



Effect of *Salvadora persica* on reproductive behavior in rats exposed to cigarette smoke

[Efecto de *Salvadora persica* sobre el comportamiento reproductivo en ratas expuestas al humo del cigarrillo]

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Abstract

Context: The components of cigarette smoke are known to adversely affect the reproductive behavior in men and women. *Salvadora persica* commonly used in oral hygiene was found to exhibit lipid lowering, hypoglycemic, anti-ulcer, anti-depressant activities.

Aims: To evaluate the effect of *Salvadora persica* on reproductive behavior in rats exposed to cigarette smoke.

Methods: The lyophilized decoction of *S. persica* was administered daily for four weeks by oral route at three doses (50, 100 and 200 mg/kg) to eight-weeks' cigarette smoke-exposed rats. Reproductive behavior in male rats was recorded by the number of approaches, mounts and intromission while in the female it was done by the number of approaches and escape frequency to male approach. Relative weights of testis and ovaries were determined. Ginseng at 100 mg/kg was used as a standard aphrodisiac. The results were analyzed statistically by one-way ANOVA followed by Tukey test. $P < 0.05$ was considered to indicate the significance of results.

Results: The results indicated that tobacco smoke exposure adversely affected the reproductive behavior in both male and female rats, besides increasing the relative weights of testis/ovaries. Among the tested doses, only the highest dose of *S. persica* (200 mg/kg) produced significant ($p < 0.05$) increase in number of approach, frequency of mounts and latency of intromission but also significantly ($p < 0.05$) enhanced the relative weight of testis and reduced the relative weight of ovaries in cigarette smoked animals. The marginal improvement in the reproductive behavior could be related to the phytoconstituents of the decoction. Ginseng, on the other hand, produced significant aphrodisiac activity and reversed the changes in the relative weights of the reproductive organs induced by cigarette smoke.

Conclusions: The observation suggests that decoction of *S. persica* improved some of the parameters of male reproductive behavior but the role of the drug on the reproductive organs needs further investigation.

Keywords: cigarette smoke; *Salvadora persica*; reproductive behavior; reproductive organs.

Resumen

Contexto: Se sabe que los componentes del humo del cigarrillo afectan negativamente el comportamiento reproductivo en hombres y mujeres. Se descubrió que *Salvadora persica*, comúnmente utilizada en la higiene bucal, exhibe actividades hipolipemiantes, hipoglucemiantes, anti-úlceras y antidepresivas.

Objetivos: Evaluar el efecto de *Salvadora persica* sobre el comportamiento reproductivo en ratas expuestas al humo del cigarrillo.

Métodos: La decocción liofilizada de *S. persica* se administró diariamente durante cuatro semanas por vía oral a tres dosis (50, 100 y 200 mg/kg) a ratas expuestas a humo de cigarrillo durante ocho semanas. El comportamiento reproductivo en ratas macho se registró por número de abordajes, monturas e intromisiones, mientras que en las hembras se realizó por número de abordajes y frecuencia de escape al enfoque macho. Se determinaron los pesos relativos de los testículos y los ovarios. Se usó ginseng a 100 mg/kg como afrodisíaco estándar. Los resultados fueron analizados estadísticamente por ANOVA unidireccional seguido por la prueba de Tukey. Se consideró que $p < 0,05$ para la significancia estadística de los resultados.

Resultados: Los resultados indicaron que la exposición al humo del tabaco afectó negativamente el comportamiento reproductivo en ratas macho y hembra, además de aumentar el peso relativo de los testículos/ovarios. Entre las dosis probadas, solo la dosis más alta de *S. persica* (200 mg/kg) produjo un aumento significativo ($p < 0,05$) en el número de abordaje, frecuencia de monturas y latencia de intromisión, pero también significativamente ($p < 0,05$) mejoró el relativo peso de los testículos y redujo el peso relativo de los ovarios en animales con cigarrillos fumados. La mejora marginal en el comportamiento reproductivo podría estar relacionada con los fitoconstituyentes de la decocción. El ginseng, por otro lado, produjo una actividad afrodisíaca significativa y revirtió los cambios en los pesos relativos de los órganos reproductores inducidos por el humo del cigarrillo.

Conclusiones: La decocción de *S. persica* mejoró algunos de los parámetros del comportamiento reproductivo masculino, pero el papel de la droga en los órganos reproductivos necesita más investigación.

Palabras Clave: comportamiento reproductivo; humo de cigarro; órganos reproductivos; *Salvadora persica*.

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INTRODUCTION

Cigarette smoking is considered to be the single most preventable cause of morbidity and premature mortality worldwide and is responsible for enormous health and economic burdens (Carter et al., 2015). It has been reported that cigarette smoking contributes significantly the sexual health of both men and women. People who are passive smokers are equally at risk of developing these complications (Gades et al., 2005).

The constituents of cigarette smoke are reported to affect the neurophysiology of sexual function in men. Erectile dysfunction and impairment in the sexual arousal are some of the manifestations of chronic smoking. Studies have suggested a direct relationship between duration of tobacco smoking and these complications (Tengs and Osgood, 2001). Similarly, smoking also has adverse effects on the sexual behavior in females. Besides affecting the arousals, it can contribute in still birth, early menopause, low conception rate, miscarriage, abortions and congenital birth defects (Harte and Meston, 2008).

Plant-based medicines are traditionally being used in the treatment of various diseases and some of them are in practice for the aphrodisiac property. These medicines are reported to exhibit their action through several mechanisms; by increasing the neurotransmitter levels, enhancing the actions mediated by nitrous oxide, improving the vitality and muscular strength (Chauhan et al., 2014). Plants known to have these properties are *Asparagus racemosus*, *Camellia sinensis*, *Hibiscus macranthus*, *Panax ginseng*, *Syzygium aromaticum*, *Terminalia catappa*, *Withania somnifera*, *Zingiber officinale* (Singh and Mukherjee, 1998).

Salvadora persica L. belonging to the family *Salvadoraceae*, is an evergreen shrub, with a short trunk 4–6 m tall, smooth green leaves and white bark. It is commonly referred as 'Meswak', a chewing stick prepared from its stings and roots. The anatomical structure as well as its chemical constituent investigated in the previous studies has made this plant a choice for maintaining oral hy-

giene. The plant is being used by millions throughout the world as herbal toothbrush (Sher et al., 2010). Additionally, the plant is reported to have antibacterial, antifungal and anti-inflammatory properties suitable for both prevention as well as treatment of oral cavity diseases. The plant is also reported to possess several pharmacological activities such as antidiabetic, antiobesity, anti-ulcer, antidepressant, antipyretic, antioxidant and antiplatelets (Aumerruddy et al., 2018).

In one of the earlier studies, it was reported that *S. persica* has adverse effects on the reproductive organs in experimental animals. The treatment of the *S. persica* was observed to reduce the rate of pregnancies and altered the relative weights of testis and ovaries (Darmani et al., 2003).

The present study was planned to evaluate the effect of *Salvadora persica* on reproductive behavior as well on organs in both male and female rats exposed to cigarette smoke.

MATERIAL AND METHODS

Plant material

Fresh roots of the plant *Salvadora persica* grown in the Makkah region, (GPS coordinates: 21.33465, 39.908790) of Saudi Arabia were purchased. The plant material was authenticated by Dr. Hamdoon, Pharmacognosist in the department of phytochemistry and medicinal chemistry, College of Pharmacy, Qassim University and a voucher specimen (Specimen # 81, Herbarium, College of Pharmacy) was deposited in the herbarium.

Preparation of decoction

The decoction was prepared as per the procedure described in the earlier study. Dried powdered roots of *S. persica* (100 g) was boiled with 1-liter distilled water for 30 min. After filtration, the decoction was lyophilized (Lab Tech Freezer Dryer, DAIHAN Lab Tech Co. Ltd, Namyangju-City, Korea). The quantity of lyophilized powder obtained from 100 g of drug was 12.6 g. The lyophilized powder was administered, in the morning, by oral gavage, at doses of 50, 100 and 200 mg/kg,

dissolved in aqueous vehicle, in a volume of 0.5 mL/100 g of body weight (Galati et al., 1999).

Animals

Young adult Wistar rats of either sex (4 male + 4 female) of weight 120-140 g were used for the present study. The experimentation was conducted after obtaining the permission from the Institutional Animal Ethics Committee (Approval ID # 2019-CP-4). Animals were housed in the central animal house facility maintained under standard lab conditions with room temperature of 20-22°C. Animals were provided pelleted food and water *ad libitum* under 12 h dark and light environment.

Experimental grouping

The experimental animals were divided into six groups: Group 1 was control [saline, 0.5 mL/100 g body weight (bw) per day]; Group 2 was positive control (saline solution) where animals were exposed to cigarette smoke daily for six days/week for 8 weeks; Groups 3 to 5 were treated with *Salvadora persica* to the cigarette smoke exposed animals at three doses viz., 50, 100 and 200 mg/kg, *per oral* for 4 weeks (Bhadoriya et al., 2010) and Group 5 was standard treatment group (ginseng, 100 mg/kg, *per oral*, 4 weeks) (Moon et al., 2009).

Experimental design

The experimental animals were exposed to the cigarette smoke in the chamber, a glass box in a cube shape (aquarium shape) with the size of 30 × 40 × 80 cm for keeping the rats, and a hood over the aquarium-shaped box to evacuate the extra smoke from the environment described by Ypsilantis et al. (2013). Animals were daily exposed to cigarette smoke (2-3 cigarettes) for total duration of 30 min (with intermittent exposure to fresh air for 2 min after every 10 min of smoke exposure). After the initial 4-weeks of exposure, tests were done to find the influence of cigarette smoke on reproductive behavior. The female rat in the diestrus phase was left in a cage with a male and their behaviors were recorded with a close circuit camera (CCTV) camera (ECam-8000, Genius, Dongguan-City, China) attached to computer (Acer Veriton M-261, Acer computers, Shaanxi,

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China). Once a significant level of altered reproductive behavior was observed in the animals (8th week), groups 3-6 were subjected to respective drug treatments for four weeks and simultaneously exposing the animals to cigarette smoke.

Reproductive behavior study

The reproductive behavior was studied in both male and female rats. The female rats in the diestrus phase was screened as per the method described by Marcondes et al. (2002). In this method, the vaginal smear was observed under light microscope (10X objective) to determine the type of cells. Presence of large number of cornified irregular shaped cells indicate that the animal is in the sexual receptive diestrus phase. One male and one female rat with diestrus phase was left in the dim light and the interaction between the male and female were recorded through CCTV attached to a computer. The parameter observed in the male rats include attraction towards female, mounting frequency, mounting latency, intromission frequency and intromission latency. In the female rats, the parameters were responses towards male approach, attraction towards male rat and escape frequencies (Beck and Bialy, 2000).

Relative weight of testis/ovaries

The influence of the treatment on the organ weight was determined by finding the the weight of the testis/ovaries with respect to the body weight (Bailey et al., 2004).

Statistical analysis

The results obtained were expressed as mean ± SE. The data was analyzed using one-way analysis of variance and Tukey. P<0.05 was considered to indicate significance.

RESULTS

Effect of *S. persica* decoction on the male reproductive behavior in cigarette smoke exposed animals

The reproductive behavioral study on male rats indicated that chronic exposure to cigarette smoke

significantly reduced the number of approaches towards female rats ($p < 0.01$), reduced the frequency of mounts ($p < 0.05$), increased the latency of mounts ($p < 0.001$), reduced the frequency of intromission ($p < 0.01$) and enhanced the latency of intromission ($p < 0.001$) compared to the control animals. Administration of *S. persica* at lower doses (50 and 100 mg/kg) did not produced significant variation on the cigarette smoked-induced alterations. However, *S. persica* at 200 mg/kg significantly ($p < 0.05$) increased the number of approaches, increased the frequency of mounts and latency of intromission when compared to the cigarette smoke exposed animals. The administration of ginseng at 100 mg/kg significantly ($p < 0.01$) inhibited all the changes induced by the exposure of cigarette smoke to male rats (Table 1).

Effect of *S. persica* decoction on the female reproductive behavior in cigarette smoke exposed animals

The observations on the female reproductive behavior are summarized in Table-2. Exposure to cigarette smoke produced significant ($p < 0.05$) decrease in the number of approaches by female rats towards male rats and also reduced the number of escapes frequency when male rat approached, compared to the control group. The tested three doses of *S. persica* (50, 100 and 200 mg/kg) did not showed significant alteration in the female reproductive behavior when compared to the cigarette smoked animals. However, administration of ginseng (100 mg/kg) showed a significant ($p < 0.05$) increase in both number of approaches as well in number of escapes when compared to the challenge group.

Table 1. Effect of *S. persica* decoction on the male reproductive behavior in cigarette smoke exposed (CSE) animals.

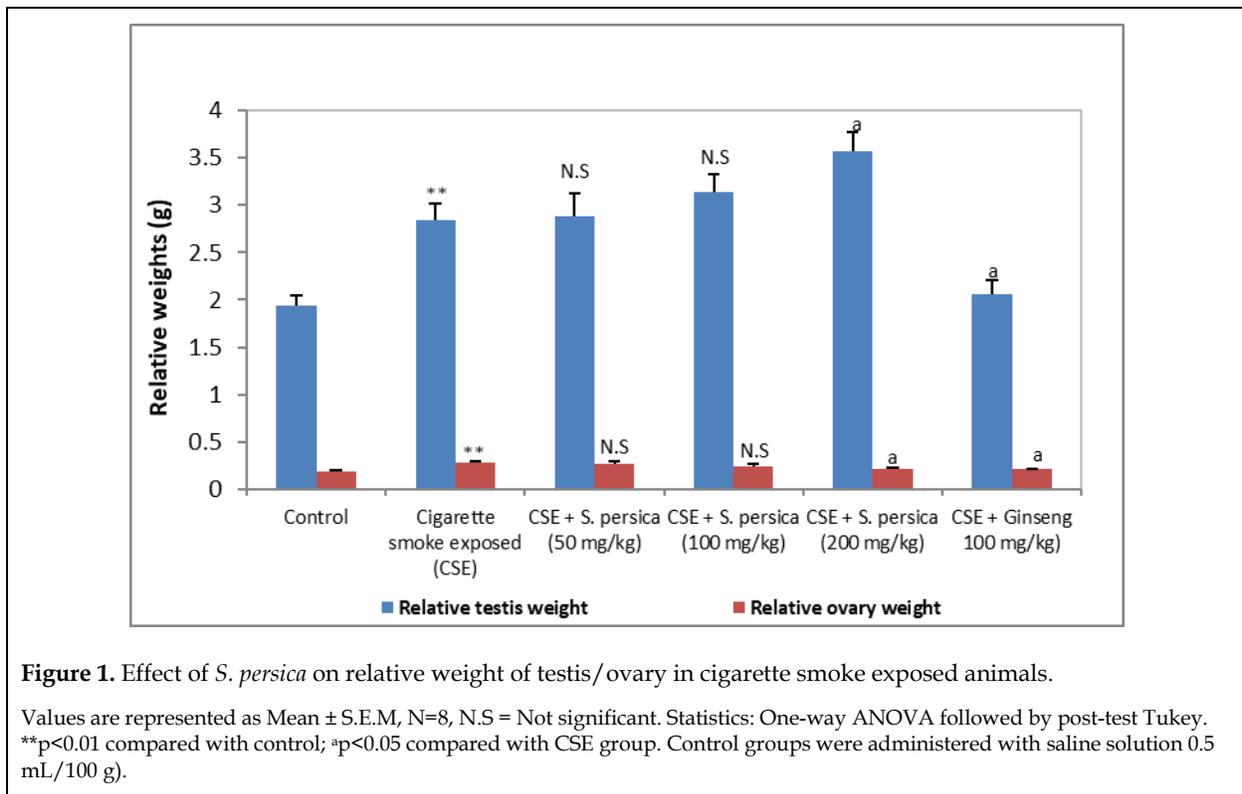
Treatment	No. of approaches	Mounts		Intromission	
		Frequency	Latency (min)	Frequency	Latency (min)
Control	39.72 ± 8.17	18.65 ± 2.59	40.68 ± 8.74	7.84 ± 1.06	67.14 ± 8.44
CSE	12.16 ± 1.57 **	8.13 ± 1.34*	84.19 ± 16.29***	2.51 ± 0.83**	208.78 ± 14.61***
CSE + <i>S. persica</i> (50)	10.76 ± 2.08 N.S	8.23 ± 1.95 ^{N.S}	168.36 ± 15.3 ^{N.S}	2.47 ± 0.93 ^{N.S}	193.39 ± 12.43 ^{N.S}
CSE + <i>S. persica</i> (100)	13.83 ± 1.94 N.S	8.75 ± 2.07 ^{N.S}	161.59 ± 15.02 ^{N.S}	2.80 ± 0.86 ^{N.S}	180.93 ± 12.03 ^{N.S}
CSE + <i>S. persica</i> (200)	17.9 ± 1.65 ^a	13.62 ± 1.51 ^a	143.38 ± 13.75 ^{N.S}	2.89 ± 0.71 ^{N.S}	164.83 ± 10.36 ^a
CSE + Ginseng (100)	27.81 ± 3.22 ^b	14.56 ± 2.02 ^a	92.44 ± 7.34 ^b	5.94 ± 1.12 ^a	137.16 ± 9.49 ^b

Values are represented as Mean ± S.E.M, N=8, N.S =Not significant. Statistics: One-way ANOVA followed by post-test Tukey. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with control; ^a $p < 0.05$, ^b $p < 0.01$ compared with CSE group. Treatment expressed in mg/kg b.w., except Control groups (saline solution 0.5 mL/100 g).

Table 2. Effect of *S. persica* decoction on the female reproductive behavior in cigarette smoke exposed (CSE) animals.

Treatment	No. of approaches	No. of escape to male approach
Control (0.5 mL/100 g)	17.05 ± 3.49	16.15 ± 2.39
CSE (0.5 mL/100 g)	6.11 ± 1.31*	8.04 ± 1.47 *
CSE + <i>S. persica</i> (50 mg/kg)	6.78 ± 1.71 N.S	7.49 ± 1.91 N.S
CSE + <i>S. persica</i> (100 mg/kg)	7.23 ± 1.84 N.S	8.62 ± 1.84 N.S
CSE + <i>S. persica</i> (200 mg/kg)	7.94 ± 1.60 N.S	10.32 ± 2.09 N.S
CSE + Ginseng (100 mg/kg)	12.67 ± 2.15 ^a	13.87 ± 1.72 ^a

Values are represented as Mean ± S.E.M, N=8, N.S =Not significant. Statistics: One-way ANOVA followed by post-test Tukey. * $p < 0.05$ compared with control, ^a $p < 0.05$ compared with CSE group. Control groups were administered with saline solution.



Effect of *S. persica* decoction on the relative organ weight in cigarette smoke exposed animals

The data from the relative organs' weight study suggested that exposure of cigarette smoke significantly ($p<0.01$) increased the relative testis weight and the ovary weight compared to the control animals. The lower doses of *S. persica* did not produce significant change on the relative testis/ovary weight in the cigarette smoke exposed animals. However, the higher dose (200 mg/kg) produced significant ($p<0.05$) increase in relative testis weight and decrease in relative ovary weight in cigarette smoked animals. On the other hand, treatment with ginseng produced significant ($p<0.05$) reduction in the relative testis weight and also the relative ovary weight when compared with the smoke induced group (Fig. 1)

DISCUSSION

Cigarette smoking is one of the leading global causes of both mortality and morbidity. The gender distribution indicated that around 26.5% of male and 9% are habituated to tobacco smoking

(Carter et al., 2015). Smoking has the tendency to affect the reproductive functions besides increasing the risks of diseases of cardiovascular, respiratory, neurological systems and variety of cancers (Gades et al., 2005; Carter et al., 2015).

The observation from this study indicated that cigarette smoke exposure adversely affected the reproductive behavior in both male and female experimental rats. The exposure altered the number of approaches, affected the mounting and intromission parameters in male rats and reduced the approaches in the female rats (Tables 1 and 2).

Earlier research indicated that tobacco smoking affects the neurotransmitter-neuroendocrine function, increases the sympathetic outflow and reduces the nitric oxide synthesis. The findings suggest the association between cigarette smoking with genital hemodynamic changes characterized by decreased penile arterial blood flow followed by disruption of veno-occlusive mechanisms leading to deficiency of genital vasoengorgement (Pomerleau, 1992). Further, the tobacco-induced changes in the metabolism leading to diabetes and hyper-

tension have also been linked to erectile dysfunction and vice versa (Gades et al., 2005). Studies also indicated that cigarette smoke in the female diminishes the vasoengorgement and arousal response that can be measured as vaginal pulse amplitude (Sala et al., 1990). These mechanisms can be suggested for the alteration in the arousals, mounting and intromissions observed in the present study.

Substances of natural origins have been traditionally used in the treatment of various ailments. Although many allopathic medicines such as sildenafil are available in the market but due to their side effects, the plant-based products are generally preferred (Singh and Mukherjee, 1998). Some of the plants as mentioned earlier have been used to improve the sexual activities in both male and female patients. *Panax ginseng* is one such folk medicine popularly used in the treatment of reproductive behavior defects in both men and women (Chauhan et al., 2014).

Our observations indicated that ginseng at 100 mg/kg significantly increased the mount and intromission frequencies in male rats compared to the cigarette smoke exposed animals (Table 1). The mount latency is known to indicate the sexual desire or motivation while, the mount frequency is considered as the indices for libido, strength, potency, sexual performance and vigor (Fouche et al., 2015). On the other hand, the intromission parameters reflect the improvement in the penile erection, its orientation and increased ejaculatory reflexes due to the drug treatment. The enhanced approaches shown by the female rats (Table 2) indicated that ginseng administration increased the desire for sexual encounters by improving the arousals (Fouche et al., 2015). However, when *S. persica* was tested, only the higher dose (200 mg/kg) increased the number of approaches and frequency of mounting, reduced the latency of intromission in male rats without affecting significantly the tested reproductive behavior parameters in female rats (Tables 1 and 2). The data suggests that *S. persica* has improved the arousal, sexual motivation and libido but the dose and duration of treatment might not be sufficient for potent aphrodisiac action.

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Earlier studies have indicated that the phytochemicals present in the herbal medicines play an important role in the aphrodisiac activity. The alkaloid components could produce estrogenic activity in causing the vasodilation of blood vessels of penis, flavonoids and sterols could change the neurotransmitter levels involved in the erectile function, and flavonoids also has the ability to increase the testosterone levels thereby enhancing the libido (Njila et al., 2018). Earlier studies have indicated the presence of some of these vital constituents such as alkaloids, flavonoids and sterols in the *S. persica* hence it can be suggested that the limited aphrodisiac activity observed in this study could be related to these constituents (Sher et al., 2010; Aumerruddy et al., 2018).

Another finding of the study is that cigarette smoke exposure increased the relative weight of testis and ovaries compared to control group (Fig. 1). This can be related to the ability of constituents of tobacco to induce inflammatory process in the body including the reproductive organs (Robbins et al., 2006). Administration of *S. persica* showed a dose dependent increase in the relative weight of testis and decrease in the weight of ovaries and a significant variation was observed only with the higher dose (200 mg/kg). The observation confirms the earlier finding wherein *S. persica* was reported to have increased the relative weight of testis and reduced the relative weight of ovaries in animals (Darmani et al., 2003). More studies in this direction are suggested to find the precise reason for these actions of *S. persica* on reproductive organs. On the other hand, ginseng reduced the relative weight of testis and ovary. The action can be linked to the anti-inflammatory and antioxidant properties of ginseng since it is known to contain one of the potent antioxidants ginsenosides (Liao et al., 2002).

CONCLUSIONS

The data from this study indicated that exposure to cigarette smoke altered the reproductive behaviors in experimental animals. *S. persica* at the highest tested dose (200 mg/kg) improved some of the sexual behavior parameters such as number of approaches, frequency of mounting and latency

of intromission in male rats. These effects can be related to the phytochemical constituents present in the plant. However, the action of *S. persica* on the reproductive organs need more studies to confirm the precise effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION:

Contribution	Rabbani SI
Concepts or ideas	x
Design	x
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Experimental studies	x
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Data analysis	x
Statistical analysis	x
Manuscript preparation	x
Manuscript editing	x
Manuscript review	x

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