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REVIEW ARTICLE

Medicinal Plants for the Treatment of Hair Loss and the Suggested Mechanisms

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Abstract: Hair loss may not be recognized as a life-threatening disorder. However, it has a great harm to a person's self-respect, mental health, and entirety quality of life. Androgenic alopecia (AGA) is the most common type of hair loss, which affects a great number of both men and women. Alopecia can be treated with various hair loss strategies, including hair transplant, cosmetics and medication. Medical treatment shows the outstanding ability in improving hair growth. Plenty of drugs prevents alopecia by inhibiting the secretion of male hormone. But these medicines exhibit some undesirable side effects. Since hair loss requires a long-term treatment and minimizing adverse side effects is extremely urgent in drug development. Accordingly, new agents are obtained from natural products with less adverse effects. Traditional Chinese medicines exhibit unique advantages in hair loss treatment. This review generalizes and analyzes the recent progress of medicinal plants for the treatment of hair loss, suggested mechanisms and outlines a number of trials taken or underway to optimize the treatment.

Keywords: Hair loss, androgenic alopecia, medicinal plant, mechanism, extracts, chemical compounds.

1. INTRODUCTION

Alopecia is one of the most common trichinosis in clinical, which results in a significant impact on human spirit and psychology. Over past years, the incidence of alopecia has been increased. The occurrence of alopecia is due to the nutritional imbalance caused by a combination of environmental pollution, stress, frequent dyeing and perm, drinking, smoking, diet and so on [1, 2]. The age of patients with hair loss tends to be younger. 40% of patients suffered from alopecia require relevant treatment [3, 4]. Although it is not defined as a severe disease, a large number of studies are still being carried out owing to the growing public demands for hairdressing and beauty. More and more attention to modern medicine and traditional medicine were put on hair growth promotion.

There are many treatments for alopecia, including hair transplant, cosmetics and medication. Medical therapy shows a great effect on improving hair growth. Plenty of drugs prevent alopecia by inhibiting the male hormone. The two famous agents, Finasteride (a synthetic 5-α-reductase inhibitor) and minoxidil (a vasodilator), are used to treat alopecia by suppressing male hormones [5, 6]. Nevertheless, the use of these two drugs is limited due to their severe side effects. Finasteride is reported to cause sexual dysfunction and minoxidil can give rise to itching, redness, and inflammation [7]. Hair loss treatment needs a long-term remedy and reducing adverse side effects is important in drug development. As a result, new ingredients are obtained from medicinal plants with less adverse effects. A lot of companies have improved productivity by using herbal medicines.

A peer-reviewed investigation has been accomplished by analyzing worldwide accepted scientific databases (Pubmed, Scopus and Web of Science, SciFinder) and scrutinizing the available information on the medicinal plants for the treatment of hair loss.

2. CAUSES OF HAIR LOSS

Hair is undergoing cyclic processes of growth which are anagen, catagen, and telogen [1]. The longest period is anagen varying with species and body site. Many disorders inducing hair loss are extensively exhibited and discussed including hypotheses on skull expansion relating to alopecia and the clinical evaluation [8, 9]. Androgenic alopecia (AGA) is the main attention of the present article based on its clinical importance. AGA is recommended as a euchromosome dominant genetic disease, which is caused by multiple-factor inheritance. More than 70% of AGA patients have a familial predisposition. AGA does not occur in puberty but always occurs under the effect of androgen. AGA will be more serious along with age. The hair follicle ratio of anagen to telogen descends from 12:1 to 5:1, which is a pathological characteristic of AGA.

Although it is widely admitted that dihydrotestosterone (DHT) causes baldness, the mechanisms involved still remains unclear. There are three mechanisms proposed by Rebora [10]: (a) miniaturization by a DHT-induced acceleration of the mitotic rate of the matrix that leaves less and less time for differentiation; (b) an increased telogen shedding as a result of the shortening of the hair cycles that increases the telogen number per unit of time; (c) and the increased number and duration of the lag phase or kenogen. The mechanism related to DHT remains unclear. Testosterone is the major androgen in the circulation, which converts to DHT, a more potent androgen, *via* 5α-reductase in tissue [3]. DHT is more likely combining with androgen receptor (AR) than testosterone in hair follicle, which promotes the process of anagen and catagen into telogen and subsequently metabolizes causing baldness.

Two types of 5α-reductase isoenzymes have been mentioned, and type II is more highly expressed in AGA follicles than in follicles of normal controls [11]. The AR is also expressed at the significantly higher level in balding than non-balding scalp follicles in AGA [12-15]. The above data suggest that the androgen-AR signaling pathway play a crucial role in AGA pathogenesis.

3. REPRESENTATIVE DRUGS AND THE SIDE EFFECTS

Combination of 5α-reductase inhibitors and hair growth promoter agents is the favorable treatment for hair loss. The treatment strategy for hair loss is different from other dermatology disorders, such as acute eczema and psoriasis. The obvious improvement of hair loss needs a long treatment process. The anti-androgen mechanisms are also classified into three parts: either inhibit or trap DHT, depress 5α-reductases and AR blocking. The first success of AGA treatment got in women via a combination of cyproterone acetate

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and estrogen [16]. This treatment increased the number of hair follicles in the anagen phase.

Minoxidil (2,6-diamino-4-piperidinopyrimidine-1-oxide), a vasodilator, was found to be effective at promoting hair growth promotion [17, 18]. However, several adverse effects were extensively reported. This vasodilator agent promotes hair growth by potassium channel opening with a stimulating effect on hair follicles [19]. The ratio of anagen to telogen was increased significantly. It has been reported that minoxidil treatment widened hair diameter at which 5% topical application was highly effective in men, whereas 2% was appropriated in women [20, 21]. As a result, the concentrations were recommended for clinical use. Owing to the wide use of minoxidil in alopecia, the mechanism involved is extensively studied and discussed. Tretinoin, another hair growth promoter, is used as minoxidil enhancer by increasing its absorption efficacy. Previous studies have demonstrated that topical minoxidil therapy may cause chest pains and palpitations [22]. In human dermal papilla cells, minoxidil increases cell proliferation through activation of Akt.

Propecia (finasteride) is a 5a-reductase inhibitor indicated for the treatment of male pattern hair loss in men only [23]. The suggested dose is 1 mg/day. It's reported that Propecia has several side effects, such as impotence, loss of interest in sex, swelling in your hands or feet, and so on [24]. Minoxidil, Propecia and other chemical agents for hair loss treatment are summarized in Table **1**. These medicines have common side effects, for example, impotence (erectile dysfunction), abnormal ejaculation, decreased ejaculatory volume, abnormal sexual function, gynecomastia, testicular pain, impairment of muscle growth, and severe myopathy [25, 26]. Therefore, the strict use needs to be concerned in the female, particularly pregnant women.

4. EXTRACTS FROM PLANTS WITH HAIR GROWTH ENHANCEMENT

There are plenty of substances from plants. Plants are regarded as an excellent source of pharmaceuticals, insecticides, flavorings, fragrances and food colorants. There are numerous plant extracts with hair growth stimulation effect to use for the treatment and prevention of hair loss. It remains unknown how these products exhibit their effects, but claims that hair growth is secondary to blood flow acceleration, anagen dermal papillae activation, DHT inhibition, anti-inflammatory activity, and nutrition increase [27]. Some extracts exhibit excellent hair-growth promotion effect, here are some examples of common plants for treating hair loss, and others are gathered in Table **2**.

Polygonum multiflorum (Polygonaceae), distributed in northeast Asia, is a well-known traditional Chinese herbal medicine, commonly known as 'He-shou-wu' in China. As a tonic, it is often used to prevent premature aging of the kidney and liver, nourish the blood, fortify the muscles, tendons and bones, and strengthen and stabilize the lower back and knees [28, 29]. It is also used in Korean traditional medicine because of its effect of anti-allergy, anti-tumor, anti-bacterial, hemostatic, spasmolytic, and analgesic properties [30]. It has also been documented that *P. multiflorum* roots possess hair growth activity in traditional medicine, and many studies showed its strong effect on hair growth and hair color. For example, a recent study demonstrated that one of active components, 2,3,5,4 0-tetrahydroxystilbene-2-O-β-D-glucoside, from *P. multiflorum* induced melanogenesis in melanocytes [31]. The hair growth-promoting activities of *P. multiflorum* extracts and the mechanism of action were reported [32].

Ginseng radix in the form of a 70% extract of red ginseng (steamed and dried roots of *Panax ginseng* C.A. Meyer, a type of Ginseng Radix) presents the ability to promote hair growth on cultured mouse vibrissal hair follicles. The major extract ginsenoside-Rb1 or G-Rb1 shows activity while others are ineffective. *Panax Ginseng* Root extract is considered as a cosmetic ingredient and used as a skin conditioning agent. Recent clinical treatment found that oral consumption of Korean red ginseng extract (3000 mg/d) for 24 weeks effectively promoted hair density and thickness in alopecia patients [33].

Zizyphus jujuba, a thorny rhamnaceous plant, is widely distributed in Europe and Southeastern Asia. Its fruits are edible and the different parts exhibit different medicinal properties such as antifertility, analgesic, and antidiabetes [34, 35]. In China, the seeds of *Z. jujuba* have been used for anti insomia and anxiety. And they are effective on improvement of the blood glucose and serum lipid compositions in dietary hyperlipidemic rats. In particular, *Z. jujuba* seeds are more effective as a therapeutic regimen in control of metabolic derangements in adult disease. *Zizyphus jujuba* essential oil also shows the promoting effect on hair growth [36].

Carthamus tinctorius L. (safflower) belongs to the Asteraceae family, the flowers of which have been used as a remedy for stroke, gynecological disease, coronary heart disease, angina pectoris, inflammation, and hypertension [37-39]. Its flowers have been used for promoting blood circulation in China [40]. In addition, *C. tinctorius* flowers aqueous extract has traditionally been used for hair color enhancement in Thailand [37]. Moreover, *C. tinctorius* extract (CTE) inhibited 5α-reductase activity and stimulated hair growth in mice [41]. The ethanolic extract of *C. tinctorius* flowers promoted the proliferation of both dermal papilla cells (DPCs) and human keratinocytes (HaCaT) and up-regulated hair growth-promoting genes, including VEGF and keratinocyte growth factor (KGF) [42]. CTE suppressed the expression of transforming growth factor-β1 (TGF-β1), a hair loss-related gene. Furthermore, CTE increased the length of cultured hair follicles and induced the growth of hair with local effects in mice [42].

Chamaecyparis obtusa is a conifer in the cypress family Cupressaceae, native to northeast Asia [43, 44]. Owing to antibacterial and antifungal effects, the essential oil of C. obtusa is contained in many products such as hygienic bands, aromatics, and shampoos [45, 46]. Interestingly, many people suffering from baldness and/or other forms of hair loss have reported the promoting effect of shampoos containing the oil on hair growth. *C. obtusa* oil facilitated the early phase of hair growth in shaved mice. Moreover, the effect of *C. obtusa* oil on the regulation of hair morphogenesis and hair growth was examined in the HaCaT. VEGF expression was enhanced, which has a positive regulative effect on hair growth. *C. obtusa* oil also stimulated hair growth in an animal model and the components of this oil also induced the increase of VEGF expression [47].

5. COMPOUNDS FROM PLANTS WITH HAIR GROWTH ENHANCEMENT

Chemical compounds isolated from medicinal plants also exhibit a hair-growth promotion effect. Dieckol from *Ecklonia cava* can improve hair loss by promoting the proliferation of DPCs and/or inhibiting the activity of 5α-reductase [48]. Major compounds, ginsenosides Rb1, Rb2, Rc, Rd, Re and Rg1 from *Panax ginseng* stimulate hair growth via a similar mechanism of minoxidil [49]. Ginsenoside F2, converted by ginsenosides Rb1 via incubation with *Aspergillus niger*, promotes hair growth through increasing β-catenin, Lef-1 expression and decreasing DKK-1 expression with Wnt receptor interaction [50]. Acankoreoside J, a lupane-triterpene of Acanthopanax koreanum, enhances hair growth by promoting the cell cycle progression of the DPCs, increasing the expression of nuclear β-catenin, decreasing the expression of cyclin D1, cyclin E, CDK2 and $p27^{kip1}$ [51]. Some chemical compounds isolated from medicinal plants with hair-growth promotion effect are collected in Table **3**.

Table 1. Chemical synthesis drugs with anti-alopecia effect.

Drug	Function	Side effects	Refs.
Minoxidil	Potassium channel opener and vasodilator	Scalp pruritus and scaling	[75]
Finasteride	5α-reductase inhibitor	Sexual dysfunction	[76]
Dutasteride	5α-reductase inhibitor	Sexual dysfunction	[76]
Fluridil	Anti-androgen agent	Sexual hypoactivity	[77]
Flutamide	Anti-androgen agent	Sexual dysfunction and hepatosis	[78]
Spironolactone	Anti-androgen agent	Gynecomastia	[79]
Cyproterone acetate	AR antagonist	Sexual hypoactivity	[80]
Ketoconazole	Anti-androgen agent	Sexual hypoactivity	[81]
Tofacitinib	JAK inhibitor	Infections and hyperlipidemia	[82]

AR: Androgen receptor; JAK: Janus kinase.

Table 2. The extracts from plants with hair growth potential.

Extract	Botanical Name	Family	Medicinal Part	Observation	Effect	Mechanism of Action	Refs.
Petroleum ether or ethanol extract	*Cuscuta reflexa*	Convolvulaceae	Stem	*In vivo* *In vitro*	Promote hair growth Upregulate testosterone level	Inhibit 5α-reductase activity	[83]
Methanol extract	*Eclipta alba*	Compositae	Whole plant	*In vivo*	Promote hair growth	Upregulate FGF-7 and Shh expression and downregulate BMP4 to induce anagen phase	[84]
Petroleum ether extract	*Eclipta alba*	Compositae	Aerial part	*In vivo*	Promote the proliferation of HaCaT	Downregulate TGF-β1 expression	[52]
Ethanol extract	*Fructus panax ginseng*	Araliaceae	Root	*In vivo* *In vitro*	Promote hair growth Promote the proliferation and inhibit apoptosis of human DPCs	Upregulate Bcl-2 expression, downregulate Bax expression and induce anagen phase	[85]
Essential oil	*Zizyphus jujuba*	Rhamnaceae	Seed	*In vivo*	Promote hair growth	Not investigated	[36]
Water extract	*Aconite Ciliare*	Ranunculaceae	Root tuber	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of human DPCs	Activate Wnt/-β catenin signal pathway	[61]
Ethanol extract	*Asiasari radix*	Aristolochiaceae	Root	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of HaCaT and human DPCs	Upregulate VEGF expression	[86]
70% ethanol extract	*Panax ginseng*	Araliaceae	Root	*In vivo* *In vitro*	Promote human follicles growth Promote the proliferation and inhibit apoptosis of ORS	Upregulate Bcl-2 expression, downregulate Bax expression	[87]
Essential oil	*Chamaecyparis obtusa*	Cupressaceae	Whole plant	*In vivo*	Promote hair growth	Upregulate ALP, γ-GT, IGF-1 and VEGF expression, downregulate EGF expression	[88]
Water extract	*Polygonum multiflorum*	Polygonaceae	Leaf	*In vivo*	Promote hair growth	Upregulate Shh and β-catenin expression to induce anagen phase	[68]
Water extract	*Polygonum multiflorum*	Polygonaceae	Root	*In vivo*	Promote hair growth	Upregulate FGF-7 expression	[89]

ALP: Alkaline phosphatase; BMP4: Bone morphogenetic protein4; DPCs: Dermal papilla cells; FGF-7: Fibroblast growth factor; HaCaT: Human keratinocytes; IGF-1: Insulin-like growth factor 1; ORS: Outer root sheath; Shh: Sonic hedgehog; TGF-β1: Transforming growth factor1; VEGF: Vascular endothelial growth factor; γ-GT: γ-glutamyltranspeptidase.

(Table 2) Contd….

Extract	Botanical Name	Family	Medicinal Part	Observation	Effect	Mechanism of Action	Ref
Water extract	*Polygonum multiflorum* (Preparata)	Polygonaceae	Root	*In vivo*	Promote hair growth	Upregulate Shh expression	[89]
Ethanol extract	*Carthamus tinctorius*	Asteraceae	Floret	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of both DPCs and HaCaT	Upregulate VEGF and KGF expression, downregulate TGF-β1 expression	[42]
Ethanol extract	*Phyllanthus emblica*	Euphorbiaceae	Fruit	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[41]
Ethanol extract	*Clitorea ternatea*	Fabaceae	Flower	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[41]
50% ethanol extract	*Rosmarinus officinalis*	Lamiaceae	Leaf	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of DPCs	Inhibit 5α-reductase activity	[74]
50% ethanol extract	*Pueraria thomsonii*	Leguminosae	Flower	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[90]
Ethanol extract	*Pueraria lobata*	Leguminosae	Root	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[90]
Ethanol extract	Erica multiflora	Ericaceae	Whole plant	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of DPCs	Promote hair growth by inducing the anagen phase	[91]
Hot water extract	*Thuja orientalis*	Cupressaceae	Leaf	*In vivo*	Promote hair growth	Upregulate Shh and β-catenin expression to induce the anagen phase	[92]
Methanol extract	*Ecklonia cava*	Lessoniaceae	Whole plant	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of ORS and DPCs and elongation of human hair shaft	Induce anagen phase Upregulate IGF-1 expression	[55]
Enzymatic extract	*Ecklonia cava*	Lessoniaceae	Whole plant	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of human DPCs	Induce anagen phase Inhibit 5α-reductase activity	[48]
Methanol extract	*Chrysanthemum zawadskii*	Asteraceae	Whole plant	*In vivo*	Promote hair growth	Repair the follicular keratin differentiation defect	[93]
70% ethanol extract	*Chrysanthemum zawadskii*	Asteraceae	Whole plant	*In vivo*	Promote hair growth	Promote the proliferation and differentiation of hair matrix	[94]
Methanol extract	*Platycarya strobilacea*	Juglandaceae	Whole plant	*In vivo*	Promote hair growth	Upregulate SCF, IGF-1, KGF, downregulate TGF-β and mast cell production	[95]

DPCs: Dermal papilla cells; HaCaT: Human keratinocytes; IGF-1: Insulin-like growth factor 1; KGF: Keratinocyte growth factor; ORS: Outer root sheath; SCF: Stem cell factor; Shh: Sonic hedgehog; TGF-β: Transforming growth factor; VEGF: Vascular endothelial growth factor.

(Table 2) Contd….

Extract	Botanical Name	Family	Medicinal Part	Observation	Effect	Mechanism of Action	
Water extract	Sophora flavescens	Leguminosae	Root	*In vitro*	Promote the proliferation of HaCaT and elongation of human hair follicles	Not investigated	[96]
85% ethanol extract	*Schisandra nigra*	Schisandraceae	Fruit	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of DPCs	Downregulate TGF-β2 expression	[57]
Ethyl acetate and butanol extract	*Alpinia zerumbet*	Zingiberaceae	Leaf	*In vitro*	Promote the proliferation of hair cells	Inhibit PAK1	[97]
Methanol extract	*Geranium sibiricum*	Geraniaceae	Whole plant	*In vivo* *In vitro*	Promote hair growth Promote the proliferation and migration of human DPCs	Upregulate IGF-1, VEGF, HGF, SCF, ki-67 expression downregulate TGF-β and the number of mast cells	[58]
Vinegar and water extract	*Delphinium staphisagria*	Ranunculaceae	Seed	*In vitro*	Promote proliferation of HaCaT and human endothelial cells	Induce angiogenic activity	[98]
95% ethanol extract	*Rumex japonicus*	Polygonaceae	Root	*In vivo* *In vitro*	Promote hair growth Induced antiapoptsis and proliferation of DPCs and HaCaT	Upregulate Bcl-2/Bax ratio, ERK, Akt, ki-67 and β-catenin, downregulate GSK-3β expression	[99]
75% ethanol extract	*Platycladus orientalis*	Cupressaceae	Leaf	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[100]
Methanol extract	*Acanthopanax koreanum*	Araliaceae	Leaf	*In vitro*	Promote the proliferation of DPCs	Not investigated	[51]
Petroleum ether extract	*Citrullus colocynthis*	Cucurbitaceae	Fruit	*In vivo*	Promote hair growth	Not investigated	[101]
Water extract	*Crataegus pinnatifida*	Rosaceae	Fruit	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of DPCs	Upregulate Bcl-2/Bax ratio, activate MAPK(ERK, p38, JNK) signal pathway to induce anagen phase	[102]
Ethanol extract	*Allium tuberosum Rottler ex Spreng*	Liliaceae	Whole plant	*In vivo*	Promote hair growth	Upregulate IGF-1 expression	[103]
80% methanol extract	*Sargassum muticum*	Sargassaceae	Whole plant	*In vivo* *In vitro*	Promote anagen initiation Promote the proliferation of DPCs	Not investigated	[56]

Akt: Protein kinase B; DPCs: Dermal papilla cells; ERK: Extracellular regulated protein kinases; GSK-3β: Glycogen synthase kinase 3β; HaCaT: Human keratinocytes; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor 1; JNK: c-Jun N-terminal kinase; PAK1: p21-activated kinase 1; MAPK: Mitogen-activated protein kinase; SCF: Stem cell factor; TGF-β: Transforming growth factor; VEGF: Vascular endothelial growth factor.

Extract	Botanical Name	Family	Medicinal Part	Observation	Effect	Mechanism of Action	
Ethanol extract	*Malva verticillata*	Malvaceae	Seed	*In vitro*	Promote the proliferation of DPCs	Activate Wnt/β-catenin signal pathway	[104]
Ethyl acetate extract	*Lycopersicon esculentum*	Solanaceae	Fruit	*In vivo*	Promote hair growth	Not investigated	[105]
Petroleum ether extract	*Glycyrrhiza Glabra*	Fabaceae	Root	*In vivo*	Promote hair growth	Not investigated	[106]
Titrated extract	*Centella asiatica*	Apiaceae	Whole plant	*In vitro*	Promote the proliferation of human DPCs	Inhibit STAT signal pathway	[107]

DPCs: Dermal papilla cells; STAT: Signal transducers and activators of transcription.

Table 3. The Chemical compounds isolated from different plants with hair growth potential.

Chemical Compound	Sort	Botanical Name	Medicinal Part	Observation	Effect	Mechanism of Action	Refs.
Stigmast-5-en-3-O-glucopyranosidetriacetate-51-ol	Petroleumether extract	*Cuscuta reflexa*	Stem	*In vivo* *In vitro*	Promote hair growth Upregulate testosterone level	Inhibit 5α-reductase activity	[83]
Torachrysone-8-O- b-D-glucoside	Ethanol extract	*Polygonum multiflo-rum*	Root	*In vitro*	Promote the proliferation of DPCs	Not investigated	[31]
(E)-2,3,5,4 0-tetrahydroxystilbene-2-O- b-D-glucoside	Ethanol extract	*Polygonum multiflo-rum*	Root	*In vitro*	Promote the proliferation of DPCs	Not investigated	[31]
(Z)-2,3,5,4 0-tetrahydroxystilbene-2-O- b-D-glucoside	Ethanol extract	*Polygonum multiflo-rum*	Root	*In vitro*	Promote the proliferation of DPCs	Not investigated	[31]
Emodin-8-Ob-D-glucopyranoside	Ethanol extract	*Polygonum multiflo-rum*	Root	*In vitro*	Promote the proliferation of DPCs	Not investigated	[31]
Ginsenosides Rb1, Re and Rg1	70% methanol extract	*Panax ginseng*	Root	*In vitro*	Promote proliferation of human DPCs	Upregulate VEGF expression and activate potassium channel	[49]
Ginsenoside Re		*Panax ginseng*	Root	*In vivo*	Promote hair growth	Inhibit TGF-β signal pathway	[59]
Ginsenoside F2	70% methanol extract	*Panax ginseng*	Root	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of human DPCs and HaCaT	Upregulate β-catenin and LEF-1, downregu-late DKK-1 expression	[50]
Dieckol	80% ethanol extract	*Ecklonia cava*	Whole plant	*In vitro*	Promote the proliferation of DPCs	Inhibit 5α-reductase activity	[48]
Dioxinodehydroeckol	Ethyl acetate extract	*Ecklonia cava*	Whole plant	*In vitro*	Promote the proliferation of ORS and DPCs and elonga-tion of human hair shaft	Upregulate IGF-1 expression	[55]
Soyasaponin I	Ethanol extract	*Pueraria thomsonii*	Flower	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[90]
Kaikasaponin III	Ethanol extract	*Pueraria thomsonii*	Flower	*In vivo*	Promote hair growth	Inhibit 5α-reductase activity	[90]
7-Phloroeckol	Methanol extract	*Ecklonia cava*	Whole plant	*In vitro*	Promote the proliferation of ORS and DPCs	Upregulate IGF-1 expression	[108]

DKK: Dickkopf 1; DPCs: Dermal papilla cells; HaCaT: Human keratinocytes; IGF-1: Insulin-like growth factor 1; LEF-1: Lymphoid enhancing factor-1; ORS: Outer root sheath; TGF-β: Transforming growth factor; VEGF: Vascular endothelial growth factor.

Chemical Compound	Sort	Botanical Name	Medicinal Part	Observation	Effect	Mechanism of Action	Refs.
Baicalin		*Scutellaria baicalensis*	Root	*In vitro* *In vivo*	Promote proliferation of human DPCs Promote hair growth	Activate Wnt/β-catenin signal pathway and upre-gualte ALP expression	[109]
Cedrol	70% ethanol extract	*Platycladus orientalis*	Leaf	*In vivo*	Promote hair growth	Not investigated.	[110]
3-Deoxysappanchalcone		*Caesalpinia sappan*	Heartwood	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of human DPCs	Modulate Wnt/β-catenin and STAT signal pathway	[111]
Icariin		*Epimedium Herba*	Leaf	*In vivo* *In vitro*	Promote hair growth Promote the proliferation of HaCaT	Upregulate IGF-1 expres-sion	[112]
Kaempferol-3-O-β-D-glucuronide	Water extract	*Alpinia zerumbet*	Leaf	*In vitro*	Promote the proliferation of hair cells	Inhibit PAK1	[97]

(Table 3) Contd….

Chemical Compound	Sort	Botanical Name	Medicinal Part	Observation	Effect	Mechanism of Action	Refs.
Labdadiene	Hexane extract	*Alpinia zerumbet*	Rhizome	*In vitro*	Promote the proliferation of hair cells	Inhibit PAK1	[97]
2,5-bis(1E,3E,5E)-6-methoxyhexa-1,3,5-trien-1-yl)-2,5-dihydrofuran	Ethanol extract	*Alpinia zerumbet*	Rhizome	*In vitro*	Promote the proliferation of hair cells	Inhibit PAK1	[97]
(E)-2,2,3,3-tetramethyl-8-methylene-7-(oct-6-en-1-yl)octahydro-1H-quinolizine	Methanol extract	*Alpinia zerumbet*	Seed	*In vitro*	Promote the proliferation of hair cells	Inhibit PAK1	[97]
12-methoxycarnosic acid	Hexane and ethyl acetate extract	*Rosmarinus officinalis*	Leaf	*In vivo* *In vitro*	Promote hair growth Upregulate testosterone level	Inhibit 5α-reductase activity	[74]
L-maackiain	Water extract	*Sophora flavescens*	Root	*In vitro*	Promote the proliferation of HaCaT	Not investigated	[96]
Medicarpin	Water extract	*Sophora flavescens*	Root	*In vivo*	Promote the proliferation of HaCaT	Not investigated	[96]
Acankoreoside J	Methanol extract	*Acanthopanax koreanum*	Leaf	*In vitro*	Promote the proliferation of DPCs	Upregulate β-catenin, cyclin D1, cyclin E and CDK2, downregulate $p27^{kip1}$	[51]

ALP: Alkaline phosphatase; CDK2: cyclin-dependent kinases; DPCs: Dermal papilla cells; HaCaT: Human keratinocytes; IGF-1: Insulin-like growth factor 1; PAK1: p21-activated kinase 1; STAT: Signal transducers and activators of transcription.

Chemical Compound	Sort	Botanical Name	Medicinal Part	Observation	Effect	Mechanism of Action	Ref
Apo-9′-fucoxanthinone	Methanol extract	*Sargassum muticum*	Whole plant	*In vitro*	Promote the proliferation of DPCs	Activate Wnt/β-catenin and VEGF-R2 signal pathway, inhibit 5α-reductase activity	[56]
Myristoleic acid	Ethanol extract	*Malva verticillata*	Seed	*In vitro*	Promote the proliferation of DPCs	Upregulate IGF-1, KGF, HGF, and VEGF expression, enhance the phosphorylation of Akt, p38 and CREB	[104]
Forsythiaside-A		*Forsythia suspensa*	Fruit	*In vivo* *In vitro*	Promote hair growth Inhibit the apoptosis of human HaCaT and DPCs	Downregulate TGF-β, caspase-9, caspase-3 and Bax, Upregulate Bcl-2 expression	[113]

Akt: Protein kinase B; CREB: cAMP-response element binding protein; DPCs: Dermal papilla cells; HaCaT: Human keratinocytes; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor 1; KGF: Keratinocyte growth factor; TGF-β: Transforming growth factor; VEGF: Vascular endothelial growth factor; VEGF-R2: Vascular endothelial growth factor- receptor2.

6. SUGGESTED MECHANISMS

6.1. Cytokines Regulation

Hair follicles are the most prominent mini organ of the skin [52], it contains several different types of cells, including the dermal sheath, dermal papilla (DP), outer root sheath (ORS), inner root sheath and matrix cells. The dermal papilla cells (DPCs) are major components of hair, which play a critical role in inducing anagen phase and maintaining hair growth. Several growth factors from the DPCs are known to have the function of modulating the proliferation of follicular epithelium and act as a cytokine network controlling follicle development and hair cycling [42, 53-55]. These growth factors, such as insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF) and transforming growth factor-β (TGF-β), could positively or negatively regulate hair growth. Among them, TGF-β, the most important regulator in hair growth and hair cycle, could induce the transition of the catagen phase in the hair cycle [56]. Some herbs or compounds could modulate the expression of TGF-β to increased hair growth, such as *Schisandra nigra* [57], *Geranium sibiricum* [58] and *ginsenoside Re* [59]. Moreover, stem cell factor(SCF) is also produced by DPCs and participate in the growth of hair follicles [60].

6.2. Signal Pathway Regulation

The Wnt/β-catenin pathway is known to be important for the initiation, development, and growth of hair follicles and has a significant role in anagen induction [61]. β-catenin, the transducer of Wnt signaling, plays an essential role in the proliferation of hair follicles [62]. Binding of Wnt ligand to the Frizzled receptor and lipoprotein receptor-related protein (LRP) on the cell surface leads to the inhibition of glycogen synthase kinase-3β (GSK-3β) activity and stabilization of β-catenin in the cytosol [63, 64]. The final effect of Wnt pathway is to activate the transcription of downstream target genes by combining β-catenin with T-cell factor/lymphoid-enhancing factor-1(TCF/LEF-1) in the nucleus [65]. Indeed, LEF-1 has been demonstrated to have potent to regulate the growth of hair follicles [66]. However, evidence strongly indicates that Dickkopf-1 (DKK-1) could inhibit Wnt signaling pathway [67]. Consequently, increasing LEF-1 and inhibiting DKK-1 or GSK-3β may enhance hair growth via β-catenin accumulation. Another critical anagen-

inducing signaling molecule involved in the proliferation of hair follicles is Sonic hedgehog (Shh). It was reported that the water extract of *Polygonum multiflorum* could promote hair growth by inducing the anagen phase via upregulating Shh and β-catenin in telogenic C57BL6/N mice [68]. In addition, signal transducer and activator of transcription (STAT) and its upstream regulator Janus kinase (JAK) can mediate the hair cycle. It is reported that inhibition of JAK-STAT pathway results in rapid onset of anagen and subsequent hair growth by stimulating the activation and/or proliferation of hair follicular stem cells [69]. 3-Deoxysappanchalcone, isolated from *Caesalpinia sappan*, could promote proliferation of DP and stimulate hair growth partly through activation of Wnt/β-catenin signaling and inhibition of STAT6-mediated quiescence of hair follicular cells [52].

6.3. Hormonal Regulation

As we know, 5α-reductase is a microsomal enzyme that catalyzes the conversion of testosterone to DHT, which binds to AR and induce the apoptosis of hair follicles cells through stimulating the transcription of TGF-β and DKK-1 [70-72]. The present study also shows that DHT could decrease IGF-1 production in DP through interaction with AR to inhibit hair growth in mice [73]. Therefore, inhibition of 5α-reductase is recognized as a suitable treatment, as well as inhibiting the binding of DHT and AR in the treatment of AGA. For example, *Rosmarinus officinalis* leaf extract and 12-methoxycarnosic acid promote hair growth in an AGA model and inhibit androgen-dependent proliferation of LNCaP cells, suggesting that they inhibit the binding of DHT to AR [74].

From the above discussion, the underlying mechanisms of medicinal plants or their active compounds to promote hair growth could induce the proliferation or inhibit the apoptosis of hair follicular cells by stimulating or suppressing growth factors, cytokines, hormones, an enzyme as well as modulating signaling pathways. More evidence is needed to confirm or find new mechanisms for treating hair loss. The common mechanisms for treating hair loss are showed in Fig. **1**.

CONCLUSION AND PERSPECTIVES

This article has presented the lists of the extracts and constituents from various plants in the treatment of hair loss. Although many natural drugs have been discovered, it is still necessary to search for novel hair promotion agents with more effective and less toxicity. Furthermore, the underlying mechanisms of many compounds with hair-growth promotion activity have not been studied or elucidated in detail.

Although some common molecular signal pathways and several distinct targets have been disclosed, the responses of molecular targets to compounds remain unclear. Recent studies focusing on molecular targets of the plant-derived compounds have yielded promising results, but the details of the anti-hair loss mechanisms involved need to be clarified further. Meanwhile, the preclinical and clinical studies need to be carried out to determine their anti-hair loss potential.

Novel information gathered from the current data is important to protect the folk indigenous knowledge and discover novel and more effective compounds against hair loss. Therefore, the purpose of this review was to present and analyze the plant species against hair loss. The extract and CC of plants, medicinal part of plants, effect and underlying mechanism are given in Table **2** and Table **3**. Even though some effective hair-growth promotion drugs have been developed from botanical sources, there still remains an untapped resource in herbal medicines. Although some bioactive components of diets or medicinal plants have been identified for their hair growth promoting potential, many others remain unknown

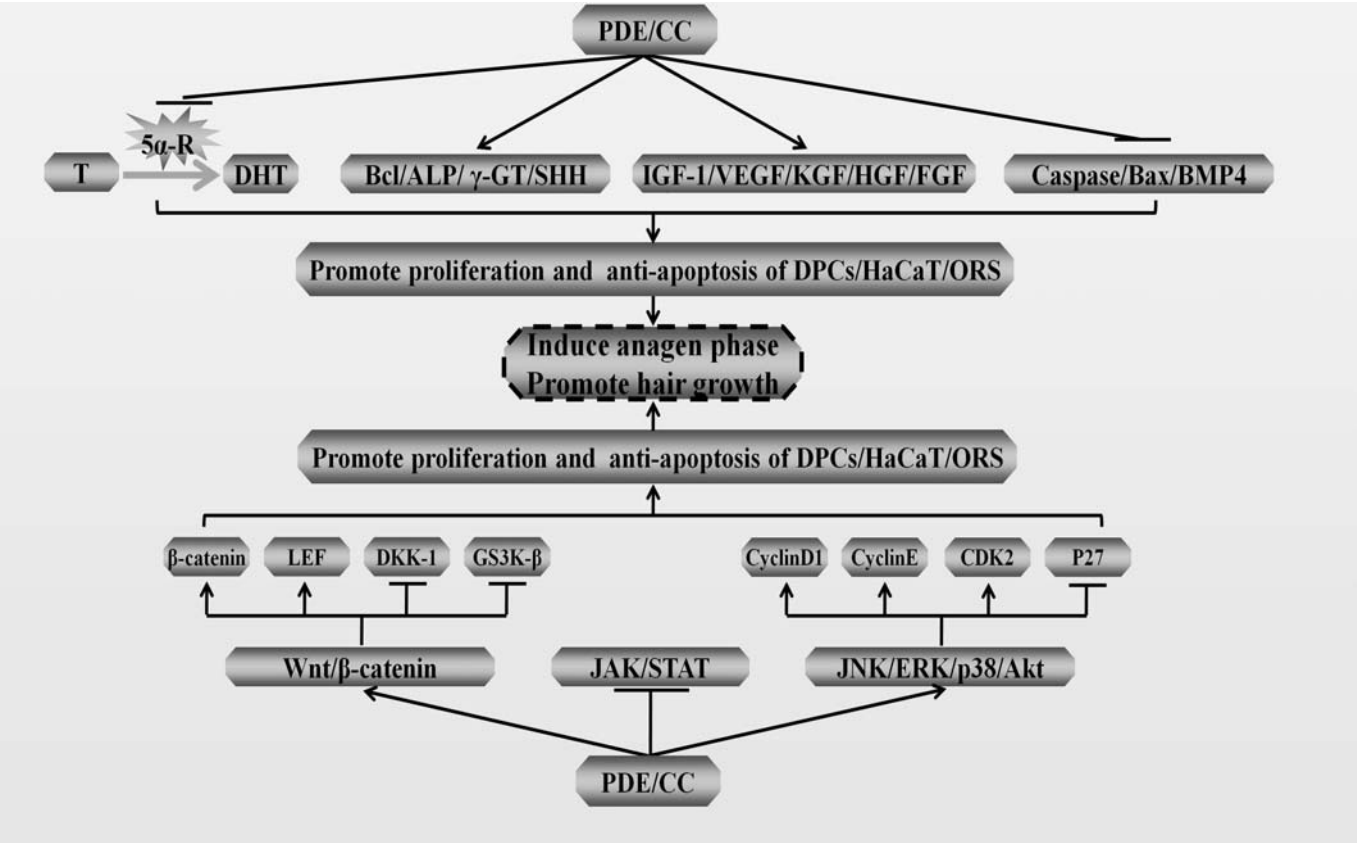

Fig. (1). The schematic diagram of the Promote hair growth effects of PDE/CC.

and/or untested. Therefore, numerous plants deserve further investigations *in vitro* and *in vivo* due to their significant anti-hair loss activity.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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