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# Effects of *Salvadora persica* L. (Miswak) Aqueous Extract on Some Physiological Indices of Female Albino Rats

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## Abstract

Objective: *Salvadora persica* (Miswak) is one of the folk medicinal plants commonly used by some women to delay menses. This study was conducted to evaluate the physiological effects-induced in female albino rats after administration of *Salvadora persica* aqueous extract. Methods: 20 female rats weighing between 160-180 g were randomized into two groups of 10 animals each. Group 1 (Control group) was orally administered with distilled water (1 ml/100 g bw) while Groups 2 (Miswak-treated group) was orally administered with 7 mg/100 g bw of the plant aqueous extract for 30 consecutive days. Estrus cycle pattern was monitored by daily observation of vaginal smears whereas glucose, total proteins, albumin, globulin, lipid profile, liver function and kidney function indices in addtion to reproductive hormones (estradiol and progesterone) and tumor markers (CA 15-3 and CA-125) were determined in sera at the end of the experiment. Results: In comparison to the control group, *S. persica* aqueous extract significantly elevated the level of high-density lipoprotein cholesterol (HDL) and decreased serum glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) and TC/HDL and LDL/HDL ratios while the values of body weight, liver function indices, kidney function indices and the estimated tumor markers in the extract treated group were approximately similar to those of control animals. Furthermore, Miswak aqueous extract showed adverse effects on sexual hormones, by reducing estradiol and increasing progesterone levels accompained with an irregular estrous cycle with shortened proestrus, estrus and metestrus phases and with lengthened diestrus phase. Conclusions: Overall, Miswak aqueous extract is safe as a natural agent for postponement of menstruation and can be used as a contraceptive plant.

## Keywords

Miswak, *Salvadora persica*, Rats, Physiological Parameters, Tumor Markers

## 1. Introduction

*Salvadora persica* L., commonly known as Miswak, is a desert evergreen shrub grows in different areas of the world including the middle east and Africa (Elvin-Lewis, 1980; Eid *et al*., 1990). Roots and small branches of this plant have been used for teeth cleaning since ancient times (Al-Sadhan and Almas, 1999). *S. persica* has been shown to contain biologically active chemical constituents as salvadorine, trimethylamine, fluoride, chloride, sulphur, silica, mustard oil, vitamin C, resins and traces of saponins, tannins, flavonids and sterol (Elvin-Lewis, 1982; Kamil *et al.*, 1999). These components have a variety of beneficial oral hygiene effects (Hardie and Ahmed, 1995). Therefore, *S. persica* sticks are widely used in medicine as toothpaste.

Some religious rites of Hajj (mandatory religious duty for Muslims that must be carried out at least once in their lifetime by all adult Muslims who are physically and financially capable of undertaking the journey) cannot be performed during menstruation. Thereore using certain drugs including oral contraceptive pills for postponement of menstruation has been a common practice for women traveling to the holy city of Mecca (Durosinlorun *et al.,* 2012).

In the same context, Miswak extract is used by some women to delay menses. The major goal of the present

investigation is to evaluate the physiological effectsinduced in female albino rats after administration of the aqueous extract of *S. persica* and if it could be used as a safe contraceptive plant.

## 2. Materials and Methods

### 2.1. Plant Material

Miswak (*Salvadora Persica*) chewing sticks were purchased from a local market in Cairo (Egypt). The identity of the plant was confirmed by a botanist at Department of Biological and Geological Sciences, Faculty of Education, Ain Shams University, Cairo, Egypt.

### 2.2. Preparation of Miswak Extract

25 g of powdered sticks of S. *persica* were boiled with 500 ml distilled water for 30 min. The obtained extract was allowed to cool at room temperature then filtered through Whatman No. 2 filter Paper. The extract was pooled and concentrated using a Büchi rotary evaporator (Büchi Labortechnik, Flawil, Switzerland) set at 40-50°C to reach to the concentrated solution of 25 ml (1:1w:v). The resultant extract was stored in a glass container at 4°C till animals administration. This extract was freshly prepared each two days.

### 2.3. Experimental Animals

The present investigation was carried out on 20 adult female albino Wistar rats of similar age (3-4 months) and weight (160-180 g). They were obtained from the animal house of Theodor Bilharz Research Institute, El-Giza, Egypt and were housed in clear plastic cages (2 animals/cage) with wood chips as bedding and given pellet rodent diet, in addition of water ad-libitum. The rats were maintained under standard laboratory conditions with a temperature range of 25 ± 2°C and relative humidity of 55 ± 5% and normal photoperiod (12h light/dark cycle) throughout the experimental period. All animal experiments were performed under protocols approved by the local Institutional Animal Ethics Committee of Ain Shams University.

### 2.4. Experimental Design

Female rats were randomly divided into two groups of 10 animals each. They were treated daily at 9 a.m. for 30 days as following:

Group I (Control group): Rats were orally received distilled water (1 ml/100 g bw) by gastric tube.

Group II (Miswak-treated group): Rats were orally given Miswak extract (7 mg/100 g bw) dissolved in 1 ml distilled water by gastric tube.

All rats were weighed at day 0 and day 30 of the experiment.

### 2.5. Estrus Cycle Evaluation

Estrus cycle phases were determined by vaginal smears every morning between 7:00 and 8:00 a.m. following the method described by Marcondes *et al.* (2002). The vagina was flushed two or three times with a plastic pipette filled with 100 µL of normal saline (0.9% NaCl) and the vaginal fluid was placed on a clean glass slide. A different slide was used for each animal and the unstained secretion was observed under a light microscope. The three types of cells recognized were round and nucleated epithelial cells, anucleated cornfield cells and little round leucocytes. The proportions among these cells were used to determine estrus phases according to Mandl (1951). Number of days in each phase of the cycle and cycle length were determined. A normal cycle was defined as being 4 to 6 days and containing 1 to 2 days of estrus. A complete estrus cycle was defined as the day after estrus to the day after the subsequent estrus.

### 2.6. Blood Collection

At the end of 30 days, polyestrus female rats were used for biochemical estimations at proestrus stage of estrus cycle. They were fasted overnight and then anaesthetized through a slight diethyl ether exposure. Blood samples were collected from the retro-orbital plexus. Blood samples were centrifuged at 1500 ×g for 10 min at 4°C. The clear supernatant sera were quickly removed and immediately stored at -20°C till used for further analysis of biochemical parameters.

### 2.7. Biochemical Estimations

Serum samples were analyzed for estimating the levels of glucose, creatinine, urea and uric acid by colorimetric methods according to Tietz (1995), while levels of aspartate transaminase (AST), alanine transaminase (ALT) and glutamyltransferase (γGT) in sera were determined colorimetrically following Schumann and Klauke (2003). Serum albumin and total proteins were measured according to the method of Burtis *et al.* (2006). Globulin was calculated by subtracting albumin from total proteins (Tietz, 1995). levels of serum total lipids, total cholesterol (Henry *et al.,* 1997); triglycerides (Fossati and Principle, 1982) and HDL (Burstein and Scholnick, 1972) were estimated colorimetrically using high quality kits according to manufacturer's protocol; while LDL was calculated applying the Friedwald's equation (Friedewald, 1972).

Friedewald's equation: LDL (mg/dl) = TC-HDL - [TG/5].

Risk factor 1 = TC/HDL

Risk factor 2 = LDL/HDL

Commercially available radioimmunoassay (RIA) kits were used to measure serum concentrations of estradiol and progesterone (Diagnostic Products Corp., Los Angeles, CA).

### 2.8. Tumor Markers

Levels of the tumor markers CA 15-3 (ES 700; Enzymun, Roche Diagnostics, Germany) and CA-125 (R&D Systems

Inc.) in sera were determined by automated test systems using ELISA assay kits according to the protocols provided by the manufacturers.

### 2.9. Statistical Analysis

Data are expressed as mean ± S.E.M. of 10 rats per group. Differences between control and test group were analyzed using Student's 't' test of the SPSS/17.0 software. Values were considered statistically significant when $P < 0.05$.

## 3. Results

Table 1 depicts that administration of Miswak aqueous extract for 30 days did not alter the values of body weight gain in comparison with the corresponding controls.

The values of hormonal assay (Table 2) revealed that administration of aqueous extract of Miswak for 30 days caused a significant decline ($P<0.05$) in levels of serum estradiol (-33.00%) paralleled with a significant elevation in levels of serum progesterone (56.34%) when compared to the control group.

Results regarding the changes in duration of estrus cycle stages are detailed in Table 3. These data showed that *S. persica* aqueous extract significantly ($P<0.05$) extended the period of diestrus phase and shortened the the duration of proestrus, estrus and metestrus with average estrus cycle length two folds compared with the control group.

Serum total proteins and albumin of animals treated with *S. persica* aqueous extract didn't exhibit any significant differences ($P>0.05$) in comparable to the control group while administration of *S. persica* aqueous extract significantly decreased glucose and A/G ratio by - 11.82% and - 13.33% respectively and increased globulin concentration by 12.42% after 30 days of adminstration (Table 4).

Activities of AST, ALT and ɤGT in sera of control and experimental groups of female rats are presented in Table (5). Treated rats showed insignificant change ($P>0.05$) in activities of these enzymes as compared with the control group.

Apart from a significant increase ($P<0.05$) in HDL (2.56 %) in animals treated for 30 days with the aqueous extract of Miswak, TC (-3.39 %), TG (-3.40 %) and LDL (-8.89 %) concentrations in addition to the ratios of TC/HDL (-5.73%) and LDL/HDL (-11.03%) showed marked decline ($P<0.05$) as compared with the corresponding control animals (Table 6).

Kidney function assessed parameters (Table. 7) showed that aqueous extract of Miswak has no adverse effects on renal functions as treating experimental animals with Miswak extract for 30 days did not affect the values of renal markers (creatinine, urea and uric acid) as compared with the corresponding controls.

The levels of the tumor markers CA 15-3 and CA-125 in sera of control and Miswak adminstrated groups are presented in Table (8). No significant change was recorded in the values of these parameters in rats adminstrated Miswak aqueous extract for 30 days as compared with the control animals.

***Table 1.*** *Effects of Miswak aqueous extract on body weight of female albino rats.*

| Parameters (g) | Groups | |
|---|---|---|
| | Control | Miswak |
| Initial body weight (0 day) | 163.20±1.53 | 164.20±1.16 |
| Final body weight (30 day) | 205.20±3.69 | 207.20±5.44 |
| Net gain | 42.00±2.55 | 43.00±5.39 |

Values are expressed as mean ± S.E.M for 10 rats in each group.

***Table 2.*** *Effects of Miswak aqueous extract on estradiol and progesterone levels in sera of female albino rats.*

| Parameters (µu/ml) | Groups | |
|---|---|---|
| | Control | Miswak |
| Estradiol | 35.02±1.63 | 23.46±1.53* |
| Progesterone | 9.62±1.43 | 15.04±0.89* |

Values are expressed as mean ± S.E.M for 10 rats in each group. * $P < 0.05$.

***Table 3.*** *Effects of Miswak aqueous extract on the estrus cycle of female albino rats.*

| parameters | Groups | |
|---|---|---|
| | Control | Miswak |
| Days in diestrus | 10.64±0.12 | 16.24±0.12* |
| Days in proestrus | 5.48±0.11 | 4.40±0.07* |
| Days in estrus | 8.84±0.12 | 5.32±0.17* |
| Days in metestrus | 5.04±0.11 | 4.04±0.09* |
| Number of cycles | 6.76±0.12 | 4.24±0.10* |
| Cycle length[a] | 4.46±0.17 | 7.12±0.30* |

Values are expressed as mean ± S.E.M for 10 rats in each group. * $P < 0.05$.
[a] Cycle length is defined as the day after estrus to the day after the subsequent estrus.

***Table 4.*** *Effects of Miswak aqueous extract on levels of serum glucose, total proteins, albumin, globulin and A/G ratio of female albino rats.*

| parameters | Groups | |
|---|---|---|
| | Control | Miswak |
| Glucose (mg/dl) | 99.16±0.44 | 87.44±0.78* |
| Total proteins (g/dl) | 7.40±0.08 | 7.60±0.23 |
| Albumin (g/dl) | 4.14±0.02 | 4.04±0.06 |
| Globulin (g/dl) | 3.06±0.04 | 3.44±0.02* |
| A/G ratio | 1.35±0.01 | 1.17±0.02* |

Values are expressed as mean ± S.E.M for 10 rats in each group. * $P < 0.05$.

***Table 5.*** *Effects of Miswak aqueous extract on hepatic marker enzymes in sera of female albino rats.*

| Parameters (U/L) | Groups | |
|---|---|---|
| | Control | Miswak |
| AST | 35.34±0.53 | 36.94±0.77 |
| ALT | 23.60±1.20 | 23.72±0.57 |
| ɤGT | 2.48±0.07 | 2.74±0.18 |

Values are expressed as mean ± S.E.M for 10 rats in each group. AST: aspartate transferase, ALT: alanine transferase, ɤGT: gamma-glutamyl transferase.

***Table 6.*** *Effects of Miswak aqueous extract on serum lipid profile indices and values of TC/HDL and LDL/HDL ratios of female albino rats.*

| Parameters (mg/dl) | Groups | |
|---|---|---|
| | Control | Miswak |
| Total lipids (g/l) | 6.58±0.42 | 5.74±0.08 |
| TC (mg/dl) | 144.92±0.23 | 140.00±0.39* |
| TG (mg/dl) | 135.32±0. 28 | 130.72±0.14* |
| HDL (mg/dl) | 46.12±0.23 | 47.30±0.30* |
| LDL (mg/dl) | 67.06±0.54 | 61.10±0.40* |
| TC/HDL | 3.14±0.02 | 2.96±0.02* |
| LDL/HDL | 1.45±0.01 | 1.29±0.01* |

Values are expressed as mean ± S.E.M for 10 rats in each group. * $P < 0.05$. TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol.

***Table 7.*** *Effects of Miswak aqueous extract on indices of renal function in sera of female albino rats.*

| Parameters (mg/dl) | Groups | |
|---|---|---|
| | Control | Miswak |
| Creatinine | 0.91±0.01 | 0.94±0.02 |
| Urea | 33.58±0.20 | 35.12±0.72 |
| Uric acid | 2.38±0.14 | 2.76±0.10 |

Values are expressed as mean ± S.E.M for 10 rats in each group.

***Table 8.*** *Levels of the tumor markers CA 15-3 and CA-125 in sera of control and Miswak adminstrated groups.*

| Parameters (µu/ml) | Groups | |
|---|---|---|
| | Control | Miswak |
| CA 15-3 | 0.027±0.00 | 0.030±0.00 |
| CA-125 | 0.032±0.00 | 0.040±0.01 |

Values are expressed as mean ± S.E.M for 10 rats in each group. CA 15-3: Cancer Antigen 15-3, CA-125: Cancer Antigen 125.

## 4. Discussion

The aqueous extract of *S. persica* (Miswak) is used by some women to delay menses. The present study was undertaken to evaluate effects of Miswak aqueous extract on some physiological indices of female albino rats.

In the present work no significant change in body weight gain was observed in Miswak-treated group after 30 days of administration (Table 1). These results are in complete agreement with a previous study carried out by Abdoon *et al.* (2014).

The hypothalamic–pituitary–gonadal axis (HPG axis) is important for the proper function of the reproductive system hence any distortion to this axis can be deleterious (Koneri *et al.,* 2006; Amah *et al.,* 2012). The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which regulates release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from specialized cells in the anterior pituitary gland. FSH and LH promote ovulation and stimulate secretion of the sex hormones estradiol and progesterone from the ovaries (Elaine and Katja, 2007). In the current study we have demonstrated that exposure of the adult female rats to meswak extract resulted in a statistically significant decrease in the levels of serum estradiol and a significant increase in levels of serum progesterone. These results indicate that Miswak is considered as an endocrine disruptor affecting HPG axis, therefore it caused hormonal imbalances. The results presented are in coincided with Al-Humesh et al. (2012) who stated that exposure of female mice to Miswak extract caused reduction in the levels of estradiol accompained with elevation in the levels of progesterone relative to control mice.

The time between periods of estrus (period of sexual receptivity) is known as the estrus cycle which consists of four phases: diestrus, proestrus, estrus and metestrus. It involves many histological, physiological, morphological and biochemical changes within the ovary. These changes takes place under the combined and balanced influence of ovarian and extraovarian hormones (Smith *et al*., 1987). Any imbalance in these hormones leads to disruption in the function of the ovary and irregular changes in the duration of estrus cycle. In the present study, the decrease in the estradiol level and elevation of the progesterone level upon administration of the aqueous extract of Miswak may explain the decrease in the duration of proestrus, estrus and metestrus phases and prolongation of the diestrus phase that has been recorded in Miswak-treated rats. Also, this is suggestive of negative influences on the estrus cycle as this reduces the number of days/ova ovulated during the proestrus and estrus phases. Similar observations were reported with *Mimosa pudica* root methanolic extract on female mice (Ganguly *et al*., 2007), *Salvadora persica* stem and leaves aqueous extracts on female rats (Abdoon *et al.*, 2014) and *Aspilia africana* leaves methanolic extract on female rats (Oluyemi *et al.,* 2007).

Administration of *S. persica* aqueous extract for 30 days caused a significant decline in serum glucose level of the treated rats. The hypoglycemic effect of *S. persica* has been confirmed by previous investigators (Khan *et al.,* 2014; Trovato *et al.,* 1998). This effect may be attributed to the active compounds of *S. persica* that may facilitate peripheral utilization of glucose, either by direct stimulation of glucose uptake or by enhanced insulin secretion. In addtion, the elevation in globulin concentration with Miswak supplementation and increasing globulin concentration over albumin concentration as idicated from the values of A/G ratio are indicators for increasing the immunity in Miswak-trated rats. These findings are in accordance with Fortun-Lamothe and Drouet-Viard, (2002). Miswak includes flavenoids, certain alkaloids and polyphenolic compounds that seem to stimulate immune function (EI-Kholy *et al.* 2008a and Ibrahim *et al.* 2005).

Activities of ALT, AST and ɤGT serve as potential markers of hepatocyte injury (Pari and Kumar, 2002; Kim *et al.,* 2004). No significant differences were observed in the activities of these enzymes in Miswak-treated group relative to the corresponding control group. These results suggest that *S. persica* is safe to liver cells and has no adverse effects with

liver functions. These results are in agree with those obtained by Ibrahim *et al.* (2005), EI-Kholy *et al.* (2008b) and El-Neney *et al.* (2013) using the same plant.

Hyperlipidemia is a common disorder of lipid metabolism and it is the major cause for the manifestation and development of atherosclerosis and coronary heart diseases (Choudhary *et al.,* 2005). Our data revealed that *S. persica* has a hypolipidemic effect marked by decline in the levels of TC, TG and LDL with concomitant elevation of HDL level in sera of rats treated with Miswak for 30 days. In the same context, Galati *et al.* (1999), Saini and Yadav (2013) and Khan *et al.* (2014) confirmed that *S. persica* exerts significant antihyperlipidemic activity. A study by Kinosian *et al.* (1995) showed that, the changes in LDL/HDL and TC/HDL ratios were better predictors of coronary heart diseases than the changes in LDL alone. In the present investigation, Miswak-treated animals showed marked decline in the ratios of LDL/HDL and TC/HDL that demonstrates a possible protection against the risk of coronary heart diseases. *S. persica* contains flavonoides, which significantly increase LDL receptor mRNA levels causing increase in the rate of hepatic uptake and degradation of LDL leading to a decrease in serum LDL levels (Wilcox *et al.,* 2001).

Creatinine, urea and uric acid are important markers reflecting the proper function of the kidney. Oral adminstration of Miswak aqueous extract for 30 days did not show detectable abnormalities on renal markers which mean its safety to the kidney cells at the tested dose. These findings go in parallel with those of Ibrahim and El-Gengaihi (2012) who proved that Miswak aqueous extract is safe concerning kidney functions.

CA 15-3 and CA-125 are two tumor markers used in oncology to help detect the presence of breast cancer (Keshaviah *et al.,* 2006) and ovarian cancer (Osman *et al.,* 2008), respectively. No significant changes in the level of these markers were recorded after treatment of female albino rats with Miswak aqueous extract for 30 consecutive days. This goes to show that *S. persica* exhibits no malignant potential on breast and ovary tissues. Previous investigation carried out by Darmani *et al.* (2006) showed that the aqueous extract of Miswak enhanced the growth of fibroblasts and inhibited the growth of carcinogenic bacteria. Moreover, Ibrahim *et al.* (2011) proved that petroleum ether extract of *S. persica* has a significant cytotoxic activity against lung carcinoma cell line-A549 and colon carcinoma cell line-HCT116.

In conclusion, no adverse alterations were found in the assesed physiological parameters of female albino rats after administration of *S. persica* aqueous extract for 30 consecutive days. Therefore, this extract can be safely used for postponement of menstruation.

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