ferulic acid via K_{ATP} channels is displayed by the interaction within these receptor systems. Hence, it should be emphasized that in this study, it was determined that the production of cGMP contributes partially and not primarily to ferulic acid analgesia. Therefore, it can be considered that aside from the increase in cGMP production, activation of K_{ATP} channels triggered by different mechanisms contributes to the peripheric analgesic effect of ferulic acid.

CONCLUSION

The outcomes of this study reveal that ferulic acid has peripheral analgesic effect and cGMP partially, activation of K_{ATP} channels predominantly are involved in this effect. Because it seems NO does not contribute to the peripheral analgesic effect of ferulic acid, it is considered that cGMP production and especially K_{ATP} channel activation are mediated by other systems. In light of these findings and considering that ferulic acid is a natural antioxidant with low toxicity, it is possible to claim that ferulic acid can be thought as a target molecule for K_{ATP} channel-mediated management of pain. Additionally, evidence was instantiated for the plants that are valuable in traditional medicine for pain treatment to be used in modern medicine.

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