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Review Article

A Literature Review of the Microneedle Therapy System for Hair Loss

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ABSTRACT

This literature review was designed to investigate the effects of the microneedle therapy system (MTS) on alopecia in experimental, and clinical studies. The MTS is acupuncture needling therapy delivered by a roller. A literature review of studies published before May 2020 was conducted using 9 online databases, and a total of 13 studies (4 in vivo studies and 9 clinical trials) were included. Most studies showed that the MTS was effective when used in combination with other treatments. In vivo studies reported an increased level of hair growth factors following treatment. Typically, 1.5 mm needles were used in the MTS treatment and photographic evaluation (by either camera or microscope) was reported in most studies. Oriental medicine research included 2 in vivo studies, which reported positive effects when combined with the MTS. There were no reported severe side effects. the MTS might be safe and has a drug delivery effect. Further studies need to be conducted regarding the frequency and needle length depending on the type of alopecia using Oriental and Western medicine.

Introduction

Hair loss can adversely affect an individual's self-esteem regardless of gender, therefore, hair loss treatment is receiving greater attention. Hair loss can be classified as scarring or non-scarring depending on scar formation or hair follicle destruction, respectively. Since scarring hair loss permanently damages the hair follicles, treatment is not feasible. Conversely, non-scarring hair loss can be treated. Examples of non-scarring hair loss include androgenetic alopecia (AGA), alopecia areata (AA), and telogen effluvium (TE) [1]. Oral finasteride, topical minoxidil (MXD), and systemic corticosteroid have been typically used for hair loss. However, it is not feasible for some patients to be treated using these drugs, and the risk of side effects such as erectile dysfunction, dermatitis, and immunosuppression cannot be excluded [2].

Recently, Western medicine has used treatments such as platelet-rich plasma(PRP) and photodynamic therapy (PDT), whereas oriental medicine treatment for hair loss involves pharmacopuncture, thread-embedding acupuncture, and herbal medicine [1,2].

The microneedle therapy system (MTS) is a treatment in the spotlight. It is mainly in the form of a cylinder or pen which has several fine needles. In oriental medicine, these needles correspond to plum-blossom needles. In the West, the MTS is used in the beauty industry for skin treatment.

The MTS has been reported to activate the expression of various factors that stimulate hair growth by stimulating the dermis and hair follicles, and helps in topical drug delivery through micropores generated during the rolling of the cylinder [3]. For drug delivery in the treatment of hair loss, topical MXD (West) and herbal extracts (Korean medicine) are mainly studied [4].

A previously published review on the MTS and hair loss included only clinical studies and this excluded many oriental medicine treatment studies [4]. This current review was conducted to investigate the efficacy of the MTS on hair loss and to summarize the research approaches to date. This review includes experimental and clinical effects of the MTS in both Western and Oriental medicine studies.

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Materials and Methods

Search strategies

Articles published before May 2020 were retrieved using national and international databases [National Digital Science Library (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS), Research Information Sharing Services (RISS), Korean Studies Information Services System (KISS), PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Citation Information by NII (CiNii), Japan Science and Technology Information Aggregator, and Electronic (J-STAGE)]. The following search terms were used: "microneedle," "microneedling therapy system," "percutaneous collagen induction," "alopecia," and "hair loss" (Table 1).

Study selection and data extraction

Experimental studies and clinical trials with the full text available and using the MTS as treatment for alopecia were included in the search. Articles on an unrelated subject, protocols, reviews, and letters were excluded from the literature review. Articles with insufficient experimental design and outcome measures were also excluded. Two independent researchers reviewed the titles and abstracts of the 147 studies after the removal of duplicate articles. Another 2 independent researchers screened the remaining articles by reading the full text.

Results

Among the 215 studies initially retrieved from 9 databases, 13 studies were eligible for review (Fig. 1). There were 4 experimental in vivo studies originating from Korea, and 9 clinical trials originating from Korea (n = 1), Italy (n = 2), India (n = 4), and China (n = 2; Tables 2 and 3).

In vivo studies

In the in vivo studies, C57BL/6 mice were used. Mice were epilated and hair follicles were removed. In 3 studies [5-7], the control group, the MXD group, and the MTS group were compared. In addition, in 2 of the 3 studies [8,9], the combination of Korean herbal extract (Hwangyeonhaedoktang and Yeongji extract) and the MTS was also examined.

Kim et al [9] reported the difference between the number of rolling's in the MTS and the depth of the needle was studied. In a 3-week study [9], the greatest effect was observed when the rolling was performed 10 times with a 0.25 mm or 0.5 mm needle. In other in vivo studies, the MTS was performed 2-3 times per week for 16 to 21 days [6,8,9].

In all studies, the density and thickness of the hair were observed through a folliscope or dermoscopy. Hematoxylin and eosin stain were used to perform histological observations of the size and number of the hair follicles, and the length of the hair bulb. Vascular endothelial growth factor (VEGF), insulin-like growth factor, prolactin, transforming growth factor, fibroblast growth factor (FGF), epidermal growth factor (EGF), Wnt3α, Wnt10β, and β-catenin levels were measured by immunohistochemical staining, Western blot, and real-time polymerase chain reaction (RT-PCR) [6-9]. In the comparative studies with MXD, the MTS had a significant effect on almost all indices of hair growth compared with the control group, although the effect was not as beneficial as MXD treatment. The MTS and Hwangyeonhaedoktang or Yeongji extract group exhibited a better outcome than the MTS alone group, though with a lesser effect than MXD [8,9].

To check the stress and toxic effects, body weight was periodically measured. After animal sacrifice, the weight and form of the organs were observed; there were no abnormalities observed.

Clinical studies

There were 4 randomized controlled trials (RCTs) in 9 studies, where AGA, TE, and AA were studied (N = 544 people). There

Table 1. Search Strategy in English Language Databases.

#1	Microneedle*
#2	Microneedling therapy system
#3	Percutaneous collagen induction
#4	#1 OR #2 OR #3
#5	Alopecia
#6	Hair loss
#7	#5 OR #6
#8	#4 AND #7

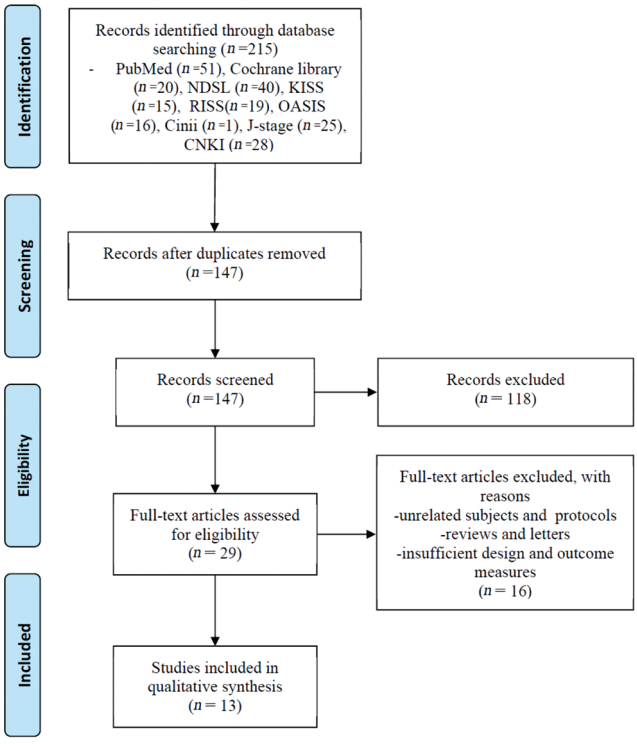

Fig. 1. PRISMA flow chart of selecting process.
NDSL, National Digital Science Library; OASIS, Oriental Medicine Advanced Searching Integrated System; RISS, Research Information Sharing Services; KISS, Korean Studies Information Services System; CNKI, Cochrane Library, China National Knowledge Infrastructure; Cinii, Citation Information by NII; J-STAGE, Japan Science and Technology Information Aggregator, and Electronic.

Table 2. Data of In Vivo Studies.

Author (nation, y)	Mouse species (sex/no.)	Intervention	Interval/no./ needle depth (mm)	Evaluation index	Results
Kang (Korea, 2016) [9]	C57BL6 (male/unknown)	1) CON 2) MXD 3) MTS 4) HRHDT + MTS	2× wk/5-6× (unknown)/0.2	1) Hair growth and length 2) Hair density and diameter 2) RT-PCR 3) Western blotting 4) Histological changes of hair follicles 5) Weight of body and organs	1-4) MXD > MTS + HRHDT > MTS > CON 5) No changes in all groups
Ju (Korea, 2014) [8]	C57BL6 (male/unknown)	1) CON 2) MXD 3) MTS 4) GLE + MTS	2× wk/6×/0.2	1) Hair growth and length 2) Hair density and diameter 2) RT-PCR 3) Western blotting 4) Histological changes of hair follicles 5) Weight of body and organs	1-4) MXD > MTS + HRHDT > MTS > CON 5) No changes in all groups
Lee (Korea, 2014) [6]	C57BL6 (male/15)	1) CON 2) MXD 3) MTS	q1d/16×/ unknown	1) Histological changes of hair follicles 2) Hair density and diameter 3) Immunohistochemical staining: FGF, VEGF 4) RT-PCR: VEGFR-2, FGF-2, EGF	1-3) MXD > MTS > CON 4) RT-PCR: MXD > MTS > CON (FGF-2), MTS > MXD > CON (VEGFR-2, EGF)
Kim (Korea, 2016) [5]	C57BL6 (female/16)	1) CON 2) MTS 10 cycles) 0.15, 0.25, 0.5, 1.0 mm -0.5 mm) 3, 6, 10, 13×	5× wk/15×/10 cycles) 0.15, 0.25, 0.5, 1.0	1) Hair density and diameter 2) Hair growth 3) RT-PCR: Wnt3a, β-catenin, VEGF, Wnt10b 4) Immunohistochemistry: Wnt3α, β-catenin, VEGF, Wnt10β	1-2) In the 10-cycle group, 0.25 and 0.5 mm were better. In the 0.5 mm group, 10 cycles were better. 3-4) All the indices increased in 0.5 mm and 10 cycles.

CON, control; MXD, minoxidil; MTS, microneedle therapy system; HRHDT, Hwangyeonhaedoktang; wk, week; d, day; RT-PCR, Real time polymerase chain reaction; GLE, Ganoderma Lucidum extract; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; EGF, epidermal growth factor.

were 395 AGA patients (366 men, 29 women), 7 TE patients (7 women), and 49 AA patients (19 men, 30 women) studied. About 33% of the AGA patients were given topical MXD or oral finasteride (conventional treatment), and the rest of the treatments were not reported. It was reported that all AA patients had been treated for many years with the conventional treatment (but the treatment was not mentioned) which were not effective [7,10]. The MTS treatment intervals were as follows: 0-1 week (1), 1-2 weeks (4), 3 weeks (2), and 4 weeks (2). The total number of treatments was as follows: 1-3 times (2), 4-6 times (2), 7-9 times (1), 10-19 times (2), and 20 times or more (2; Table 4). In the AGA and TE studies, 1.5 mm needles in the rollers were used except for in 2 RCTs [11,12]. However, in the AA study, 5 mm needle roller and a 1 mm needle pen were used [7,10,13].

There were 4 RCTs [14-17] that compared the MTS with 5% MXD treatment, and there was 1 clinical study where platelet-rich plasma was used [12]. Two studies compared the MTS to conventional (not reported) treatments [11,13], and another 2 AA studies [7,10] compared PDT with the MTS.

All patients, with 1 exception [16], were evaluated for the degree of hair growth by taking photographs using a camera or a microscope and a camera. Two studies evaluated the effects of treatment by the hair pull test [11,12], and 4 studies assessed treatment success by perceived personal satisfaction [14-17]. There was another study that performed hematoxylin and eosin staining of biopsies [7]. The side effects of the MTS were investigated in several studies [11,12,14,16], and severe side effects were not observed in any study.

A study on alopecia totalis [7] showed that none of the treatments had a beneficial effect. In the study of moderate to severe AA [10], only the MTS was not effective however, the MTS + PDT group showed significant improvement compared with the PDT alone group.

In the 2 RCT studies [14,15], the increase in hair count was about 5 to 6 times higher in MXD treatment combined with the MTS group compared with the MXD alone group.

The self-assessment also made a lot of difference. In the study by Kumar et al [14], 67.7% perceived a 30-50% improvement in the MXD + MTS group, whereas 93.1% reported a 0-20% improvement in the MXD alone group. In the study by Dhurat et al [15], 82% perceived an improvement of more than 50% in the MXD + MTS group, whereas 95.5% reported improvement to be less than 50% in the MXD alone group. In other studies of AGA and TE [11,12], when the MTS treatment was added, hair growth improved significantly compared with the group that did not have the MTS.

Discussion

Although hair loss itself does not pose a health risk, many patients want treatment for aesthetic reasons. AGA, AA, and TE are typical non-scarring hair loss conditions that can be treated.

In AGA, testosterone is converted to dihydrotestosterone in the skin, which causes hair loss. As a treatment for men oral finasteride, and topical MXD are usually prescribed. However, oral finasteride can have sexually adverse effects such as erectile dysfunction in men and in females it is not recommended due to the potential for teratogenicity. MXD has been used topically due to its hypertrichosis effect but may cause side effects such as contact dermatitis when used long term [18].

The exact cause of AA is thought to be related autoimmunity, and immunotherapy or corticosteroid treatment is commonly used

Table 3. Data of Clinical Studies.

Author (nation, year)	Gender/no. (type of hair loss)	Study design	Intervention	Interval/no./ needle depth (mm)	Evaluation index	Results
Yoo (Korea, 2010) [7]	Female/6, male/2 (AA)	Non-RCT	Left: MAL + PDT Right: MAL + PDT + MTS	q4wk/3×/5	1) Hair growth 2) Histopathologic changes	1) No difference was found 2) No difference was found
Giorgio (Italy, 2020) [10]	Female/24, male/17 (AA)	Non-RCT	A: MTS (9) B: ALA + PDT (15) C: ALA + PDT + MTS (17)	q3wk/6×/1	1) Hair growth	1) No response to treatment in group A. No response: (B:4, C:1). Response more than 50%: (B: 7, C: 10)
Starace (Italy, 2020) [11]	Female/29 (AGA), male/14 (AGA), female/7 (TE)	Non-RCT	Conventional treatment (topical MXD) + MTS	q4wk/3×1.5	1) Hair pull test 2) No. and diameter of the hairs	1) Negative in all patients 2) Frontal density (36.64%), vertex density (35.10%). Frontal diameter (9.75%). Vertex diameter (9.08%)
Jha (India, 2019) [12]	Male/93 (AGA)	Non-RCT	A: MXD (31) B: MXD + PRP (31) C: MXD + PRP + MTS (31)	q3wk/4×/ unknown	1) Hair pull test 2) Hair growth 3) Terminal-to-vellus hair ratio(T:V ratio) 4) Self-satisfaction	1) Negative ratio: A(15), B(20), C(27) 2) Improved: A (10), B (17), C (26) 3) Mean variation of T:V ratio: A (1.00), B (1.19), C (1.78) 4) Very satisfied: A (10), B (16), C (24)
Dhurat (India, 2015) [13]	Male/4 (AGA)	Non-RCT	Conventional treatment (oral finasteride + topical MXD) +MTS	q1wk or q2wk/15×/1.5	1) Hair growth (standardized 7-point evaluation scale) 2) Self-satisfaction	1) Improved: Grade +2 to +3 2) 75% improvement in 3 patients and 50% improvement in 1 patient
Kumar (India, 2018) [14]	Male/68 (AGA)	RCT	A: MXD + MTS (34) B: MXD (34)	q1wk or q2wk/8×/1.5	1) Hair count 2) Patient satisfaction (VAS)	1) Mean increase: 12.82 ± 6.82 (A), 1.89 ± 8.94 (B) 2) Mean variation of VAS: 2.97 ± 1.28 (A), 1.21 ± 0.90 (B)
Dhurat (India, 2013) [15]	Male/100 (AGA)	RCT	A: MXD + MTS (50) B: MXD (50)	q1wk/ 12×/1.5	1) Hair count 2) Investigator evaluation 3) Patient satisfaction	1) Mean increase: 91.40 ± 49.27 (A), 22.2 ± 19.34 (B) 2) Improvement: +2 to +3 (A: 80%), 0 to +1 (B: 100%) 3) More than 50% improvement: (A: 82%), (B: 4.5%)
Li (China, 2020) [17]	Male/90 (AGA)	RCT	A: MXD + MTS (30) B: MTS (30) C: MXD (30)	q2wk/48× / unknown	1) Hair growth 2) Patient satisfaction	1) More than moderate improvement: (A: 28), (B: 11), (C: 13) 2) More than 50% improvement: (A: 24), (B: 4), (C: 6)
Liu (China, 2019) [16]	Male/90 (AGA)	RCT	A: MXD + MTS (30) B: MXD (30) C: scalp nutrient solution (30)	q1wk/20×/ unknown	1) Hair growth 2) Investigator evaluation 3) Patient satisfaction	1) A was better than B and C ($p < 0.05$). B and C were equally effective. 2) Improved: (A: 26), (B: 25), (C: 26) 3) Improved: (A: 26), (B: 23), (C: 25)

AA, alopecia areata; RCT, randomized controlled trials; MAL, methyl aminolevulinate; PDT, photodynamic therapy; MTS, microneedle therapy system; wk, week; ALA, 5-aminolevulinic acid; AGA, androgenetic alopecia; TE, telogen effluvium; MXD, minoxidil; MTS, microneedle therapy system; PRP, platelet rich plasma; VAS, visual analog scale.

Table 4. Interval and Number of MTS Treatment.

Treatment interval (wk)	0-1	1-2	3	4	
Clinical studies (*n*)	1	4	2	2	
Treatment (*n*)	1-3	4-6	7-9	10-19	20-
Clinical studies (*n*)	2	2	1	2	2

MTS, microneedle therapy system.

to treat this condition [19]. However, side effects such as eczema, lymphadenopathy, dermatitis, immunosuppression, hypertension, and hyperglycemia may occur.

Temporary hair loss due to TE occurs about 3 months after an event such as stress, fever, infection, hormonal changes, diet, and consumption of certain drugs, and diffuse hair loss lasts about 6 months. The goal of treatment is to correct the cause of the trigger event [20].

The MTS makes tiny holes during rolling, which allows drug delivery. An advantage is that drugs that may cause unwanted effects when taken systemically can be delivered topically at a low dose to specific sites [21]. In addition, the MTS activates stem cells in the hair bulge area and induce the expression of vascular endothelial growth factor(VEGF), β-catenin, Wnt3α, and Wnt10β. [8,9] Furthermore, the MTS has been reported to promote the secretion of platelet-derived growth factors and epidermal growth factor, thus helping hair growth [3,11,14]. The MTS causes dermal remodeling and skin resurfacing through the formation of collagen and elastin in the wound healing process. [3] In oriental medicine, it is equivalent to roller acupuncture needling therapy or cha-acupuncture (車鍼) or plum-blossom acupuncture (梅花鍼). The method of stimulating shallow depths through the skin is similar to many acupuncture methods (半刺, 豹文刺 of 五刺法, 毛刺 of 九刺法, 揚刺 of 十二刺法) mentioned in the Huangdi Neijing (黃帝內經) of oriental medicine [22]. This study reviewed the effect of the MTS on hair loss in animal, and clinical studies (regardless of nationality).

C57BL/6 mice were the animal model used to evaluate hair growth effects. The dorsal hair of C57BL/6 mice has a time-synchronized growth cycle and truncal pigmentation that is produced only during the anagen phase of hair growth [23]. Animal models for AA and AGA were not used in this literature review. The C3H/HeJ mouse model or the Dundee experimental bale mouse are used as the murine model for AA, and the transgenic rat model (human androgen receptor) is used as the AGA animal model, however these animal models are not highly effective [24,25].

In clinical studies, AGA, AA, and TE temporary hair loss were examined. Whether the effect of the MTS differed according to the type of alopecia was not evaluated. In this literature review, while the effect of the MTS was positive on symptoms of AGA and TE, its effect on AA was not positive. Since the MTS was performed at a low frequency for 3 to 4 weeks, once in both studies [7,10] that deal with AA, it cannot be asserted that the MTS is ineffective. In order to determine this, in vivo studies as well as clinical studies with high treatment frequency should be conducted.

In animal models, the MTS was effective alone however, it was more effective when used in combination with herbal extracts. [8,9] Although it is less effective than MXD treatment, it is an alternative treatment to patients who do not respond to MXD or have developed side effects to MXD. Clinically, there have been studies of various herbal extracts topically applied in the treatment of hair loss, and most extracts have been reported to have a few side effects. [1,2] The combination of herbal extracts with the MTS may have a synergistic function due to drug delivery effects and effects of the MTS itself. Therefore, experimental, and clinical studies on various herbal extracts with the MTS are needed.

In the study by Lee et al [6], it was reported that a needle that is not too short or too long was effective. Almost all AGA studies used 1.5 mm needles, and were effective. Considering the results, stimulation to the depth of the dermal layer where the hair follicles are, is believed to enhance the effectiveness of treatment. The hair follicles are in the dermal layer, and the general depth of the dermis of the scalp is 3-4 mm [26,27]. Therefore, the 1.5 mm needle is deep enough to stimulate the dermal layer of the scalp. Further research is needed to determine whether a needle length sufficient to stimulate the hair follicle will be more effective.

While the difference in efficacy according to the number of rolling was studied in an in vivo study [5], the difference in frequency of treatment has not been studied. The research methods of the 2 RCT studies [14,15] were similar, although there were differences in the number and frequency of treatments. Dhurat et al [15] conducted the MTS once a week for 12 weeks, and Kumar et al [14] conducted the MTS once a week for 4 weeks and every other week for the next 8 weeks. Despite the fact that Dhurat et al [14] evaluated smaller surface areas, the mean change in hair count was greater than the Kumar et al study [14]. Although self-assessment indicators are subjective, 50% improvement was best in the Kumar et al study [14], 82% of those who rated 50% or more improvement were identified in the Dhurat et al study [15] Two RCT studies originating in China conducted the MTS 1-2 times per week. In a study that performed the MTS once a week, hair growth was significant in the MTS combined with MXD group, though personal satisfaction was insignificant. Conversely, in the study that conducted the MTS twice a week, there was a significant difference in personal satisfaction, and the MTS alone group and the MXD alone group showed similar personal satisfaction. Since the difference in efficacy may occur depending on the frequency of treatment, the efficacy according to the frequency should be studied in the future.

In 3 clinical studies, MXD was not applied topically for 24 hours after the MTS [11,14,15]. This allows the effect of the MTS itself to be observed rather than the drug delivery effect due to MXD. Two Chinese RCT studies [16,17] conducted the MTS and topical application of MXD at the same time, and 2 studies on AA [7,10] applied methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA) cream with the MTS. In these articles, drug delivery effects could be observed. As the other clinical studies did not reveal the timing of the MTS, it was not known whether it was for drug delivery purposes. In in vivo studies, it was reported that the absorption of Hwangyeonhaedoktang and Yeongji extracts during the MTS had a better outcome. In Korean medicine, pharmacopuncture treatment using herbal extracts is currently used for hair loss [1,2]. In particular, bee venom pharmacopuncture was reported to be effective in the treatment of hair loss as well as topical application of bee venom [28]. If these substances can be absorbed by the scalp, a synergistic effect may be produced and thus have a better outcome.

In the studies that examined the adverse effects of the MTS, there were no reports of severe adverse effects [11,14-16]. In vivo studies have also reported no effect of stress or toxicity [8,9] Common adverse effects of the MTS known to date are erythema and bruising [29]. The MTS may be a relatively safe and effective treatment method alone or in combination, though further research on safety will have to be performed. This study was conducted to determine what role the MTS may play in the treatment of hair loss. In the West, the treatment focus was on drug-delivery rather than the MTS itself. In oriental medicine, treatment of hair loss studies was abundant however, most were not included in this review due to insufficient experimental design. This review may be useful for reference when establishing the design of future research of the MTS and hair loss.

Conclusion

It was observed histologically that the MTS had a positive effect on thickness and number of hair follicles and had significant clinical effects on hair loss conditions including AGA and TE,

although with no effect observed for AA. Both the MTS alone and in combination were reported as effective, and no serious adverse effects were reported. The MTS can be applied to treat hair loss with or without oriental medicine or Western drugs. Future studies focusing on the MTS and its use in combination with external preparations will be helpful in the development of effective treatments for hair loss.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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