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ARAŞTIRMA MAKALESİ **RESEARCH PAPER**

Evaluation of Bee Venom-Induced Toxicity: Toxicity and Management

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Abstract: Inflammation and increased cellular ROS levels caused by bee venom can increase the formation of necrotic tissue and allergies. Many treatment methods are used for bee venom-induced toxicity. These treatment options include two agents with therapeutic effects and pharmacological value to decrease induced toxicity. L-tryptophan causes a decrease in the level of inflammation and the amount of ROS. Similarly, Amygdalin, which also targets the mTOR/AKT pathway and reduces inflammation, causes a decrease in FAK, ILK, and β-catenin concentrations by inhibiting the expression of β1 and β4 integrins. Application of high doses of bee venom causes sensitization of nociceptors by activating TRPV1 via the PLA2 cascade, which contains mellitin. This may result in pain and inflammation. We aimed to examine the toxic effects of bee venom by creating a wound model in the fibroblast cell line. After a linear wound was opened, the cells were exposed to bee venom (25 µg/mL) for 15 minutes. L-tryptophan and amygdalin doses were applied at the end of 15 minutes. After 24 hours of incubation, wound healing was visualized, and cell viability and oxidative damage tests were performed. The results showed that the BV+ B-17 + LT dose had a 60% effect on viability compared to the bee venom control group, resulting in wound closure. It was also determined that the cellular ROS level decreased. All these results show that the combination of L-tryptophan and amygdalin has therapeutic efficacy on difficult-to-heal wounds.

Keywords: Amygdalin, bee venom, l-tryptophan, nitric oxide, toxicity.

Arı Zehri Kaynaklı Toksisitenin Değerlendirilmesi: Toksisite ve Yönetim

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Öz: Arı zehrinin neden olduğu iltihaplanma ve artan hücresel ROS seviyeleri nekrotik doku oluşumunu ve alerjileri artırabilir. Arı zehri kaynaklı toksisite için birçok tedavi yöntemi kullanılmaktadır. Bu tedavi seçeneklerine, indüklenen toksisiteyi azaltmak için terapötik etkileri ve farmakolojik değeri olan iki ajan dahil edilmiştir. L-triptofan, iltihaplanma seviyesinde ve ROS miktarında azalmaya neden olur. Benzer şekilde, mTOR/AKT yolunu da hedef alan ve iltihabı azaltan Amygdalin, β1 ve β4 integrinlerinin ekspresyonunu inhibe ederek FAK, ILK ve β-katenin konsantrasyonlarında azalmaya neden olur. Yüksek dozda arı zehri uygulaması, mellitin içeren PLA2 kaskadı aracılığıyla TRPV1'i aktive ederek nosiseptörlerin duyarlılaşmasına neden olur. Bu, ağrı ve iltihaplanmaya neden olabilir. Fibroblast hücre hattında bir yara modeli oluşturarak arı zehrinin toksik etkilerini incelemeyi amaçladık. Doğrusal bir yara açıldıktan sonra hücreler 15 dakika boyunca arı zehrine (25 µg/mL) maruz bırakıldı. 15 dakikanın sonunda L-triptofan ve Vit B17 dozları uygulandı. 24 saatlik inkübasyondan sonra yara iyileşmesi görüntülendi ve hücre canlılığı ve oksidatif hasar testleri yapıldı. Sonuçlar özellikle BV+ B17 + LT dozunun arı zehri kontrol grubuna kıyasla canlılık üzerinde %60'lık bir etkiye sahip olduğunu ve yaranın kapanmasına neden olduğunu gösterdi. Ayrıca hücresel ROS seviyesinin azaldığı belirlendi. Tüm bu sonuçlar L-triptofan ve amigdalin kombinasyonunun iyileşmesi zor yaralarda terapötik etkinliğe sahip olduğunu göstermektedir.

Anahtar kelimeler: Amigdalin, arı zehri, nitrik oksit; l-triptofan; toksisite.

INTRODUCTION

Wounds are usually the result of mechanical abrasions and cuts (Özkorkmaz & Özay, 2009). Homeostasis is disrupted in the area where the wound occurs, and secondary pathogens in the surrounding area become active. As a result of the invasion of secondary pathogens, high levels of inflammation, pain, and spread to surrounding tissues can be observed (Eron, 1999). Wound healing is regulated by multiple cellular, humoral, and molecular processes (Tepebaşı & Calapoğlu, 2016). The most important cell type involved in this pathway is the fibroblast. Fibroblasts are found in many tissues in the body, are normally in a relatively quiescent state, and are primarily

responsible for the production and regeneration of extracellular matrix (ECM) molecules (Addis et al., 2020; Bomalaski, Neilson, & Jimenez, 1986).

Bee venom is a liquid substance with a strong odor, acidic, yellowish color, formed in the venom bag of bees and containing mainly mellitin, apamin, MCD-peptide, histamine, hyaluronidase, phospholipase-A2 (PLA2) (Khalil, Elesawy, Ali, & Ahmed, 2021). Although it has a therapeutic effect thanks to the compounds it contains, high doses of melittin, which constitutes 50-60%, cause toxicity. Mellittin is formed by activating the thermal nociceptor transient receptor potential vanilloid 1 (TRPV1) via the PLA 2 cascade, which causes sensitization of primary nociceptors (Oršolić, 2012). It is also responsible for cell lysis and death. Accumulated melittin peptides disrupt phospholipid packaging in the cell membrane, causing cell lysis. Melittin and bee venom PLA 2 act synergistically with lipid membranes, leading to cell damage (G. Lee & Bae, 2016). In light of this information, a linear wound model was created on fibroblast cells, and toxicity was performed using high doses of bee venom (25 µg/mL).

Vitamin B17 (Amygdalin) has been known for many years to have therapeutic effects on many diseases. These effects include anti-cancer, anti-inflammatory, anti-asthmatic and anti-fibrotic effects (Dasari et al., 2024). However, the most common anticancer effects in recent years are mostly characterized by the induction of apoptotic pathways and the reduction of inflammation (Liczbiński & Bukowska, 2018). Amygdalin inhibits the expression of β1 and β4 integrins, resulting in decreased concentrations of FAK, ILK, and β-catenin, and also inhibits the mTOR/AKT pathway (Al-Khafaji & Tok, 2020). In a study conducted to determine the anticancer and antioxidant effects of amygdalin, it was observed that amygdalin at a dose of 8 µg/mL decreased TAS levels and increased TOS levels in human glioblastoma cells (Genç et al., 2024).

L-Tryptophan is an essential aromatic α-amino acid. It is necessary for protein synthesis and as a precursor of important biomolecules such as serotonin, melatonin, tryptamine, niacin, quinolinic acid, and kynurenic acid, nicotinamide adenine dinucleotide (Maes et al., 1993). Melatonin is one of the antioxidants used to reduce ROS levels in the cell. Like amygdalin, it plays a role in regulating the mTOR/AKT signaling pathway and reduces inflammation and cellular ROS levels (Florido et al., 2022). In a study, it was observed that melatonin at a dose of 10 µM/L reduced inflammation and decreased nitric oxide levels in IL-1-induced human intestinal epithelial cells (Mannino et al., 2019).

In this study, the antioxidant and anti-inflammatory effects of L-tryptophan and amygdalin were determined in a fibroblast wound model created using a toxic dose of bee venom (25 µg/ml).

MATERIAL AND METHOD

Preparation of Reagents: Bee venom was obtained from New Techniques Laboratory Ltd. (Tbilisi, Georgia). Vit B17 and LT substances were obtained from VEFA Ltd. (Ankara, Türkiye). Each substance was weighed on a precision balance to be 1 mg. Then, 1 ml of each was taken from Dulbecco's Modified Eagle (DMEM) medium containing 0.1% Penicillin/Streptomycin and 10% Fetal Bovine Serum (Euroclone, Milan, Italy) prepared for cell culture and dissolved. After the dissolution process, dilution procedures were performed according to the doses to be used. Experimental groups were determined as given in the table below.

Table 1. Experimental groups.

Control
Wound Control
Bee venom (BV) control 25 µg/mL
BV + B17 5 µg/mL
BV + B17 10 µg/mL
BV + B17 25 µg/mL
BV + L- tryptophan 1 µg/mL
BV + L- tryptophan 5 µg/mL
BV + L- tryptophan 10 µg/mL
BV + B17 25 µg/mL+ L- tryptophan 1 µg/mL
BV + B17 25 µg/mL+ L- tryptophan 5 µg/mL
BV + B17 25 µg/mL+ L- tryptophan 10 µg/mL

Cell Culture: The fibroblast cell line (L929, ATCC) was provided by our institution, Bilecik Seyh Edebali University, Faculty of Medicine, Department of Medical Pharmacology. Briefly, cells were grown and developed in Dulbecco's Modified Eagle (DMEM) medium containing 0.1% Penicillin/Streptomycin and 10% Fetal Bovine Serum (Euroclone, Milan, Italy). Cells were incubated at 37 °C in a 5% CO_2 environment. Cells that reached 80% confluency were passaged for seeding in 96-well plates. The number of cells per 1 µL was determined using the cell counting kit (Thermofisher Scientific). 10^3 cells were seeded per well. Cells were incubated again to reach 80% confluency. After incubation, a linear wound model was created in all groups except the control group and reagents were added to the medium. Bee venom was applied to all groups except control and kept in the incubator for 15 minutes for toxication. After adding treatment doses, it was kept for 24 hours again. At the end of 24 hours, the groups were photographed to observe wound closure (Sevim, Taghizadehghalehjoughi, & Mehtap, 2020).

MTT Analysis: A commercial kit from Sigma-Aldrich (USA) was used to perform the MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) test. In conclusion, 10 µL of MTT (5 µg/mL) was added to each well, and the mixture was incubated for 4 hours at 37 °C with 5% CO_2. DMSO was then applied to each well to dissolve the formazan crystals. The optical density (OD), measured at 570 nm with a spectrophotometer (BioTek, 800TS), was used for determining the percentage of viable

cells. The OD value of the control group was determined as 100, and the viability rate of other groups was calculated by taking the control group as reference (Avci et al., 2022).

Total Antioxidant Capacity (TAC) and Total Oxidative Stress (TOS) Analysis: The TAC value was measured calorimetrically using the Total Antioxidant Capacity Kit as described in our previous studies (Rel Assay Diagnostics kit). The TAC value obtained was calculated as mmol Trolox Equiv./L according to the formula below (Nalci, Nadaroglu, Genc, Hacimuftuoglu, & Alayli, 2020).

A2-A1= $^{\Delta}$Absorbance (standard, sample, or H_2O)

$$TAC = \frac{H2O\Delta Abs - Sample\Delta Abs}{H2O\Delta Abs - Standard\Delta Abs}$$

The TOS assay was evaluated calorimetrically using the Total Oxidative Stress Kit as described in our previous studies (RL0024, Rel Assay Diagnostics kit). The TOS value obtained was calculated as mmol H_2O_2 Equiv./L according to the formula below (Nalci et al., 2020).

A2–A1 = ΔAbsorbance (standard or sample).

A2– A1 = ΔAbsorbans

$$TOS = \frac{Sample\ \Delta Abs}{Standard\ \Delta Abs} \times 10$$

Biochemical Analysis: Nitric oxide (NO) (H0030, BT Lab) and Lactate Dehydrogenase (LDH) (E-BC-K046-M, Elabscience) tests were performed according to the kit procedure. Samples were measured with a spectrophotometer device at 450 nm.

Statistical Analysis: Statistical assessments throughout groups were calculated using the one-way ANOVA method. For statistical analysis, SPSS 20 software was used for all computations ($P<0.05$). The standard deviation and mean of the results (mean ± SD) are reported.

RESULTS

Cell Proliferation Results: After 24 hours of treatment, photographs of the groups were taken under a light microscope (Nikon, Tokyo, Japan) at 4x magnification, and cell proliferation processes were determined (Figure 1). The BV + B17 25 µg/ml + LT 10 µg/ml group had the highest proliferation. After this group, the best proliferation was observed in the BV+ B17 25 µg/ml + LT 1 µg/ml group.

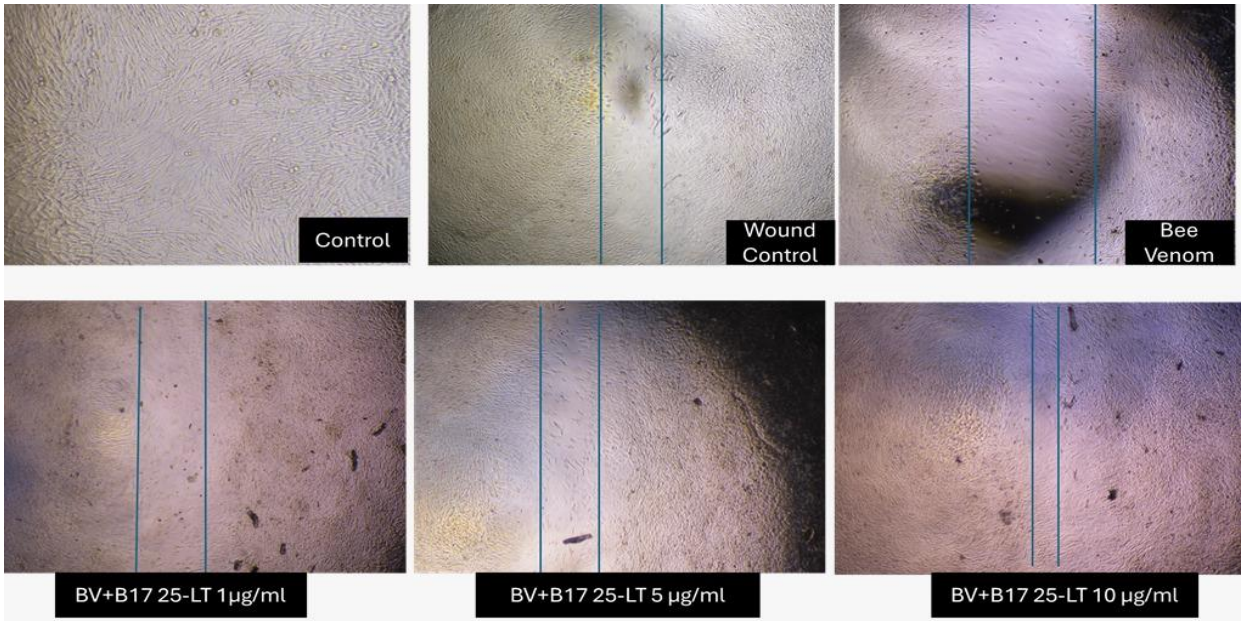

Figure 1. Cell proliferation results after 24 hours of treatment (BV: Bee venom, B17: Vitamin B17, LT: L-tryptophan) Bar x4.

MTT Analysis Results: The effects of LT (1, 5, and 10 µg/ml) and vitamin B17 (5, 10, and 25 µg/ml) applied as a treatment against bee venom (25 µg/ml), which causes toxicity on the wound model, on fibroblast cells were determined after 24 hours using the MTT method. The spectrophotometric measurement results of the control group were evaluated as 100% and other groups were compared with the control group. When the results obtained were examined, the cell viability of the bee venom control group decreased by 41.1% compared to the control group ($P<0.01$). No significant result was obtained against toxicity in the low-dose groups of LT. A 41.21% increase in cell viability was observed in the L. tryptophan 10 µg/mL treatment group compared to the bee venom control group ($P<0.5$). The most significant result in the combined treatment was obtained in the BV + B17 25 µg/ml + LT 10 µg/ml groups ($P<0.01$). These results show the effect of the B17 25 µg/ml + LT 10 µg/ml combined treatment on cell viability (Figure 2).

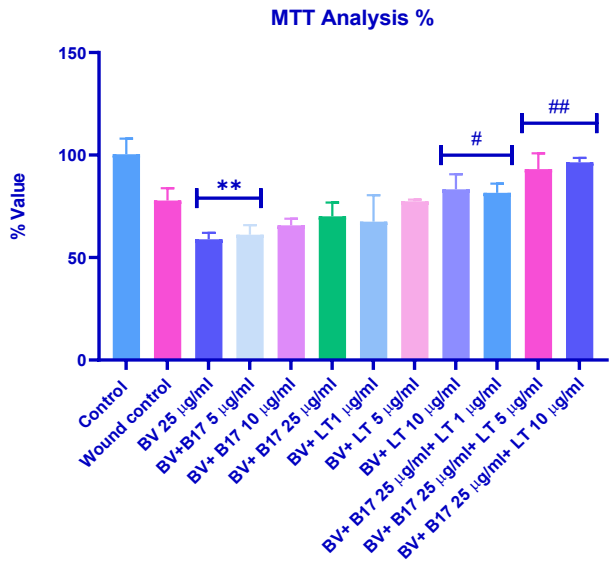

Figure 2. Cell viability of fibroblast cells at 24 h. The significance level was determined as (**P<0.01) in the BV 25 µg/ml dose group compared to the control. The significance level was determined as (#P<0.05) when compared to LT 10 µg/ml and BV + B17 25 µg/ml + LT 1 µg/ml bee venom control group. The significance level was determined as (##P<0.01) when compared to the BV + B17 25 µg/ml + LT 10 µg/ml bee venom control group (BV: Bee venom, B17: Vitamin B17, LT: L-tryptophan

TAC and TOS Results: To determine oxidative damage, TAC and TOS values were examined from cell media taken at the end of 24 hours; all findings are shown in Figure 3. An increase in TAC level was observed in correlation with the result in cell viability. BV 25 µg/mL showed a significant decrease (approximately 39.48%) compared to the control (P<0.01). BV + B17 25 µg/ml + LT 10 µg/ml showed a significant increase (approximately 52.88%) compared to the bee venom control group (P<0.01). Considering these findings, it is seen that antioxidant activation in fibroblast cells also increased with the increase in cell viability. Contrary to the increase in antioxidant activity, oxidative stress decreased at the cellular level, and a significant change was observed in TOS level (Figure 3B). A significant increase was observed compared to the BV 25 µg/mL control (P<0.01). Compared to bee venom control, a significant decrease (approximately 63.93%) was observed in BV + LT 10 µg/ml and BV + B17 25 µg/ml + LT 1 µg/ml dose groups (P<0.5). The highest decrease was observed in the high-dose combined treatment groups (BV + B17 25 µg/mL + LT 5 µg/mL and BV + B17 25 µg/mL + LT 10 µg/mL) (P<0.01). According to our results, it was shown that when applied in combination with vitamin B17 and LT, it was effective on wound healing by reducing oxidative stress in fibroblast cells.

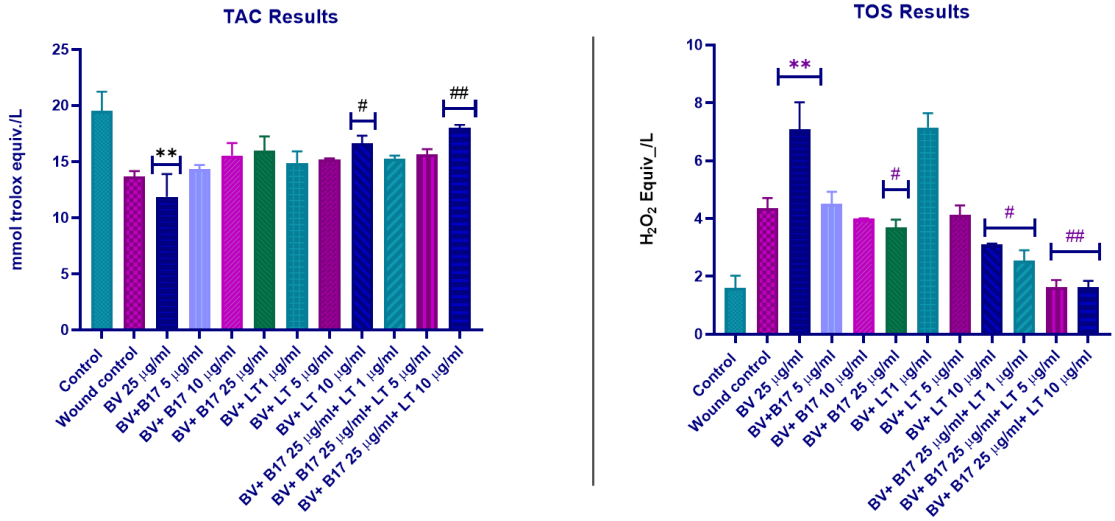

Figure 3. TAC and TOS levels of control, wound control, bee venom, and treatment groups. A) TAC result; BV 25 µg/mL is significant compared to control (**P<0.01). Among the BV+ B17 25 µg/mL + LT 10 µg/mL treatment groups, it has the highest significance compared to the bee venom control group (##P<0.01). B) TOS result; BV 25 µg/mL is significant compared to control (**P<0.01). A highly significant decrease was observed in the combined treatment groups (BV + B17 25 µg/mL + LT 5 µg/mL and BV + B17 25 µg/mL + LT 10 µg/mL) compared to the bee venom control group (##P<0.01) (BV: Bee venom, B17: Vitamin B17, LT: L-tryptophan).

Biochemical Analysis: NO and LDH levels on fibroblast cells of L. tryptophan (1, 5, and 10 µg/mL) and vitamin B17 (5, 10, and 25 µg/mL), which were applied as a treatment against bee venom (25 µg/ml) causing toxicity in the wound model, were determined by ELISA test after 24 hours (Figure 4 and 5). Spectrophotometric measurement results of the control group were evaluated as 100% and other groups were compared with the control group. When the obtained results were examined, an increase of 93.02% in NO was detected in the wound control group compared to the control group and 82.87% in the bee venom group. Among the treatment doses, the combination of BV + B17 25 µg/mL + LT10 µg/mL was the most effective dose, with a decrease of 42.08% compared to the bee venom control group.

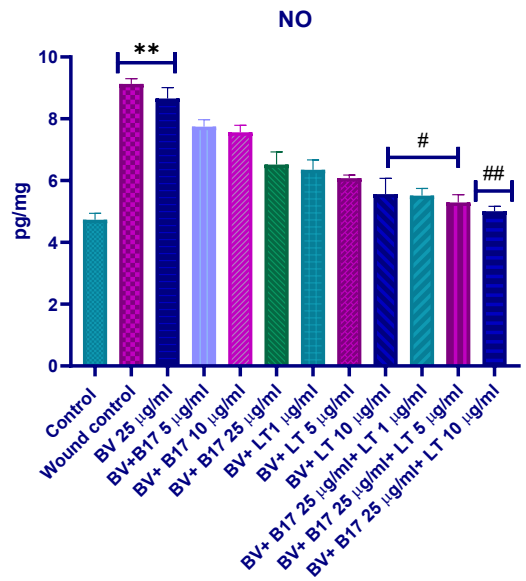

Figure 4. NO levels of the groups. A high increase was observed in the wound and bee venom control group compared to the control group (**P<0.01). The treatment group closest to the control showed a significant decrease compared to BV + B17 25 µg/mL + LT10 µg/mL bee venom (##P<0.01) (BV: Bee venom, B17: Vitamin B17, LT: L-tryptophan).

The bee venom control group showed a 174.90% increase in LDH level compared to the control group. BV + B17 25 µg/mL + LT 1µg/mL and BV + B17 25 µg/mL + LT10 µg/mL doses showed a 28.1% and 41.21% decrease in LDH levels compared to the bee venom group, respectively.

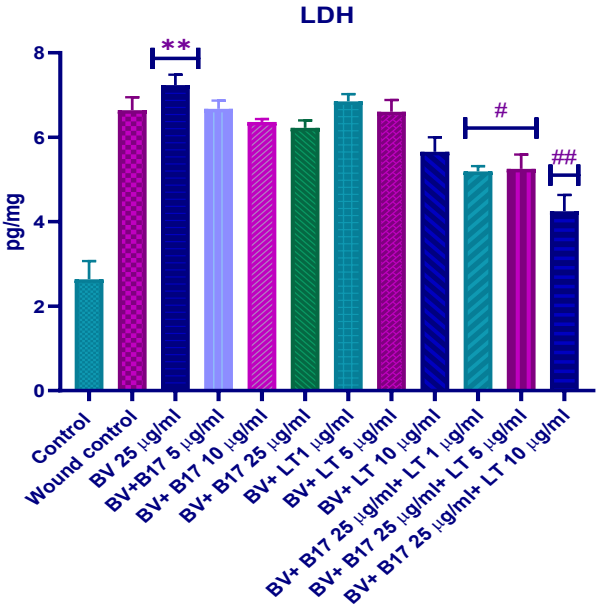

Figure 5. LDH levels of the groups. A high increase was observed in the bee venom control group compared to the control group (**P<0.01). The treatment group closest to the control, BV + B17 25 µg/mL + LT10 µg/mL, showed a significant decrease compared to bee venom (##P<0.01) (BV: Bee venom, B17: Vitamin B17, LT: L-tryptophan).

DISCUSSION

Tryptophan has anti-oxidative and anti-nitrosative effects. Some studies prove that L-tryptophan has an anti-inflammatory effect on neurons and gastric cells (Shizuma, Mori, & Fukuyama, 2013; Wei et al., 2022). In this study, the antioxidant and anti-inflammatory effects of L-tryptophan and amygdalin were determined in a fibroblast wound model created using a toxic dose of bee venom (25 µg/mL). The wound model has been widely used to evaluate the toxic effects of different materials (Comakli et al., 2019; Wilson, Mills, Prather, & Dimitrijevich, 2005). Bee venom is a natural component produced by bees. Bee uses venom that contains different active ingredients for the protection of the colony (Celebi, Celebi, Baser, & Taghizadehghalehjoughi, 2023; H.-S. Lee et al., 2021). Despite its therapeutic effect thanks to the compounds it contains, high doses of melittin, which constitutes 50-60%, cause toxicity. After 24 hours of exposure to bee venom in fibroblast cultures, the cellular regeneration mechanism will be shut down, and migration will be suppressed at a dose of 25 µg/mL (Figure 1). In the current study, for the treatment of induced toxicity, LT and vitamin B17 were used. According to Prerna A (2020) study, LT protects fibroblast cells against ochratoxins. They showed that LT reduced oxidative stress and increased the cell viability ratio (Agarwal, Singh, Raisuddin, & Kumar, 2020). In the current study, the protective effects of LT were shown, and the protective effect in 10 µg/mL was obvious (P<0.05). This result also has a correlation with Xiaoshi W (2022) study (Wei et al., 2022). In addition, vit B17 has a protective effect, but not as much as the LT groups. Combination of vit B17 and LT successfully decreased the toxicity induced by BV. In the other studies, it was shown that vit B17 alleviates DNA damage and apoptosis induced by the Trenorol (Al-Otaibi, 2024). Our study showed that in fibroblast cells where cellular migration was inhibited and viability was reduced due to bee venom toxicity, viability increased after treatment with vitamin B17 and LT (MTT test). Aljohara M Al-Otaibi (2024) showed that treatment of rats with Trenorol + VitB17 decreased the testicular toxicity, sperm parameters, DNA damage, and apoptosis. The study showed that the toxicity induced by Trenorol, cause DNA damage and apoptosis in rat testis, whereas treatments with Vit B17 improved these parameters (Al-Otaibi, 2024).

The highest regeneration was seen in the B17 25 µg/mL + LT 10 µg/mL group. Protective mechanisms of the components were investigated in oxidative stress. Shatha G. (2020) showed vit B17 decreased the toxicity of the methotrexate-induced oxidative stress. Vit B17 acts as a free-radical scavenger and lipid peroxidation inhibitor. In addition, it has protective effects on the levels of GSH, SOD, and CAT (Celebi et al., 2023; Felemban, Aldubayan, Alhowail, & Almami, 2020). Dinh QH (2024) showed that

L-tryptophan can decrease oxidative stress levels by scavenging free radicals (Quy Huong et al., 2024). The data shows a correlation with our study. Oxidative damage, as determined by LDH, NO, TAC, and TOS analyses resulting from the application of high-dose bee venom to fibroblast cells, was shown to be reduced by combinations of vitamin B17 and LT. Although an increase in total antioxidant capacity was observed, a decrease in total oxidative stress, such as LDH and NO, was observed ($P<0.01$).

CONCLUSION

Bee venom, called apitoxin, can lead to inflammation and irritation in the area of a bee sting. The apitoxin induces oxidative stress. Vitamin B17 and L-tryptophan amino acids, as seen in the current study, decreased oxidative levels and increased cell viability in conclusion. We suggest that Vitamin B17 and L-tryptophan can be used for the treatment of inflammation induced by apitoxin, but future study needs to clarify the mitochondrial and endoplasmic reticulum stress.

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Conflicts of Interest: The authors declare no conflicts of interest.

Ethical Approval: Not Applicable.

Abbreviations:
BV: Bee Venom
B-17: Amygdalin
LT: L-tryptophan
ROS: Reactive oxygen species
mTOR: Mammalian target of rapamycin
AKT: A strain transforming
NO: Nitric oxide
FAK: Focal adhesion kinase
FBS: Fetal bovine serum
PLA 2: Phospholipase A 2

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