

# Hair loss and herbs for treatment

Nattaya Lourith, PhD & Mayuree Kanlayavattanakul, PhD

School of Cosmetic Science, Mae Fah Luang University, Chiang Rai, Thailand

## Summary

*Baldness* or androgenetic alopecia directly distresses self-confidence affecting the individual's quality of life. Hair loss is therefore a significant psychosocial manifestation that worth much expense on treatment. Androgenetic alopecia is noticed as a slow transformation of large scalp terminal hair follicles to shorter, thinner, and less deep vellus hair with a much shorter anagen. Although minoxidil, finasteride, and dutasteride including other synthetic therapeutic agents are mostly used for alopecia treatment, their adverse effects encourage sorting of alternative efficient treatment agent with a limited side effect particularly herbs. Thus, this review briefly summarized causes of hair loss and emphasized on active ingredients for treatment in particular currently used herbs and the potential candidates. Treatment choices will be further wider and conclusively select herbs that fitting the consumers' preference.

*Keywords:* androgenetic alopecia, baldness, hair loss, herbal cosmetics

## Introduction

Human hair plays an important role in social and sexual communication with pronounced differences between ages and sexes in addition to protective function.<sup>1,2</sup> Baldness or androgenetic alopecia (AGA) as well as the other androgenic control on hair growth directly distresses self-confidence affecting the individual's quality of life<sup>3</sup> of which Caucasian men are largely affected.<sup>4</sup> The significant psychosocial manifestation of hair loss<sup>5</sup> worth much expense on treatment.<sup>6</sup> Thus, this review summarizes therapeutic agents and proposes those of natural remedies extensively herbs potential for hair loss treatment with a briefly details of hair loss.

## Causes of hair loss

Hair undergoes cyclic periods of growth which are anagen, catagen, and telogen. The longest phase is

anagen varied with species and body site. That, scalp anagen hair may last for longer than 3 years,<sup>7</sup> whereas finger anagen lasts longest only 3 months.<sup>8</sup> Human hair growth is altered by thyroid and those of pregnancy hormones including androgens as well. Pregnancy hormones maintain hair follicles in anagen and after parturition getting back the follicles to catagen and telogen resulting in hair shedding.<sup>9</sup> The genetic precisely influences androgen affecting hair growth, of which male pattern baldness<sup>10</sup> and heavy beard growth are obviously similar in families.<sup>11,12</sup> Although there are several disorders causing hair loss as there were extensively presented and discussed<sup>7–14</sup> regarding pattern alopecia<sup>15</sup> including hypotheses on skull expansion relating to alopecia<sup>16</sup> and the clinical evaluation,<sup>17</sup> AGA is the main focus of this article respecting to its clinical importance.

Androgen regulates vellus hair changing into terminal hairs which are longer, thicker, and darken in color.<sup>12</sup> However, this hormone functions differently on the scalp by hair follicles regression turning terminal hairs into vellus ones. The severity directly relates with age, that is, androgenetic alopecia that widely recognized as male pattern baldness.<sup>9–12</sup> Androgenetic

\*Correspondence: N Lourith, School of Cosmetic Science, Mae Fah Luang University, Chiang Rai 57100, Thailand. E-mail: 'nattayal@mfu.ac.th

Accepted for publication March 30, 2013

alopecia (AGA) is noticed as a slow transformation of large scalp terminal hair follicles to shorter, thinner, and less deep vellus hair with a much shorter anagen. A histopathological study reveals that follicular micro-inflammation plays an integral role in the AGA in early cases<sup>14</sup> particularly IL-1 $\alpha$ .<sup>18</sup> AGA is well defined on male and female scalp.<sup>17</sup> In men, the initial frontal recession is followed by balding on the crown or central scalp and vertex. The hair loss in men is discrete in frontal, temporal, mid, and vertex,<sup>11</sup> which associated in easily assignment of Hamilton–Norwood hair loss pattern.<sup>17</sup> The occipital and parietal regions are often uninvolved. In women, baldness frequently begins on the top of the head. Hair density diffusing starts without the temporal recession. Besides the Ludwig hair loss pattern,<sup>19</sup> which profound in a late stage of hair loss, a frontal accentuation of hair loss or Christmas tree pattern is commonly present preliminary.<sup>20</sup> Unlike men, women with mild-to-moderate hair loss do not have the same degree of hair miniaturization in affected scalp areas.<sup>11</sup> Determination of hair loss by measuring of hair width on scalp or Savin scale is well assisted in clinical diagnosis.<sup>12,13,20</sup> However, it is different from age associated in hair thinning<sup>21</sup> with a decline of anagen follicles and hair diameter.<sup>22</sup> In men without hair loss, a terminal hair (>40  $\mu$ m diameter) should occupy  $276 \pm 10/\text{cm}^2$  at age 18–32 years old<sup>23</sup> and hair density at a midtop scalp of normal women age 35 years old is  $293/\text{cm}^2$ ,<sup>24</sup> as observed in Caucasian.

Testosterone (T), a major male androgen, enzymatically converts to 5 $\alpha$ -dihydrotestosterone (DHT) by 5 $\alpha$ -reductase with NADPH as a cofactor prior to bind with androgenic receptor.<sup>25</sup> Further transcription of androgen-dependent genes exhibits baldness<sup>26</sup> of which 5 $\alpha$ -reductase and androgen receptor (AR) are clearly involve in baldness.<sup>27–29</sup> There are 5 $\alpha$ -reductase type I and type II, which differently convert weak androgen (T) into more potent androgen (DHT)<sup>27</sup> respecting to a localization ability of these isozymes in sebaceous glands and hair follicles that potently to mediate androgen action.<sup>30</sup> 5 $\alpha$ -reductase type I is found predominantly in the scalp, whereas type II is largely distributes in hair follicles and the prostate.<sup>31</sup> In addition to T that is enzymatically metabolized into 5 $\alpha$ -DHT, dehydroepiandrosterone (DHEA) is potentially converted into T. T is subsequently metabolized causing baldness.<sup>32</sup> Other enzyme relating to hair loss is aromatase located in the other root sheath of hair follicles. Aromatase converts T (precursor of DHT) and androstenedione to estrogens estradiol and estrone, respectively. This therefore explains less severity of

hair loss in women who have 2–5-folds greater in aromatase than men confirming frontal hairline sparing in women accordingly.<sup>33</sup> Thus, overall causes of hair loss are androgen, genetic, and age. The readers would find more details regarding molecular mechanism of androgenetic alopecia that had been presented elsewhere.<sup>34</sup>

## Therapeutic agents for alopecia

Ideal treatment for hair loss is a combination of 5 $\alpha$ -reductase inhibitors with hair growth promoter substances.<sup>9</sup> Treatment for hair loss is different from other dermatology disorders for instance psoriasis and atopic dermatitis as it will need a longer period of treatment until significant improvement has been noticed.<sup>35</sup> Anti-androgen mechanisms are generally categorized into three actions; either inhibit or trap DHT or inhibit 5 $\alpha$ -reductases or AR blocking.<sup>32</sup>

Treatment for AGA was firstly success in women using a combination of cyproterone acetate and estrogen. This treatment induced the number of hair follicles in anagen phase.<sup>35</sup> On the meantime, minoxidil was found to stimulate hair growth in men.<sup>36–38</sup>

Minoxidil, 2,6-diamino-4-piperidinopyrimidine 1-oxide, is commercialized in regaine/rogaie for alopecia treatment.<sup>37</sup> Although it was found effective on hair growth stimulation, several adverse effects were extensively summarized.<sup>38</sup> This vasodilator agent induces hair growth by potassium channel opening with stimulating effect on hair follicles. The ratio of anagen/telogen was increased.<sup>39</sup> Minoxidil treatment had been reported to widen hair diameter at which 5% topical application was highly effective in men, whereas 2% was appropriated in women.<sup>40,41</sup> Therefore, these concentrations were recommended. Respecting to the widely used of minoxidil, the mechanism of actions toward alopecia was extensively studied and reviewed.<sup>38</sup> In addition, tretinoin, a hair growth promoter,<sup>42</sup> was used as minoxidil enhancer by increasing absorption efficacy.<sup>43,44</sup>

Finasteride is the 5 $\alpha$ -reductase type II inhibitor by an induction of scalp T reducing scalp and serum DHT consequently.<sup>45,46</sup> The recommended dose is 1 mg/day for anagen hair induction<sup>47</sup> and hair weighten<sup>48</sup> without a serious adverse effect and drug interaction in men unless negative effect on sperm<sup>49</sup> and sexual side effects. However, strictly use is needed to be concerned in female particularly in expecting mothers.<sup>38</sup>

Modification of a treatment agent was achieved diminishing drawback effects of finasteride yielding dutasteride. Dutasteride significantly reduced hair loss

progression<sup>50</sup> by inhibiting both isozymes of 5 $\alpha$ -reductases with a stronger activity against type II and type I by 3- and 100-folds compared with finasteride.<sup>51</sup> This potent activity was relevant to serum DHT reduction that was highly affected by dutasteride of which 0.5 mg daily was the recommended dose.<sup>50</sup> However, it may accumulate in prostate cancer setting.<sup>52</sup> In addition, expecting women should refrain from this agent treatment in similar to the above agents, although dutasteride found no serious effect on sperm.<sup>38</sup>

Spironolactone was used as orally treatment for AGA, hirsutism, and acne at a dose of 100 mg/day.<sup>53</sup> Although it was found more effective than finasteride<sup>54</sup> but less than flutamide,<sup>55</sup> it poses adverse reactions and drug interactions.<sup>32</sup> Furthermore, later study found no significant on hair regrowth.<sup>56</sup>

Flutamide, a nonsteroidal anti-androgen, works in 2-hydroxyflutamide form by blocking the binding between DHT and AR.<sup>57</sup> It is the treatment for choice when hair loss and hirsutism are associated.<sup>58,59</sup> Similar to spironolactone, it not only poses adverse reactions but also drug interactions.<sup>32</sup>

Anti-androgen and androgen inhibitor capability were performed by progesterone that has similar structure to T leading similar affinity toward AR and T. However, topical application of progesterone found rarely improves on AGA treatment.<sup>32</sup>

Cyproterone suppresses balding by a competitive action with DHT for AR binding in a less efficacy compared with minoxidil.<sup>60</sup> However, its adverse effect in pseudohermaphroditism is similar to the above agents.<sup>32</sup>

Cimetidine that has anti-androgen property binding to AR was used at a dose of 800–1600 mg per day. However, this agent poses adverse effect on libido and impotence as others.<sup>57</sup> In addition, hair loss treatment efficacy of cimetidine may be of anecdotal value that negative feedback mechanism increases androgen secretion and needed a strictly controlled of clinical evaluation.<sup>59</sup>

Mineral salt also imply in hair loss treatment. Zinc sulfate was found to inhibit DHT production and deduce NADPH.<sup>61</sup>

In addition to zinc salt, vitamin is associating in hair growth particularly in female pattern alopecia. Topically, application of niacins significantly increased hair density widens options for female alopecia treatment.<sup>62</sup>

Aminexil or 2,4-diaminopyrimidineoxide was claimed on deduction of telogen hair with anagens inducible activity and prolong hair follicle age as well.<sup>63</sup>

Ketoconazole, a well-known antidandruff agent, was reported to improve alopecia,<sup>62,63</sup> but its mechanism of action remains unclear.

Cyclosporin A functions as a potent immune suppressive agent and an antihypertensive agent with a stimulating effect on hair growth similar to minoxidil.<sup>64</sup> It remodels injured hair follicles in anagen phase by restarting hair production instead of turning into telogen hair.<sup>65</sup>

Functions of therapeutic agents used for hair loss treatment are therefore summarized as shown in Table 1. Those with clinical evidences are concluded in Table 2. In addition to those mentioned, there were several anti-androgen agents mainly steroids and nonsteroid compounds had been synthesized and *in vitro* evaluated on their activities. Selective 5 $\alpha$ -reductase type I inhibitor, MK386 or (4,7-dimethyl-4-azacholestane-3-one), was evaluated resulting in IC<sub>50</sub> against type I and type II of <20 and 3100 nM, respectively.<sup>68</sup> Furthermore, PNU157706 or N-(1,1,1,3,3,3-hexafluorophenylpropyl)-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide, a dual 5 $\alpha$ -reductase type I and II (IC<sub>50</sub> = 3.9 and 1.8 nM) was more potent than finasteride (IC<sub>50</sub> = 313 and 11.3 nM).<sup>69</sup> A number of anagen follicles were found increased with a reduction of telogen follicles including density, thickening, and length inductions of hair by a nonsteroidal anti-androgen, RU58841, following topical application on bald scalp.<sup>70</sup> In addition, 3-carboxy-20-keto steroids and indole-3-alkanoic acids were found potently inhibited 5 $\alpha$ -reductase.<sup>71,72</sup> Structural development of 3-substituted pregna-4,16-diene-6,20-dione derivatives consisting of finasteride core structure was carried out to improve affinity against 5 $\alpha$ -reductase.<sup>73</sup> Furthermore, 3,3-diphenylpentane skeleton was used in structural development and found that 4-(3-(4-(N-methylacetamido)phenyl)pentan-3-yl)phenyl dibenzylcarbamate showed a great activity against 5 $\alpha$ -reductase type I at IC<sub>50</sub> of 0.84  $\mu$ M.<sup>74</sup> However, clinical evaluation of these steroids on toxicity should be clarified for their safety. To avoid side effects of steroidal agents,<sup>75</sup> 7-hydroxycoumarin derivatives were synthesized and evaluated on inhibitory effect against 5 $\alpha$ -reductase that posed potent activity particularly toward type I<sup>76</sup> as well as pyridones with a substitution at 4'-position enhanced inhibitory efficacy.<sup>77</sup> In addition, biphenyl compounds were found potently against 5 $\alpha$ -reductase type II at a low concentration.<sup>78</sup> Despite there are several patents claim on alopecia treatment by syntheses and application of anti-androgen agents, biological clarifications are needed because contrary results were indicated.<sup>79</sup>

**Table 1** Functions of actives in hair loss treatment

Compound	Function
Minoxidil	Vasodilator (long-lasting anagen)
Finasteride	5 $\alpha$ -reductase type II inhibitor
Dutasteride	5 $\alpha$ -reductase inhibitor
Flutamide	AR blocker
Cyproterone	AR blocker
Cimetidine	AR blocker
Zinc	hair growth promoter, 5 $\alpha$ -reductase type I inhibitor
Niacin	Hair growth promoter
Aminexil	anagen prolongation, telogen deduction
Ketoconazole	AR blocker
Cyclosporin A	hair growth stimulator, anagen promoter

Although minoxidil and finasteride are the most widely used agents for alopecia treatment,<sup>7,38</sup> their undesired adverse effects encourage sorting of alternative efficient treatment with a limited side effect. In addition, gene therapy had been discussed and found appropriated for hair follicle treatment.<sup>6</sup> In addition, several treatments particularly herbal remedies have been provoked.<sup>80–82</sup>

### Biologically actives and herbs for hair loss treatment

Aliphatic unsaturated fatty acids were found specifically inhibited 5 $\alpha$ -reductase.<sup>83,84</sup> The essential fatty acids, which are linolenic, linoleic, palmitoleic, oleic, myristoleic, and stearic acids, are claimed on their 5 $\alpha$ -reductase inhibitory effect<sup>85</sup> and hair regrowth promoter particularly linolenic acid. Linolenic acid is used as a positive control on 5 $\alpha$ -reductase inhibitory activity

accordingly. In addition, vitamin B, phytoestrogens, and iron are complementary treatments of hair loss.<sup>59</sup>

Essential oils were traditionally incorporated in hair care product giving shine and conditioning effects. Rosemary, West Indian bay and chamomile oils are able to improve hair growth as well as lavender and bergamot oils that used for dandruff treatment.<sup>86</sup> Tea tree oil was used for dandruff treatment as it possesses antifungal properties<sup>87</sup> with anti-inflammatory effect<sup>88</sup> accumulating in hair loss protection. A combination of essential oils with a light massage of the scalp was found effectively improved AGA. The blend of *Pimenta racemosa*, *Myrtus communis*, *Cedrus atlantica*, *Laurus nobilis*, *Pogostemon patchouli*, *Rosmarinus officinalis*, *Salvia officinalis*, *S. sclarea*, *Thymus satureioides*, *Cananga odorata*, and electromagnetic pulse increased hair density and ratio of anagen hair per total hair.<sup>89</sup> Fatty acids in essential oils<sup>90</sup> are responsible to this activity. Traditional aromatherapy massage on scalp with a combination of *T. vulgaris*, *Lavendula angustifolia*, *R. officinalis* oils in jojoba, and grape seed oils was found significantly increased hair growth<sup>91</sup> in addition to an application with electromagnetic pulse-enhancing absorption.<sup>89</sup>

*Serenoa repens* or saw palmetto, a 5 $\alpha$ -reductase inhibitor,<sup>92</sup> was commercialized in Permixon®, which is a lipido-sterolic extract containing high essential fatty acids content<sup>85</sup> with phytosterols,  $\beta$ -carotene, and tocopherols including  $\beta$ -sitosterol.<sup>93–95</sup> This phytotherapeutic agent for hair loss treatment is very popular in Germany and France<sup>82,96</sup> and found effective without any enhancer.<sup>97</sup> Although there was hepatotoxicity of saw palmetto reported in rat,<sup>98</sup> its confirmed safety was later proven.<sup>99</sup>

**Table 2** Clinical study of active compound in hair loss treatment

Compound	Type of study	Subject	Duration	References
Minoxidil	<i>In vivo</i> , randomized double-blind placebo-controlled	393 men	48-week	40
Finasteride	<i>In vivo</i> , randomized double-blind placebo-controlled	212 men	48-week	47
		66 men	192-week	48
Dutasteride	<i>In vivo</i> , randomized double-blind placebo-controlled	34 men	48-week	50
Flutamide	<i>In vivo</i> , randomized double-blind	46 women	48-week	58
Cyproterone	<i>In vivo</i> , randomized double-blind	66 women	48-week	60
Zinc	<i>In vitro</i>	na		61
Niacin	<i>In vivo</i> , randomized double-blind placebo-controlled	60 women	24-week	62
Aminexil	<i>In vivo</i> , randomized single-blind placebo-controlled	351 men	24-week	63
Ketoconazole	<i>In vivo</i>	27 men	21-week	64
		6 men	24-week	65
Cyclosporin A	<i>In vivo</i>	Female and male mice		66,67

na, not available.



Pygeum (*Pygeum africanum*) has been commercialized vastly in Europe in Tadenan<sup>®100</sup> because it is a 5 $\alpha$ -reductase inhibitor.<sup>101,102</sup> However, effective treatment for *P. africanum* individually or in combination is worth further discussed.<sup>103</sup>

Stinging nettle (*Urtica dioica*) was used as a traditional remedy in Europe<sup>104</sup> and commercialized in many dosage forms<sup>102</sup> as it possesses anti-androgenetic effects<sup>105–107</sup> according to its biologically active phenolics, fatty acids, phytosterols, and lignans.<sup>108–112</sup> Although an adverse effect of its treatment is very low, complete clinical safety should be conducted.<sup>104</sup>

Naturally derived compounds posing efficiency in hair growth promoter and prevention of hair loss as well are additionally included as shown in Table 3. In particular, functions of the above commercialized herbs for alopecia are summarized in Table 4.

### Candidate herbs for hair loss treatment

In addition to the above well-known herbs, those with a potential activity candidate for hair loss treatment are included.

Natural saponin from *Acacia concinna* imparts its application in hair cleansing with additional benefit on antidandruff including adequate activity inhibited 21% of 5 $\alpha$ -reductase at 200  $\mu$ g/mL.<sup>113</sup>

Topical application of onion (*Allium cepa*) juice on scalp was found effectively stimulated hair regrowth both in male and female.<sup>114</sup> This might be regulated by its anti-inflammatory and antimicrobial effects due to its flavonoids.<sup>115–117</sup>

Benign prostatic hyperplasia could be treated by garlic (*Allium sativum*) respecting to its anti-inflammatory and antioxidant effects.<sup>118</sup> In addition, it was used for dandruff controlling regarding to its antimicrobials.<sup>119</sup>

*Aloe vera* gel was traditionally used for hair loss, and it was claimed to improve hair growth following alopecia<sup>120</sup> respecting to aloenin that promotes hair growth without irritation<sup>121</sup> including its enrichment in multivitamin B.<sup>122</sup>

*Artocarpus incisus* showed potent 5 $\alpha$ -reductase inhibitory activity.<sup>113</sup> The constituents were characterized as chlorophorin, artocarpin, and chalcone with IC<sub>50</sub> of 37, 85, and 104  $\mu$ M, respectively.<sup>123,124</sup>

*Asiasari radix* is an oriental medicine for treating hair loss because it has hair growth-promoting potential stimulating telogen to anagen transformation with cellular proliferation induction.<sup>125</sup>

Tea (*Camellia sinensis*) has been continuously used and very famous as a daily beverage according to its pharmacological properties.<sup>126,127</sup> Polyphenolic compounds in tea significantly increased hair regrowth.<sup>128</sup> Catechins are biologically active ingredient in green tea possess several activities including aromatase inhibition.<sup>129</sup> Furthermore, epigallocatechin-3-gallate, which is a main constituent of polyphenols in tea, was reported on its potential of AGA by an inhibition of 5 $\alpha$ -reductase<sup>130</sup> with hair growth enhancing in human.<sup>131</sup>

Capsaicin from chili (*Capsicum frutescens*) was found to accumulate in hair follicle results in anagen induction<sup>132</sup> and promoted hair growth in volunteers with alopecia.<sup>133</sup>

Inhibition of 5 $\alpha$ -reductase was reported by *Cimicifuga racemosa* or black cohosh extract of which more potent than finasteride.<sup>134</sup>

Butterfly pea or *Clitoria ternatea*, which is a natural antioxidant, has been used as a folk lore for gray hair recovery in Thailand. However, its activity against 5 $\alpha$ -reductase is moderate as only 29% of enzyme was inhibited at the extract concentration of 200  $\mu$ g/mL.<sup>113</sup>

**Table 3** Natural-derived compounds imparting hair growth improvement

Compound	Herb
Fatty acids: linolenic, linoleic, palmitoleic, oleic, myristoleic and stearic acids	<i>Pimenta racemosa</i> , <i>Myrtus communis</i> , <i>Cedrus atlantica</i> , <i>Laurus nobilis</i> , <i>Pogostemon patchouli</i> , <i>Rosmarinus officinalis</i> , <i>Salvia officinalis</i> , <i>S. sclarea</i> , <i>Thymus satureioides</i> , <i>Cananga odorata</i> , <i>T. vulgaris</i> , <i>Lavendula angustifolia</i> , <i>Serenoa repens</i> , <i>Urtica dioica</i> , <i>Ocimum sanctum</i> , <i>Persea americana</i> , <i>Roystonea regia</i> , <i>Thuja occidentalis</i> , <i>Zizyphus jujuba</i>
Vitamin B	<i>Aloe vera</i> , <i>Persea americana</i>
Phytoestrogens: isoflavone; daidzein, genistein, glycitein lignans; enterodiol, enterolactone	<i>Serenoa repens</i> , <i>Urtica dioica</i> , <i>Cucurbita</i> spp.
Proanthocyanidins	<i>Vitis vinifera</i>
Capsaicin	<i>Capsicum frutescens</i>
(–)-Epigallocatechin-3-gallate	<i>Camellia sinensis</i>
Soymethide-4	<i>Glycine max</i>

**Table 4** Herbs with biological activities potential for hair loss treatment

Herb	Activity	Remark
<i>Serenoa repens</i>	5 $\alpha$ -reductase inhibitor	Commercial available
<i>Pygeum africanum</i>	5 $\alpha$ -reductase inhibitor	
<i>Urtica dioica</i>	5 $\alpha$ -reductase inhibitor	
<i>Acacia concinna</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Allium cepa</i>	Hair growth stimulator, anti-inflame, antimicrobial	<i>In vivo</i> , single blind in human volunteers, 4 week
<i>Allium sativum</i>	Anti-inflame, antioxidant, antimicrobial	<i>In vitro</i>
<i>Artocarpus incisus</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Asiasari radix</i>	Cellular proliferator, telogen transformer to anagen	Mice
<i>Camellia sinensis</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i> , Human volunteers, 3-day
<i>Capsicum frutescens</i>	Anagen induction	Mice, human volunteers, 20-week
<i>Cimicifuga racemosa</i>	5 $\alpha$ -reductase inhibitor	Rat
<i>Clitoria ternatea</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Citrus hystrix</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Cuscuta reflexa</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Elipta alba</i>	Increase hair follicle number and scalp thickness, anagen induction	Mice
<i>Ganoderma lucidum</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Ginkgo biloba</i>	Hair regrowth promoter, epidermis growth stimulant, astringent, anti-inflame	Mice
<i>Glycyrrhiza glabra</i>	DHT inhibitor, anti-inflame	<i>In vitro</i>
<i>Junglan regia</i> and <i>Junglan nigra</i>	Scalp itching and peeling treatment, antidandruff	Traditional used
<i>Lawsonia inermis</i>	Hair growth promoter	Traditional used
<i>Ocimum sanctum</i>	Anti-inflame	Active constituent
<i>Panax ginseng</i>	Anti-inflame, cell proliferation improvement, prolong anagen hair	Mice
<i>Persea americana</i>	Anti-itching, antidandruff, sebum reduction, 5 $\alpha$ -reductase inhibitor	Human cell cultures
<i>Rosmarinus officinalis</i>	Sebum reduction, antioxidant, antidandruff	<i>In vivo</i> , randomized double-blind placebo-controlled, 28-week
<i>Roystonea regia</i>	5 $\alpha$ -reductase inhibitor	<i>In vitro</i>
<i>Salvia officinalis</i>	Hair growth stimulator, antidandruff	<i>In vivo</i> , randomized double-blind placebo-controlled, 26-week
<i>Sophira flavescens</i>	5 $\alpha$ -reductase inhibitor	Mice, human hair dermal papilla cell cultures
<i>Thuja occidentalis</i>	5 $\alpha$ -reductase inhibitor	Rat, mouse and cell cultures
<i>Vitis vinifera</i>	Hair follicle proliferation stimulator, telogen transformer to anagen	Mice
<i>Zizyphus jujuba</i>	Hair growth promoter	Mice

*Citrus hystrix* is able to smooth skin and scalp suppressing antidandruff with exfoliation refreshing effect. Despite it is Thai folk remedy for hair loss, it posed moderately 5 $\alpha$ -reductase inhibitory activity but higher (25%) than *C. ternatea* at the same concentration.<sup>113</sup>

Pumpkin (*Cucurbita* spp.) contains several phytosterols with depressive function against androgenetic-mediated diseases<sup>135</sup> because its carotenoids and fatty acids that suppress androgenetic expression as prostate cancer<sup>136</sup> particularly its high content of linoleic, oleic, palmitic, and stearic acids.<sup>137,138</sup>

*Cuscuta reflexa*, a traditional purgative herb in Indian exhibited hair growth promotion via 5 $\alpha$ -reductase inhibitory effect. Although its IC<sub>50</sub> was higher than finasteride (1.78 mg and 0.77  $\mu$ g), this herbal extract

was highlighted as a potential agent promising for hair loss treatment.<sup>139</sup>

*Ganoderma lucidum* is a mushroom that has been used as a folk medicine in East Asia<sup>140</sup> was found dual inhibition against both isozymes of 5 $\alpha$ -reductase<sup>141</sup> respecting to its triterpenoids.<sup>142</sup>

*Ginkgo biloba* is another universal natural remedy, which has been used as hair regrowth promoter with its epidermis growth stimulant, astringent, anti-inflammatory, and radical activities.<sup>143</sup>

Soy (*Glycine max*) protein particularly soymetide-4 isolated from trypsin digestion was one of herbal product-suppressing alopecia.<sup>144</sup>

*Glycyrrhiza glabra* or licorice was traditionally used for hair loss treatment as it inhibits DHT formation in

addition to its anti-inflammatory effects respecting to glycyrrhizin and glycyrrhetic acid.<sup>145,146</sup>

Walnuts (*Juglan regia* and *J. nigra*) were used to treat scalp itching and peeling relevant to dandruff, which accumulate in hair loss.<sup>147</sup>

Natural red shades color herb, henna (*Lawsonia inermis*), was used as hair growth accelerator since ancient time.<sup>148,149</sup>

Holy basil (*Ocimum sanctum*), the natural anti-inflammatory agent, containing linolenic acid highlighting its capability to treat hair loss.<sup>150</sup>

Cell regeneration herb, ginseng (*Panax ginseng*), with anti-inflammatory and blood circulation effect was also used for skin and scalp treatment limiting hair loss.<sup>151</sup> Potential of ginseng extract contributing in hair regeneration was again confirmed in cell proliferation improvement including an *in vivo* efficacy evaluation in animal at 1 mg/mL topical application on mice regulated earlier anagen phase and prolong the mature anagen phase comparable to 5% minoxidil.<sup>152</sup>

Avocado (*Persea americana*) was known for anti-itching and antidandruff that indirectly accumulated in hair loss. In addition, it's capable to reduce sebum secretion that explains antidandruff property. Furthermore, 5 $\alpha$ -reductase type I was found to deactivate by Avocado. Biological activities of Avocado particularly against androgenetic expression<sup>153</sup> rely on its fatty acid constituents, vitamin B, and other biologically active compounds.<sup>154,155</sup>

*Rosmarinus officinalis* or rosemary that was reported to increase hair growth<sup>91</sup> was further evaluated for alopecia treatment individually. It stimulated hair growth with a reduction of sebum secretion, which additionally suitable for greasy hair treatment. Rosmarinic acids and other caffeic acid derivatives in rosemary are responsible for the biological activities according to their antioxidant effects.<sup>156</sup> Furthermore, rosemary can be daily used for dandruff treatment.

*Roystonea regia* or Cuban royal palm is fatty acid enrichment that inhibits 5 $\alpha$ -reductase.<sup>157–159</sup>

Sage (*S. officinalis*) in a combination with other herbs increased hair density.<sup>89</sup> Sage itself was traditionally used for hair conditioning as it maintains the sheen of curly hair, strengthens and stimulates hair growth in addition to its ability for dandruff, hair loss, and gray hair treatment.<sup>148</sup>

*Sophira flavescens* is another oriental medicine for hair loss treatment, which proven on hair growth promoting by 5 $\alpha$ -reductase type II inhibitory effect.<sup>160</sup>

*Thuja occidentalis* was found potently inhibit 5 $\alpha$ -reductase type II at the IC<sub>50</sub> of 2.6  $\mu$ g/mL, which stronger than linolenic acid (a positive control).<sup>161</sup>

Grape (*Vitis vinifera*) seeds contain many biologically active compounds including polyphenolic proanthocyanidins that consequently convert to procyanidins which posse stronger antioxidative effect.<sup>162</sup> Proanthocyanidins from grape seeds stimulated hair follicle proliferation and accelerated hair converting from telogen to anagen phases.<sup>163</sup>

Hydrodistillation of *Zizyphus jujuba* seed giving essential oil that potentially promoted hair length, diameter, and density following clinical evaluation in mice particularly at 1% treatment. This hair-promoting efficacy would be delineated by fatty acid constituents including palmitic, oleic, linoleic, linolenic, and arachidonic acids.<sup>164</sup>

Biological activities of these candidate herbs substantially used for hair growth improvement are included in Table 4. This will widen the alternative choices of herbal products in alopecia. In addition, herbs that obviously cultivated in Thailand, which are *Flagellaria indica*, *Leucaena leucocephala* and *Eucalyptus* sp., *Piper betle*, *Mitragyna hirsute*, and *Ixora maerothyra*, posed slight, moderate, and potent 5 $\alpha$ -reductase inhibitory activities, respectively.<sup>113</sup> Furthermore, ayurvedic medicine composing of *C. reflexa*, *Citrullus colocynthis*, and *Eclipta alba* that potentially increased hair follicle number and scalp thickness particularly induction of anagen hair comparing with minoxidil<sup>165</sup> were formulated. Cream comprising the herbs was evaluated on hair growth promoting efficacy in albino rats. The formulation exhibited a promising result in hair loss treatment.<sup>166</sup>

## Conclusions

Natural-derived compounds, which are phytosterols, phytoestrogens, fatty acids, and terpenoids particularly of plants, are able to prevent androgenetic-mediated disease by free radical scavenging activity, blocking the harmful effects of sex hormone resulting in a reduction of serum excretion/production accordingly.<sup>167</sup> In addition, zinc and biotin deficiency are associated in hair loss. Iron had been addressed in an association of alopecia recently.<sup>168</sup> Therefore, adequate dietary supplementation is accumulated on limiting hair loss in addition to application of herbal products.

This review embedded commonly used herbs for hair loss prevention and treatment with alternative choices of potential herbs. Although natural remedies are the main concept on health concerning,<sup>169</sup> including for hair loss treatment due to the perception of human that phytotherapeutic treatment is safer.<sup>170</sup> Standardized herbal products are necessary to ensure the

qualities, which are efficacy, safety, stability, and usability. Furthermore, herb-drug interactions should be seriously concerned.<sup>169</sup> Moreover, herb should be used at an adequate dose for safety consideration. In addition, psychological treatments limiting stress and other psychiatric disorders by relaxation improving are encouraging hair growth induction.<sup>171</sup>

## Acknowledgment

The authors acknowledge Mae Fah Luang University on facility support for this manuscript preparation.

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