

The potential of androgenic alopecia management from plant derivatives

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Abstract

Hair loss or alopecia is a common dermatological issue that can affect millions of human population of all ages and both gender, male and female. Frequently, alopecia has been found to be associated with significant adverse effects or reduction of psychological and self-esteem. Consequently, this may lead to psychological problems such as depression and anxiety, thus it may negatively impact the quality of life as well. There are several types of hair loss including androgenetic alopecia (AGA), alopecia areata (AA), alopecia totalis (AT), Alopecia Universalis (AU), cicatricial alopecia (CA), senescent alopecia (SA), traction alopecia (TA) and telogen effluvium. However, this review will focus on the androgenic alopecia only. Androgenic alopecia (AGA) also known as male pattern baldness is referred to as hair loss that often occurs in men after puberty caused by the androgen. In addition, this review will discuss on the hair growth cycles and their mechanism on the androgenic alopecia and lastly the management of androgenic alopecia using plant derivatives and methods used in order to prolong the efficacy of androgenetic alopecia treatment.

1. Introduction

Generally, the human may have between 90,000 and 150,000 of hairs on their head and loss between 50 and 100 per day (Erdoğan, 2017; Sengar *et al.*, 2018). Though, the hair loss does not noticeable, as the new hair will grow at the same times. However, if the hair growth cycle was interrupted or the hair loss is more than 100 per day, then hair loss disorder that associated with pathological issues is seen (Shaikh *et al.*, 2016). Hence, it is important to understand the causes of hair loss thoroughly as it can be the key part of the treatment or prevention of the alopecia. There are numbers of causal factors for alopecia to take place including the hereditary thinning, diseases, hormonal imbalance and stress, medication and nutrition. However, in this review, the focus will be on the androgenic alopecia. This review will discuss the anatomy and physiology of hair and it's growth cycle, causes of androgenic alopecia, and treatment and management of hair loss using plant derivatives. This review also will discuss on the

application of nanoparticles as one of the delivery systems potentially used for androgenic alopecia treatment.

2. Hair anatomy and physiology

Hair mostly can be found on all mammals and not on other animals. Hair is a derivative of the epidermis which physically is thin, flexible tubes of a dead, fully keratinized cell. Hair from the macrostructural point of view, hair has varied in term the hair length, diameter, colour and cross-sectional shape (Buffoli *et al.*, 2014). Hair serves as many functions in which the main function is to protect the surface of the skin and act as the thermoregulator. Human hair also helps in sweating thermoregulation and also act as a sensory organ. Besides, provide protection against UV radiation and elements, the hair also plays an important role as a psychological function for identity and self-confident in human.

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Hair consists of two different structure fibre which is follicle and hair shaft. The hair follicle is said as the living part of the hair that located under the skin while the hair shaft is fully keratinized dead part that can be found above or on the skin surface (Buffoli *et al.*, 2014; Cooper, 2015; Erdoğan, 2017; Murphrey *et al.*, 2020). The hair shaft is the hair that visible on the skin surface. Hair shaft consisted of three layers of keratin (a hardening protein) that are cuticle, cortex, and medulla. The cuticle is the outermost layer that is formed by tightly packed scales resemble roof shingles in an overlapping structure. Cuticle cell covers the hair from the root to the tip of the epidermis that also has important protective properties also act as barrier function against physical and chemical insults (Buffoli *et al.*, 2014; Cooper, 2015). Next, the middle layer called cortex which makes up the majority of the hair shaft and the innermost layer is medulla. Both cortex and medulla contain pigmented cell that responsible for the hair colour.

The essential part of the hair growth structure is follicle. The hair follicle is like a stocking-like structure that contains cells and connective tissue. The base of the follicle where the papilla can be found. The papilla contains tiny blood capillaries that help to give nutrition to the cells. The follicle basically consists of two distinct parts, the upper and lower part (Buffoli *et al.*, 2014; Cooper, 2015). First, the upper part has infundibulum and isthmus. The infundibulum is the uppermost portion of the hair follicle from the opening of the sebaceous gland to the surface of the skin and the isthmus is the lower portion of the upper part that located between the openings of the sebaceous gland and the erector pili muscles. The lower part of the follicles consists of hair bulb and suprabulbar region where it has continuous cycles of regeneration (Erdoğan, 2017). The suprabulbar region of the follicle composes of three layers, outer root sheath, inner root sheath, and hair shaft. The outer root sheath act as the reservoir of stem cells, keratinocyte and melanocytes stem cells. The inner root sheath has three layers, Henle's layer, Huxley's layer, and cuticle layer. The inner root sheath cells produce keratins that give strength to support the growing hair shaft and guide the upward movement. The inner root sheath also acts as the separator that separates the hair shaft from the outers root sheath. The hair bulb is the stocking like structure that surrounds the papilla and germinal matrix that take nutrient from the capillaries around it. The follicular papilla is an essential source of growth factor that responsible for the hair growth cycle which the volume and secretory activity of follicular papilla with the number of matrix stem cells help determine the size of the anagen hair bulb, the duration of the anagen phase and the diameter of the hair shaft (Buffoli *et al.*, 2014;

Cooper, 2015).

The whole of human body surface nearly covers with hairs except palms, soles and mucosal region (lips and external genitalia). There are three basic hair types on the human body which are vellus, intermediate and terminal hair (Buffoli *et al.*, 2014; Cooper, 2015). Vellus hair covering the majority part of body surface both children and adults. Vellus hair are characterized with short (<2 mm), fine (<30 μ m) and non-pigmented hair, this hair synthesis by non-sexual hair follicles which does not affect by hormones (Buffoli *et al.*, 2014; Cooper, 2015). Hair that characterizes as thicker (> 60 μ m), longer (>2 cm) and pigmented are called terminal hairs and can be found on the scalp, eyebrow, eyelash, armpit and pubic area (Cooper, 2015). Human hair classified using the ethnic subgroup which is African, Asian and European however recently the classification had expanded to eight main subgroups. Usually, the classification of hair involves the measurement of the three main parameters such as the curve diameter, the curl index and the number of waves (Buffoli *et al.*, 2014; Cooper, 2015).

3. Growth cycle of hair

Hair growth is a continuous and cyclical process that control by the changes in the activity of hormones in individual hairs on the body at different stages of the growth cycle. The hair growth cycle can be divided into three significant difference phases, involve anagen phase, catagen phase and telogen phase (Buffoli *et al.*, 2014; Erdoğan, 2017; Murphrey *et al.*, 2020). All the phases would have different duration can depend on the location of the hair, individual age, hormone status and also an individual nutritional level.

Figure 1 shows the growth cycle of hair on the scalp. The anagen phase is also known as the growing phase of the hair follicle that can last for several years and about 85% to 90% of scalp hair is in this phase (Cooper, 2015; Erdoğan, 2017). This phase is characterized by the formation of the hair shaft stick out or protrude from the surface of the skin. During this phase, hair can grow approximately one centimetre every 28 days, short anagen phase would have difficulty growing hair beyond some length due to short anagen phase and this would be opposite to person that has long anagen phase (Randall and Botchkareva, 2008). Eyelashes, eyebrows, leg and arm hair are shorter than the hair on the scalp due to this hair have very short anagen phase that lasts only 30 to 45 days as compared to scalp hair that can last for several years. Fibre length or hair length often depends on the duration of the actively growing phase of the follicles (Erdoğan, 2017). In the anagen phase, there is some article that divided this phase more into six stages of

anagen. The early phase of anagen is where hair progenitor cells start to proliferate and envelop the growing dermal papilla and begin to differentiate into the hair shaft and inner root sheath (Buffoli *et al.*, 2014; Erdoğan, 2017). In mid anagen phase where the hair starts to show pigment due to melanocytes in the hair matrix and start to develop newly formed hair shaft. The end of the anagen phase, full restoration of hair fibre-producing unit achieved were characterized by the formation of the epithelial hair bulb surrounding the dermal papilla and the new hair shaft also start to appear from the skin surface (Randall and Botchkareva, 2008; Buffoli *et al.*, 2014; Erdoğan, 2017). Activity that involves hair shaft synthesis and pigmentation can only take place in the anagen phase. The new hair bulb is formed at the base of the follicle and inside the hair bulb, specialized dermal papilla cells start to grow new hair shaft. If the old hair has not been shed, the newly growing hair helps push the old hair out of the follicle (Randall and Botchkareva, 2008). During anagen, there would have active signalling exchange activity occur between the epithelial cells of the hair bulb and the fibroblasts of the dermal papilla that aid in hair growth and proliferation (Randall and Botchkareva, 2008).

blood supply. The first sign of the catagen phase is the termination of the melanogenesis in the hair bulb (Cooper, 2015). At the end of the anagen phase, the mitotic activity of the hair matrix cell diminished and all the differentiation and proliferation of hair matrix keratinocytes decrease significantly (Buffoli *et al.*, 2014). Also include the pigment-producing activity of melanocytes stops and hair shaft production is completed. During the catagen phase, the follicles compartment involved in hair production is reduced to sizes that can allow the regeneration for the next hair cycle after receiving stimulation (Randall and Botchkareva, 2008). The specialized structure is known as club hair, that characterize with outer root sheath shrinks and attaches to the root of the hair.

Telogen phase takes over after the catagen phase, also known as the resting phase where the hair does not grow and the dermal papilla stays in the resting phase that lasts for months. This phase accounts for 10% to 15% of all hair and the hair follicle is at rest and club hair completely formed (Randall and Botchkareva, 2008; Buffoli *et al.*, 2014; Cooper, 2015). The telogen phase is characterized by lack pigment-producing melanocytes, the hair shaft transformed to club hair and at the end shed off. The follicles will remain in telogen phase until the hair germ receive and responsive to the signal for initiating anagen phase from the dermal papilla (Lourith and Kanlayavattanakul, 2013). A solid, dry and has white material at the root of the hair will reveal when the hair is pulled that in this telogen phase.

3.1 Common hair problem

Recently, many studies have proved that hair disorder may cause psychological affliction where the resultant effects may worsen the hair problem scenarios (Sengar *et al.*, 2018). This is due to the facts that hair is an appendage which correlated with the brain in many ways. For example, when the brain in a stressful event, it may alter the adaptive immunity of the skin and hair where consequently this may lead to the premature death of the hair. Therefore, identifying the common hair disorder that affected in the human population may play a vital role in preventing these undesirable effects. Hence, the main problems that may possibly be associated with hairs are premature greying of hair (PGH), dandruff and also hair loss (balding) (Patel, Sharma, Chauhan, Thakur and Dixit, 2015).

Hair loss or alopecia is a common dermatological issue that can affect millions of human population of all ages and both gender, male and female. Frequently, alopecia has been found to be associated with a significant adverse effect or reduction of psychological and self-esteem (Montgomery *et al.*, 2017).

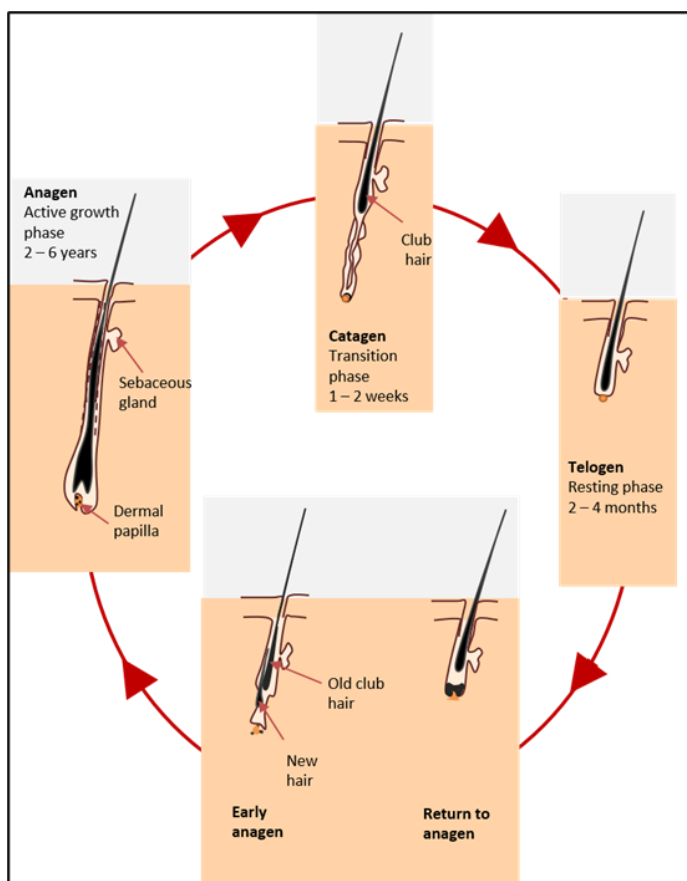


Figure 1. Normal hair growth cycle

The phase where the hair stops growing and hair follicles start to shrinking known as catagen phase. This phase is also known as regression period that lasts for two to three weeks. The lower part of hair follicle break apart and the hair follicles need less nourish from the

Consequently, this may lead to psychological problems such as depression and anxiety, thus it may negatively impact the quality of life as well (Phillips *et al.*, 2017). There are several types of hair loss including androgenetic alopecia (AGA), alopecia areata (AA), alopecia totalis (AT), Alopecia Universalis (AU), cicatricial alopecia (CA), senescent alopecia (SA), traction alopecia (TA) and telogen effluvium. The summary of the etiology and histopathology for each type of hair loss were illustrated in Table 1 (Daniels *et al.*, 2019).

4. Androgenetic alopecia (AGA)

Androgenetic alopecia (AGA) is the most common type of progressive hair loss that may affect both men and women. This condition is called male pattern hair loss or common baldness in men and as female pattern hair loss in women (Fabbrocini *et al.*, 2018; Lulic *et al.*, 2017). Basically, the histopathology of female pattern hair loss often can be seen with the diffuse thinning of the hairs in the frontal and parietal region (Ramos and Miot, 2015). Besides that, for the male-pattern baldness is hair loss occurs on the temples and crown of the head with sparing of the sides and back which is also known as “M”- shaped pattern. This pattern reflects the distribution of androgen-sensitive follicles in most

people that are usually starting at puberty (Springer *et al.*, 2003).

Alopecia in these cases is characterized by shortening of the anagen phase and continuous miniaturization of sensitive hair follicles (Springer *et al.*, 2003). As the results, the thin terminal hair transformed to a fine vellus that may lead to the bald appearance. Additionally, studies have demonstrated that high production of androgen, dihydrotestosterone (DHT) may play a significant role in causing AGA as this may cause miniaturisation of hair follicle and its subsequent effect (Lolli *et al.*, 2017). The study also has suggested that the androgen receptor and the metabolism of androgen are two factors that can influence the production of DHT. The 5 α -reductase Type-2 enzyme is an essential catalyzer in metabolism of the androgen by converting the testosterone to dihydrotestosterone (DHT) (Lulic *et al.*, 2017).

4.1 Causes of androgenetic alopecia (AGA)

Hereditary thinning is also known as androgenetic alopecia (AGA), the most common types of alopecia that may affect in both men and women recently. There are ample of genetic factors may possibly play a role in causing the hereditary thinning. However, only one gene has been identified and confirmed by the scientific

Table 1. The summary of the different types of alopecia, their etiology, and manifestations as well as the typical proscribed treatment (Daniels *et al.*, 2019).

Alopecia progenies	Etiology	Histopathology	Treatment
Androgenic Alopecia (AGA)	Androgen dependent (testosterone/DHT) follicle miniaturisation	Female – diffuse hair loss (Ludwig), often Male – often manifests as a receding hairline and hair loss in the vertex region (Hamilton-Norwood)	Topical Minoxidil (2%) Topical Minoxidil (5%) Oral Finasteride/ Dutasteride Hair transplantation
Alopecia Areata (AA)	T cell-dependent auto-immune disorder	Regions of ‘patchy’ hair-loss, which predominantly manifest in the scalp.	Topical Minoxidil (5%) Topical or oral corticosteroids
Alopecia Totalis (AT)		Complete absence of terminal scalp fibres	Wig/ Hair transplantation
Alopecia Universalis (AU)		Complete absence of scalp and bodily fibres	Wig
Cicatricial Alopecia (CA)	Inflammation of the upper part of the HF leading to irreversible damage of the hair bulge and the loss of stem cells.	Permanent loss of hair in the affected patches, visible scarring may occur	Topical or oral antibiotics, Scalp reduction surgery Hair transplantation
Senescent Alopecia (SA)	Stochastic ‘ageing’ of the follicle caused by UV, reactive oxygen species and other endogenous and exogenous stressors	Gradual decrease in fibre-diameter and the number of anagen-follicles, resulting in a diffuse hair-loss across the entirety of the scalp (non-androgenic)	Topical Minoxidil Cosmetic intervention Topical antioxidants
Traction Alopecia (TA)	Persistent or significant strain to the follicle, caused by particular grooming practices (Inc. braiding,	Scarring of follicles and hair-loss at the frontotemporal margin of the scalp	Acute: anti-inflammatory Chronic: Hair transplantation
Telogen Effluvium (TE)	Numerous ‘triggers’ including physiological and metabolic stress	Non-scarring diffuse hair-loss, characterized by the simultaneous shedding of telogen fibres	Cosmetic interventions: topical antioxidants and 5- α reductase inhibitors

studies, androgen receptor (AR) gene (Ellis *et al.*, 2002). Initially, this gene is essential in providing the instructions for producing a protein called androgen receptors. Nevertheless, variation in the AR gene is associated with an elevated risk of AGA. The changes might the results from small variation in the type or numbers of DNA building blocks that make up the AR gene (Ellis *et al.*, 2002). Many research have believes

these isozymes are involved in steroid metabolism in particular areas and interact with the androgen receptors. In androgen synthesis, the 5α -reductase enzyme acts as a catalyst converting testosterone to the more potent dihydrotestosterone. By introducing a 5α -reductase inhibitor, the conversion of testosterone to DHT can be decreased and help in reducing hair loss (Figure 2).

For instance, dihydrotestosterone (DHT) may interfere with the Wnt signalling pathway in the hair (Ramos and Miot, 2015). Initially, the Wnt pathway is important mechanism that use to maintain the anagen phase in the body by inducing the dermal papilla cells. Hence, the disruption of Wnt pathway by the presence of excess DHT may interfere with the hair growth cycle. The androgenic imbalance in the body can be due to several reasons. For example dysregulation of the hypothalamic-pituitary-adrenal cortex, polycystic ovary syndrome (PCOS), hormonally-active tumours and idiopathic hirsutism (Urysiak-czubatka *et al.*, 2014).

4.2 Treatment and management of hair loss

Medication that currently has claims their indication to treat AGA have target a steadily growing market worldwide. However, the availability of specific therapies is still deficient and concomitant with several side effect. Frequently, the treatment status for alopecia is based on etiology and progression (Patel, Sharma, Chauhan, Thakur and Dixit, 2015). The major non-surgical therapeutic strategies for hair growth promotion are including angiogenesis (through endogenous substances), androgen antagonism, vasodilation through potassium channel opening 5α -reductase inhibition and modulation of the hair cycle. There are two US FDA-approved synthetic drugs finding that can be used for the treatment of androgenic alopecia including 2-5% topical solution of minoxidil (useful in both male and female pattern baldness) and 1 mg of finasteride (useful in male pattern baldness), however, the presence of side effects have reduced their usage (Adil and Godwin, 2017). The side effects associated with the use of these synthetic compounds include erythema, scaling, pruritus, gynecomastia, dermatitis, itching or skin rash (Etminan and Member, 2016; Patel, Sharma, Chauhan, Thakur and Dixit, 2015). Recently, another medication such as 0.5 mg of dutasteride has been approved and used for the treatment of AGA in a few countries including Korea and Mexico (Kelly *et al.*, 2016). Studied have revealed that dutasteride may help to improve hair growth and reverse the androgenic alopecia. Nevertheless, the usage of the medication in therapies of alopecia may also be associated with sexual dysfunction side effect including decreased libido and ejaculation dysfunction (Tsunemi *et al.*, 2016). Hence, this leads to an increased interest of

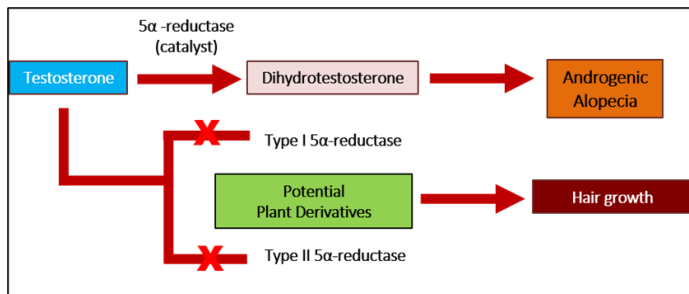


Figure 2. Schematic diagram of inhibition of 5α -reductase from plant derivatives in androgenic alopecia management

that the variation may increase the activity of the androgen receptor in the scalp, though the actual mechanism still remains unclear. These genetic variation is happening more frequently in men with early age of hair loss. Additionally, studies suggest that having closed relatives with patterned hair loss can increase the risk factor for developing the condition.

Androgen is a hormone that can be produced naturally in the human body and usually found higher in men (Davey and Grossmann, 2016). The key pathophysiological features of male androgenic alopecia are alteration in hair cycle development, follicular miniaturization and inflammation (Cranwell and Sinclair, 2016). Testosterone and dihydrotestosterone are the major androgens that regulate hair growth. Dihydrotestosterone (DHT) has approximately a five-fold greater affinity for the androgen receptor than testosterone (Kaufman, 2002). In hair loss patients, the 5α -reductase enzyme acts as a catalyst that converts testosterone, which is the primary androgen, to the more potent androgen, DHT which makes the hair follicle miniaturise and shed hair (Olsen *et al.*, 2006).

Due to the effect of the potent androgen (DHT), their normal hair starts as long, thick and pigmented, then changes to be thin, short and less pigmented at the end of the process. The new hair colour becomes less pigmented from one cycle to another, the hair shaft becomes thinner, and there is the appearance of baldness. Two isozymes participate in androgen synthesis; namely, Type I 5α -reductase isozyme which is present in the skin, hair follicles and sebaceous glands, liver, prostate, and kidney and Type II 5α -reductase isozyme which is present in hair follicles, male genitalia and the prostate (Russell and Wilson, 1994; Kandavilli *et al.*, 2010). Both

researches in finding alternative treatments to overcome the hair loss problem with fewer side-effects such as formulation containing herbs or their active constituents.

Nowadays, many studies have proven that natural drugs made from plant derivative may give a promising impact to treat the AGA (Herman *et al.*, 2017). Ample of herbal topical or natural product formulations have been marketed worldwide to prevent hair loss or promote hair growth. There are numerous advantages of using natural based compound. For examples, improve patient compliance, fewer side-effects, and easy availability, low-cost, more than one mode of biochemical action for hair loss treatment and some of it may also work synergistically with the drugs to reduce the hair loss. Based on the previous study, Karatas *et al.*, (Karatas *et al.*, 2016) found that treatment with topical 5 α reductase inhibitors and supplementation of Vitamin C and omega-3 fatty acids are likely appeared to be the most appropriate treatment agents for the management of hair loss. Therefore, a lot of researches are looking for new herbs and active constituents that could be potentially used as alternative tools for the drugs in therapies of alopecia. In this review, some of the plants or herbal sources that have been found could be used for the treatment of AGA will be discussed.

4.2.1 *Avicennia marina*

Avicennia marina (*A. marina*) is a pioneer tree species of the mangrove forest ecosystem that widely distributed along with the tropical and subtropical environment. This plant belongs to the family *Acanthaceae* and commonly called grey or white mangrove (Jain *et al.*, 2016). *A. marina* exhibits various pharmacological activities that have been used in many countries as dermatologic disorder treatment, such as Egypt (Zhu *et al.*, 2009; Jain *et al.*, 2014). Extraction of the *A. marina* contains avicequinone C compound using methanolic heartwood extract shown potent activity of inhibition of 5 α -reductase enzyme and shown decrease in dihydrotestosterone production which can be used in the treatment of androgenic alopecia (Jain *et al.*, 2014; Yardimci, 2017). Among all thirty Thai medicine plant, *A. marina* has high 5 α -reductase inhibitor and cause reduce dihydrotestosterone production about 52% as compared to other medicine plants tested (Jain *et al.*, 2016).

4.2.2 *Boehmeria nipoonivea*

Boehmeria nipoonivea, *B.nivea* is a perennial herb that belongs to the family of *Urticaceae* (Ancora, 2009). The chemical constituents that have been found in the plant including 10%-30% fatty acid, 10% chlorogenic acid, linoleic acid, protocatechuic acid, caffeic acid and α

-linolenic acid (Patel, Sharma, Chauhan, Thakur and Dixit, 2015). Studies have demonstrated that the plants may also have various pharmacological properties and used as medicines such as antioxidant, antidiabetic, hepatoprotective and anti-cancer and to be effective in neurodegenerative diseases (Marjahan *et al.*, 2018). The acetone extract of *B. nivea* reported having both potent 5 α - reductase inhibitory effect and hair re-growth promotion effect on mice (Nahata, 2017). The inhibitory effect of 5 α -reductase is due to the presence of fatty acids in the plant. For example α -linolenic, linoleic, palmitic, elaidic, oleic, and stearic acids (Rondanelli *et al.*, 2015).

4.2.3 *Camellia sinensis*

Camellia sinensis in the family of *Theaceae* is one of the common plants since ancient times, especially in China. Extraction from the *Camellia sinensis* leaves is known as green tea that grown in subtropical climates and is a popular drink worldwide. There are many pharmacological effects that have been shown such as ant metastatic, anticancer, anti-inflammatory, antidiabetic, antibacterial, antiviral and antioxidant effects (Patel, Sharma, Chauhan, Thakur and Dixit, 2015; Yardimci, 2017). Green tea also used in many dermatological diseases such as acne, rosacea, keloids, genital warts and atopic dermatitis (Zink and Traidl-Hoffmann, 2015). Besides, green tea also reported has the activity of actively inhibiting 5 α -reductase that can be used for the treatment of androgenic alopecia (Yardimci, 2017). It thought that green tea contains epigallocatechin-3-gallate (EGCG) which a major polyphenol that can give antioxidant and anti-cancer effect (Patel, Sharma, Chauhan, Thakur and Dixit, 2015). Reported that the tea polyphenolic EGCG compound can stimulate human hair growth when it tested among mice that show positive significant elongation of hair follicle (Amin *et al.*, 2014). Apart from EGCG compound present that gives pharmacological effect, there also has catechins in the green tea that can also quickly reduce the 5 α -reductase that can act as treatment and prevention agent for hair loss problem (Zink and Traidl-Hoffmann, 2015).

4.2.4 *Citrullus colocynthis*

Citrullus colocynthis herb in family *Cucurbitaceae* that grow in the most barren environment is one of plant that recommended in much traditional literature that can act as a growth promoter for hair. This plant is also known as *Indrayam* in India that also recommended in Indian traditional medicine to treat hair loss problem (Roy *et al.*, 2007; Yardimci, 2017). The fruit from this plant is the part of the plant that has constitutes that has promising effects to hair problem. The dried pulp of the

unripe with full-grown fruit freed is used to treat hair loss problem. Besides that, the oil from the seeds of the plant also has reported can help to control premature falling of hair and greying of hairs (Patel, Sharma, Chauhan, Thakur and Dixit, 2015). The fruit has a pungent smell, bitter and has a purgative characteristic. Extraction of *C. colocynthis* can act as antihelmintic, antipyretic, can treat ulcers, asthma, bronchitis, enlargement of the spleen, dyspepsia, constipation, anaemia and throat disease (Roy et al., 2007; Dhanotia et al., 2011). This plant also has several pharmacological effects such as antibacterial, hypoglycemic, immunostimulating and antiandrogen beside act as hair promoting effect (Yardimci, 2017).

4.2.5 *Curcuma aeruginosa*

Curcuma aeruginosa or curcumin (*Zingiberaceae*) is traditional medicines that commonly used in Thailand for gastrointestinal disturbances, uterine pain, postpartum uterine, and perimenopause bleeding (Srivilai, Waranuch, Tangsumranjit et al., 2018). Preclinical studies have suggested that *C. aeruginosa* may have several medical indications including antimicrobial, anti-inflammatory, antipyretic and analgesic properties (Srivilai, Nontakhot, Nutuan et al., 2018). Besides that, many research also have revealed that the curcumin able to inhibit 5 α -reductase, this is due to the presence of sesquiterpenes compound of which the germacrone was most potent (Herman et al., 2017). Recently, studies have proved that co-application of curcumin along with minoxidil may enhance the reversion of androgen-induced alopecia compared to the substance applied alone (Srivilai, Waranuch, Tangsumranjit et al., 2018). This is due to *C. aeruginosa* may help increase the epidermal penetration of minoxidil, thus improving the delivery of the drugs into the target sites.

4.2.6 *Cucurbita pepo*

Pumpkin seed oils also are known as *Cucurbita pepo* (*C. pepo*) is belong to the family of *Cucurbitaceae* and (Dhariwala and Ravikumar, 2019). Frequently the oils were extracted from the oval seeds of *C. pepo* and it has been found that the solvent extraction method is one of the most efficient with 98 % of the oil was obtained (Cho et al., 2014). There are various chemical constituents found in the pumpkin seeds oil including fatty acids, sterols, phytoestrogen, and tocopherols. The inhibition of 5 α -reductase and anti-androgenetic effect of the pumpkin seeds oil is due to its high content of phytosterols. Studies have reported that pumpkin seed oils may show the inhibition of 5 α -reductase properties with a dose of 400 mg/day for 24 months (Dhariwala and Ravikumar, 2019). According to the study, the presence of the

phytosterols and as well lipid in the pumpkin seeds oil may synergistically treat the AGA. *C. pepo* has been used traditionally by many countries to treat numerous diseases. For instances anti-inflammatory, analgesic urinary, disorders antiviral, antidiabetic, anti-ulcer, and antioxidant (Perez Gutierrez, 2016).

4.2.7 *Cuscuta reflexa* Roxb

Cuscuta reflexa Roxb is a parasitic plant fit into the family of *Convolvulaceae* (Yardimci, 2017). The plants have a low level of chlorophyll and they cannot produce their own food by photosynthesis (Saini et al., 2018). Therefore, they completely depend on the host plant in order to obtain foods and nutrients. There are various chemical constituents obtained in the plants may have ample of pharmacological functions. For instances cuscutin, cuscotalin, sitosterol, luteolin, bergenin, kaempferol and others (Singh et al., 2016). *C. reflexa* has been used traditionally as numerous purposes of treatment such as antitumor, antimicrobial, hepatoprotective, anticonvulsant, antioxidant, relaxant and spasmolytic action, positive inotropic and cardiogenic activities, cholinergic action, anti-HIV, anti-steroidogenic, hypoglycemic, diuretic, anti-inflammatory and induced alopecia have been previously reported (Dutta et al., 2017; Yardimci, 2017). Researches have revealed that the petroleum ether extract solution of *C. reflexa* can inhibit the 5 α -reductase and as well as the conversion of testosterone to DHT, consequently, this may help in reversing the androgen-induced alopecia (Pandit et al., 2008).

4.2.8 *Glycyrrhiza glabra*

Glycyrrhiza glabra, *G. glabra* or licorice (family of *Leguminosae*) have been used in Chinese herbal medicine with long usage history and it is usually can be obtained from root and stem of the plant (Kowalska and Kalinowska-Lis, 2019). Many studies have demonstrated that licorice can be used as an alternative treatment for the AGA (Utami et al., 2017; Pastorino et al., 2018). This is due to the facts that the plant may show antagonizing testosterone effect through the presence of glycosides, terpenoid, phenolics, and flavonoids. Besides that, the existence of phytosterols in the licorice may also help to inhibit the 5 α -reductase enzyme, hence reducing the production of DHT and as well as AGA. In another study also have revealed that the hydro-alcoholic extract of *G. glabra* in 2% concentration showed a better hair growth activity compared to 2% of standard minoxidil. Hence, this proved that the plant has a potent hair growth activity (Pandey et al., 2017). Additionally, other pharmacological activities of *G. glabra* are anti-tussive, anti-demulcent, antioxidant, anti-malarial, anti-fungal, immuno-stimulatory, anti-ulcer, anti-dyslipidemia, anti-

thrombotic, skin lightening and anticancer properties (Pandey et al., 2017; Al-Snafi, 2018).

4.2.9 *Sophora flavescens* Aiton

Sophora flavescens Aiton root extract belongs to the family of *Leguminosae* and commonly used in traditional medicine (Lee et al., 2018). It has been used to treat various of disease including viral hepatitis, cancer, viral myocarditis, heat dysentery, hemifacial, jaundice, anuresis, leucorrhoea with reddish, discharge, vulval swelling, pruritus vulvae, eczema, and trichomonas vaginalis (Yardimci, 2017). The extract may have a strong inhibitory 5 α -reductase effect and anti-androgen effect that can be used in treating the problematic hair issues of AGA (Roh et al., 2002). Nevertheless, the research evidence of *S. flavescens* in suggesting the extract able to promote hair growth and treat the hair loss are lacking. Additionally, studies have demonstrated that there is two active compounds of pterocarpan derivatives in the extract may help to promote the proliferation of human hair keratinocytes, L-maackiain, and medicarpin (Takahashi et al., 2016).

4.2.10 *Phyllanthus niruri*

This plant is a small plant that grows in tropical and subtropical regions in Central and South American countries, India and East Asia. This plant of genus *Phyllanthus* is also known as 'chanka piedra', 'zhuzicao', 'dukung anak' and 'chanca piedra' (Yardimci, 2017). *Phyllanthus niruri* family of *Euphorbiaceae* widely used in traditional medicine especially in promoting hair growth. Beside can promote hair growth, this plant also commonly used for the treatment of jaundice, asthma, hepatitis, fever, malaria, antidiabetic, analgesic, wound healing and immunomodulatory effect (Patel, Sharma, Chauhan, Thakur and Kumar, 2015; Yardimci, 2017). *P. niruri* can increase the activity of hair growth through the mechanism of inhibition of 5 α -reductase enzyme due to the present of lignans and terpenoids that belief can contribute to the promoting of hair growth (Patel, Sharma, Chauhan, Thakur and Kumar, 2015; Yardimci, 2017; Luliana et al., 2018). It had been identified that this plant contains phenols compound that can be lignans (methylated phenols) which play a role in inhibiting the activity of 5 α -reductase enzyme to help in reducing the conversion of testosterone into active testosterone (dihydrotestosterone) that potentially cause hair loss (Luliana et al., 2018). A study conducted had proven that *P. niruri* ethanol extract that contains methanol as the penetration enhancer showed high activity of hair growth that has been useful for the hair loss treatment.

4.2.11 *Serenoa repens*

Serenoa repens with botanical family *Areaceae* is one of a native plant in West Indian that grown in large quantities on the Atlantic southeast coast of North America (Yardimci, 2017). *S. repens* also commonly known as saw palmetto has been used as one of natural treatment for mild to moderate androgenic alopecia and showed to be more effective than other pharmaceutical drug treatment such as finasteride (Cho et al., 2014). Saw palmetto is extracted from the berries that reported have an inhibitory effect on 5 α -reductase enzyme. Saw palmetto not only shown activity toward the 5 α -reductase enzyme but it may also cause a decrease in dihydrotestosterone uptake by the hair follicle and decrease the binding of dihydrotestosterone to androgenic receptors (Murugusundram, 2009; Yardimci, 2017). A study conducted in a group of patient with mild to moderate androgenic alopecia were treated with saw palmetto for 24 months and the result showed improvement in hair growth compared to a group of patients that treated with finasteride (Rossi et al., 2012). The side effect of the plant as alternative treatment said to be uncommon but one that can usually found when patient taking as oral form causes mild stomach discomfort. Saw palmetto can lower the prostate-specific antigen level after 6 months of treatment that can mask the early detection of prostate cancer patient (Murugusundram, 2009).

4.2.12 *Thuja orientalis*

Thuja orientalis is an evergreen coniferous tree in the family of *Cupressaceae* that can be found in East Asian that has been commonly used in herbal medicine. In Eastern, this plant is also known as *T. occidentalis* and this plant has been used to treat any type of diseases such as respiratory, skin disorder and urinary system (Yardimci, 2017). In India and China traditional medicine claims that plants of genus *Thuja* have hair growth-promoting effect that used as hair growth tonic however this claims lack of scientific data of their use (Thukral et al., 2017). Therefore in the present study, these plants have been used to study its promoting effect of hair growth. This plant was found potentially inhibit 5 α -reductase that said help in treating or prevent hair loss due to the androgenic effect (Kumar et al., 2012; Lourith and Kanlayavattanukul, 2013). *T. orientalis* leaves are used as part of the plant that contains the promoting effect of hair growth. Kaempferol and isoquercetin are compounds that were found using hot water extract. Kaempferol is a natural flavonoid that contains potent antioxidant activity and anti-inflammatory while isoquercetin also in flavonoids group that has the effect of anti-oxidant, anti-inflammatory and protective effect

in cancer due to it can react on lipid peroxidation (Di Camillo Orfali *et al.*, 2016; Yardimci, 2017; Deng *et al.*, 2019; Wei and Martirosyan, 2019). In animal studies, this plant extract can induce earlier anagen phase and help in longer the mature anagen phase that can help promote hair growth and treat hair loss. *T. orientalis* is one of plant derive that observed that can promote more hair growth more prominently than pharmaceutical treatment such as minoxidil (Zhang *et al.*, 2013).

5. Nanoparticles as one of the delivery systems potentially used for androgenic alopecia treatment

Nowadays, many modern medicines have been derived and obtained from natural resources such as plants and herbs that were used for the purpose of health promotion and treatment of diseases (Thomford *et al.*, 2018). This is because of their unique advantages and as well as characteristics that lead to the discovery of the plant's based drugs. For instance, it may produce lower toxicity, side effects and cost, and good therapeutic potential. Nevertheless, studies have reported that most of the plants' derivatives failed to complete the clinical trial phase due to a few problems (Thomford *et al.*, 2018). The usage of the large-sized materials in the drug delivery poses a major concern in these issues. Therefore, the study has revealed that changing of the drug delivery system using nanotechnology or nanoparticle may play a significant role in overcoming these critical issues. Nanoparticle exhibit a remarkable ability to carry and deliver the medication into the target sites with an optimum dosage range (Carter *et al.*, 2019). As the results, this may alleviate the therapeutic efficiency of the drugs, reduced the side effects and subsequently improved patient compliance. The main interest of this method is delivery of the plant derivatives to the follicular or transdermal site in order to improve or reverse the androgenetic alopecia.

6. Conclusion

Overall, most of the plant derivatives or extract used in treating androgenic alopecia are targeting the inhibition of the 5 α -reductase enzyme. In the meantime, there is no permanent treatment for treating androgenic alopecia unless the patient chooses to proceed with the hair transplantation which is quite costly. Due to patient compliance, they prefer to choose the oral or topically applied ingredients even though they know that this method is impermanent in order to manage their hair loss problem. Due to that, a lot of plants have been screened by researchers to figure out that it can be used to manage the androgenic alopecia alternatively. Combining the plant extract would be work synergistically in order to

increase the inhibition of 5 α -reductase enzyme. One of the methods to target and deliver the active ingredients either by orally or topically in order to prolong the efficacy of hair loss treatment is using nanoparticles delivery system. This delivery system is suggested in order to enhance the efficacy and delivery of plant derivatives by inhibiting the 5 α -reductase enzyme which is the main catalyser in the metabolism of the androgen by converting the testosterone to dihydrotestosterone. However, this system should be further investigated especially on their safety aspect due to their size and materials used. In addition, a lack of clinical trial has been found for those using plant derivatives compound in treating androgenic alopecia. More clinical trials using plant-derived compound should be undergone in order to prove the findings.

Conflict of interest

The authors declare no conflict of interest.

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