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## Alternative Medicine for Hair Loss

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### Abstract

In recent years, people have begun to give further emphasis to the external beauty, especially for their hair. Except drugs with proven effectiveness, complementary and alternative treatment options that have not yet been clarified of their effectiveness and side effect profiles have been used for centuries. Many plants or their extracts are widely used to prevent hair loss and treat alopecia (e.g., androgenetic alopecia, alopecia areata, or traction alopecia) worldwide, especially in Far Eastern countries. The mechanisms of action of these plants are still unknown. Although there are little randomized-controlled studies investigating the effectiveness in the treatment of hair loss, reported results have demonstrated that complementary and alternative medicine will become much more popular in the near future.

**Keywords:** hair loss, complementary, alternative, medicine, herbal, acupuncture, hypnosis

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### 1. Introduction

The social and sexual communication roles of hair as well as its protective function have absolutely undeniable for both sexes for many years [1, 2]. Although the loss of hair is not a life-threatening condition, the loss of hair at an early age or sudden onset hair loss may cause serious psychological distress, thus it may directly affect the quality of life negatively [1, 3]. For this reason, patients with suffering from hair loss should be considered finically in order to distinguish ordinary hair shedding from pathologic hair loss. A loss of 100 or less hair falling per day should not be considered as pathological hair loss. But in case of hair loss more than 100 per day, a pathological condition should be mentioned [3].

Hair loss is a common dermatological problem that has been estimated to affect between 0.2 and 2% of the world's population. There are several factors leading to hair loss including

major physical-emotional stress, chemotherapy, genetic predisposition, dihydrotestosterone (DHT), excessive sebum, cardiovascular diseases, smoking, and endogenous substances [3]. The common hair diseases that dermatologists are often faced in daily practice are androgenetic alopecia (AGA), alopecia areata (AA), telogen effluvium, anagen effluvium, and traumatic alopecia such as trichotillomania and traction alopecia [1]. AGA, known as male pattern hair loss in men and as female pattern hair loss in women, is the most common form of hair loss in adults [1, 4, 5]. Approximately 60% of males between the ages 30 and 50 years and 17% of women under 50 years of age suffer from AGA [4]. The role of DHT which is reduced from testosterone by enzyme  $5\alpha$ -reductase is clearly known in the mechanism of AGA [6]. In early stage, the process begins with shortening of the anagen phase and continuous miniaturization of sensitive follicles [1]. During this process, terminal hairs are replaced by vellus hairs which are shorter, finer and nonpigmented in the frontal and vertex regions of the scalp [3, 4]. Year after year, permanent baldness occurs at the site of miniaturized hair [1]. AA is a common, chronic inflammatory disease that is characterized by non-scarring alopecic patches on the scalp. It affects approximately 2% of the United States (US) population [7, 8]. Although the mechanism of AA is exactly unknown, it is thought that a necessary secondary event or cofactor such as febrile illness, pregnancy, or a major life crisis in addition to genetic predisposition [8, 9]. Even though AA may regress spontaneously, the disease may remain stable or even may spread to the entire scalp (known as alopecia totalis) or body (known as alopecia universalis). Telogen effluvium is a disease that occurs as a result of passing of a portion of hair from anagen phase to telogen phase. It is characterized by diffuse hair shedding. While trichotillomania is an impulse control disorder, traction alopecia is association with patients' hairstyle. These two diseases that occur after recurrent and chronic trauma are frequently seen in females than males. Both of them can result with permanent scarring [9].

In recent years, complementary and alternative medicine (CAM) is becoming increasingly popular all over the world. In fact, CAM is still the only option to cure and treat some diseases in some regions of Africa, Asia, and South America [10]. Alternative medicine refers to the use of CAM in place of conventional medicine, while complementary medicine refers to the use of CAM along with conventional medicine [11]. According to The National Center for Complementary and Alternative Medicine (NCCAM) in the United States, CAM is defined as 'a group of diverse medical and health-care system, practices, and products that are not presently considered to be a part of conventional medicine' [12]. In some countries like Korea, oriental medicine has been officially approved and has gained support from legal system using the licensing system [13]. The number of visits to alternative care practitioners increased by about 1.5 times in 7 years (from 427 billion in 1990 to 629 billion in 1997) in the United States [14]. The National Health Interview Survey estimated that in 2007 alone, 38% of adults in the United States used CAM [15].

CAM is separated by NNCAM into four categories: alternative medical systems, biologically based therapies, manipulative and body-based therapies, and mind-body therapies. The details of these therapies are shown in **Table 1** [16]. In a survey study conducted in the United Kingdom (UK) in 2010, the most popular CAM therapies were reported as acupuncture, hypnotherapy, and chiropractic, while the least preferred CAM were noted as aromatherapy, reflexology, and medical herbalism [17]. The annual expenditure on CAM is about \$30 billion in the United States and £1.6 billion in the UK [18, 19].

|  |  |
|--|--|
| <b>Alternative medical system</b>            | Acupuncture                            |
|  | Ayurveda                               |
|  | Homeopathy                             |
|  | Naturopathy                            |
| <b>Biologically based therapies</b>          | Chelation                              |
|  | Folk medicine                          |
|  | Nonvitamin nonmineral natural products |
|  | Diet-based therapies                   |
|  | Megavitamin therapy                    |
|  |  |
| <b>Manipulative and body-based therapies</b> | Chiropractic care                      |
|  | Massage                                |
| <b>Mind-body therapies</b>                   | Biofeedback                            |
|  | Relaxation techniques                  |
|  | Hypnosis                               |
|  | Yoga                                   |
|  | Tai Chi                                |
|  | Qi Gong                                |
|  | Healing rituals                        |
|  | Energy healing                         |
|  | Reiki                                  |

**Table 1.** Various treatments used in complementary and alternative medicine.

Similarly, using of CAM is quite often among patients suffering from dermatologic disorders such as acne, atopic dermatitis, psoriasis, dermatophytes, actinic keratosis, vitiligo, hair loss, cosmetic indications, melanoma, and lupus erythematosus [20–27]. A survey data from UK indicated that 35–69% of patients who have various skin diseases have used CAM in their lifetime [27]. The prevalence of CAM use by dermatology patients were 25.7 and 41% in Singapore [28] and Taiwan [29], respectively, while it ranges from 33.5 [30] to 43.7% in Turkey [31]. As the most frequently complementary medicines used by patients to treat their dermatological diseases have been reported as homeopathy, herbalism, diets, and food supplements in the UK [19, 27], the most used types of CAM have been recorded as herbal remedies, special diet, and megavitamin in Taiwan [29]. In one study, positive feedbacks from patients using CAM, especially herbal therapies, were noteworthy for both skin-related and non-skin-related conditions. Approximately 85% of patients with skin-related conditions, many of those with chronic diseases such as acne and eczema, noted improvement with CAM use [32]. To treat hair loss, the first two groups shown in **Table 1** are more preferred than the others.

Ideal treatment of hair loss should include the drugs that have both 5 $\alpha$ -reductase inhibition effect and hair growth promoter substances, together. The most used conventional treatments

are topical minoxidil, finasteride, dutasteride, combination of cyproterone acetate and estrogen, spironolactone, flutamide, topical progesterone, cimetidine, zinc sulfate, topical niacin, topical aminexil, topical ketoconazole, and cyclosporine-A [2]. In particular, minoxidil and finasteride are widely used for treating hair loss. But adverse effects of all of these agents have limited to their usage [1, 2]. Hence, patients suffer from hair loss have begun to turn to alternative therapies, even though there is little scientific evidence to prove their effectiveness.

## 2. Complementary and alternative medicines for hair loss

### 2.1. Herbal drugs

Herbal medicine is extremely popular since ancient times in Ayurveda, Siddha, Chinese, and Unani systems of medicine [3, 33]. Many plants and/or their extracts have been used to prevent hair loss and treat alopecia. These plants and their properties are summarized in **Table 2**.

#### 2.1.1. *Thuja orientalis*

*Thuja orientalis* (*T. orientalis*, family *Cupressaceae*), also known as *T. occidentalis* in Eastern or Arbor vitae or white cedar, is a plant that is widely distributed in East Asia [34, 35]. In addition to grown as an ornamental tree in Europe, it has been used to treat various diseases concerning respiratory system, skin disorders, and urinary system. Nowadays, it is often used in homeopathy and evidence-based phytotherapy [35]. It has also been traditionally used to promote hair growth in the oriental medicine. Although *T. orientalis* has a strong 5 $\alpha$ -reductase inhibitor effect, the exact mechanism of hair-promoting effect of *T. orientalis* is still unknown. In the literature, there are few studies investigating the association between *T. orientalis* and hair growth. In animal studies, it was demonstrated that topically application of *T. orientalis* extract induced an earlier anagen phase and prolonged the mature anagen phase. In immunohistochemistry analysis, it was also shown that the expression levels of  $\beta$ -catenin and sonic hedgehog (Shh) were upregulated in *T. orientalis* extract-treated group at 14 days, compared to those in the control or 1% minoxidil-treated group. In mice treated with *T. orientalis*, authors observed an increase in both the number and size of hair follicles [34, 36]. Even, cubosomal suspension of *T. orientalis* extract was found to be more effective due to increased skin penetration of the *T. orientalis* [37].

#### 2.1.2. *Citrullus colocynthis*

*Citrullus colocynthis* (*C. colocynthis*) Shrad (family *Cucurbitaceae*), known as *Indrayan*, is one of the numerous herbal drugs recommended by the traditional system of medicine for hair growth promotion in India [38, 39]. It contains  $\beta$ -sitosterol, campesterol, stigmasterol,  $\alpha$ -spinasterol, and cucurbitacin glycosides. It has several pharmacological effects such as immunostimulating, antiandrogenic, antibacterial, and hypoglycaemic in addition to hair-promoting effect [39]. There are few animal studies evaluating hair growth-promoting activities of the *C. colocynthis*. Roy et al. reported that topical application of *C. colocynthis* plant, especially petroleum ether extracts, had an astonishing effect on hair growth initiation time, complete hair growth,

| Botanical name                                       | Family           | Possible mechanisms of action   |
|--|------------------|---|
| <i>Thuja orientalis</i>                              | Cupressaceae     | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Citrullus colocynthis</i>                         | Cucurbitaceae    | Antiandrogenic effect   |
| <i>Rosmarinus officinalis</i>                        | Lamiaceae        | Increasing the circulation of the scalp   |
| <i>Camellia sinensis</i>                             | Theaceae         | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Asiasari radix</i>                                | Aristolochiaceae | Inducing early telogen-to-anagen conversion   |
| <i>Allium cepa</i> L.                                | Liliaceae        | Unknown   |
| <i>Polygonum multiflorum</i>                         | Polygonaceae     | Proliferation of dermal papilla cells, expression of FGF-7, up-regulating Shh and $\beta$ -catenin expression                               |
| <i>Allium tuberosum</i> Rottler ex Spreng            | Liliaceae        | Stimulating expression of IGF-1   |
| <i>Cucurbita pepo</i>                                | Cucurbitaceae    | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Serenoa repens</i>                                | Arecaceae        | Inhibition of 5 $\alpha$ -reductase enzyme, decreasing DHT uptake by hair follicle, decreasing the binding of DHT to androgenetic receptors |
| <i>Panax ginseng</i> C.A. Meyer                      | Araliaceae       | Expression of VEGF, antiapoptotic activity  |
| <i>Eclipta alba</i>                                  | Asteraceae       | Anagen phase induction, reducing level of TGF- $\beta$ 1  |
| <i>Zizyphus jujuba</i>                               | Rhamnaceae       | Unknown   |
| <i>Allium sativum</i>                                | Liliaceae        | Unknown   |
| <i>Avicennia marina</i>                              | Acanthaceae      | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Phyllanthus niruri</i>                            | Euphorbiaceae    | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Oryza sativa</i>                                  |                  | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Sophora flavescens</i> Aiton                      | Leguminosae      | Inhibition of 5 $\alpha$ -reductase enzyme, vasodilator and antiandrogen effects  |
| <i>Chrysanthemum zawadskii</i> var. <i>latilobum</i> | Asteraceae       | Anti-inflammatory effect  |
| <i>Scutellaria baicalensis</i>                       | Lamiaceae        | Inhibiting nuclear translocation of the androgen receptor, enhance proliferation of human dermal papilla cells                              |
| <i>Cuscuta reflexa</i> Roxb                          | Convolvulaceae   | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Pueraria thomsonii</i>                            | Leguminosae      | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Curcuma aeruginosa</i>                            | Zingiberaceae    | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Hura crepitans</i>                                | Euphorbiaceae    | Inhibition the neurotrophin (NT)-4 activation   |
| <i>Tobacco leaves</i>                                | Solanaceae       | Inhibition of 5 $\alpha$ -reductase enzyme  |
| <i>Tectona grandis</i> Linn                          | Verbinaceae      | Unknown   |
| <i>Boehmeria nipoonivea</i>                          | Urticaceae       | Inhibition of 5 $\alpha$ -reductase enzyme  |

**Table 2.** Some plants used for hair loss and their properties.

and the length of hair follicle in albino rats. In qualitative studies, hair growth was initiated in the denuded area on the 4th day and 5th day with 5 and 2% ointment of petroleum ether extract of *C. colocynthis*, respectively. But, hair growth initiation was noted on the 6th day and the second week in minoxidil-treated standard group and in control group, respectively. Complete hair growth was recorded on the 16th, 18th, 19th, and 24th days in the 5% petroleum ether extract group, 2% petroleum ether extract group, minoxidil group, and control group, respectively. In quantitative studies, at 30 days after treatments with extracts of *C. colocynthis*, anagenic population were recorded as 67 and 47% in the minoxidil group and control group, whereas it was noted as 75 and 72% in the 5 and 2% petroleum ether extract groups, respectively. In both 2 and 5% petroleum ether extract groups, approximately 50% of hair population had length of 0.5 mm and above at 30 days after treatment [38]. In another study, Dhanotia et al. evaluated the hair growth-promoting activities of the petroleum ether extract from the fruit of *C. colocynthis* on albino mice using a testosterone-induced alopecia model. As a result of both qualitative and quantitative studies on hair growth, they suggested to present the inhibition of androgenic activity and altered anagen/telogen ratio and follicular density [39]. Polyherbal formulation including *C. colocynthis* was also shown to present hair growth-promoting activity on rats. Hair growth initiation time was markedly reduced to one-third on treatment with the prepared formulation compared to control group. The time required for complete hair growth was also reduced by 32%. Quantitative analysis of hair growth cycle after treatment with formulations and 2% minoxidil solution (positive control group) exhibited greater number of hair follicles in anagenic phase compared with control [40].

### 2.1.3. *Rosmarinus officinalis*

*Rosmarinus officinalis* (*R. officinalis*), commonly known as Rosemary, is a plant that belongs to family *Lamiaceae* and naturally grows in all Mediterranean countries [41, 42]. It has antiandrogenic effect and hair growth-promoting activity apart from antioxidative, anti-inflammatory, antibacterial, and antitumor effects [43]. In CAM, *R. officinalis* is often used in aromatherapy to treat anxiety-related conditions and increase alertness, although it has occasionally been used to stimulate hair growth [41]. The exact mechanism of hair growth is still unclear, but it is believed to act by increasing the circulation of the scalp. Murata et al. showed that topical administration of *R. officinalis* extracts solution (2 mg/day/mouse) improved hair regrowth in the testosterone-treated C57BL/6NCrSlc mice. They also showed significant promotion of hair growth after 16 days of topical administration. Among the some constituents of *R. officinalis* [i.e., rosmarinic acid, ursolic acid, 12-methoxycarnosic acid (12-MCA)], it was demonstrated that inhibitory activity of 12-MCA on 5 $\alpha$ -reductase was higher than rosmarinic acid and ursolic acid (82.4, 14.2, and 2.5% inhibition at 200  $\mu$ g/ml, respectively) [43].

### 2.1.4. *Green tea*

Green tea (*Camellia sinensis*, family *Theaceae*) is a well-known plant since ancient times, especially in China. It has been regarded to possess numerous pharmacological effects such as antimetastatic, anticancer, hepatoprotective, antidiabetic, antiobesity, anti-atherosclerotic, antibacterial, antiviral, anti-inflammatory, and antioxidant effects. It has been preferred in various dermatological diseases due to its mentioned beneficial effects worldwide. Human papilloma

virus (HPV)-induced cervical cancer, genital warts, acne, rosacea, wound healing, atopic dermatitis, and keloids are diseases that green tea is commonly used. Apart from these diseases, it can be used to prevent or treat AGA by selectively inhibiting  $5\alpha$ -reductase activity. Catechins, a group of very active flavonoids, are a major component of green tea representing 60–80% of all polyphenols [44, 45]. There are four major catechins in green tea: epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin gallate, and epicatechin [46, 47]. EGCG is the most highly bioactive catechin among these constituents [45]. In a study, EGCG was found to cause significant human hair follicle elongation *ex vivo*. Indeed, it was also shown proliferative and antiapoptotic effects of EGCG on dermal papilla cells through the upregulations of phosphorylated *Erk* and *Akt* and by an increase in the ratio of Bcl-2/Bax ratio [48]. Esfandiari et al. also reported that 33% of the mice that received 50% fraction of polyphenol extract from dehydrated green tea in their drinking water had significant hair regrowth within a period of 6 months compared with control group received regular drinking water [49].

#### 2.1.5. *Asiasari radix*

*Asiasari radix* (*A. radix*, family *Aristolochiaceae*) or the radix of *Asiasarum heterotropoides var. mandshuricum* F. Maekawa usually grows in Korea, Japan, and China. *A. radix* is also called as 'seshin' in Korea, as 'saishin' in Japan, or Chinese wild ginger in English [50, 51]. It is used to treat various oral mucosal diseases such as aphthous stomatitis, gingivitis, local pain, and toothache apart from hair loss. A study from Korea showed its potent hair growth effect in mice. Though *A. radix* had not inhibitory effect on  $5\alpha$ -reductase enzyme, authors suggested that the extract of the plants induced early telogen-to-anagen conversion. They also demonstrated expression of vascular endothelial growth factor (VEGF) in human dermal papilla cells cultured *in vitro* [52].

#### 2.1.6. *Allium cepa* L

Onion juice (*Allium cepa* L., family *Liliaceae*) may be used in patients with AA because of garlic-like activity. Both herbal medicines have similar chemical constituents, especially *Allicin*. The exact mechanism of onion juice in the treatment of AA is still unknown [53, 54]. In the study by Sharquie and Al-Obaidi, at 4 and 6 weeks after topical application of onion juice twice a day, hair regrowth was observed as 73.9 and 86.9% of patients with AA, respectively. Patients should be informed about skin irritation on the skin surface in contact with the onion juice [53].

#### 2.1.7. *Polygonum multiflorum*

*Polygonum multiflorum* (*P. multiflorum*, family *Polygonaceae*) is a very popular plant that has been widely used to treat various diseases in traditional Chinese medicine due to its different pharmacological effects such as antiaging, immunomodulating, antihyperlipidemia, hepatoprotective, anticancer, and anti-inflammatory. Besides these pharmacological effects, some studies have been reported related to hair growth promotion activity and hair-blackening effect [55, 56]. An active component of *P. multiflorum*, known as 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside (THSG), has melanogenesis-stimulating effect in melanocytes [55]. A new



compound isolated from *P. multiflorum*, known as torachryson-8-O- $\beta$ -D-glucoside, induces a strong increase in the proliferation of dermal papilla cells and significantly increases the hair-fiber length of rat vibrissa follicles [57]. Li et al. investigated hair growth promotion activities and their possible mechanism of *P. multiflorum* Radix (PMR) and *P. multiflorum* Radix Preparata (PMRP), both of them originated from *P. multiflorum*, in C57BL/6J mice. While hair covered skin ratio was higher in oral PMR groups than in PMRP groups, hair covered skin ratio was lower in topical PMR groups compared with topical PMRP groups. It was also demonstrated that the most possible cytokines regarding hair growth-promoting activity were fibroblast growth factor-7 (FGF-7) and Shh [58]. Another animal study suggested that anagen phase was induced in resting hair follicles through upregulating Shh and  $\beta$ -catenin expression after topical application of *P. multiflorum* [55].

#### 2.1.8. *Allium tuberosum* Rottler ex Spreng

*Allium tuberosum* Rottler ex Spreng (*ATRES*, family *Liliaceae*) is one of the *Allium* species like *Allium tuberosum* and *Allium cepa* L. It is widely distributed in East Asia and has been used for treating abdominal pain, diarrhea, hematemesis, and asthma in traditional medicine. Choline acetyltransferase activity of *ATRES* was also reported [54, 59]. In the first study, evaluating the hair growth-promoting activity and its mechanism of action, *ATRES* has strong hair-promoting activity through stimulating expression of insulin-like growth factor-1 (IGF-1). Especially, the n-butanol extract of *ATRES* was found to have most hair growth-promoting activity among the other compared groups including minoxidil, ethanol, n-hexane, distilled water groups on telogenic C57BL6/N mice [59].

#### 2.1.9. Pumpkin seed oil

Pumpkin seed oil (PSO, family *Cucurbitaceae*) has been used for treating symptomatic benign prostatic hyperplasia through its inhibitory effect on  $5\alpha$ -reductase and antiandrogenic effect [60, 61]. In a randomized, double-blind, placebo-controlled study, self-rated improvement score, and self-rated satisfaction scores in the PSO-treated group were higher compared with the placebo group after oral administration of PSO at dosage of 400 mg/day for 24 weeks. At 24 weeks, mean hair count was recorded as increase of 40 and 10% in the PSO-treated group and placebo group, respectively. But, there was no significant difference in hair thickness between groups [60].

#### 2.1.10. *Serenoa repens*

*Serenoa repens* (*S. repens*, family *Arecaceae*) is a native plant in West India and is grown in large quantities on the Atlantic southeast coast of North America. Saw palmetto is extracted from the berries of this plant. It is one of the herbal medicines that have inhibitory effect on both types 1 and 2 of  $5\alpha$ -reductase enzyme. In addition to inhibitory effect on  $5\alpha$ -reductase, *S. repens* may also decrease DHT uptake by hair follicle and decrease the binding of DHT to androgenic receptors [62, 63]. Anti-inflammatory effect has been demonstrated with a composition containing saw palmetto, carnitine, and thioctic acid in hair follicle keratinocytes [64]. Both oral and topical use of *S. repens* could be effective for treating androgen-induced

alopecia in both sexes [63]. In an open label study, 50 male patients with mild to moderate AGA were treated with *S. repens* 320 mg/day for 24 months. After this period, only 38% of patients had an increase in hair growth. But, this improvement was lower than the group treated with finasteride (68% of patients) [62]. Satisfactory results were also observed after application of topical products containing *S. repens* extract for 24 weeks in male patients with AGA [65]. Recommended dose is 320 mg/day orally [63]. Side effects of *S. repens* are minimal. The most known side effects are related to gastric symptoms, although contact dermatitis, feeling of coldness, mild burning sensation, undesirable smell, itching, and acne are the reported adverse events after topical application [63, 65, 66].

#### 2.1.11. Ginseng

Ginseng (family *Araliaceae*) is traditionally used as an important herbal medicine in East Asian countries such as China, Korea, and Japan. It is divided into three categories: fresh ginseng, red ginseng, and white ginseng [67, 68]. Red ginseng is extracted from the steamed root of *Panax ginseng* C.A. Meyer, or known as Korean ginseng, and has various effects such as anti-aging, antidiabetic, immunoregulatory, anticancer, neuroregulation, lipid-regulating and antithrombotic activities, and wound- and ulcer-healing activity [68, 69]. In addition to these properties, it has also been used for treating numerous hair diseases such as AGA and AA due to its promoting hair growth activity [70, 71]. There are very important chemical constituents such as polysaccharides, ginsenosides (or known as saponins), alkaloids, glucosides, and phenolic acid in ginseng [68]. Ginsenosides are the major pharmacologically active ingredients of ginseng. To date, approximately 70 ginsenosides have been isolated from ginseng. In a study, it has been demonstrated that ginsenoside Rg3 had upregulated the expression of VEGF in human dermal papilla cells and mouse hair follicles [72]. Antiapoptotic activity of *fructus panax ginseng* was also shown in human dermal papilla cells [73].

#### 2.1.12. *Eclipta alba* (L.) Hassk

*Eclipta alba* (L.) Hassk. (*E. alba*, family *Asteraceae*) is a medicinal plant commonly used for treating gastrointestinal disorders, respiratory tract disorders, fever, liver disorders, skin disorders, spleen enlargement, and cuts and wounds as well as hair loss and graying of hair. Numerous pharmacological activities including hepatoprotective, hair growth-promoting activity, antidiabetic, analgesic, anti-inflammatory, neuropharmacological activities, antioxidant, antimicrobial, antimalarial, cardiovascular effects, immunomodulatory, antiepilepsy, anticancer, antiulcer, and antihelmintic activities have been demonstrated. *E. alba* phytoconstituents including wedelolactone, eclalbasaponins,  $\alpha$ -amyryn, oleanolic acid, ursolic acid, luteolin, and apigenin are responsible from main medicinal effects [74]. Hair growth-promoting activity has been investigated on animals. The methanol extract of *E. alba* has been tested for its efficacy for hair growth in pigmented C57/BL6 mice. While the transition of telogen phase to anagen phase of hair growth was observed in approximately 87.5% animals treated with 3.2 mg/15 cm<sup>2</sup> of methanol extract of *E. alba*, 50% of the animals treated with 1.6 mg/15 cm<sup>2</sup> of methanol extract of *E. alba* was observed transition from telogen phase to anagen phase of hair growth. The rate of anagen induction was dependent on concentration of methanol extract of *E. alba* [75]. The petroleum ether extract of *E. alba* was also investigated for its hair

growth stimulatory effects in nude mice. This fraction of *E. alba* significantly reduced the levels of transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) expression during early anagen and anagen-catagen transition, so that authors suggested that the duration of terminal differentiation was extended [76]. Roy et al. also reported that the petroleum ether and ethanol extracts of *E. alba* (incorporated into ointment base in concentration of 2 and 5%, respectively) significantly reduced the time taken for hair growth initiation and completion in albino rats treated with the extracts [77].

#### 2.1.13. *Zizyphus jujuba*

The plant, *Zizyphus jujuba* (*Z. jujuba*, family *Rhamnaceae*), is a widely distributed both in the Mediterranean regions and in the tropical and subtropical region of Asia and America. It can be used for several diseases such as diabetes, diarrhea, skin infections, liver complaints, urinary disorders, obesity, fever, pharyngitis, bronchitis, anemia, insomnia, and cancer [78]. There is no sufficient data related to its hair growth-promoting effect. In a study by Yoon et al., a greater effect on length of hair was reported in mice treated with 1 and 10% of *Z. jujuba* essential oil after 21 days of treatment as compared to control group. Although the length of hair was measured as 9.96 mm with 1% of oil and 10.02 mm with 10% of oil, respectively, the length of hair was measured as 8.94 mm in the control group [79].

#### 2.1.14. *Allium sativum*

*Allium sativum* (family *Liliaceae*), known as garlic, is one of the most popular herbal medicine and can be used in the treatment of various dermatologic conditions such as psoriasis, AA, keloid scar, wound healing, cutaneous corn, viral and fungal infection, leishmaniasis, and skin-aging and rejuvenation. Constituents of garlic include enzymes (e.g., alliinase), sulfur-containing compounds (e.g., alliin), compounds produced enzymatically from alliin (e.g., allicin), arginine, oligosaccharides, flavanoids, and selenium [80]. In a double-blind randomized-controlled study, Hajheydari et al. reported that combination of topical garlic gel and betamethasone valerate cream was more effective than betamethasone valerate cream alone in patients with localized AA at the 3rd month. The number of total and terminal hairs in the group treated with garlic gel was significantly higher than those of the control group at the third months [81].

#### 2.1.15. *Avicennia marina*

*Avicennia marina* (*A. marina*), also known as grey or white mangrove, is a traditional herbal plant belonging to family of *Acanthaceae*. However, it is traditionally used to treat various skin diseases in Egypt, antiandrogenic activity of *A. marina* and a compound, avicequinone C, isolated from the hearthwood of *A. marina* was firstly reported by Jain et al. [82]. The results revealed that *A. marina* was a potent 5 $\alpha$ -reductase type 1 inhibitor, reducing the 5 $\alpha$ -DHT production by 52% at the final concentration of 10  $\mu$ g/mL [82]. Moreover, among the thirty different extracts, the highest inhibitory activity was observed from the crude extract of *A. marina* at a final concentration of 10 g/ml through the reduction in 5 $\alpha$ -DHT formation by more than 50% [83].

#### 2.1.16. *Phyllanthus niruri*

*Phyllanthus niruri* (*P. niruri*, family *Euphorbiaceae*) is a widely used plant of genus *Phyllanthus* in traditional medicine. It is also known as 'chanka piedra,' 'bhuiamlki,' 'zhuzicao,' 'dukung anak,' 'quebra-pedra,' and 'chanca piedra.' *P. niruri* usually grows in tropical and subtropical regions in Central and South American countries, India and East Asia and has several biologic activities such as antidiabetic, analgesic, wound healing, and immunomodulatory effects. It is traditionally used to cure of jaundice, fever, malaria, stomachache, urolithiasis, vaginal candidiasis, varicella, and tuberculosis by people living in these countries [84, 85]. Newly, inhibitory activity of petroleum ether extract of *P. niruri* on 5 $\alpha$ -reductase type 2 enzyme was shown, and it has been suggested to be useful in the treatment testosterone-induced alopecia [85].

#### 2.1.17. Rice bran

It has been believed that rice bran extract, which is produced by milled rice (*Oryza sativa*), has antioxidant, anticancer, and antihyperlipidemic effects as well as 5 $\alpha$ -reductase inhibitory activity [86]. The compounds having antioxidant activity are phenolic acids, flavonoids, anthocyanins, proanthocyanidins, tocopherols, tocotrienols,  $\gamma$ -oryzanol, and phytic acid [87]. Very few studies exist to support the claims of the efficacy of rice bran. The hair growth-promoting activity of rice bran supercritical CO<sub>2</sub> extract (RB-SCE) and its two components (linoleic acid and  $\gamma$ -oryzanol) were shown using real-time reverse transcriptase-polymerase chain reaction in C57BL/6 mice by Choi et al. [86]. In a double-blinded randomized-controlled study, dermal application of 0.5% of RB-SCE (8 ml/day) to the head skin significantly increased hair density and hair diameter in male patients with alopecia for 16 weeks [88].

#### 2.1.18. *Sophora flavescens* Aiton

*Sophora flavescens* Aiton (*S. flavescens*, family *Leguminosae*) is one of the important plants used in traditional Chinese medicine [89, 90]. It has been used for treating viral hepatitis, cancer, viral myocarditis, heat dysentery, hemaferia, jaundice, anuresis, leucorrhoea with reddish discharge, vulval swelling, pruritus vulvae, eczema, and trichomonas vaginalis [90, 91]. It is a strong inhibitor of 5 $\alpha$ -reductase enzyme in addition to its vasodilatory and antiandrogen effects. Despite lack of proper clinical trials to support its efficacy for hair loss, the mechanism of affect on hair loss treatment is thought to be through these activities. It was demonstrated that the isolated two pterocarpans, L-maackiain and medicarpin, promoted the proliferation of human hair keratinocytes [89].

#### 2.1.19. *Laminaria japonica*

*Laminaria japonica* (*L. japonica*) is a kind of brown algae and called as 'kombu' in Japanese, 'dashima' in Korean, and 'haidai' in Chinese. The most consumed countries of *L. japonica* are Far Eastern countries such as Korea, Japan, and China. *L. japonica* is believed to have beneficial effects for health; however, the mechanism of beneficial effects is not fully understood [92, 93]. The combination of *L. japonica* extract and *Cistanche tubulosa* extract has the potential to promote hair growth. Oral administration of both *L. japonica* extract at dosage of 54 mg/kg and *Cistanche tubulosa* extract at dosage of 162 mg/kg exhibited an excellent hair regrowth activity

on mice. It has been thought that anti-inflammatory activities of the both plant extracts could play an important role to prevent hair loss and improve alopecia [94].

#### 2.1.20. *Chrysanthemum zawadskii* var. *latilobum*

*Chrysanthemum zawadskii* var. *latilobum* (*C. zawadskii*, family *Asteraceae*) has been used for the treatment of pneumonia, bronchitis, cough, common cold, pharyngitis, bladder-related disorders, gastrointestinal disorders, and hypertension in traditional medicine for ages. Essential oil of the plant contains 27 hydrocarbons, 12 alcohols, 7 ketones, 4 esters, 1 aldehyde, 1 amine, and 3 miscellaneous components [95, 96]. Although recent studies have expressed anti-inflammatory effect and protective effects from liver damage of *C. zawadskii*, there is little experimental evidence suggesting that the extract stimulates hair growth in humans and animals. In mice study, topical methanol extract of *C. zawadskii* was more effective compared to minoxidil-treated group. In the *C. zawadskii*-treated and minoxidil-treated groups, while the maximum hair scores in the first hair-growth generation were recorded as  $2.5 \pm 0.29$  and  $2.5 \pm 0.28$ , hair coverage scores in the second hair-growth generation were noted as  $2 \pm 0.41$  and  $1.5 \pm 0.29$ , respectively. Rapid hair loss seen in minoxidil-treated mice was not observed in *C. zawadskii*-treated group after the first hair growth generation [95].

#### 2.1.21. *Scutellaria baicalensis*

*Scutellaria baicalensis* (*S. baicalensis*, family *Lamiaceae*), also known as *Huang Qin*, mostly grows in China, Japan, Korea, Mongolia, and Russia [97, 98]. *S. baicalensis* is likely to have hair growth-promoting effect by means of its active substances. It has been reported that the compound possessing this activity is an active flavonoid isolated from *S. baicalensis* named 'Baicalin'. In recent years, it has also suggested that both the extract of *S. baicalensis* and baicalin inhibit nuclear translocation of the androgen receptor stimulated by DHT in human dermal papilla cells and enhance proliferation of human dermal papilla cells in vitro [98].

#### 2.1.22. *Cuscuta reflexa* Roxb

*Cuscuta reflexa* Roxb. (*C. reflexa*, family *Convolvulaceae*) is a parasitic plant that is used as herbal medicine. It is also known as 'Tukhm-e-Kasoos (dodder)', 'Aftimoon,' or 'Kasoos' in Unani Tibbi, 'Akashabela,' or 'Amarabela' in Hindi, 'Swarnalata' in Bengali, and 'Akakhilata' in Assamese, in vernacular [99, 100]. It commonly grows on different host plants, mostly thorny herbs in all geographical regions of India [99, 101]. Many pharmacological activities such as relaxant and spasmolytic action, positive inotropic and cardiogenic activities, cholinergic action, anti-HIV, antioxidant, anti-steroidogenic, antibacterial, hepatoprotective, hypoglycemic, diuretic, anti-convulsant, anti-inflammatory and anticancer activities as well as hair growth activity have been previously reported [100]. A number of experimental observations have indicated that *C. reflexa* has hair growth-promoting and  $5\alpha$ -reductase inhibitory activities. Hair growth was shown after treatment of the petroleum ether extract solution (250 mg/kg, orally) of *C. reflexa* and the ethanolic extract solution (250 mg/kg, orally) of *C. reflexa* in male albino rats with cyclophosphamide-induced alopecia at 19 days [99]. In another animal study by Pandit et al. suggested that petroleum ether extract of *C. reflexa* reversed androgen-induced alopecia

by inhibiting conversion of testosterone to DHT [101]. Polyherbal formulation including *C. reflexa* was also shown to present hair growth-promoting activity on rats. Hair growth initiation time was markedly reduced to one-third on treatment with the prepared formulation compared to control group. The time required for complete hair growth was also reduced by 32%. Quantitative analysis of hair growth cycle after treatment with formulations and 2% minoxidil solution (positive control group) exhibited greater number of hair follicles in anagenic phase compared with control [40].

#### 2.1.23. *Ishige sinicola*

*Ishige sinicola* (*I. sinicola*) is a brown alga that has antibacterial and anti-inflammatory effects against acne. In 2013, a study firstly demonstrated that *I. sinicola* extract and its component, octaphloretol A, have the potential to promote hair growth via the proliferation of dermal papilla cells followed by the activation of  $\beta$ -catenin pathway, and the  $5\alpha$ -reductase inhibition [102].

#### 2.1.24. *Grateloupia elliptica*

*G. elliptica* is the edible seaweed in some Asian countries. Although it is thought that potential anticancer activity, there is not enough evidence investigating the protective effect against hair loss and hair growth-stimulating effect of *G. elliptica* [103, 104]. Possible mechanisms including the proliferation of dermal papilla cells, inhibition of  $5\alpha$ -reductase enzyme, increase in prostaglandin E2 (PGE2) production, decrease in pro-inflammatory cytokine production, and inhibitory activity against *Pityrosporum ovale* (*P. ovale*) have been shown in the prevention of hair loss. A study showed that *G. elliptica* extract promoted the proliferation of dermal papilla cells by 169.5% at the concentration of 100  $\mu$ g/ml compared with the vehicle-treated control group. The study also indicated that *G. elliptica* extract inhibited  $5\alpha$ -reductase enzyme and this activity increased with dosage [104].

#### 2.1.25. *Puerariae flos*

*Puerariae flos* (the flowers of *Pueraria thomsonii*, family *Leguminosae*) extract (PF-ext) has inhibitory activity on testosterone  $5\alpha$ -reductase. The two major compounds, soyasaponin I and kaikasaponin III, are responsible for this inhibitory activity. In addition to inhibitory activity on testosterone  $5\alpha$ -reductase of both compounds, soyasaponin I possesses hepatoprotective, sialyltransferase inhibitory, and renin inhibitory activities, while kaikasaponin III possesses anti-hepatotoxic, hypoglycemic, hypolipidemic, and anti-herpes virus activities [105, 106]. Inhibitory activity of PF-ext on  $5\alpha$ -reductase is stronger than *Puerariae Radix* extract (PR-ext). In testosterone-sensitive male mice, hair regrowth was improved after the application of PF-ext solution in a dose-dependent manner via antiandrogenic activity. PF-ext can stimulate the induction of the hair cycle to anagen phase, but this mechanism has not been proven definitely [105].

#### 2.1.26. *Curcuma aeruginosa*

*Curcuma aeruginosa* (*C. aeruginosa*, family *Zingiberaceae*) is a native plant of India and Southeast Asia. The rootstock of *C. aeruginosa* has long been used in traditional medicine for various

indications such as dysmenorrhea, exanthemas and fungal infections. The oils derived from this plant consist of 1,8-cineole, curserenone, furanogermerone, camphor, (Z)-3-hexenol, zedoarol, furanodienone, curcumenol, isocurcumenol,  $\beta$ -alemene, curzerene, and germacrone, among others. *C. aeruginosa* hexane extract effects by inhibiting 5 $\alpha$ -reductase activity, consecutively impairing the conversion of testosterone to DHT [107, 108]. Pumthong et al. investigated the effect of *C. aeruginosa* hexane extract on male-pattern baldness with a randomized, double-blind, placebo-controlled study. The study has shown that 5% hexane extract of *C. aeruginosa* especially combined with 5% minoxidil increased hair growth and decreased hair shedding [107].

#### 2.1.27. *Hura crepitans*

*Hura crepitans* (*H. crepitans*, family *Euphorbiaceae*) has been used as a traditional medicine to treat some diseases such as Hansen's disease and syphilis in the Amazon region. A compound in *H. crepitans*, daphne factor F3, can play an effective role the mechanism of the hair growth. But, interestingly, the amount of daphne factor F3 is very important for hair growth. While *H. crepitans* from Peru possesses hair regrowth activity, *H. crepitans* from Brazil is not affect hair growth. Because, the daphne factor F3 content of *H. crepitans* from Peru is about 30 times more than *H. crepitans* from Brazil [109, 110]. It has been suggested that *H. crepitans* inhibits the retardation of hair regrowth by DHT through inhibition the neurotrophin (NT)-4 activation induced by DHT [109].

#### 2.1.28. Tobacco leaves

Tobacco leaves (family *Solanaceae*) are used in traditional medicine for promoting of hair growth. The leaves also used to treat bronchitis, asthma, skin diseases, headache, etc. Alkaloid nicotine is the main constituent of tobacco leaves. Alkaloids such as nicotine, nicotianin, nicotinine, nicotine, and nicoteline, which are the constituent parts of tobacco leaves, selectively inhibit 5 $\alpha$ -reductase activity. The microbial bio transformed extract of tobacco leaves in cow urine has been investigated to treat AGA, and it has been found that it promotes hair growth at concentration dependent manner. The study confirms that 30% concentrated lotion treatment is at par with 2% minoxidil treatment in potentiating hair growth promotion in male albino Wister rats [111, 112].

#### 2.1.29. *Tectona grandis* Linn

*Tectona grandis* Linn. (*T. grandis*, family *Verbinaceae*) (teak tree) has been used to cure many diseases in traditional Indian medicine. *T. grandis* is called as 'saka' in Sanskrit, 'sagun' in Hindi, 'sagwan' in Marathi, and teak tree in English. It has also been used as a hypoglycaemic agent. According to the traditional Indian medicine, *T. grandis* roots are useful in anuria and urinary retention. The flowers have used to treat bronchitis, biliousness, and urinary discharge. The oil from the seeds is useful in scabies. The wood is used to relax and sedate the gravid uterus, heal headache and burning pains, cure liver problems, and even dysentery. *T. grandis* has been investigated in some studies for its anti-inflammatory and wound healing effects and is used as a topical treatment for burn wounds [113, 114]. Jaybhaye et al. investigated the

effect of petroleum ether extract of *T. grandis* Linn. seeds on hair growth activity of albino mice. According to this study, topical application of the petroleum ether extract of *T. grandis* induced hair growth initiation and was superior to standard therapy with minoxidil 2% solution. The combination of the petroleum ether extract (5%) with 2% minoxidil has the strongest effect on hair growth initiation [113].

#### 2.1.30. *Boehmeria nipononivea*

*Boehmeria nipononivea* (*B. nipononivea*, family *Urticaceae*) is a Japanese plant and the use of acetone extract derived from this plant has been investigated for treatment of androgen-dependent alopecia. One study indicates that the acetone extract of *B. nipononivea* has  $5\alpha$ -reductase inhibitory activity. The acetone extract derived from *B. nipononivea* was investigated on mice for its hair growth effect, and it resulted with a significant hair regrowth starting on 15th day and continues until 22th day. The  $5\alpha$ -reductase inhibitory activity of the acetone extract of *B. nipononivea* is attributed to fatty acids contains such as  $\alpha$ -linolenic acid, palmitic acid, oleic acid, elaidic acid, and stearic acid. The study reveals that both the acetone extract of *B. nipononivea* and three fatty acids ( $\alpha$ -linolenic, elaidic, and stearic acids) have  $5\alpha$ -reductase activity and stimulates hair regrowth [115].

## 2.2. Acupuncture

Acupuncture is an ancient holistic system of Chinese medicine and has been practiced there so many years. China had the cultural and traditional exchange with its neighbors, and therefore, it spread to all over the world in time. Today, it is one of the most frequently used forms of complementary medicine [116].

Acupuncture aims to bring a complete cure, not only managing the outstanding symptom but to heal the whole body. Even though various acupuncture techniques are available, the fundamental techniques are needling, moxibustion, cupping, suction, and acupressure. Over the centuries, acupuncture has been used to treat a wide variety of diseases including skin disorders such as acne, alopecia, eczema and dermatitis, pruritus, pityriasis, psoriasis, rosacea, systemic lupus, urticaria, herpes zoster, chicken pox, impetigo, leprosy, and vitiligo. The exact mechanism of action of acupuncture treatment in skin disorders is not clear but investigations revealed that acupuncture stimulation effects on three key points: the hypothalamus-pituitary-adrenal axis, the autonomic nervous system, and brain-derived neurotrophic factor. There may be an increase on serum levels of cortisol by the effect of acupuncture. It has also been demonstrated by functional MRI that manual needle acupuncture distinctively activates the hypothalamus-limbic system [116].

Degranulation of mast cells significantly increases in autoimmune diseases such as AA and chronic inflammation. A mouse model for AA study has shown that severe mast cell degranulation and accumulation around the anagen hair follicle cause a self-attack of the hair follicle cells by migration of the inflammatory cells. This attack induces the hair matrix cell phase to the telogen phase that results with hair loss. Acupuncture treatment reduces  $T_1$ -cell attacks on hair bulb and activates blood circulation by warming the local collaterals; therefore, it may help to reduce hair loss. The same mouse study indicated that electro-acupuncture reduces



mast cell degranulation in the dermis. It is reported that may be the cause of the pathological changes causing AA but reliable evidence is not yet available [117, 118].

Even though acupuncture treatment in dermatological diseases is safe and inexpensive, improperly performed acupuncture can cause potentially serious adverse effects such as vasovagal events, local infections, damage to internal organs, pneumothorax, spinal cord injury, and hepatitis B infection [116].

### 2.3. Hypnotherapy

The hypnotic phenomenon has been used over thousands of years, and it is a form of trance induction. Recently, the use of hypnotic therapy in somatic medicine has been supported by the British Medical Association in 1955 and the American Medical Association in 1958. A hypnotic trance can be described as an altered state of consciousness with “inward focus.” It can be differed from other states of consciousness by electroencephalography (EEG) and imaging modalities. A hypnotic state can be induced by a therapist or an individual can induce hypnotic trace in himself or herself (self-hypnosis) [119, 120].

Hypnosis has been used for several indications such as induction of anesthesia or to heal irritable bowel syndrome and psychosomatic diseases as well as a variety of skin disorders including AA and trichotillomania. Nowadays, medical hypnosis is performed by physicians whom have received appropriate training in many countries all over the world. For some selected skin disorders, with proper training and selection of appropriate patients, medical hypnosis can relieve symptoms and in some cases can cure the illness [119, 120].

Hypnosis is a cost-effective and nontoxic therapy and can be used in dermatological treatment especially in patients with psychosomatic component [119, 120]. In a preliminary study, hypnotic sessions including relaxing suggestions and symptoms-oriented suggestions were held as a complementary or the only treatment once every 3 weeks in patients with severe AA, alopecia totalis, or alopecia universalis. Twelve of 21 patients showed significant improvement after 4–13 (mean 5.5) sessions of hypnosis, while treatment success could not be achieved in 9 patients. But also, minimal relapses were observed in all patients responded well [121]. In another prospective cohort study, it has been suggested that hypnosis had no significant contribution on hair regrowth in patients with refractory AA [122].

Despite confusing conclusions have been reported about the efficacy in the treatment of AA, hypnosis seems to be salubrious in the treatment of both children and adolescents with trichotillomania. Cohen et al. reported that complete resolution of their complaints was seen in two children after 7–8 weeks and in one child after 16 weeks. Even if just a recurrence was observed in one patient during follow-up, the patient completely recovered again with hypnotic retreatment [123]. Iglesias A observed that three pediatric cases completely disappeared to their trichotillomania behavior after 7 or less hypnotic sessions [124]. In addition to children, hair pulling was significantly reduced with imaginative techniques in adolescents with trichotillomania [125]. According to these results, hypnotherapeutic approach

can be considered as a quite effective and preferred option in both children and adolescents with trichotillomania.

### 3. Side effects

The side effects reported after CAM is often minimal. Contact dermatitis was reported with onion juice in patients with AA, thus patients should be informed about skin irritation on the skin surface in contact with the onion juice (**Figure 1**) [53]. *S. repens* that can be used as both orally and topically may cause undesirable adverse effects such as mild stomach discomfort, contact dermatitis, feeling of coldness, mild burning sensation, undesirable smell, itching, and acne [63, 65, 66]. Vasovagal events, local infections, damage to internal organs, pneumothorax, spinal cord injury, and hepatitis B infection are some of the side effects that can be encountered after acupuncture therapy [116]. Prurigo nodularis also reported on extremities of a patient shortly after acupuncture [126].



**Figure 1.** Contact dermatitis developed after topical application of onion and garlic on face of a patient with AA.

## 4. Conclusion

In recent years, although the increasingly widespread use of CAM, scientific data are still not enough. The observed results with herbal medicine are promising in the treatment of hair loss, especially AGA and AA. According to acceptable results, hypnosis may be an effective and safe alternative option in patients with hair loss, especially AA and trichotillomania. Even so, there is need for more scientific data proving its effectiveness and reliability.

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