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Original article

Effects of AiQingHua oil on microcirculation disturbance and alopecia mice model

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ABSTRACT

Purpose: Study the effect of AiQingHua (AQH) oil on auricle microcirculation disorder mice caused by epinephrine and the effect of promote hair regeneration in mice with pathological alopecia caused by testosterone. Methods: Model of auricle microcirculation disorder in mice induced by intravenous injection of epinephrine hydrochloride (10 mg/kg), observed the auricle capillary vein and arteriole diameter, blood flow velocity and the amount of capillary opening before and 2 min after injection. The model of alopecia was established in mice induced by testosterone, the mold-making process was also externally applied to the drug for 21 consecutive days. On the day when the hair began to grow, the hair growth status was graded every four days. The serum levels of testosterone (T) and estradiol (E2) were measured on 21 d. The alopecia part of the skin was taken and the pathological changes were observed. Results: Compared with the blank group, minoxidil tincture group and the large and small dosage of AQH oil group can expand the diameter of auricle capillary vein and arteriole, increase the number of capillary opening and improve blood flow of mice with auricle microcirculation disorder. All mice in each group had hair growth from the 8th day of administration. Hair growth score in each administration group was superior to the model group on the 12th day, the 16th day and the 20th day. Each administration group can reduce the serum T and E2 level of mice with hair loss to different degrees, and reduce the ratio of T/E2, and improve the number of hair follicles, sebaceous glands and sweat glands in hair loss area. Conclusion: AQH oil can improve the microcirculation of mice and promote hair regeneration in mice with hair loss.

Alopecia (alopecia) is a skin disease characterized by reduced hair. It has many kinds such as congenital alopecia, alopecia and androgenic alopecia. Androgenic alopecia (AGA) is the most common type. According to the epidemiological survey, the prevalence rate of androgenic alopecia in China is 21.3% for men and 6.0% for women (Wang et al., 2010). It is generally believed that alopecia is associated with heredity, endocrine function, infection focus, autoimmune function, mental factors and nutritional status (Jin and Zhang, 2017; Deepika et al., 2018), but the increase of androgen level is the main cause of AGA. Due to its prevalence in teenagers, it affects the mental health of patients, easily leads to the occurrence of other diseases, and even leads to the total shedding of hair (Strazzulla et al., 2018). Therefore, the study of hair loss drugs has always been the direction of Chinese and western medicine. The causes of hair loss are complex and diverse, and the pathologic mechanism is still unclear. However, it is difficult to obtain related tissues such as the scalp in clinical studies. Therefore, animal models are often used to study the mechanism and treatment of hair loss. Androgenic depilation model, similar to the pathogenesis of clinical AGA, is suitable for the study of the pathological mechanism of hair loss and the confirmation of the efficacy (Shun et al., 2017).

HuangDi NeiJing is the earliest record of alopecia, which is called hair plucking and hair falling. Chinese medicine believes that the nutrition of the hair is derived from blood, blood gas enough is conducive to the hair dark and shiny; Liver blood deficiency and kidney qi deficiency make hair pale and easy to fall off, there is theory of "hair for the rest of blood". If the blood flow is not smooth and blocked in meridian, it is difficult to cultivate hair and skin. Therefore, the hair roots are empty and flake off (Zhan et al., 2014). Traditional Chinese medicine believes that the AGA

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pathogenesis is closely related to liver, spleen and kidney; The pressure of social survival and the pressure of learning and working lead to dark loss of Yin and blood and loss of hair; Youthful vigor, blood heat injury Yin, hair losing embellish shed; Disordered diet leads to abnormal spleen and stomach transport, or dwelling in wetland for a long time, fumigation with dampness, poor blood and qi, resulting in sticky and greasy hair and falling off (Zhang et al., 2018). Therefore, traditional Chinese medicine usually classifies the disease into three syndromes: liver and kidney deficiency, damp-heat infiltration and blood hot wind dryness, which are used to guide clinical syndrome differentiation and treatment (Wei, 2015). AGA disease is located in the skin, is suitable for external use of drugs. In consideration of the existence of skin barrier, this experiment used AQH oil for external use to observe its effect on mice with auricle microcirculation disorder and the effect of hair-grow in alopecia mice model induced by rosin and paraffin combined with testosterone.

1. Experimental animals

KM mice, male, 18–22 g, SPF, 40 subjects, certificate of quality of experimental animals: No. 37009200013723; KM mice, male, 20–24 g, SPF, 60 subjects, certificate of quality of experimental animals: No. 37009200011653; Provided by shandong experimental animal center, license number: SYXK (Lu) 20140007; Laboratory license no.: SYXK (Yu) 2015–0005.

2. Experimental reagents and instruments

2.1. Experimental reagents

Adrenalin hydrochloride injection, produced by sui cheng pharmaceutical Co., Ltd., batch no. 1707252; Cedar oil, manufactured by Shanghai yiyang instrument Co., Ltd., batch no. 20170403; Rosin, Yuanye biological production, batch number C11A8Z33639; Paraffin, Shanghai hualing rehabilitation machinery factory, batch no. 160323; Testosterone, Solarbio, batch no. 316B031; Minoxidil tincture, produced by xiamen meishang pharmaceutical Co., Ltd., batch no. 170727; T and E2 ELISA kit, batch no. 20180601SR; AQH oil is composed of mugwort oil, holly oil and rose oil and so on, all were provided by Henan university of traditional Chinese medicine.

2.2. Experimental instruments

JM 1000 electronic scale, yuyao Ming weighing and checking equipment Co. Ltd.; AL204 electronic balance, mettler Toledo instrument (Shanghai) Co., Ltd.; Image analysis system bi-2000, chengdu taimeng scientific instrument Co., Ltd.; Type 680 Bio-rad, USA; KDC-160HR high speed freezing centrifuge, keda innovation co.

2.3. Grouping and modeling

2.3.1. Effects of AQH oil on auricle microcirculation disorder induced by adrenaline in mice

Forty male mice with a body weight of 18–22 g were randomly divided into 4 groups, with 10 mice in each group. The patients were treated with minoxidil tincture (0.02 mL), AQH oil (0.02 mL each in the morning and afternoon) and small doses (0.02 mL in the morning), respectively, and the control group was treated with normal saline of the same volume. Give the medicine once a day. For 5 consecutive days, and the test was started when the drug was administered for 1 h (fasting water for 12 h) on the 5th day (Wang and Miao, 2013; Liu et al., 2018b).

2.3.2. Effects of AQH oil on alopecia mice model induced by testosterone

The mice were adapted to feeding for 3 days. Rosin and paraffin were mixed after melting by 1:1 heating and soaked in 2 cm × 2 cm gauze. After cooling to the appropriate temperature, they were taken out and covered in the back of the back of anesthetized mice. After cooling and solidification, from the tail to remove the gauze and remove the hair, inducing the hair follicles of mice to enter the growing period from the static period. On the second day of depilation, 50 mice with clean hair removal and no skin damage were selected and randomly divided into blank group, model group, minoxidil tincture group, large (0.2 mL each day) and small (0.1 mL each day) dosage of AQH oil group, 10 mice in each group. Mice in addition to the blank group were treated with 0.1% testosterone (prepared by 50% ethanol) 0.2 mL every day, established the pathological hair loss model. The blank group was treated with 50% ethanol. After 30 min of testosterone application, the drug was applied in groups, sterile water was applied in the blank group and the model group, once a day for 21 consecutive days (Murata et al., 2012; Zhang et al., 2016).

3. Test indicators

3.1. Effects of AQH oil on auricle microcirculation disorder mice induced by adrenaline

After intraperitoneal injection of 5% chloral hydrate (0.2 mL/10 g), the abdomen of the anesthetized mice was upward and fixed on the observation table. Adjust the height of the auricle so that the auricle is flat on the auricle. Add a little cedar to the surface of the auricle and place the observation table on the microscope stage. The auricle arteriole (A), auricle capillary vein (V) diameter, blood flow velocity and capillary opening in each group were observed by bz-2000 microcirculation microscope and microcirculation microanalysis system. Then, adrenalin hydrochloride injection (Adr, 10 mg/kg) was injected into the tail vein, and the auricle microcirculation of each group was observed immediately after 2 min of injection. The control group was only injected with normal saline of the same volume, and the observation was the same.

3.2. Effects of AQH oil on alopecia mice induced by testosterone

3.2.1. Hair growth observation and scoring

On the day when the hair began to grow, the hair growth status was graded every four days. Scoring criteria: 0 points for glabrous growth; 1 points for 20% growth; 2 points for 20%–40%growth; 3 points for 40%–60% growth; 4 points for 60%–80% growth; 5 points for 80%–100% growth (Liu et al., 2014).

3.2.2. Determination of hormone content in blood

The mice were sacrificed 1 h after the drug was applied on the 21st day, and the blood was collected, and the serum was centrifuged at 3000 r/min at room temperature for 10 min. The contents of testosterone (testosterone, T) and estradiol (estradiol, E2) in blood were determined according to the instructions of the kit, and the value of T/E2 was calculated.

3.2.3. Histological observation

On the 21st day, 1 cm × 1 cm of skin tissue from the depilated area of mice was taken and attached to the hard plastic plate to prevent it from curling and contracting. 4% formalin was fixed and prepared for routine HE pathological section, which was observed by 100 times larger under the microscope.

4. Statistical methods

SPSS19.0 statistical software was used to statistically process the experimental results. The measurement data are expressed as mean plus or minus standard deviation ($\bar{X}$±s). Single factor analysis of variance was used for inter-group comparison. The homogeneity of variance was tested by LSD method, and the heterogeneity of variance was tested by Games-Howell method. The hierarchical data is validated with Ridit.

5. Experimental results

5.1. Effects of AQH oil on auricle microcirculation disorder mice induced by adrenaline

5.1.1. Effect of AQH oil on the diameter of auricle capillary vein of microcirculation disorder mice induced by adrenaline

It was known from Table 1 that there was no significant difference in auricle capillary vein diameter of each group before injection of epinephrine. After injection of epinephrine, the auricle capillary vein diameter of each group was significantly reduced. However, compared with the blank group, minoxidil tincture group and large, small dosage AQH oil group could significantly expand the animal auricle capillary vein diameter ($P < 0.01$).

5.1.2. Effect of AQH oil on the diameter of auricle arteriole of microcirculation disorder mice induced by adrenaline

As shown in Table 2, there was no significant difference in auricle arteriole diameter in each group before administration of epinephrine. After the injection of epinephrine, the diameter of the auricle arteriole decreased significantly in each group. However, compared with the blank group, the diameter of animal auricle arteriole was significantly enlarged in minoxidil tincture group, and large, small dosage AQH oil group ($P < 0.01$).

5.1.3. Effect of AQH oil on the number of capillary opening of microcirculation disorder mice induced by adrenaline

According to Table 3, there was no significant difference in the number of auricle capillary opening before injection of epinephrine. After injection of epinephrine, the number of auricle capillary opening in each group decreased significantly. However, compared with the blank group, the minoxidil tincture group, the AQH oil large and small dose group could significantly increase the number of auricle capillary opening ($P < 0.01$).

5.1.4. Effect of AQH oil on blood flow of microcirculation disorder mice induced by adrenaline

According to Table 4, after the injection of epinephrine, the auricle blood flow in each group changed to different degrees. However, compared with the blank group, minoxidil tincture group, the AQH oil large and small dose group all could improve the animal auricle microcirculation blood flow. However, the effect of minoxidil tincture and large dose AQH oil were superior to low doses AQH oil.

5.2. Effects of AQH oil on alopecia mice induced by testosterone

5.2.1. Effect of AQH oil on hair regeneration score of alopecia mice induced by testosterone

As shown in Table 5: On the 12th day of modeling, the hair regeneration score of the model group was obviously lower than that of the blank group. Hair regeneration scores were obviously higher in the minoxidil tincture group than in the model group ($P < 0.05$). On the 16th and 20th day of modeling, hair regeneration score of the model group was significantly lower than that of the blank group ($P < 0.01$). Hair regeneration scores were significantly higher in the minoxidil tincture group and large dose AQH oil group ($P < 0.01$), and obviously higher in small dose AQH oil group than in the model group ($P < 0.05$).

5.2.2. Effects of AQH oil on serum hormone levels of alopecia mice induced by testosterone

As shown in Table 6, compared with the blank group, T and T/E2 in the model group increased significantly and E2 decreased significantly ($P < 0.01$). Compared with the model group, T and T/E2 were significantly decreased and E2 was significantly increased in the minoxidil tincture group and large dose AQH oil group ($P < 0.01$). The T and T/E2 were obviously decreased ($P < 0.05$), and E2 was increased, but there were no statistically significant in small dose AQH oil group.Table 7.

5.2.3. Effects of AQH oil on skin pathology of alopecia mice induced by testosterone

As can be seen from Fig. 1: In the blank group, the skin epidermis was covered with 2–3 layers of flat epithelium with a thickness of 18–30 um. The length of hair is 500–800 um, and the diameter of hair follicle is 50–100 um. The number of hair follicles, sebaceous glands and sweat glands were normal. In the model group, the skin epidermis was close to normal, hair follicles were atrophied and the number of sebaceous glands and sweat glands were decreased. In minoxidil tincture group, the epidermis was normal, the number of hair follicles was moderate, and the volume of hair follicles decreased. Hair bulb atrophy, the length of the hair 300–500 um, slightly short. In large dosage of AQH oil group, the thickness of epidermis and dermis is normal, the number of hair follicles and hairs is slightly reduced, the bulb shrinks, and some hair follicles disappear. In the small dose group of AQH oil, the thickness of epidermis and dermis is close to normal, the thickness of dermis is 500–800 um, the number of hair follicles and hairs is reduced, the bulb shrinks, and some hair follicles disappear.

It is known from Table 3 that, compared with the blank group, the skin tissues of the model group showed significant changes such as hair follicle reduction and hair bulb disappearance ($P < 0.01$). Compared with the model group, each administration group can also increase the number of hair follicles and the volume of the bulb to different degrees, thus improving the skin lesions of mice with alopecia ($P < 0.01$ or $P < 0.05$).

Table 1
Effect of AQH oil on the diameter of auricle capillary vein of microcirculation disorder mice induced by adrenaline ($\bar{X}$ ± s, um).

Group	n	Dose (g/ml)	auricle capillary vein before adrenalin injection	auricle capillary vein after adrenalin injection
Blank group	10	–	20.82 ± 0.63	14.56 ± 0.64
Minoxidil tincture	10	0.04	21.35 ± 0.75	16.74 ± 0.79**
AQH oil	10	0.04	21.29 ± 0.49	16.78 ± 0.52**
AQH oil	10	0.02	21.07 ± 0.57	15.36 ± 0.54**

Note: * compared with the blank group, $P < 0.05$; **compared with the blank group, $P < 0.01$.

Table 2
Effect of AQH oil on the diameter of auricle arteriole of microcirculation disorder mice induced by adrenaline ($\bar{X} \pm s$, um).

Group	n	Dose (g/ml)	auricle arteriole before adrenalin injection	auricle arteriole before adrenalin injection
Blank group	10	–	9.53 ± 0.42	6.49 ± 0.28
minoxidil tincture	10	0.04	9.73 ± 0.40	7.64 ± 0.28**
AQH oil	10	0.04	9.68 ± 0.38	7.64 ± 0.27**
AQH oil	10	0.02	9.62 ± 0.36	7.07 ± 0.37**

Note: *compared with the blank group, $P < 0.05$; **compared with the blank group, $P < 0.01$.

Table 3
Effect of AQH oil on the number of capillary opening of microcirculation disorder mice induced by adrenaline.

Group	n	Dose (g/ml)	capillary opening before adrenalin injection	capillary opening after adrenalin injection
Blank group	10	–	7.0 ± 0.67	3.2 ± 0.42
Minoxidil tincture	10	0.04	7.5 ± 0.53	5.2 ± 0.79 **
AQH oil	10	0.04	7.5 ± 0.53	5.0 ± 0.82 **
AQH oil	10	0.02	7.2 ± 0.42	4.4 ± 0.84 **

Note: *compared with the blank group, $P < 0.05$; **compared with the blank group, $P < 0.01$.

Table 4
Effect of AQH oil on blood flow of microcirculation disorder mice induced by adrenaline.

Group	n	Dose (g/ml)	Line flow	Line grain flow	Grain flow	Pendulum flow
Blank group	10	–	0	3	7	0
Minoxidil tincture	10	0.04	1	7	2	0
AQH oil	10	0.04	2	7	1	0
AQH oil	10	0.02	1	6	3	0

Table 5
Effect of AQH oil on hair regeneration score of alopecia mice induced by testosterone.

Group	The 8th day	The 12th day	The 16th day	The 20th day
Blank group	0.6 ± 0.52	1.3 ± 0.95*	3.1 ± 0.74**	4.8 ± 0.42**
Model group	0.5 ± 0.53	0.9 ± 0.57	2 ± 0.67	3.7 ± 0.48
Minoxidil tincture	0.6 ± 0.52	1.7 ± 0.82*	3.1 ± 0.57**	4.6 ± 0.52**
Large AQH oil	0.6 ± 0.52	1.7 ± 0.82*	3 ± 0.67**	4.5 ± 0.53**
Small AQH oil	0.6 ± 0.52	1.2 ± 0.79	2.6 ± 0.52*	4.3 ± 0.48*

Note: *compared with the model group, $P < 0.05$; **compared with the model group, $P < 0.01$.

Table 6
Effects of AQH oil on serum hormone levels of alopecia mice induced by testosterone.

Group	T (pmol/mL)	E2 (pmol/mL)	T/E2
Blank group	28.36 ± 2.94**	11.06 ± 0.83**	2.57 ± 0.29**
Model group	38.44 ± 2.69	8.37 ± 0.94	4.64 ± 0.6
Minoxidil tincture	30.98 ± 1.93**	9.96 ± 1.03**	3.13 ± 0.35**
Large AQH oil	33.84 ± 4.09**	9.37 ± 0.48**	3.63 ± 0.56**
Small AQH oil	35.95 ± 1.81*	9.09 ± 1.01	4.00 ± 0.46*

Note: *compared with the model group, $P < 0.05$; **compared with the model group, $P < 0.01$.

6. Discussion

AGA also known as male type alopecia, is a common chronic disease in dermatology. Hair follicles undergo progressive miniaturization under the effect of androgens, leading to hair gradually reduced and thinning. The disorder of hair follicle blood supply may be one of the mechanisms of hair loss (Wu, 2018; Gerkowicz et al., 2013). The western medicine treatment of AGA mainly consists of systemic oral anti-androgen metabolites such as fenastamine and spironolactone, and local topical drugs to improve local microcirculation such as flurodil, minoxidil and hair

Table 7
Effects of AQH oil on skin pathology of alopecia mice induced by testosterone.

Group	Number	–	+	++	+++	*P* value
Blank group	10	10	0	0	0	<0.01
Model group	10	0	2	6	2	–
Minoxidil tincture	10	6	3	1	0	<0.01
Large AQH oil	10	2	6	2	0	<0.01
Small AQH oil	10	0	6	4	0	<0.05

(–) The thickness of epidermis and dermis is normal, the length of hair is normal, the volume of bulb and activity of cells are normal, and the appendages of skin are normal. (+) The thickness of epidermis and dermis is normal, the length of hair is slightly shorter, the volume of hair follicle and bulb is reduced, and the skin accessories are close to normal. (++)The thickness of epidermis and dermis is normal, the length of hair is shortened obviously, the volume of hair follicle and hair bulb shrinks and decreases, and the skin accessory decreases with the decrease of hair follicle. (+++) The length of hair is shortened, the hair follicle and hair bulb disappear, a little hair root remain, the skin accessory decreases with the decrease of hair follicle.

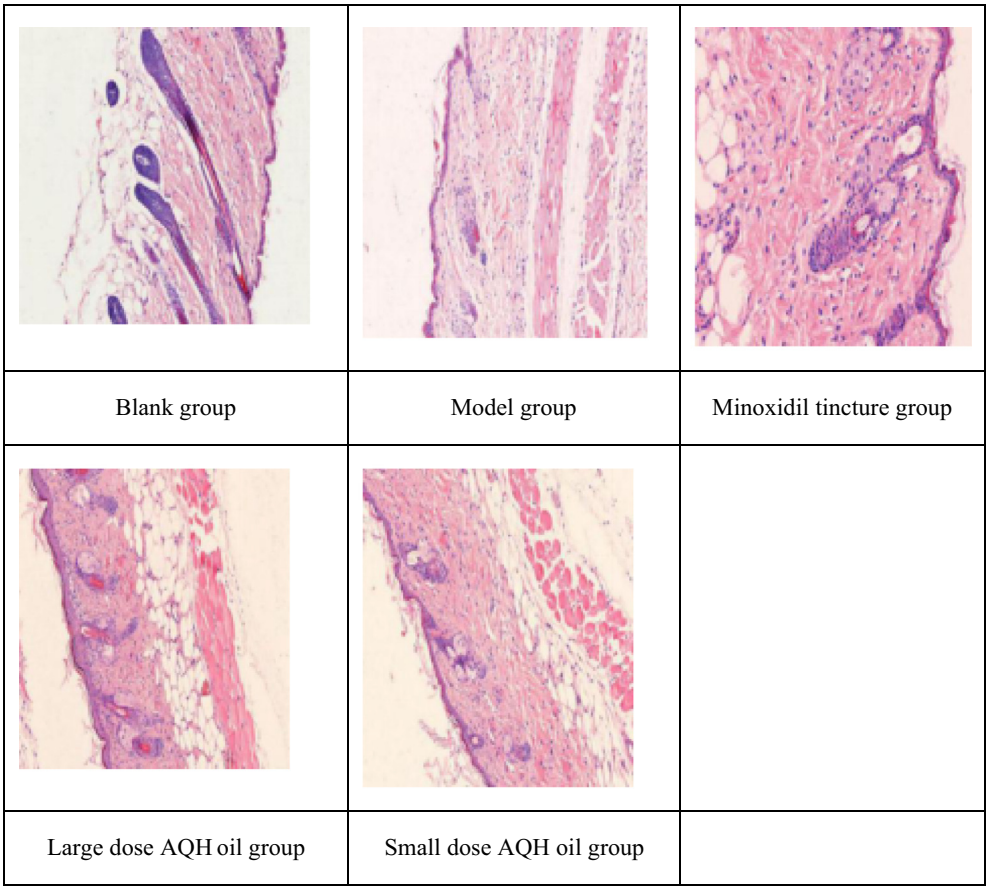

Fig. 1. Effects of AQH oil on skin pathology of alopecia mice induced by testosterone.

transplantation, etc. The curative effect is accurate, but the long-term oral drug has certain risk, and the patient compliance is poor; Hair transplantation has some problems such as surgical risk and continued shedding after operation (Liu et al., 2018a). In Chinese medicine, alopecia belongs to the category of "hair loss s" "mothiness and" "white dandruff wind". Both men and women can have diseases, but the young and middle-aged male patients are mostly seen. The growth and regeneration of hair depends on the abundant blood supply to hair follicles. The disturbance of microcirculation perfusion leads to the decrease of blood perfusion velocity and flow in the microcirculation, which affects the normal oxygen supply to hair follicles of the scalp, leading to alopecia. Therefore, improving the local microcirculation of the scalp and enhancing the blood supply of hair follicles is one of the important mechanisms to treat alopecia (Zhang et al., 2011).

Hair growth, moist not only depend on blood run raise, also depend on kidney essence fill raise (Cui and Shun, 2016). Liver and kidney deficiency, qi and blood deficiency, spleen, stomach, and gallbladder dampness and heat are the recognition of alopecia in Chinese medicine, treatment is mainly used to supplement liver and kidney, supplement qi and blood, clear heat and nourish Yin, remove wind and dehumidifying (Zhao et al., 2014). In this experiment, AQH oil containing artemisia argyi, ginger, angelica sinensis, safflower and chilli, with the functions of promoting hair regeneration and dehumidification, warming menstruation and blood tonic, clearing heat and detoxification and relieving liver depression. Among them, capsaicin contained in chilli has a protective effect on cardiovascular metabolism, and its target, TRPV1, is involved in the regulation of vascular function and blood pressure (Zhu et al., 2011; Hao et al., 2011). Artemisia argyi has the effect of warming channel- hemostasis and channeling-activating collaterals (Cao et al., 2018), which is in line with the characteristics of "hemostasis" and "activating blood" in the treatment of alopecia. Angelica sinensis is a common tonic medicine for nourishing blood and clearing damp, safflower is commonly used in gynecological diseases. It can promote blood circulation and remove blood stasis (Mu and Sun, 2017; Li et al., 2014). This formula is consistent with the understanding and treatment principle of traditional Chinese medicine for alopecia, and is a fat-soluble ingredient, which is conducive to absorption. Therefore, AQH oil was used as a test drug for external application to observe the effect of improving microcirculation and hair growth.

The growth of hair is related to the blood of the body. If the blood does not run well, the hair will lose its nourishing ability and is difficult to regenerate or maintain growth. Therefore, promoting blood circulation can promote hair regeneration and normal growth to a certain extent. The experimental results showed that aiqing flower essential oil could expand the diameter of the capillary vein and the arteriole, increase the number of capillary opening, and promote blood circulation in mice with auricle microcirculation disorder caused by epinephrine, so it was speculated that the tested drug could through improve the microcirculation of mice to promote hair regeneration. For diseases related to alopecia, the growth of hair at the hair loss site is the most intuitive and favorable evaluation standard for drug efficacy. In this study, the hair was observed and scored from the time of hair growth, which was the most intuitive way to evaluate the efficacy. The results of the epigenetic evaluation were consistent with the measurement of biochemical indexes and the pathological observation of skin tissue, indicating the validity and feasibility of this method as a

method to evaluate the efficacy of drug germination. AGA is a kind of androgen-dependent polygenic genetic disease (Piraccini and Alessandrini, 2014). Testosterone (T) is the main male hormone in the body, which can be converted into dihydrotestosterone under the catalysis of related enzymes, and then binds to related receptors, resulting in different biological effects. The different effects of androgens on the hair of various tissues are called "androgen paradox", which promotes the hair growth in the facial hair of men. To increase the secretion of transformed growth factor of hair follicle and hair papilla, and promote the transformation of hair follicle to degenerative stage, so as to reduce hair thinning (Inui and Itami, 2013). The imbalance of androgenic hormone level is an important cause of AGA. The increase of serum T level and the decrease of estradiol (E2) level leads to the imbalance of T/E2 ratio and intensifies the hormone disturbance phenomenon in the body (Sun et al., 2011). The experimental results showed that the serum T/E2 and E2 level of AGA mice could be increased to different degrees by different drugs, and the level of T could be decreased. In other words, hair growth could be promoted by regulating hormone imbalance.

To sum up, the external application of AQH oil can improve the blood circulation of mice with auricle microcirculation disorder caused by epinephrine and improve estrogen and androgen disorders. It was speculated that the AQH oil might through regulate the blood microcirculation and regulate hormone imbalance of AGA mice to promote hair regeneration in alopecia area.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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