

THE ANALGESIC EFFECTS OF MISWAK

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دراسة الاعتقاد العام بأن للمسواك (جذور نبات السلفادور بيسيكا) تأثيراً مسكناً لبعض آلام الأسنان . وعليه فإن الهدف من هذا البحث إثبات حقيقة هذا الاعتقاد وتقييم آلية من هذا المفعول . تم دراسة تأثير المسواك المزيل للألم على استجابة الجرذان لثلاثة مؤثرات محدثة للألم من خلال ثلاثة اختبارات هي اختبار السطح الساخن، واختبار التقلصات الانعكاسية لعضلات البطن واختبار نقره الذيل . قبل إجراء الاختبارات السالفة بـ ١٥ دقيقة حقنت الجرذان من نوع ام اف اى بخلصة المسواك في جرعات تتراوح بين ٠.٢ - ١٢.٥ مل كجم في البرتونيوم .

وقد وجد أن حقن الخلاصة المائية للمسواك يقلل من استجابة الجرذان للمؤثرات الكيميائية والحرارية المحدثة للألم . مقدار التأثير المسكن للألم للمسواك مرتبط إحصائياً بجرعة المسواك . الجرعة الوسطية الفعالة (اي دي ٥٠) للاختبارات الثلاثة كانت على النحو التالي ٣,٥ مل/كجم للسطح الساخن و ٠,٤٥ كل/كجم . لاختبار التقلصات الانعكاسية لعضلات جدار البطن و ٥,٥ مل/كجم لاختبار نقره الذيل . يقل التأثير المسكن للمسواك في الاختبارات الثلاثة إذا ما حقنت الجرذان بمادة النالكسون (مادة مقفلة لمستقبلات المورفين) ٤,٠ مجم/كجم قبيل الحقن بخلصة المسواك . وعليه خلص أن للمسواك تأثيراً مسكناً للألم في الجرذان ربما سببه تداخل خلاصة المسواك مع النظام الطرفي أو المركزي لمستقبلات المورفين .

Miswak (the root and branches of *Salvadora persica*) decoction was traditionally implicated as possessing analgesic activities against some form of dental pain. The purpose of this study was to determine whether miswak decoction has an analgesic effect and to describe the antinociceptive profile of miswak. Three analgesic tests (hot plate, writhing reflex, and tail flick) were used. Miswak decoction was injected intraperitoneally into MFI mice in dose volumes of 0.3 - 12.5 ml/kg 15 min. before the analgesic tests. Results showed that miswak decoction lowers mice's response to chemical and thermal stimuli in dose dependent manner. The effective dose 50 (ED50) were 3.5, 0.45, and 5.5 ml/kg for hot plate, tail flick, and writhing reflex tests, respectively. The analgesic effects of miswak decoction in the three tests were antagonized by prior treatment by Naloxone (0.4 mg/kg). It was concluded that miswak has an analgesic effect which is apparently mediated via interaction with central and/or peripheral opiated pathway.

Introduction

Miswak (*Salvadora persica*) is a desert plant of salvadoraceae family. Its roots and branches are used as a tooth cleaning stick in many third world countries.¹³ The history of miswak use as chewing sticks is dated back to period longer than fourteen centuries. Several workers reported that its frequent use improved oral health. For example, Al-Khateeb

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et al⁴ found that frequent miswak users needed lower periodontal treatment than non-users. It was also noted that miswak users showed lower dental decay than non-users.⁵ Traditionally, several miswak users claimed that the application of miswak decoction to oral mucosa relieved some dental pain. Although there is no control study to confirm this claim, earlier study in this laboratory indicated the presence of a sedative or neuroleptic substances in its decoction.⁶

In the present study, the authors attempted to examine the effects of miswak decoction on the analgesic behavior of mice to verify the traditional claim.

Materials and Methods

Four hundred male MFI mice, 30-140 gm, were used in this study. Mice were obtained from the Animal Unit of King Fahd Medical Research Center in Jeddah, Saudi Arabia. They were housed in groups of 5 at a room temperature of 23 °C and light schedule of 12 and 12, 18.00 - 6.00 hr dark, and 6.00 - 18 hr. light. They were fed standard food and tap water.

Miswak Decoction Preparation

Miswak chewing sticks were purchased from the local market and were identified in this laboratory as the roots of *Salvadora persica*. The roots were cut into small pieces and powdered. Ten gms. from the miswak powder was heated in 50 ml distilled water at 80°C for 10 minutes. The mixture was filtered of which filtrate volumes ranged from 40-45 ml. Miswak decoction was prepared daily just before the examination started.

Writhing Reflex Test

Mice were injected intraperitoneally (IP) with 0.6% v/v acetic acid in dose volume of 10 ml/kg to induce writhes reflex in mice. Writhes were counted over a 5-minute period, commencing 15 minutes after acetic acid injection. Mice were randomly divided into groups of test and control. Five minutes before the acetic acid injection test, mice were injected with the miswak decoction and an equivalent volumes of saline. Results were expressed as percent of the matched control values.

The ED50 was determined by linear regression analysis.

Hot Plate Assay

Mice were individually placed on the surface of copper base heated at 55 °C. Each mouse was observed, at a maximum period of 1 min, for signs of discomfort such as licking or paw shaking. They were randomly divided into 12 groups of 8 mice each. Groups 1 to 6 were injected with miswak at 5, 1, 2, 4, 7 and 10 ml/kg IP, respectively. Groups 7 to 12 were injected with equivalent volumes of saline.

Miswak decoction or saline were administered 15 min. before placing on the hot plate. Latent period (reaction time) was determined for each mice. The results were expressed as percent of that of the matched control. The ED50 was determined by linear regression analysis.

Tail Flick Test

Mice were individually placed in close fitting tubular perspex cages for 30 mins. to accustom them to restraining situations. Mice tail tips were exposed to a light source of which reaction time for their tails to flick from the heat source was determined in seconds. Mice were injected with miswak decoction in dose volumes of 0.5, 2, 4, 7, 10 and 12.5 ml/kg (N = 5 mice for each dose) 15 min before exposure to light source. Control mice received equivalent volumes of saline of which reaction time was determined in seconds. Test results were expressed as percent of that of the matched control for each dose. The ED50 was determined by linear regression analysis.

Influence of Naloxone

To examine the relevance of opiate's system to miswak action, the three analgesic antinociceptive tests were repeated and miswak decoction dose-response curves were reconstructed in new groups of mice in the presence of Naloxone 0.4 mg/kg injected IP 5 min before miswak decoction was administered (N = 5/dose). All experiments were performed blindly by the same investigators.

Statistical Analysis

Results were analyzed by Student's t-test and analysis of variance (ANOVA). Results were considered statistically significant at P<0.05.

Results

Effects of Miswak decoction on Writhing Reflex.

Mice injected with miswak decoction (0.5-12.5 ml/kg IP) showed lower writhes reflex than those injected with an equivalent volumes of saline (Table 1). The writhes number in miswak injected mice ranged between 5 ± 2 and 15 ± 4.8 writhes/min vs. 13 ± 4 and 20 ± 5 writhes/min for mice injected with an equivalent volumes of saline. The decrease in writhes reflex in mice injected with miswak decoction ranged between 0% and 74% of that of the saline-injected mice. This decrease was linearly and negatively related to the injected miswak volumes ($r = -.95, P = .0007$). Yet, there was no correlation between the writhes reflex and saline volumes in the control mice ($r = .7, P = .06$) The ED50 for mice injected with miswak decoction was 5.5 ml/kg.

Mice injected with Naloxone (0.4 mg/kg) before miswak injection showed higher writhes than that of mice injected with miswak alone. As shown in Figure 1, the miswak dose-response curve was shifted upwards and to the right. The ED50 for miswak decoction in the presence of Naloxone increased by 1.45 folds higher than that of mice treated with miswak alone (Table 2).

Table 1. Effects of miswak decoction on writhing reflex in the presence and absence of naloxone (0.4 mg/kg) in mice.

Dose (ml/kg)	Control	Miswak	Miswak + Naloxone
0.5	13 ± 4	13 ± 2.5	13 ± 1.2
1	16 ± 2.9	16 ± 4.1	16 ± 3.2
2	17 ± 3.1	15 ± 4.8	15.6 ± 4
4	15 ± 3.8	9 ± 3.1	13.8 ± 2.5
7	20 ± 2.2	8 ± 3.7	15.6 ± 1.9
10	17 ± 2.9	5 ± 2.9	6.5 ± 1.9
12.5	20 ± 5	5 ± 2	6.5 ± 2

Table 2. Effects of naloxone (0.4 mg/kg) on miswak (ED50 mg/kg) in mice.

Tests	Miswak	Miswak + Naloxone
Tail flick	0.4	1.3
Hot plate	3.5	6.0
Writhing reflex	5.5	13.5

Effects of Miswak on mice response to hot plate

Mice injected with Miswak decoction (0.5 - 10 ml/kg IP) showed longer latency period than the matched mice injected with equivalent volumes of saline (Table 3). The latency period in miswak injected mice ranged between 9.65 ± 3 and 20.5 ± 4.1 seconds vs. 8 ± 2 and 13 ± 4 seconds for mice injected with equivalent volumes of saline. The increase in latency period in mice injected with miswak decoction ranged between 10% and 82% of that of the saline injected mice. This decrease was positively related to the injected miswak volumes ($r = .06, P = .9$). The ED50 for mice injected with miswak decoction was 3.5 ml/kg.

Mice injected with Naloxone, 0.4 mg/kg before Miswak injection showed longer latency period than that of the mice injected with Miswak alone. As shown in Figure 2, the miswak dose-response curve was shifted downwards and to the left. The ED50 for miswak-naloxone treated mice was 71.4% higher than that of the miswak alone treated mice (Table 2).

Effects of Miswak on mice response to Tail Flick Test

Mice injected with Miswak decoction (0.2 - 12.5 mg/kg IP) showed longer latency period than the

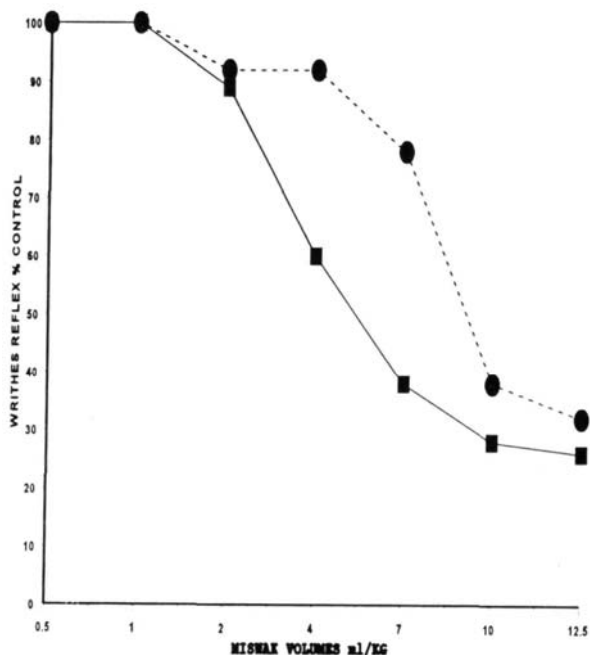


Figure 1. Effects of miswak decoction injected intraperitoneally on writhing reflex in mice (N = 6) for each point, in the presence (●), and absence of naloxone (■).

Table 3. Effects of miswak decoction in the presence and absence of naloxone (0.4 mg/kg) on mice response to hot plate test.

Dose (ml/kg)	Control	Miswak	Miswak + Naloxone
0.5	12.5 ± 2.1	13.95 ± 1.2	12.6 ± 1.6
1	8 ± 2	9.6 ± 3	8.5 ± 1
2	10.9 ± 3.5	13.6 ± 1.6	11.6 ± 1.1
4	13 ± 4	20.5 ± 4.1	16 ± 6.5
7	9 ± 2	15.3 ± 2	16 ± 2.4
10	11 ± 2.9	20.2 ± 8.4	16.6 ± 3.2

Table 4. Effects of miswak decoction in the presence and absence of naloxone (0.4 mg/kg) on mice response to tail flick test.

Dose (ml/kg)	Control	Miswak	Miswak + Naloxone
.2	10 ± 2.1	12.5 ± 2.1	12 ± 1.2
0.5	11 ± 2.7	15 ± 2	13 ± .65
1	6 ± 1.8	8.5 ± .5	9.5 ± 1.4
2	14 ± 3.7	20.5 ± 1.8	20 ± 2
4	11 ± 1.6	16.5 ± .75	16.6 ± 1.4
7	12 ± 3.1	19 ± 2.9	17 ± 2
10	12.1 ± 2.7	19.2 ± 3	20.3 ± 2.4
12.5	8 ± 2.4	13.04 ± 1	15.5 ± 1.5

matched mice injected with an equivalent volume of saline (Table 4). The latency period in Miswak injected mice ranged between $8.5 \pm .5$ and 20.5 ± 1.8 seconds vs. 6 ± 1.8 and 14 ± 3.7 seconds for mice injected with an equivalent volumes of saline. The increase in latency period in mice injected with Miswak decoction ranged between 25% and 63% of that of the saline injected mice. This decrease was positively related to the injected miswak volumes ($r = .9, P = .002$). Yet, there was no correlation between the latency period and the saline volumes in control mice ($r = .4, P = .24$).

The ED50 for mice injected with Miswak decoction was .4 ml/kg. Mice injected with naloxone 0.4 mg/kg before miswak injection showed longer latency period than that of the mice injected with miswak alone. As shown in Figure 3, the miswak dose-response curve was shifted downward and to the right. The ED50 for miswak-naloxone treated mice was 3.25 folds higher than that of the miswak alone treated mice (Table 2).

Discussion

Results presented in this study showed that miswak decoction injected intraperitoneally into

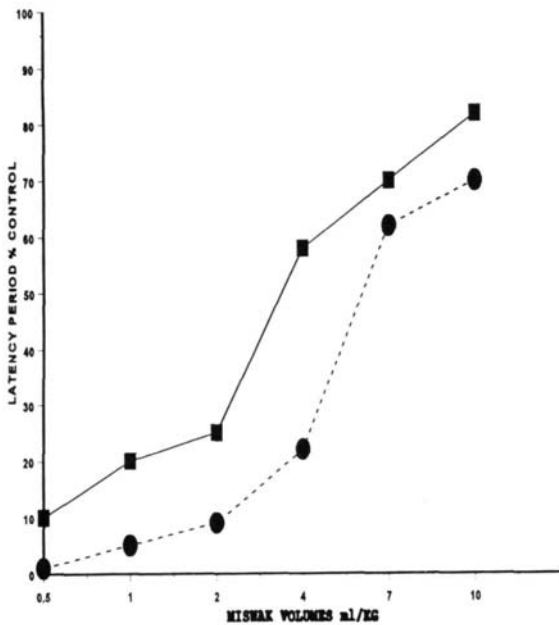


Figure 2. Effects of miswak decoction injected intraperitoneally on mice response to hot plate (N = 8) for each point, in the presence (●), and absence of naloxone (■).

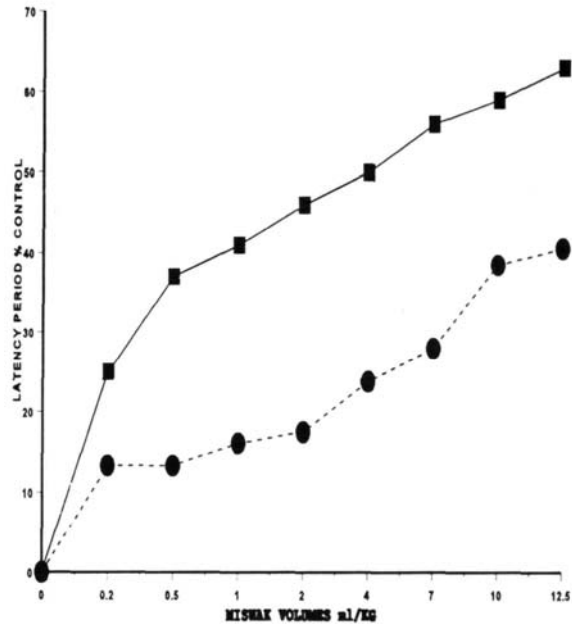


Figure 3. Effects of miswak decoction injected intraperitoneally on latency period in tail flick test (N = 5) for each point, in the presence (●), and absence of naloxone (■).

mice, lower their response to chemical and thermal stimuli in the three analgesic tests. Miswak was more effective against thermal stimuli than against chemical stimuli. It is generally accepted that response to thermal stimuli is mediated via skin pain receptors while response to chemical stimuli in writhing reflex test is mediated via visceral receptors.⁷ Therefore, it was assumed that miswak is more effective against peripheral pain than visceral pain. This may explain the traditional claim that miswak decoction relieves oral pain by its application to oral mucosa. The underlying mechanism for miswak analgesic action was unclear. However, as the effect of miswak was antagonized by naloxone, it was speculated that the effects could be mediated via interaction with the opiate system. This deduction is consistent with early findings in this laboratory in which miswak decoction lowers the spontaneous locomotor activity in mice.⁶ The conclusion is consistent with the notion that opiates, e.g. morphine, produce immobility or decrease locomotor activity in different rodent species.⁸ Further evidence for morphine-like action in miswak decoction was obtained from its effect on gastrointestinal motility in rats in vivo. Injection of miswak decoction IP lowers the GIT motility. This effect was also antagonized by naloxone injection. Photochemical analysis of miswak decoction showed an alkaloid. However, further screening of miswak decoction for morphine-like substance by radioimmuno assay showed no sign for morphine. Chemical analysis of the miswak chewing sticks showed the presence of trimethylamine, tannin, saponin, sterol and alkaloid.^{9,10} However, it is unclear whether any of these substances is responsible for the analgesic effects of miswak decoction. If the analgesic effect of miswak was confirmed in clinical dental pain, e.g. superficial pain due to dental hypersensitivity to thermal, tactile or to chemical stimuli, miswak will be of practical value. In theory, miswak has some advantage over other conventional analgesics of being natural, inexpensive, has anti-astringent effect, detergent and has anti-inflammatory action.¹¹

Therefore, it could be of some value in some cases of primary periodontal inflammatory condition due to local causes such as trauma, overstraining or dental treatment.

In summary, the traditional claim that miswak has an analgesic effect has been investigated. Miswak was found to possess a relatively moderate analgesic effect in mice which could be due to interaction with the central and/or peripheral opiate system. Therefore, the traditional claim may have some scientific basis. However, more experiments are still required to identify and isolate the active agents and to draw firm conclusions on its efficacy in dental pain.

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