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Formulation and Evaluation of Herbal Tablets from the Shimshin-6 Prescription and Its Effect on Postpartum Involution in Rats

Dejidmaa Buyantogtokh[1], Erdenechimeg Chuluunbaatar[2]*, Anu Altangerel[1], Nyamdolgor Uranbileg[3] and Chimedragchaa Chimedtseren[1]

[1]Department of Pharmacology, Research center, Institute of Traditional Medicine and Technology, Ulaanbaatar, Mongolia.
[2]Department of Chemistry and Technology, Research center, Institute of Traditional Medicine and Technology, Ulaanbaatar, Mongolia.
[3]Department of Pathology, Institute of Veterinary Medicine. Ulaanbaatar, Mongolia.
*Corresponding Author e-mail: Erdenechimeg.ch805@gmail.com

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The Shimshin-6 prescription has been used to treat female patients for blood clots, back and waist pain, and menstrual cramps. It is intended to support the recovery of the uterus after both childbirth and abortion. The purpose of this study is to create a tablet form of the Shimshin-6 formula and examine its effects on the recovery of the uterus after childbirth. The granules were developed using wet granulation, and the tablets were made using a direct compression method. Our test product in tablet form was manufactured following the quality parameters specified in the Mongolian National Pharmacopoeia. Shimshin-3 tablet was considered the best formulation; it used 5% cane sugar as a binder. In this study, Shimshin-6 treatment significantly reduced the uterus index and blood estrogen levels compared to the control group showing no difference in progesterone concentration. We found that Shimshin-6 decreased Tumor Necrosis Factor (TNFa) and regulated growth factors in postpartum rats. Shimshin-6 also regulated postpartum uterine recovery, as indicated by histological analysis. Our results showed the infiltration of inflammatory cell and hemorrhagic changes in the uterine wall. In conclusion, the formulation and evaluation of herbal tablets were satisfactory, and it has been found to enhance uterine recovery postpartum in rats.

Keywords: Cane sugar; Herbal formulation; Involution of uterus; Rheum undulatum Postpartum care.

In 1990, the crude birth rate, which represents the amount of live births per 1000 population in a given year, was 35.3 in Mongolia. This rate dropped twice to its lowest level in 2005, and it has increased steadily since 2006 to 24.0 in 2020. The total number of registered complications in pregnancies, childbirth, and postpartum was 58,947 in 2020. This is equivalent to 779 per 1000 live births. The two most crucial periods for newborn and maternal survival are during childbirth and immediately postnatal. Mongolia became a member of the countries that authorized abortion in 1989. The total cases of abortion that year registered were 14,622, which means a ratio of 191.7 per 1000 live births. Therefore, the general abortion rate, which is the number of abortions occurring during the specified period per 1000 women of reproductive age, was 17.8 in 2020[1].

Postpartum care involves the medical attention and support provided to a woman after

childbirth to ensure her physical and emotional well-being, as well as that of her newborn. One common issue addressed during postpartum care is postpartum bleeding, also known as postpartum hemorrhage (PPH), which is excessive bleeding following childbirth. Deficiency of uterine involution has been shown to be closely related to maternal morbidity and, in particular, postpartum hemorrhage[2].

Uterotonics are medications used to prevent or manage postpartum bleeding by inducing uterine contractions, which help to control bleeding by compressing blood vessels. Oxytocin is one of the most commonly used uterotonics. Other uterotonics include misoprostol, ergometrine, and carboprost[2]. But natural uterotonic is a substance that rise the tone of the uterus, and it often have laxative, purgative, diarrheagenic, cathartic, abortifacient, and emmenagogues effects in traditional and herbal medicine[3].

Traditional medicine and food play a significant role in postpartum care various cultures, offering natural remedies to support recovery and wellness after childbirth. Traditional Mongolian postpartum care is composed of three features dietary therapy with a mushroom sheep meat soup and with milk tea and postpartum women for daily routine protect a cold and windy or wear a hat/, consume an herbal therapy. According to the dietary and daily and herbal therapy, during the 45 days after labor, the consumption of food considered to be "cold, sour" in meal and drinks are also restricted in the women[4].

In the past twenty years, several Traditional Mongolian Medicine formulas have been developed into modern dosages. These have the demonstrated benefits of being easier to use, improved quality and safety, effects that are approved by modern research methods, and improved packaging that extends the shelf life of the products. The Shimshin-6 tablet is one of these modernized formulas.

The Shimshin-6 tablet is derived from Shimshin-6 talkh or 'fine powder', a well-known traditional Mongolian medicine prescription that has been widely used for postpartum care in Mongolia for many years. Shimshin-6 helps to amenorrhea and some women's disease, promote blood flow, resolve blood stasis, alleviate back pain[5].

Shimshin-6 consists of six herbs: Radix *Rheum undulatum*, *Tronae veneni*, Radix *Kaempferia galanga*, Fructus *Hippophae rhamnoides*, Radix *Saussurea Lappa*, and *Sal ammoniac*. Shimshin-6 talkh has been used to support uterine recovery after both childbirth and abortion in Traditional Mongolian Medicine. Shimshin-6 talkh has a pale-brown and yellow color, has a specific odor, and tastes salty and bitter[5]. The Shimshin-6 prescription was studied that administrates the metabolic process of energy, amino acids, and fatty acids, to treat amenorrhea in animals[6].

Rhubarb *(R.undulatum* L.) is accepted East-Asian traditional medicine for the therapeutic of inflammation, allergies, dental diseases and blood stagnation[7]. Radix and rhizomes of Rhubarb have been applied as medicine for symptoms of blood stasis and as a substance that eases defecation in Eastern traditional medicines such as China, Korea, and Japan. This Rhubarb which holds stilbenes like emodin, piceatannol 32 -O-â-d-glucopyranose, and rhaponticin is most effective on symptoms of blood stagnation but has a less cathartic effect[8].

In addition, these substances have been known that contains anthraquinones and their derivatives chrysophanol, emodin, physcion, aloe-emodin, rhapontin, rhein, and stilbene diglycoside[9,10].

In some traditional medicine systems, including Traditional Chinese Medicine (TCM) and Ayurveda, Rhubarb has been used historically to help regulate menstrual cycles and address symptoms associated with menstruation, such as irregular periods or excessive bleeding[11].

One of the ingredients in this Shimshin-6 tablet is Radix *K.galanga* which has been used for the treatment flu, dry cough, toothaches, rheumatism, and hypertension. The rhizomes contain monoterpenoids, sesquiterpenoids, and phenylpropanoids[12]. The herb *K.galanga* was used for colic, dyspepsia and postpartum care in Malaysia[13].

This study's primary objective was to investigate the opportunity to combine the effects of these herbs into the Shimshin-6 tablet and analyze how it could increase the involution of the uterus after childbirth in rats.

MATERIALS AND METHODS

Materials

The Radix of *R.undulatum* L. were collected from Gachuurt, Mongolia in 2021 and *H.rhamnoides* had been cultivated in Dashinchilen, Bulgan province, Mongolia. *T.veneni*, Radix *K.galanga* and *S.lappa*, and *S.ammoniac* used in the study were bought from the Traditional manufacture in Institute of Traditional Medicine and Technology of Mongolia.

The species of plants were identified by T. Munkh-Erdene, an expert of botany at the Botanic Garden and Research Institute, Mongolian Academy of Science, Ulaanbaatar, Mongolia.

Plant Extraction

We decided to use the extract of the *R.undulatum* L in technological study due to *R.undulatum* L is a main ingredient in Shimshin-6 prescription. The dried raw material of *R.undulatum* L. was chopped and extracted in a 60% ethanol solution using the remaceration method[14]. Extracts were combined and filtered. The solvent was evaporated with a vacuum rotary evaporator (RE-1002, China). This yielded a 1:1 liquid extract of the *R.undulatum* L. was prepared.

Animals

All of the study procedure was in accordance with the "Guide for the care and use of laboratory animals" proposed by the Biomedical ethics committee of Ministry of Health Mongolia. The protocol of permission number is 23/032. The experimental animals used in this study were female Wistar rats 9-11 weeks old, 250-300 grams were obtained from the experimental animal house of Institute of Traditional Medicine and Technology. The rats were provided in the cages kept with a 12-h light/dark cycle. Those rats feed with rodent's diet and tap water containers.

Method of the Pre-formulation study

Development of the tablet formulation

The tablets were produced by preparation as a wet granulation with subsequent direct compression. The ingredients of the tablet are illustrated in Table 1. The tablets were pressed on a 17 punch-tablet machine (ZP 17E, China) with 9 mm diameter punches. The mixture of the powdered herb was moistened with the required amount of solution of cane sugar with various concentrations and liquid extract of the *R.undulatum* L. The mass was then granulated using the sieve that have 18-mesh diameter and were dried at 25^0C for 48 h. After drying, the granules were added and mixed talc and magnesium stearate.

Bulk density

Bulk density is determined as the dry weight of the granule per unit volume of the granule. 25g of sample was added into a 100ml cylinder with the initial volumes were measured. The bulk density was determined using Equation 1[15, 16].

$$\text{Bulk density} = \frac{\text{Weight of the granule (g)}}{\text{Volume occupied by the granule (ml)}} \quad ...(1)$$

Tapped density

The tapped density is an increased bulk density attained after mechanically tapping a cylinder containing the granule. A sample that was used to determined bulk density was used and the cylinder was tapped until a constant volume. The last volume was measured. The tapped density was determined following the Equation 2[15, 16].

$$\text{Tapped density} = \frac{\text{Weight of the granule (g)}}{\text{Tapped volume occupied by the granule (ml)}} \quad ...(2)$$

Compressibility

The Compressibility Index or the Hausner Ratio illustrates an index of the ability of the powder to flow. The compressibility was established to compare the bulk and tapped density. It was represented by the percentage and was calculated Equation 3[15, 16].

$$\text{Carr index} = (TD - BD)/TD \times 100 \quad ...(3)$$

Hausner's ratio

Hausner's ratio is the proportion of the tapped and bulk density. It represents an index of the flowability and was calculated by Equation 4.

$$\text{Hausner ratio} = TD/BD \quad ...(4)$$

Method of the physical evaluation of tablets

Weight variation

The experiment was carried out by weighing 20 tablets individually measuring an analytical balance. The weight variation was then

represented as percentage and defined by using the Equation 5[16].

Weight variation=(Average weight-Individual weight)/(Average weight) x100 ...(5)

Hardness

The hardness of the Shimshin-6 tablet forms was quantified using a SY-6D four functions tablet tester (China). 20 tablets of each formulation for hardness test and it was calculated by using Equation 6[17].

Hardness=(Force applied the anvils)/(Diameter of the tablet (mm) x High of the tablet (mm)) ...(6)

Friability

The friability was carried out by using a SY-6D four function tablet tester (China). Twenty tablets of each formulation were tested in following conditions: speed was 25 rpm per a minute (100 rotations). The friability was represented by percentage and determined using the Equation 7.

Friability,"\%"=(Tablet weight before friability-Tablet weight after friability)/(Tablet weight after friability) x100 ...(7)

Total Anthraquinone Content

The content of total anthraquinone glycosides in the tablets was determined using a UV-vis spectrophotometer. The contents were calculated as emodin. The standard curve of emodin (y = 0.0695x–0.0236; R2 = 0.9972) was determined using solutions of various concentrations (1.5–12µg/mL). This method is based on the concept that the anthraquinone would react with magnesium acetate. Absorbance of sample and standard solutions were computed at 515nm with UV spectrophotometer. Content of total anthraquinones were expressed in milligrams of emodin equivalents per the tablets[18].

Pharmacology methods

The female rats, housed in special (separate) cages were mated with two male rats kept in special (separate) cages, all groups were mated with these two male rats with the exception of the control group. (female rats without mating n=7). Pregnancy symptoms were the indicator marking the formation of mating or vaginal plug the first day.

After pregnancy, rats were divided into four groups depending on their drug: two experimental groups (n=7) to which was administered Shimshin-6 liquid formula (*tang*) (Sh-6) 162mg/kg (n=7), and two groups receiving the Shimshin-6 tablet (ShT) 160mg/kg (n=7) or Shimshin-6 tablet 90mg/kg (n=7) respectively – all orally received[19].

Sampling process

After five days of experimental drug received, the rats were anaesthetized after intraperitoneal injection of 10% chloral hydrate (0.3mL/100g), and then blood collected from the heart were sampled into tubes and centrifuged to separate the serum. Also, uterus was removed and weighed. Uterus indices were calculated divided by the total weight of each rats[19].

Enzyme-linked immunosorbent assays (ELISA)

Level of serum of estrogen (E), progesterone (P), tumor necrosis factor á (TNF-á), growth factor â1 (TGF-â1), and growth factor â3 (TGF-â3) were analyzed using commercially available assay kits Shanghai MLBIO Biotechnology Co. Ltd (China).

Histopathological analysis

Uteri were immediately fixed in 10% buffered paraformaldehyde for 24 hours at 4°C. Subsequently, standard pieces of uteri were embedded in paraffin after sequential dehydration in a graded ethanol series, and sliced into 2-5 ìm thick sections before being stained with H&E and Masson-Trichrome stain. After H&E and Masson-Trichrome staining, the thickness of the endometrium, myometrium and were measured using a li microscope with a calibrated ocular scale set to 17.

Statistical analysis

The results were expressed as mean±standard deviation (SD). Data from the ELISA assays were analyzed using a one-way analysis of variance (ANOVA) with Kruskal-Wallis test and P values of < 0.05.

RESULTS AND DISCUSSION

Evaluation of granule blend

The granule series produced for the experimental batches (Shimshin-1 - Shimshin-5)

were satisfactory. When the granules flow from the hopper, capping, holing, and sticking was not remarked. The results are shown in Table 2.

In Table 2, the all of batch granules were the same like brown in color, with a specific smell, and salty and bitter. The average of the particle size was 0.32mm to 0.43mm. The moisture of all batch granules did not significantly change and about were 11-12%.

Flow properties of the powder are good and fair (aid not needed) when Carr's index ranges from 11-20% and Hausner's Ratio is 1.12-1.25[16]. All granules were defined to have good flowability from values of the Carr's index and Hausner's Ratio noticed for granules of all batches.

Physical properties of tablets

The tablets were pressed each of 400mg weight on a 17 punch-tablet machine. During the manufacturing, any defects such as capping, lamination, and chipping were not obtained. The results of the physical property analysis of tablets were illustrates in Table 3.

All of the produced tablet forms were tested to evaluate quality control parameters including size, shape, color, and appearance. The prepared tablets were uniform, smooth surface, convex.

The maximum weight variation of the tablets was -4.79 and +4.6%, which falls within the allowable weight variation range of ±5%, as a consequence all tablets satisfied the weight variation analysis. The changes in the conformation of tablets under the action of storing, transferring, packaging, and handling previous utilization hinge upon tablet hardness. Hardness for tablets of Shimshin-1 – Shimshin-3 formulations was between 0.9 and 1.14, which satisfied the range of 0.6 to 1.2[15], but Shimshin-4 and Shimshin-5 formulation were found to be too hard. Friability value for tablets of Shimshin-3 – Shimshin-5 formulations were in the range 99.5 to 99.79%, which satisfied the limit of more than 97%. But Shimshin-1 and Shimshin-2 tablets did not meet the requirement. A non-coated tablet disintegrates within 15 minutes. The disintegration test showed that the results of all batches were determined to range from 8 minutes to 13 minutes and 30 seconds. Diameter and thickness of the tablet were determined by SATA Digital caliper (0-150 mm) (APEX tool group, China) and reported that thicknesses ranged from 5.07mm to 5.20mm, but diameters were constantly around 9.1mm indicating fairly acceptable tablets.

Result of the involution of the uterus in rats

Reduction in uterus indexes by treatment Shimshin-6

The most significant indicator during pregnancy is the size of enlargement, weight of the uterus. We measured the weight of uteri at postpartum period day 5 (Figure 1A).

According to the results the uterus indexes of the model and Shimshin-6 groups were higher than the control group, and Shimshin-6 groups were than lower the model group uterus indexes.

Evaluation of Shimshin-6 on serum Estrogen levels and progesterone on postpartum rats

We studied the estrogen and progesterone levels in serum of postpartum animals. According to the results estrogen level was lower in the ShT 90 and 180mg/kg groups than in the model group (Figure 1B) and progesterone level was no difference in the all experimental groups (Figure 1C). Although the estrogen and progesterone hormone concentrations showed different, the

Table 1. Ingredients of the tablet formulations

Ingredients	Formulation				
	Shimshin-1	Shimshin-2	Shimshin-3	Shimshin-4	Shimshin-5
1:1 liquid extract of the *R.undulatum* L.	93.75ml	93.75ml	93.75ml	93.75ml	93.75ml
Mixture of powdered herb	300g	300g	300g	300g	300g
Cane sugar	-	3.9	6.45	13.05	26.25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3

levels of both trended to return to the non-pregnant period.

The *R.undulatum* chemical constituents (aloe emodin, rhapontigenin, and chrysophanol 1-*O*-â-d-glucopyranoside) showed estrogen-like activity in the concentration range of 10 to 50ìM, by increasing the proliferation of human ER-positive MCF-7 cells[20].

The serum level of TGF-â1 by treated Shimshin-6 group was higher than the model group (Figure 2A).

However, the trends for TGF-â3 were higher than control group (Figure 4B) and after Shimshin-6 treatment groups tendency an increase on TGF-â3 level observed in the postpartum rats.

Ameliorations and histological changes in the postpartum uterine horn by Shimshin-6 treatment

The non-pregnant control group showed a normal structure of the uterine endometrium and myometrium. The endometrium was lining the columnar epithelium, and there were frequent mitoses of epithelial cells, and the laminar propria had tubular glands surrounded by stromal cells. Smooth muscle fibers, arranged both circulatory and longitudinally, and a dark purple nucleus were observed in the muscularis layer of the uterus.

There were no significant changes observed in the epithelium or tubular gland of the laminar propria of the endometrium in the control group of rats. Due to the smooth muscle cells being enlarged after delivery and hypertrophied, various-sized, pale-colored myocytes can be seen. Inflammatory cell infiltration and slight edema were observed interstitially in the muscle fibers. Slight hemorrhages were seen in the muscularis.

The Shimshin-6 tablet 90mg/kg group had mild inflammatory cell infiltration that was detected interstitially in the smooth muscle fiber of the uterine. Smooth muscle cells being enlarged or

Table 2. Micromeritic parameters of polyherbal granules

No.	Parameters	Shimshin-1	Shimshin-2	Shimshin-3	Shimshin-4	Shimshin-5
1	Color	Brown	Brown	Brown	Brown	Brown
2	Smell	Specific	Specific	Specific	Specific	Specific
3	Taste	Slightly bitter and salty	Slightly bitter and salty	Slightly bitter and salty	Slightly bitter and salty	Slightly bitter and salty
4	Average particle size, mm	0.32	0.33	0.34	0.35	0.43
5	Bulk density	0.48±0.02	0.5±0.03	0.53±0.02	0.55±0.03	0.52±0.2
6	Tapped density	0.561±0.03	0.6±0.02	0.64±0.03	0.625±0.03	0.62±0.01
7	Carr‘s index, %	14.6±1.2	15.5±1.5	17.02±1.8	11.2±1.3	14.8±1.4
8	Hausner’s Ratio	1.168±0.1	1.2±0.13	1.2±0.17	1.12±0.14	1.173±0.11
9	Moisture, %	11.35±0.2	11.3±0.1	11.2±0.1	12.01±0.1	11.81±0.2

Table 3. Physical properties of tablets

No.	Parameter	Shimshin-1	Shimshin-2	Shimshin-3	Shimshin-4	Shimshin-5
1	Shape	Round, Biconvex	Round, Biconvex	Round, Biconvex	Round, Biconvex	Round, Biconvex
2	Average weight (mg)	391±10	396±8	395±6	389±8	405±5
3	Weight variation (%)	+3.8%, -4.79	-3.2%, +2.6%	-4.2%,+2.2%	-3.72%, +3.2%	-2.52%, +4.6%
4	Thickness, mm	5.11±0.09	5.19±0.03	5.1±0.02	5.07±0.04	5.2±0.1
5	Hardness	0.9±0.4	0.95±0.3	1.14±0.08	1.32±0.24	1.34±0.59
6	Friability (%)	93.39±2.8	95.8±1.3	99.76±0.07	99.79±0.06	99.5±0.2
7	Disintegration time, min	8.3±0.93	10.3±0.5	12.5±0.5	13±0.33	13.5±0.5
8	Content uniformity, mg	0.175±0.02	0.17±0.04	0.18±0.03	0.185±0.04	0.177±0.02

hypertrophied, various-sized, deep purple-colored myocytes can be seen. In the muscularis. Slight hemorrhages were seen in the uterine wall, and a few more of blood vessels were observed compared to the control group.

There were no significant histopathological changes observed in the epithelium or tubular gland of the laminar propria of the endometrium in the Shimshin-6 tablet 180mg/kg group of rats. Due to the smooth muscle cells being enlarged after delivery and hypertrophied, various-sized, pale to deep purple-colored myocytes can be seen. Inflammatory cell infiltration and slight edema were observed interstitially in the muscle fibers. Slight hemorrhages were seen in the muscularis.

The Shimshin-6 decoction (*tang*) 162mg/kg group had focal inflammatory cell infiltration that was observed in the endometrium, and

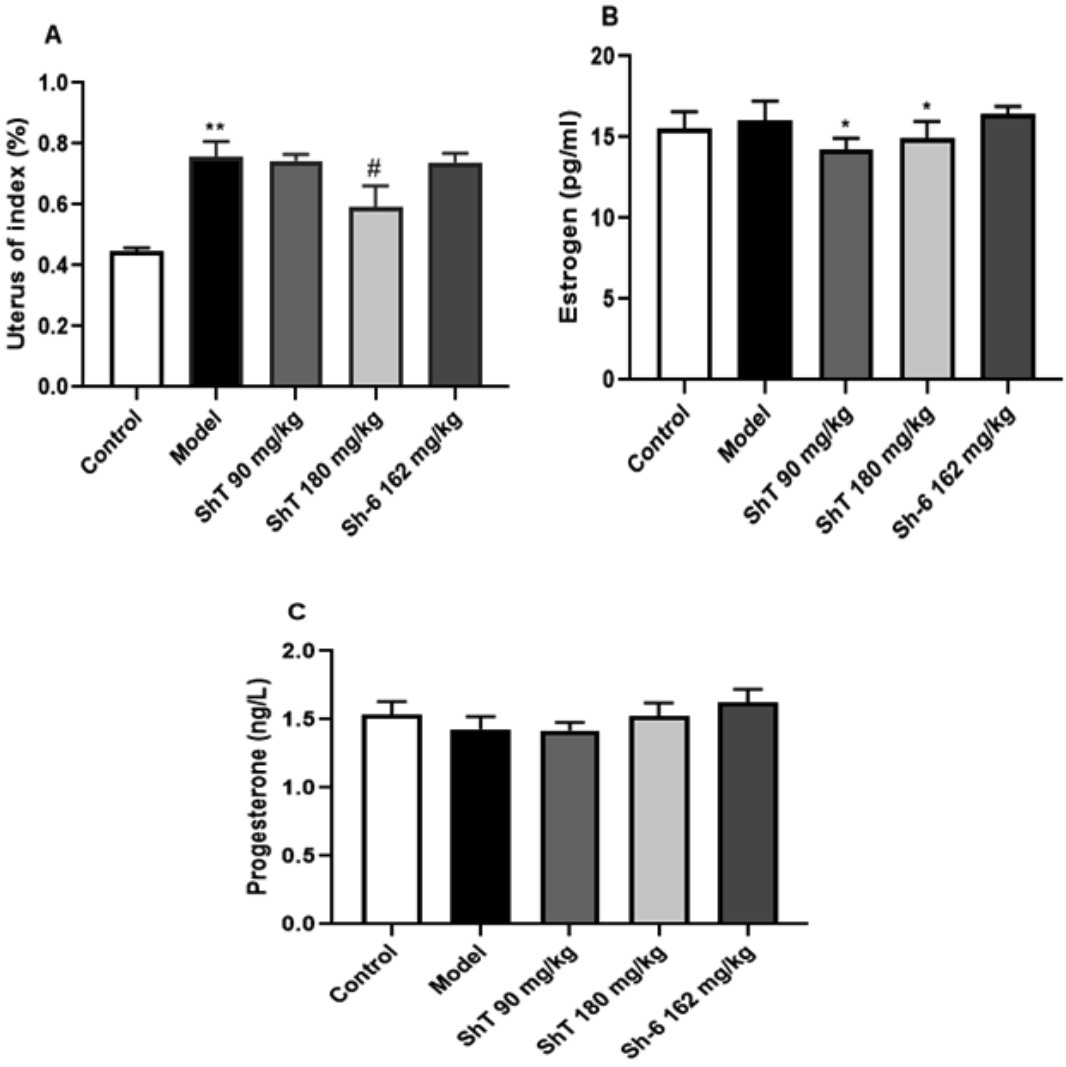

Fig. 1. Modulation of the uterus index and levels of Estrogen and Progesterone by Shimshin-6 treatment. A) Uterus index on postpartum Day 5. B) Estrogen level in serum on postpartum Day 5. C) Progesterone concentration in serum on postpartum Day 5. Control, non-pregnant rats, Model, postpartum rats; experimental group was included Sh-6 162mg/kg (n=7), ShT 180mg/kg (n=7), ShT 90mg/kg (n=7). Data was expressed as mean ±SD (n=7 per group). *p = 0.05, **p=0.01 compared with the control group; #p=0.05 compared with the model group.

Table 4. Histopathological evaluation of postnatal uterine regeneration

Experimental groups	Thickness of the uterine wall /micrometer/ Muscularis	Endometrium	Total thickness	Inflammatory cells	Hemorrhage
Normal	231.6±12	393±31.0	1173.0±98.5	-	+
Control	935.3±53***	400.2±19	1229.2±108*	+++	+++
ShT 90mg/kg	284.5±14$^{\#\#\#}$	370.0±27$^{\#}$	946.6±97.0$^{\#\#}$	+	++
ShT 180mg/kg	298.5±11$^{\#\#\#}$	398.9±21	1071.5±117.1$^{\#}$	++	++
Sh-6 162mg/kg	286±9.5$^{\#\#\#}$	443.8±54$^{\#}$	1014.5±78.9$^{\#}$	+	++

Compared to control***p=0,001, compared to experimental $^{\#}$p=0.05,$^{\#\#}$p=0.001
oneway-ANOVA, nonparametric Kruskal-Wallis test

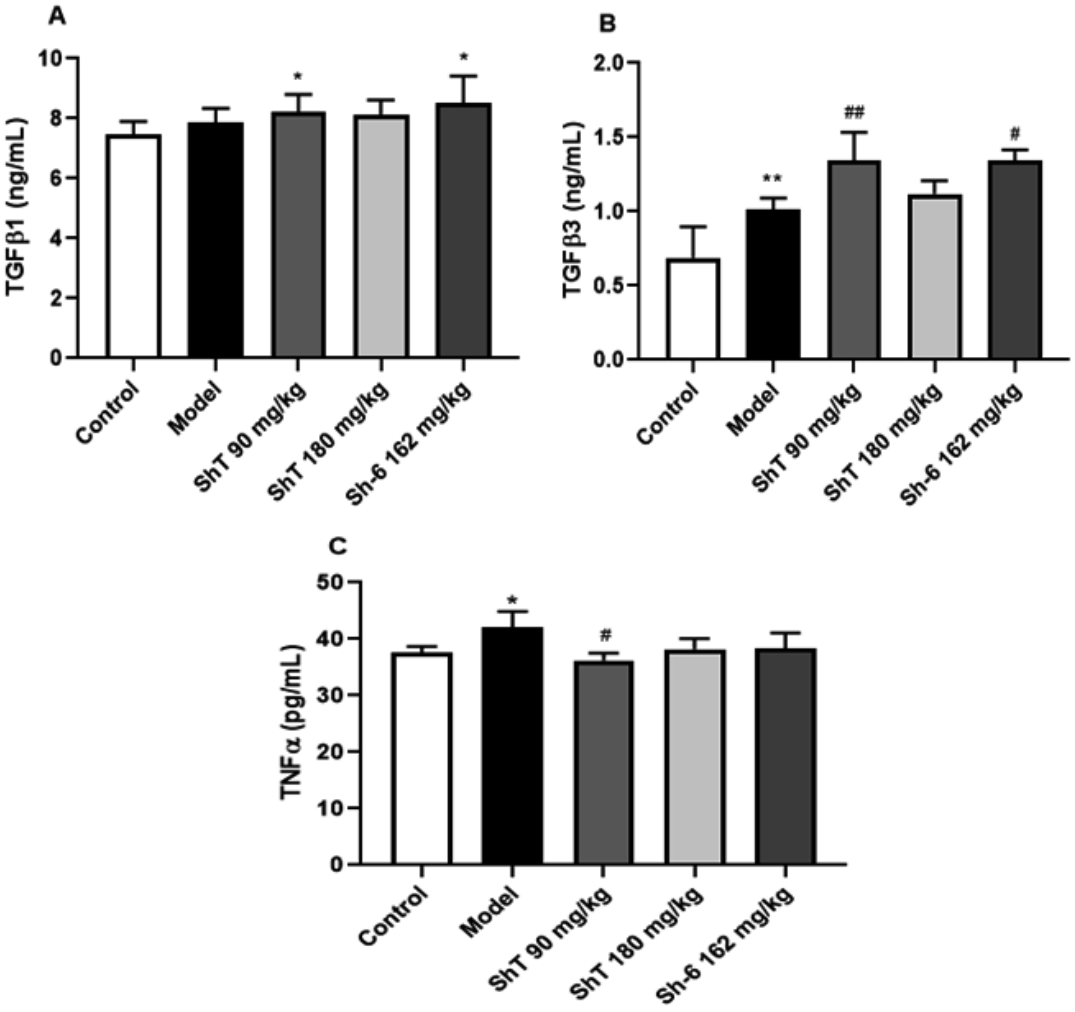

Fig. 2. Modulation of the levels of transforming growth factors and tumor necrosis factor by Shimshin-6 treatment. A, B) TGFâ1 and TGFâ3 on postpartum Day 5. C) TNFá concentration in serum on postpartum Day 5. Control, non-pregnant rats, Model, postpartum rats; experimental group was included Sh-6 162mg/kg (n=7), ShT 180mg/kg (n=7), ShT 90mg/kg (n=7). Data was expressed as mean±SD (n=7 per group). *p = 0.05, **p=0.01 compared with the control group; ##p=0.05 compared with the model group.

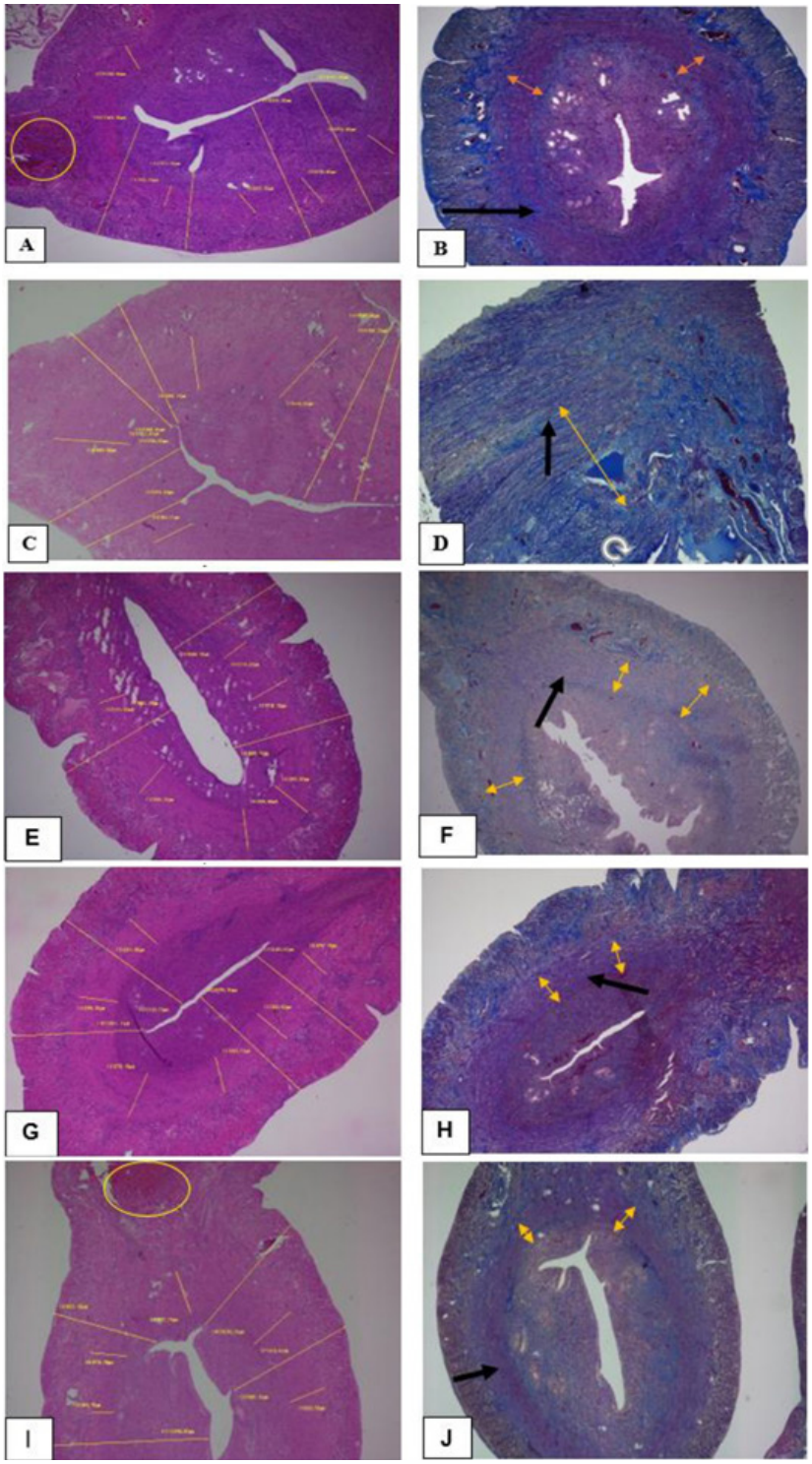

Fig. 3. Histopathological changes in the uterine on postpartum rats following treatment with Shimshin-6 (A, C, E, G, I) H&Eõ40 and (B, D, F, H, J), Trichrome Masson õ40 staining on the uterus on 5th day postpartum. A, B) Control, non-pregnant rats, C, D) Model, postpartum rats; E, F) Treatment by ShT 90mg/kg, G, H) Treatment by ShT 180mg/kg, I, J) Treatment by Sh-6 162mg/kg. Data was assessed as mean±SD (n=3 per group).

interstitially mild infiltration of inflammatory cells was seen in the smooth muscle fiber of the uterine. Smooth muscle cells are enlarged or hypertrophied; various-sized, deep purple-colored myocytes can be seen in the muscularis. Slight hemorrhages were seen in the uterine wall.

According to the histopathological results, inflammatory cell infiltration and hemorrhagic changes were observed in the uterine wall; however, no structural changes were found. These findings indicated the stage of involution in the postnatal period. The Shimshin-6 tablet 90mg/kg and Shimshin-6 decoction 162mg/kg groups had significantly less inflammatory and hemorrhagic changes and hypertrophy of the muscular fiber myocytes compared to the other groups.

Traditional Tibetan therapies have previously applied Zhi Byed 11 for the prevention and treatment of postpartum hemorrhage for above 700 years. This traditional prescription is used to raise contractions of the uterus, quicken delivery, deliver the placenta, and treat other problems of pregnancy such as hypertension and infection[20]. Compositions of the Zhi Byed 11 are similarly Shimshin-6 prescription, such as *R.Palmatum* L, *Trona*, *S.ammoniacum*, *Z.offficinale* Rose, *H.rhamnoides* L.

Postpartum involution specifically refers to the process through which the uterus returns to its pre-pregnancy state after childbirth. This involves the contraction of the uterine muscles and the shedding of excess tissue. It's a natural and important aspect of the postpartum recovery period[22,23]. Shimshin-6 a well-known Traditional Mongolian Medicine, has been widely used during the postpartum period in Mongolian women. This treatment is accelerating the involution process for maybe a strategy to avoid postpartum complications.

In the present study, the beneficial effects Shimshin-6 tablet, which is derived from Shimshin-6 decoction, Mongolian prescription used during the postpartum period in rats, were investigated on involution process.

As demonstrated in the present study, when compared with the model group, Shimshin-6 treatment was shown to markedly decrease the index of uterus, reduce the level of estrogen and not difference in concentration of progesterone.

We found that Shimshin-6 decreased TNFá and regulated growth factors in postpartum rats.

Shimshin-6-regulated postpartum uterine involution as shown by histological investigation. Our results showed inflammatory cell infiltration and hemorrhagic changes were observed in the uterine wall; however, no structural changes were found. These findings indicated the stage of involution in the postnatal period. The Shimshin-6 tablet 90mg/kg and Shimshin-6 decoction 162mg/kg groups had significantly less inflammatory and hemorrhagic changes and hypertrophy of the muscular fiber myocytes compared to the other groups.

Dahae L et al. have studied the estrogenic and anti-tumor effects of *R.undulatum* extracts on ER-positive MCF-7 and ER-negative MDA MB 231 breast carcinoma cell lines. In this study, *R.undulatum* extracts and some compounds that were isolated from the plant grew the proliferation of MCF-7 cells in a dose-related manner[20].

CONCLUSION

The best formulation was Shimshin-3 tablet that used 5% cane sugar as a binder and the formulation and evaluation of herbal tablets were satisfactory. These results, grounded on investigational considerations at the levels of hormones and cytokines, proved that Shimshin-6 can improve the involution of the uterus, and indicated the possible application of Shimshin-6 in postpartum care.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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REFERENCES

1. Center for Health Development, World Health Organization (WHO). Health Indicators 2020. Ulaanbaatar: Center for health development, 2020; 51 p.
2. Ferdousi B, Jolly B, Thomas B, Cherrie E, Claudia H, Andre L et al. FIGO and the International Confederation of Midwives endorse WHO guidelines on prevention and treatment of postpartum hemorrhage. Int. J. Gynaecol. Obstet., 2022; 158(1): 6–10.
3. Nelson R J, An Introduction to Behavioral Endocrinology, 3rd edition. Sunderlans Mass: Sinauer Associates; 2005.
4. Bensky, D., Clavey, S., & Stoger, E. (2004). Chinese Herbal Medicine: Materia Medica 3rd ed. Eastland Press.
5. Jambalchoijidanzanperenlei. "Manag Rinchin Junai". Traditional Medical Source Book. Huhhot: "Inner Mongolian medical treasurers" printing house, 1978.
6. Bao Y, Daariimaa K, Wang H, Wirginia K, Davaadagva D. Metabolomics Study of Amenorrhea After the Administration of Shimshin-6 Traditional Prescription in Rats Using the Ultra High-Performance Liquid Chromatography Coupled with Time of Flight Mass Spectrometry. Cent. Asian. J. Med. Sci., 2021; 7(1): 71-80.
7. Marina S. Kaempferia galanga L. Zingiberaceae. Ethnobotany of the Mountain Regions of Southeast Asia, 2021; 579-585.
8. Hisashi M, Supinya T, Toshio M, and Masayuki Y. Anti-allergic activity of stilbenes from Korean rhubarb (Rheum undulatum L.): structure requirements for inhibition of antigen-induced degranulation and their effects on the release of TNF-á and IL-4 in RBL-2H3 cells. Bioorg. Med. Chem., 2004; 12(18): 4871-4876.
9. Ko S. K, Lee S. M and Whang W. K. Anti-platelet aggregation activity of stilbene derivatives from Rheum undulatum. Arch. Pharm. Res., 1999; 22: 401–403.
10. Sharma H, Chandola H M, Singh G, and Basisht G. Utilization of Ayurveda in health care: An approach for prevention, health promotion, and treatment of disease. Part 2 – Ayurveda in primary health care. The Journal of Alternative and Complementary Medicine. 2012; 18(1): 63-74.
11. Ye M, Han J, Chen H, Zheng J and Guo D. Analysis of phenolic compounds in Rhubarbs using liquid chromatography coupled with electrospray ionization mass spectrometry. J. Am. Soc. Mass. Spectrom., 2007; 18: 82–91.
12. Si-Yu W, Hui Z, Hong-Tao X, Xiao-Dong H, Yun-Shan W, Fang-Fang X, et al. Kaempferia galanga L.: Progresses in Phytochemistry, Pharmacology, Toxicology and Ethnomedicinal Uses. Front. Pharmacol., 2021; 12: 675350.
13. Hirschhorn H. H. Botanical Remedies of the Former Dutch East Indies (Indonesia). Part II: Dicotyledones up to and Including Leguminosae. J. Ethnopharmacol., 1983; 8(1): 65-96.
14. Hee J. K, Seon J. P, Yun N. K, Guijae Y, Eun J. J and Seung H. K. Optimization of extraction conditions for enhancing estrogenic activity of Rheum undulatum Linné using response surface methodology. Sep. Sci. Technol., 2020; 55(11): 2080-2089.
15. Sharma V, Rani D, Kumar A and Chaurasia H. Formulation and evaluation of herbal tablet containing Terminalia Chebula extract. Lett. Appl. NanoBioScience., 2019; 8(4): 692-697.
16. Amrita M and Arun K. M. Development of herbal tablet formulation: Systematic approach. Altern. Integr. Med., 2019; 8:1.
17. Mongolian national pharmacopoeia (MNP). General requirement for tablets. First edition. Ulaanbaatar: Soyombo print; 2011. 25 p.
18. Aurapa S and Wandee G. Extraction method for high content of anthraquinones from cassia fistula pods. J. Health. Res., 2008; 22(4): 167-172.
19. Zheng Z. H, Han Y, You S. Y, Chen Z and Zheng X. D. Improvement in post-partum uterine involution in rats treated with Apios americana. J. Zhejiang. Univ. Sci. B., 2019; 20(7): 576-587.
20. Dahae L, Seon J. P, Sungyoul C, Seung H. K and Ki S. K. In Vitro Estrogenic and Breast Cancer Inhibitory Activities of Chemical Constituents Isolated from Rheum undulatum L. Molecules., 2018; 23(5): 1215.
21. Coelius R. L, Stenson A, Morris J. L, Cuomu M, Tudor C and Miller S. The tibetan uterotonic zhi byed 11: mechanisms of action, efficacy, and historical use for postpartum hemorrhage. Evid. Based. Complement. Alternat. Med., 2012; 794164.
22. Liu H, Ma W, Liu Q. I, Wang F, Cao L, Li T, et al. Effect of Wujia Shenghua capsule on uterine bleeding following medically-induced incomplete abortion in rats during early pregnancy. Exp. Ther. Med., 2015; 10(2): 635-640.
23. Tiantian Z, Guowen L. I, Zhifeng C, Jie L. I, Lijun Y. U, Yuan G, et al. Efficacy of Qiancao (Radix Rubiae Cordifoliae) and Haipiaoxiao (Endoconcha Sepiellae), a traditional Chinese herb pair, on abnormal uterine bleeding in rats with incomplete abortion. J. Tradit. Chin. Med., 2022; 42(5): 758-763.