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Analytical perspectives of chemical adulterants in herbal sexual enhancer drugs

[Análisis de medicamentos falsificados a base de hierbas utilizados para mejorar el rendimiento sexual]

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Abstract

Context: Detection of active pharmaceutical ingredients in herbal drugs has been described in numerous studies. However, few reports have been published in relation to the analysis of counterfeit herbal supplements for the detection of synthetic drugs in Iran.

Aims: To analyze herbal drugs used as sexual performance enhancer from forensic and analytical toxicology point of view.

Methods: Eighty herbal drugs gathered from herbal shops in Bushehr city, Iran were analyzed. High performance liquid chromatography and gas chromatography/mass spectrometry were used for detecting and identifying the chemical structures of probable active pharmaceutical ingredients as adulterants.

Results: Among 80 samples, 23% contained only sildenafil. Three samples contained sildenafil, tramadol and diazepam in combination with each other reported for the first time.

Conclusions: This study substantiates regular analysis of purported herbal drugs is needed for more effective quality control and health promotion.

Keywords: analytical toxicology; chemical adulterants; counterfeit; herbal drugs; sexual enhancers; sildenafil.

Resumen

Contexto: Muchos estudios han apuntado a identificar fármacos en productos vegetales. Sin embargo, se han realizado pocos estudios en Irán para el análisis de medicamentos falsificados a base de hierbas e identificar los componentes del fármaco en su estructura química.

Objetivos: Analizar el efecto de las hierbas medicinales utilizadas para aumentar el rendimiento sexual desde el punto de vista toxicológico forense.

Métodos: Se analizaron ochenta hierbas que fueron recogidas de la ciudad de Bushehr, Irán. La detección de medicamentos falsificados en productos vegetales se llevó a cabo mediante cromatografía líquida de alta resolución y cromatografía de gases/espectrometría de masas.

Resultados: Solamente el 23% de 80 muestras que fueron probadas, contenía sildenafil que es el componente activo del fármaco. Se ha informado, por primera vez, tres muestras que contenían una mezcla de sildenafil, tramadol y diazepam en un mismo producto.

Conclusiones: Este estudio sustenta la necesidad del análisis regular de los fármacos a base de plantas para un control de calidad más eficaz y promoción de la salud.

Palabras Clave: adulterantes químicos; falsificación; hierbas medicinales; potenciadores del rendimiento sexual; sildenafil; toxicología analítica y forense.

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INTRODUCTION

In the last few years the popularity of herbal drugs is increasing all over the world (Rocha et al., 2016). According to World Health Organization (WHO) report, at least 80% of the population in developing countries use traditional medicine as their primary health care needs (Skalicka-Woźniak et al., 2016). It is indisputable that herbal drugs had captured drug market in Iran and many other countries for addiction treatment, sexual performance enhancing, weight gain and weight loss purposes under the impression that herbal drugs are natural, safe and without any side effects (Jalili et al., 2015; Foroughi et al., 2017). But the efficacy and safety of herbal supplements is under discussion in many countries. One well-cited assertion in the literature is that herbal supplements may be adulterated with drugs to ensure or increase the effects of final product. However, the majority of adulteration cases are intentional (da Justa Neves and Caldas, 2015).

The United States Food and Drug Administration (FDA) reported 572 adulterated supplements from 2007-2014 in the United States, of which 41.6% were sexual enhancer drugs (da Justa Neves and Caldas, 2015). Undeclared drugs may be present in counterfeit herbal drugs at higher levels than those found in approved pharmaceutical dosage forms (Foroughi et al., 2017). Side effects assigned to undeclared synthetic drugs in adulterated pharmaceuticals include their direct side effects and drug-drug interactions resulting in health hazards (Skalicka-Woźniak et al., 2016). In this sense public awareness about the dangers of adulterated drugs should be changed to use licensed and standardized drugs to prevent side effects and even lethal consequences (Foroughi et al., 2017).

There are many reasons for growing informal pharmaceutical black markets all over the world; these include: the increase in demand for herbal supplements, poor and inadequate regulatory measures, unrestrained drug distribution chains and mixing the illicit and licit drug supply channels (Bhagavathula et al., 2016). The differentiation between authentic and counterfeit drugs is very important and need to be addressed diligent surveillances on the part of authorities and health providers (Lee et al., 2015).

Nowadays the use of herbal drugs for the treatment of erectile dysfunction has gained tremendous popularity. It is estimated that sexual problem raises over 320 million all over the world in 2025 (Bhagavathula et al., 2016). Although it is now broadly accepted that herbal drugs are safe formulations, very little is known about the undeclared active pharmaceutical ingredients (APIs) in herbal sexual performance enhancers. Also, information regarding the adulteration of herbal supplements with undeclared drugs is limited to few studies in Iran with limited number of samples (Jalili et al., 2015). Jalili et al. (2015) in a study conducted on ten samples for the detection of undeclared active pharmaceutical ingredients in herbal drugs used for weight gain and sexual activity enhancement found sildenafil and tadalafil in 3 samples and dexamethasone in 3 weight gain drugs. Evidence from the study of Skalicka-Woźniak et al. (2016) suggest that sildenafil and tadalafil were detected as adulterant in food beverages.

However, this raises the question of whether herbal drugs used as sexual performance enhancer in Iran are adulterated by synthetic drugs. The present study is crucial in analyzing sexual enhancement drugs and detection APIs other than those were reported by previous studies. In the present study we sought to analyze herbal sexual performance enhancer drugs in different pharmaceutical dosage forms to detect APIs using high performance liquid chromatography (HPLC) and gas chromatography/mass spectrometry (GC/MS) instrumentations.

MATERIAL AND METHODS

Sample collection

In the present study 80 herbal dietary supplements intended to be introduced into herbal shops in Bushehr city, Iran were submitted for analysis. There are 24 herbal shops in Bushehr city. Samples were gathered from all of the herbal shops in different pharmaceutical dosage forms including tablets, capsules, powders, oral drops and handmade solid dosage form in the shape of small balls. None of the herbal shops were registered by Ministry of Health and Medical Education, Iran.

Chemicals

Analytical grade chloroform, methanol, potassium dihydrogen phosphate, phosphoric acid, hydrochloric acid (37%) were purchased from Merck Chemical Co. (Darmstadt, Germany). Water for chromatography (Merck Millipore) was used to prepare buffer for mobile phase in HPLC system and also all aqueous solutions and eluents. HPLC grade acetonitrile was prepared from Merck Chemical Co. (Darmstadt, Germany). Helium (99.99% purity) was supplied by Roham Co. (Tehran, Iran). All chemicals and solvents used were of analytical reagent grade and high purity.

Methods

All pharmaceutical dosage forms were analyzed to detect APIs. Bulking agents, inert substances, colors and flavoring agents were not investigated in analysis procedures.

Physical attribute considerations of pharmaceutical dosage forms

Size, shape, odor and the color of tablets, capsules and powders were characterized.

Sample preparation methods

All handmade balls and tablets were crushed and grinded to fine and uniform powders. The content of gelatin capsules was emptied for analysis. Liquid forms were analyzed without dilution. All prepared powders and liquids were mixed with 2 mL 0.1 M borate buffer (pH=9.2) at concentration of 1 mg/mL in three parts. As many drugs with forensic interest have basic structures, the pH of the analysis medium was adjusted to be alkaline (pH=12) for efficient extraction of basic drugs such as benzodiazepines, antidepressants, and narcotic analgesics. For efficient extraction of drugs with acidic structure (barbiturates, phenytoin and primidone) the pH was balanced to acidic (pH=2). Adjustment of pH to isoelectric point (pH=9) was necessary for the extraction of morphine and other amphoteric drugs (Khazan et al., 2014). Dispersive liquid microextraction (DLLME) was used to extract APIs from dosage forms. Extraction procedure was prevalidated in the laboratory. Limit of detection, limit of quantification, coefficient of variation %, accuracy and precision were evaluated for all of the analytes. DLLME was used as a sample preparation method. In this procedure a triplicate solvent system (aqueous phase, disperser solvent and extraction solvent) is used for the extraction of analyte from biological and nonbiological matrices in forensic toxicology laboratories (Jain and Singh, 2015). In the present study methanol and chloroform were used as disperser and extraction solvents respectively. To one mL of prepared samples in borate buffer a mixture of 2.5 mL methanol + 30 µL chloroform was added rapidly. The mixture was subjected to ultrasonication for 5 min followed by centrifugation. Chloroform was collected in conical tube and dried with a light stream of nitrogen gas. Residue was dissolved in 30 µL methanol and analyzed using HPLC and GC/MS instrumentations.

Instrumental analysis

All of the samples in the present study had been analyzed with the two previously validated HPLC and GC/MS instrumentations routinely used for systematic toxicological analysis in forensic toxicology laboratory (Bazmi et al., 2016; Foroughi et al., 2017).

GC/MS operating conditions

An Agilent gas chromatograph (7890 A, Agilent, Sdn Bhd, Selangor, Malaysia) equipped with split/splitless injector was used. The column of the GC was HP5-MS model capillary column (cross-linked 5% methylphenyl silicone, 30 m length x 0.25 mm ID x 0.25 µm film thickness). Mass analyzer (MS 5975 C, Agilent) was connected to the column. The injection port temperature was 250°C, the transfer line temperature was 280°C. The initial column oven was set to 60°C and held constant for one minute. Temperature program rate was 2°C/min and final temperature was set to 280°C and final hold for 15 minutes. The mass spectrometer was operated by electron impact (70 ev) in positive full scan mode (50-550 m/z). Wiley, NIST and MPV 2011 libraries were used for qualitative analysis of samples.

HPLC operating conditions

KNUER HPLC system (Berlin, Germany) equipped with diode array detector (DAD, S 2800-4

channels) was used to analyze samples using Eurospher-100-5 C18 column (250 mm x 4.6 mm, 5 µm particle size, 100 Å pore size) with a Smart-1000 pump. A mixture of acetonitrile and phosphate buffer (38:62) was used as elution solvent. Analysis was performed in isocratic mode at a flow rate of 1 mL/min and 400 bar maximum pressure. All of the routine analytical procedures were validated in the laboratory. All the solvents and apparatus conditions were selected according to the results of prevalidation procedures.

Statistical analysis

Statistical analysis was performed with SPSS software (Chicago, IL, USA). Results are shown as frequency and percentages.

RESULTS

In the present study, 80 herbal products sold as sexual performance enhancer by herbal shops in Bushehr, Iran were analyzed from forensic toxicology point of view to detect undeclared APIs using HPLC and GC/MS methods. As it is shown in Fig. 1A-B herbal supplements were prepared in different dosage forms such as powders (n=35), oral drops (n=11), gelatin capsules (n=17), tablets (n=9) and herbal balls (n=8) (Table 1). All of the products had herbal odor. Physical appearances of solid dosage forms were similar to those of dried powdered herbal leaves with beige to dark green colors. None of the samples had standard labels, standard logo, batch number, identity statement, list of APIs or even the names of herbs, manufacturer's names and production and expiration dates. All of the samples had a label indicating "natural or herbal product".

Powders were the most prevalent dosage form collected to perform the present study (43.75%). Powders were wrapped tightly in plastic bags (5 g/bag) to be dissolved in water or fruit juice and taken once or three times daily. Qualitative analysis of samples showed that 22 (27.5%) samples had at least one undeclared API. In 19 samples sildenafil was the only API detected. Capsules, tablets, powders and handmade balls were the most prevalent pharmaceutical dosage form containing APIs. One interesting result is that three samples (two capsules and one handmade ball were adulterated with a mixture of sildenafil, tramadol and diazepam. Figs. 2 and 3 show the spectrum of sildenafil, tramadol and diazepam in one sample with each other and the chromatogram of sildenafil.

A

B

Figure 1. (A) Pharmaceutical dosage forms of adulterated herbal drugs used as sexual performance enhancers.

(B) Handmade herbal balls used as sexual performance enhancing drugs that were adulterated with sildenafil, tramadol and diazepam.

Table 1. Characteristics and contents of adulterants identified in the formulations analyzed.

API identified	Dosage form	Physical appearance
None	Oral drops (n=11)	Colorless liquid with herbal odor
Tramadol, sildenafil, diazepam	Gelatin capsules (n=17)	Purple/white, blue/white, yellow, gelatin capsules in different sizes
Sildenafil	Powders (n=35)	Beige to dark green powdered leaves
Sildenafil	Tablets (n=9)	Pink,o white, brown, tablets with herbal odor
Sildenafil, tramadol, diazepam	Herbal balls (n=8)	Balls made from compressed leaves with one cm diameter and beige to dark brown color

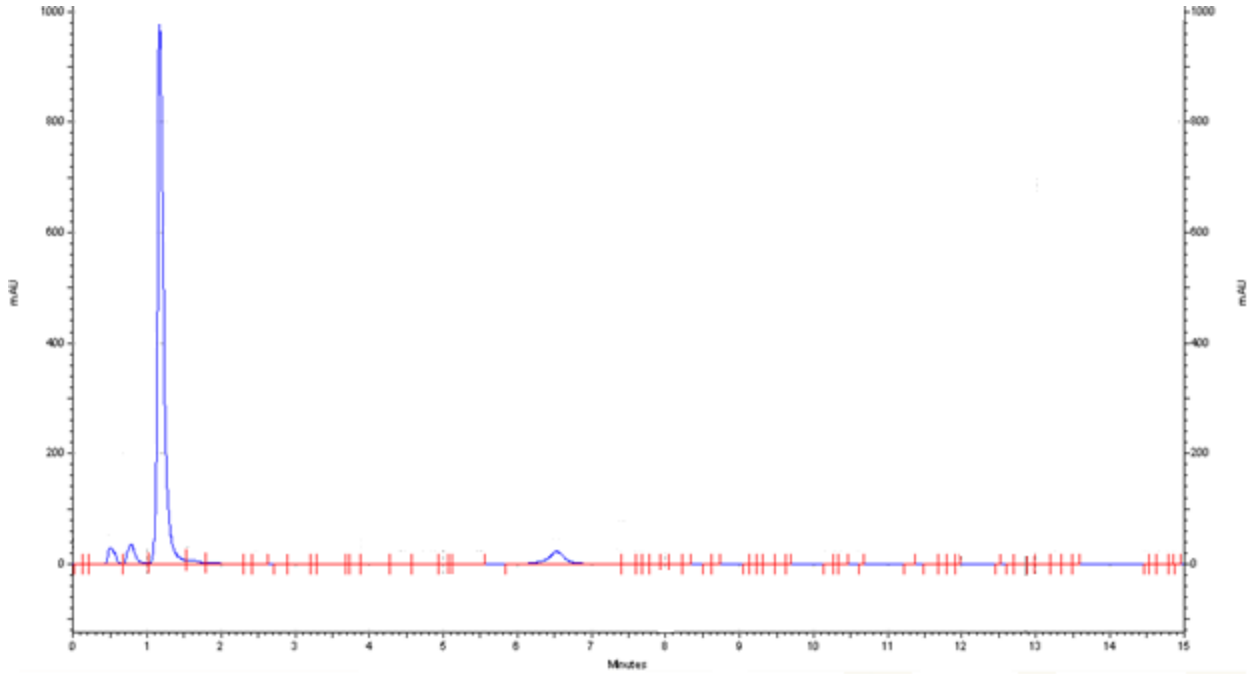

Figure 2. UV spectrum of sildenafil, tramadol and diazepam in adulterated herbal sexual enhancer drugs.

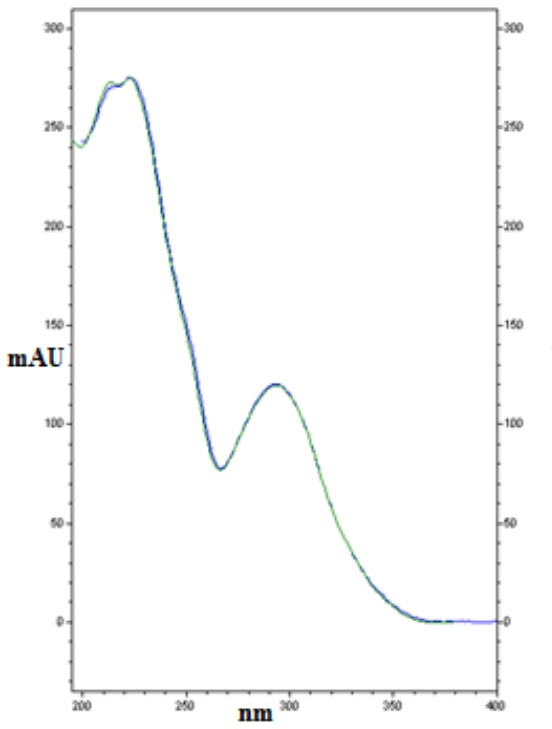

Figure 3. HPLC chromatogram of sildenafil in adulterated herbal medicine used as sexual performance enhancer.

HPLC/DAD system equipped with Eurospher-100-5 C18 column was used with acetonitrile:phosphate buffer (38:62) as elution solvent and one mL/min flow rate and 400 bar pressure.

DISCUSSION

The purpose of the present study was to analyse herbal drugs used as sexual performance enhancer to detect undeclared APIs. According to the results of the present study different pharmaceutical dosage forms were adulterated with pharmaceutical ingredients mainly sildenafil.

Many studies highlighted the erectile dysfunction as a result of psychiatric, neurological, pharmacological, vascular and hormonal causes (Thu et al., 2017). Sildenafil citrate (Viagra) was introduced to drug market in 1998. Since then it gained popularity in the management of erectile dysfunction (Xu et al., 2016). Poor compliance accounts for phosphodiesterase-5 (PDE-5) inhibitors-related adverse effects such as muscle pain, back pain, flushing and visual impairment. Patients tend to change their therapy to natural substitutes such as herbal drugs to improve sexual problems (Malviya et al., 2011; Thu et al., 2017). The other reason for high tendency towards herbal supplements desire is that herbal drugs are safe and can be used without doctors' advice (Bhagavathula et al., 2016). In the recent years, the tendency for herbal medicines as effective substitutes for synthetic drugs is increasing all over the world (Skalicka-Woźniak et al., 2016). The annual sales of dietary supplements exceed several billion euros all over the world. This cosmic market encourages intentional adulteration towards high profit margin (Skalicka-Woźniak et al., 2016). Unfortunately, many herbal shops adulterate herbal medicines with undeclared APIs and consumers are unaware of using counterfeit drugs. One of the definitions for substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medicinal products is "a product with wrong APIs". Therefore, adulterated herbal drugs with APIs are not determined as herbal medicine by WHO (2016). None of the samples in the present study had standard labels indicating their APIs and the kind of herbal ingredients used. One of the requirements for dietary supplement is to indicate ingredients in descending order by weight. In spite of the guidelines for dietary supplements labels issued by United States Food and Drug Administration (US Food and Drug Administration, 2005), none of the pharmaceutical dosage forms in the present study had identity statement, amount of dietary supplements, list of ingredients, and manufacturer, packager and distributor's names and addresses. Pharmaceuticals are always vetted to gain a proven degree of efficacy and safety. With growing number of counterfeit herbal medicines, safety in production and labelling is a great concern for different stakeholders including governmental regulators, health professionals and consumers (Rocha et al., 2016). Unfortunately, herbal drugs are not screened in this issue and it doesn't have priority for manufacturers due to high costs in many countries (Brown, 2016).

Several studies suggest that sildenafil and other PDE-5 inhibitor analogues were detected in adulterated natural products advertised on the internet and on television to resolve sexual problems (Rocha et al., 2016). Balayssac et al. (2012) characterized sildenafil analogues for the first time in counterfeit herbal sexual enhancing drugs.

In accordance with the results of the present study sildenafil and other PDE-5 inhibitors were detected in 61% of 150 herbal dietary supplements marketed for improving sexual performance in

France in the study of Gilard et al. (2015) using ^{1}HNMR spectroscopy. Other chemical adulterants such as yohimbin, flibanserin, phentolamine and testosterone were detected in their study.

All of the pharmaceutical dosage forms in the present study are prescribed for both male and female subjects. Although the role of sildenafil for the treatment of male erectile dysfunction was addressed by previous studies, the beneficial effects of sildenafil in female sexual dysfunction was proved by many researchers. Berman et al. (2003) showed that sildenafil prescription to women in postmenopausal state significantly improved sexual function. However, Basson et al. (2002) found that sildenafil had no effect on sexual response in premenopausal and postmenopausal women.

One of the undeclared APIs that was detected in analysed samples was tramadol. Use of tramadol in the improvement of sexual dysfunction is controversial. Khan et al. in their study investigated the effect of tramadol on premature ejaculation. Results of their study showed that tramadol administration had positive effect in the improvement of quality of sexual life (Khan and Rasaily, 2013). The efficacy of tramadol in the treatment of premature ejaculation was reported in previous studies (Gameel et al., 2013; McMahon, 2016). The exact mechanism of tramadol in improving premature ejaculation is not well understood. But its anesthetic-like and anti-nociceptive activities explain its effectiveness in treating sexual dysfunction. Also the inhibitory effects of tramadol on serotonin and norepinephrine reuptake in nerve terminals should not be neglected (McMahon, 2016). Yet other scholars indicated that using tramadol for the treatment of premature ejaculation is equal to live "on a knife's edge" due to the presence of other sexual dysfunctions produced by tramadol (Abdel-Hamid et al., 2016). Some sexual adverse effects of opioids are serious reproductive system toxicity, testicular oxidative damage and consequently increased sperm DNA damage (Nna et al., 2016). On the other hand, adulteration of herbal drugs cheats the consumer and can pose serious risk to health in some patients.

One of the APIs in herbal drugs in the present study was diazepam. Some studies highlighted the role of vaginal diazepam in the treatment of sexual pain due to the muscle relaxation properties of diazepam (Houman et al., 2016). It is interesting that some dosage forms containing sildenafil, diazepam and tramadol were prescribed for female subjects.

Data from other study show that some natural herbal supplements such as *Eurycoma longifolia* may have remarkable positive effects in enhancing sexual performance in male subjects (Tambi et al., 2012). Thu et al. in their systematic review investigated the role of *Eurycoma longifolia*for the improvement of sexual problems. Results of their investigation showed that in seven studies there was a remarkable association between the uses of *Eurycoma longifolia*and treatment of male sexual dysfunction (Thu et al., 2017).

The risk of adulterated drugs use overweighs their benefits (Bhagavathula et al., 2016). As herbal drugs are adulterated with undeclared APIs, they predispose the consumer to drug-drug interactions especially in patients with co-morbid conditions such as cardiovascular complications and diabetes and even polypharmacy in older adults (Gur et al., 2013; Bhagavathula et al., 2016). There are some reports that correlate age with erectile dysfunction (Thu et al., 2017). According to the Massachusetts Male Agency Study 52% of men aged 50-70 and 70% of men older than 70 have some degrees of erectile dysfunction (Chiang et al., 2017). Old population almost involves with cardiac complications. Use of sildenafil as an aid in erectile dysfunction treatment with nitrates and α-blockers may cause severe hypotension and syncope (Skalicka-Woźniak et al., 2016). Therefore, drug interactions can cause life-threatening outcomes in patients using counterfeit adulterated herbal drugs with APIs. In this concern Nissan et al. (2016) reported a case of hepatotoxicity associated with herbal medicine, "Tiger King" adulterated with sildenafil. In this case report, it was explained that within three days of hospital admission, patient's liver function and clinical status improved without any treatment.

The most probable definition for the addition of APIs to herbal supplements is to enhance their pharmacologic effects. To the best of our knowledge there have been no report regarding the presence of sildenafil, tramadol and diazepam in combination in single pharmaceutical dosage form in counterfeit herbal drugs used for the treatment of sexual dysfunction.

The power of this study is that acquired data can be analyzed in the future to see if the concentration of APIs in adulterated sexual performance enhancer drugs are in toxic level or not, and if new undeclared compounds are present in herbal drugs.

CONCLUSIONS

Among 80 herbal formulations analyzed, about 27% had at least one active pharmaceutical ingredient. Three formulations contained sildenafil, tramadol and diazepam in combination with each other. Therefore, existing law and regulations should mandate robust requirements for analyzing herbal drugs and to evaluate their safety and efficacy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Author contribution:

Contribution	Hafizi Fard H	Akhgari M
Concepts or ideas		X
Design		
Definition of intellectual content		
Literature search		
Experimental studies	X	
Data acquisition	X	
Data analysis	X	X
Statistical analysis		X
Manuscript preparation	X	X
Manuscript editing		X
Manuscript review		X

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