International Journal of Multidisciplinary Research and Growth Evaluation.

The Role of Green Tea (*Camellia sinensis*) in the Management of Androgenetic Alopecia (AGA): A Review

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Article Info

ISSN (online): 2582-7138
Volume: 04
Issue: 05
September-October 2023
Received: 17-08-2023;
Accepted: 03-09-2023
Page No: 308-316

Abstract
Alopecia is a condition that impacts over 50% of the global population. The Food and Drug Administration (FDA) only approved topical minoxidil and oral finasteride for prevention of hair loss, and hair regrowth. Numerous *in vitro* and *in vivo* studies on active herbal ingredients suggest the herbal active ingredients may help control hair loss when used alone, together, and in combination with synthetic anti-hair loss medicines. For over 100 years, thyme, lavender, rosemary, and cedar wood essential oils have traditionally used to treat hair loss. According to current researches about topical green tea in the prevention and hair re-growth, this plant may be a suitable and relatively reliable alternative to chemical drugs such as minoxidil and finasteride. Green tea contains polyphenol compounds called catechins. Catechins have a significant anti-hair loss due to their effect on the dermal papillae cells (DPCs); DPCs are specialized fibroblasts that control the hair growth cycles. This article reviews the potential impact of green tea (*Camellia sinensis*) in reducing hair loss, hair re-growth, and its particular effect on dermal papillae.

DOI: https://doi.org/10.54660/.IJMRGE.2023.4.5.308-316

Keywords: Camellia sinensis, herbal drugs, anti-hair loss, Androgenetic alopecia

Introduction

The hair growth cycle consists of four phases of hair growth cycle: anagen, catagen, telogen, and exogen [1, 2]. The four phases of hair growth repeat until the follicles are able to make hair [1] (Figure 1). The most extended hair growth cycle is anagen, which lasts 2 to 7 years. Anagen; is also called the growth phase. Anagen is the period of the follicle regeneration, and it is the most active stage of hair growth, with high mitotic proliferation and pigmentation occuring in this phase only. Mean hair growth is 2 cm per month. The catagen phase is a short transitional period, called an apoptosis-driven regression phase. Catagen lasts about three weeks. During the catagen phase, mitotic activity decreases, extensive follicle apoptosis occurs, melanocytes shrink, and melanogenesis ceases (Figure.1) [3, 4, 5]. The telogen phase begins after the catagen phase. During the telogen phase, hair enters the resting stage; although it does not grow in this phase, the dermal papilla remains in the resting phase. The telogen phase lasts approximately four months (Table.1) [3, 4].

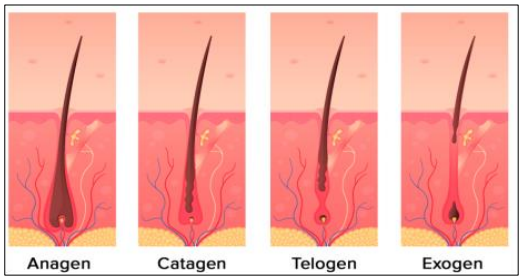

Fig 1: The Hair cycle [4]

Table 1: The main phases of hair growth [6, 7]

Stage	Key features
Anagen	Growth stage
	The most extended phase of the hair cycle
	Active growth stage
	Highly mitotic stage
	Nourishment of Hair follicles from the blood supply enables hair growth.
	Making the hair shaft from the follicles
	Decreases with age
	It lasts 2–8 years
Catagen	Transition stage
	Hair follicles begin to regress, and hair follicles detach from the dermal papilla.
	It lasts 2 weeks
Telogen	Resting stage
	Remains of the hair bulk are inactive, and papillary cells completely separate from Hair follicles.
	It lasts 5–6 weeks
Exogen	Shedding stage
	Hairs fall out at the end of life
	Mainly coupled to early anagen but also occurs in telogen.

Alopecia is the medical term for hair loss. Alopecia can affect just the scalp or the entire body. Hair loss can be caused by a variety etiology, including genetics, environmental triggers, certain chemical medications, nutritional problems, stress, or prolonged illness. It is classified into several categories based on the pattern of hair loss [8, 9]. Stressful situations lead to low self-esteem, psychological and emotional strains. The many factors can cause hair loss, including stress, genetics, hormones, diet, illness, medical conditions, and medications such as chemotherapy [10]. Alopecia is primarily include two groups: cicatricial alopecia and non-cicatricial alopecia [2, 10]. There are three common types of alopecia: androgenic (AGA), areata (AA) and chemotherapy-induced (CIA). Since there are various types of alopecia with different causes, Other possible forms of hair are: tinea capitis, trichotillomania, traction alopecia, chemotherapy alopecia, anagen effluvium, traction alopecia, telogen effluvium, and congenital alopecia [6, 8]. Androgenetic hair loss has two patterns: male pattern hair loss and female pattern hair loss. The highest prevalence occurs among people aged 30 to 65. The first symptoms of AGA may appear as early as puberty [8].

AGA is a progressive chronic disorder that highly prevalent in both males and females. It is characterized by follicular miniaturization and scalp gradual hair thinning. In 1960, Norman Orntrich used the term AGA for the first time. The highest prevalence of androgenetic loss is observed in Caucasians and Asians, respectively [8]. AGA is caused by androgenetic factors, mainly driven by the hormone dihydrotestosterone (DHT), which shortens the growth cycle of hair follicles and leads to thinner hairs. AGA is a common condition that affects up to 80% of men and 50% of women in their lifetime [11, 12]. Despite being a non-life-threatening condition, AGA can have significant psychological and social impacts, especially among women, and it often prompts individuals to seek medical or cosmetic treatments [13, 14]. The stress is due to hair loss more in women than men. Hair is the crown of a woman's beauty, pride and charm, therefore Hair loss can damage a woman's self-esteem and identity. It is also seen as premature aging for women and causes a woman to lose her sexual attraction to her mate [13].

The major factor causing AGA

AGA is the most common cause of hair loss in both sexes, which affects 30 to 58 percent of men over the age of 50, and 12 to 40 percent of women, depending on age and race. The disease manifests as androgen-induced progressive hair follicle shrinkage on genetically sensitive hair follicle epithelial cells in androgen-dependent regions. Managing AGA requires a multifaceted approach; therefore it is crucial to manage the fundamental causes like 5-dihydrotestosterone (DHT), oxidative stress, and inflammation that affect the dermal papilla cells, and accelerate hair loss [15].

Dihydrotestosterone (DHT)

DHT, the primary culprit behind hair loss in AGA, triggers the secretion of interleukin (IL-) 6 and transforming growth factor (TGF-) β2 by dermal papilla cells (DPCs). DHT suppresses the anagen phase and initiates the catagen phase (Figure 2) [15].

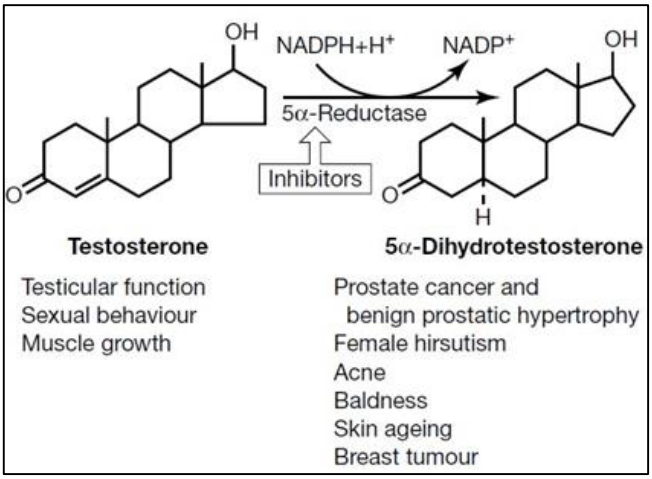

Fig 2: Testosterone is transformed into a more active androgen by 5α-reductase [16]

Dermal papilla cells (DPCs)

DPCs are particular fibroblasts in the hair follicle that play a fundamental role in controlling hair growth not only during the normal hair cycle but also in the pathogenesis of specific diseases, such as androgenetic alopecia (Figure3) [18].

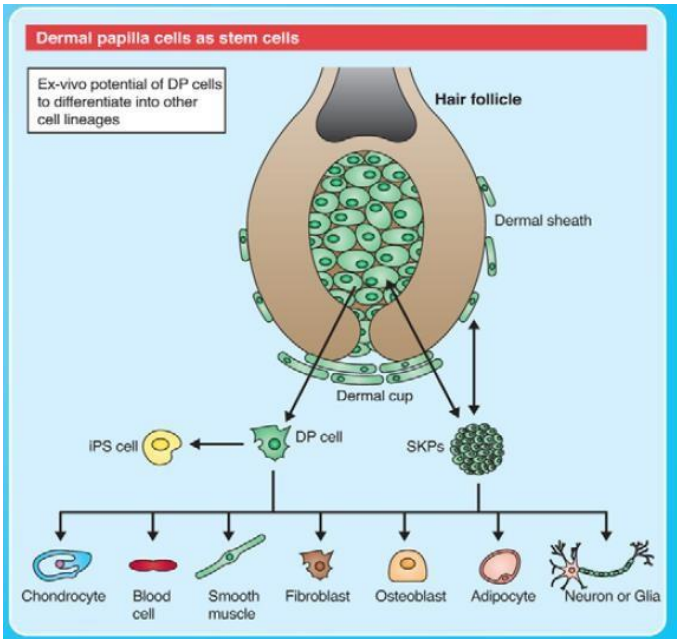

Fig 3: Dermal Papilla Cells [19]

Hair FDA-approved treatments

The various solutions have been proposed to treat hair loss, however, there are many reports of side effects and ineffectiveness of herbal and synthetic remedies. The Food and Drug Administration (FDA) only approved topical minoxidil and oral finasteride for prevention of hair loss,and hair regrowth(Figure 4) [20].

Finasteride (Propecia)

Charles B. Huggins developed finasteride in the 1930s and 1940s as a chemo-preventive drug for prostate cancer; This discovery led to the connection between the physiological role of testosterone and prostate growth. In 1992, the FDA approved Proscar or finasteride, formerly known as MK906, to cure benign prostatic hyperplasia (BPH). Merck acquired Propecia-FDA approval for treatment of AGA in 1997. Finasteride, a synthetic 4-aza-3-oxosteroid compound, is the active ingredient of Propecia. The optimized oral dose proposed to cure male loss pattern is 1 mg/day [21]. Finasteride is a 5-alpha reductase type II inhibitor (5-ARI-***2***) enzyme more selective than 5-alpha reductase type I (5-ARI-***1***) (Figure 5). Finasteride blocks the transformation of peripheral testosterone to DHT at the surface of the DPC. Therefore, this causes a considerable decline DHT in the scalp, and serum levels. Both chemical and herbal 5a-reductase inhibitors (5-ARIs). are increasingly used to treat some androgen-dependent disorders (Figure 6) [52].

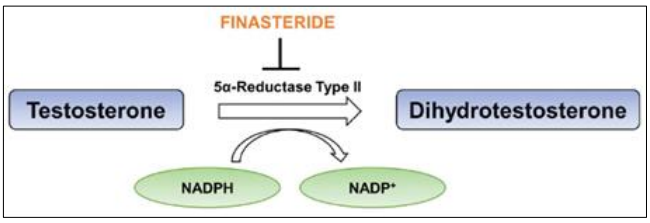

Fig 5: Mechanism of action of finasteride [21]

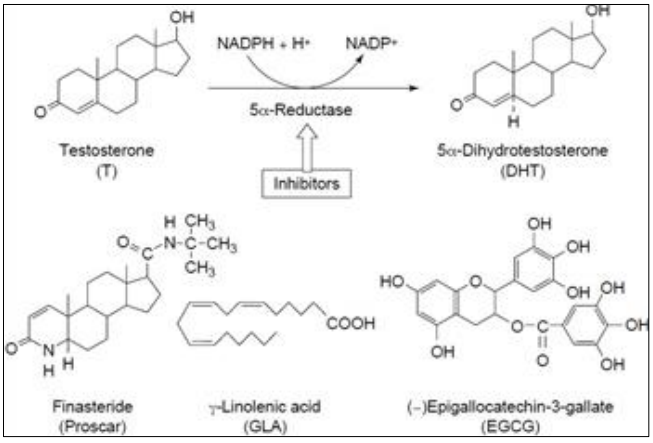

Fig 6: 5AR-synthetic inhibitors: (Proscar) and 5AR-natural inhibitors (GLA /EGCG) compounds [52]

Minoxidil

One of the FDA-approved treatments for male and female pattern alopecia is topical minoxidil, which has been approved since 1988 as a first-line choice for men with mild to moderate androgenetic alopecia (Table ***2***) [23, 24, 25].

Table 2: Topical Minoxidil use in hair disorders [16]

FDA approved Indications
▪ Androgenetic Alopecia
▪ Female Pattern Hair Loss
Over-The-Counter Use
▪ Alopecia Areata
▪ Beard Enhancement
▪ Cicatricial Alopecia
▪ Chemotherapy-induced Alopecia
▪ Eyebrow Enhancement
▪ Frontal Fibrosing Alopecia
▪ Loose Anagen Hair Loss Syndrome
▪ Telogen Effluvium

Minoxidil was introduced in the 1970s as an oral medication to cure severe hypertension. Coincidentally, The physicians discovered hair regrowth and general hirsutism in bald individuals using minoxidil, leading to the development of topical minoxidil to treat AGA. For the initial time, 2% minoxidil solution used in 1986, and then 5% solution introduced in 1993. Contrary to the universal acceptance of minoxidil for more than 30 years, the mechanism of minoxidil in increasing hair growth is still not completely understood [24].

Table 3: Side effects of minoxidil and finasteride [20]

Topical Minoxidil	Oral Finasteride
▪ Irritation	▪ Loss sperm count
▪ Itching	▪ Loss of libido
▪ Contact dermatitis	▪ Reduced ejaculation volume
▪ Facial Hair (unwanted hair)	▪ Erectile dysfunction
▪ Reversible hair loss upon stopping the medication	▪ Ejaculation dysfunction
▪ Burning sensation	▪ Enlargement of breast
▪ Dry scalp	▪ Menstrual abnormalities
▪ Emergency of rash	▪ Hair growth on an undesigned places like the face
▪ Redness	▪ A dizzy feeling
	▪ Hypersensitivity reactions
	▪ Testicular pain

Topical Finasteride

Another treatment for androgenetic alopecia is topical finasteride. First evaluated in 1997 by Mazzarella *et al*., a study on 52 subjects reported promising results in hair regrowth without any side effects. An investigation revealed that topical finasteride gel is as effective as the oral form. However, studies comparing the two have only been over a 6 months [25]. The two AGA-approved drugs reported to have side effects in some patients [20]. Side effects associated with these drugs include scalp dryness, irritation, rashes, redness, burning, decreased libido, impotence, erectile dysfunction, testicular pain, ejaculation problems, breast enlargement, and headache (Table **5**). Herbal therapy may be a potential alternative to dominate chemical drug side effects. Saw palmetto, green tea, pumpkin seeds, and licorice have been reported to 5-ARIs, while rosemary improves scalp blood circulation, and grape seed induces the proliferation of hair follicles. Topical herbal medicines used may be more effective than conventional medicines [8].

Dutasteride

Dutasteride, 0.5 mg/day, an inhibitor of 5-ARI-1 and 5-ARI-2, is an approved treatment of BPH. It is 100 times and about three times more effective in inhibiting 5-ARI-1 and 5-ARI-2 than finasteride, respectively. Dutasteride has been indicated in clinical tests to significantly increase scalp hair, decrease extra hair loss, and enhance patient consent when used as the primary drug for treating AGA [26]. It facilitates hair growth compared with finasteride in AGA and well tolerated. Dutasteride showed greater potency than finasteride in treating AGA and had the same or possibly less adverse effects [26]. It may provide an effective and safe cure choice for male AGA. Its efficacy and safety data are primarily short-term and limited. Therefore, there is a need for long-term evidence about the effectiveness of dutasteride [27].

Herbal Extracts Induce Hair Growth

For over 100 years, thyme, lavender, rosemary, and cedarwood essential oils have traditionally used to treat hair loss [28]. Recently, several herbs and medicinal plants have been investigated for clinical effects in preventing hair loss and growth [10, 29]. Multiple herbal compounds and extracts including, *Punica granatum*, *Pumpkin seed oil*, saw palmetto extract, Citrullus colocynthis, Morus alba, Zizyphus jujuba, Eclipta alba, Phlantus embelica, Carthamus Tinctorius, Panax ginseng. The role of preventing hair loss and regrowth with different mechanisms [Table 6]. Numerous *in vitro* and *in vivo* studies on active herbal ingredients suggest that these compounds may help control hair loss when used alone, together, and in combination with synthetic anti-hair loss medicines [30, 31, 32, 42].

Table 4: Summary of herbal extracts have hair growth-promoting activity

Herb	Mechanism	Topical / Oral / *In vitro*/*In vivo*/ Cell culture	Human/Animal/Cell	References
Camellia sinensis	Anti-apoptosis Increase DPC proliferation Decrease oxidative cell damage	Topical	Human	[18, 33, 34]
Pumpkin seed oil	5-ARI	Oral& Topical	Human	[35, 36, 37]
Saw palmetto extract	5-ARI	Topical	Human	[31, 38]
Citrullus colocynthis	5-ARI Transformation of hair follicles from telogen to anagen phase	Topical	Animal	[39, 40]
Morus alba	Transform telogen to anagen	Cell culture	DPC	[41]
Zizyphus jujuba	Unknown	Topical	Animal	[42]
Eclipta alba	Transform anagen in the resting phase	Topical	Animal	[43]
Phlantus embelica	5-ARI	Topical/cell culture	Human/ Hair follicles	[44, 45, 46]
Carthamus Tinctorius	5-ARI The proliferation of DPC & HaCaT	*In vitro* & *In vivo*	Animal/DPC	[47, 48]
Panax ginseng	5-ARI	Topical	Human/Animal/ Hair follicles	[49]

Material and Methods

This research conducted to explore of investigate the topical effect of green tea, and its role in preventing Androgenetic alopecia and hair re-growth. This research data collected from 1995 to 2023 across academic search systems, including Google Scholar, PubMed Central, ScienceDirect, Springer, ResearchGate, Elsevier, and Google Scholar searches.

Chemical Compounds Present in Green Tea

The chemical structure and main ingredients of green tea are below

Polyphenols

Camellia sinensis mainly contains high amounts of antioxidants called polyphenols. The highest amounts of polyphenols in green tea are 20-30%, making it an excellent natural antioxidant [50, 51]. The primary catechin types found in green tea mainly include catechin (C), epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG). As shown in Figures 4 and 5 [51, 52]. According to previous research, all tea catechins have been described as powerful antioxidant agents *in vitro* and *in vivo* (Figure 8) [34].

Catechins

The effect of tea catechins on free radicals is multi-faceted and includes the following:

- Direct scavenger of reactive oxygen species (ROS) and nitrogen (RNS).
- Chelation of trace elements (such as copper and iron) involved in free radical generation;
- Increasing the production of endogenous antioxidant enzymes (SOD (superoxide dismutase) and glutathione);
- Inhibition of enzymes involved in the production of ROS (glutathione S transferase, microsomal monooxygenase, mitochondrial succinoxidase, or NADH oxidase);
- Protection and regeneration of antioxidant compounds (vitamin C or E) (Figure 7, 8) [34].

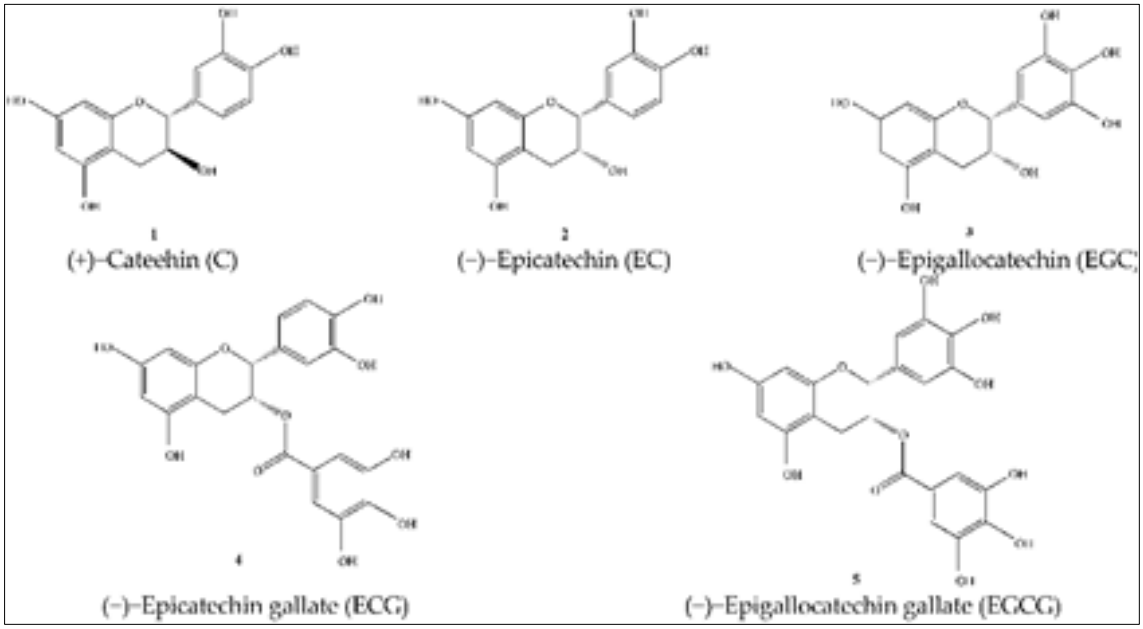

Fig 7: Phytochemical structures of *Camellia sinensis* catechins [50, 51, 52]

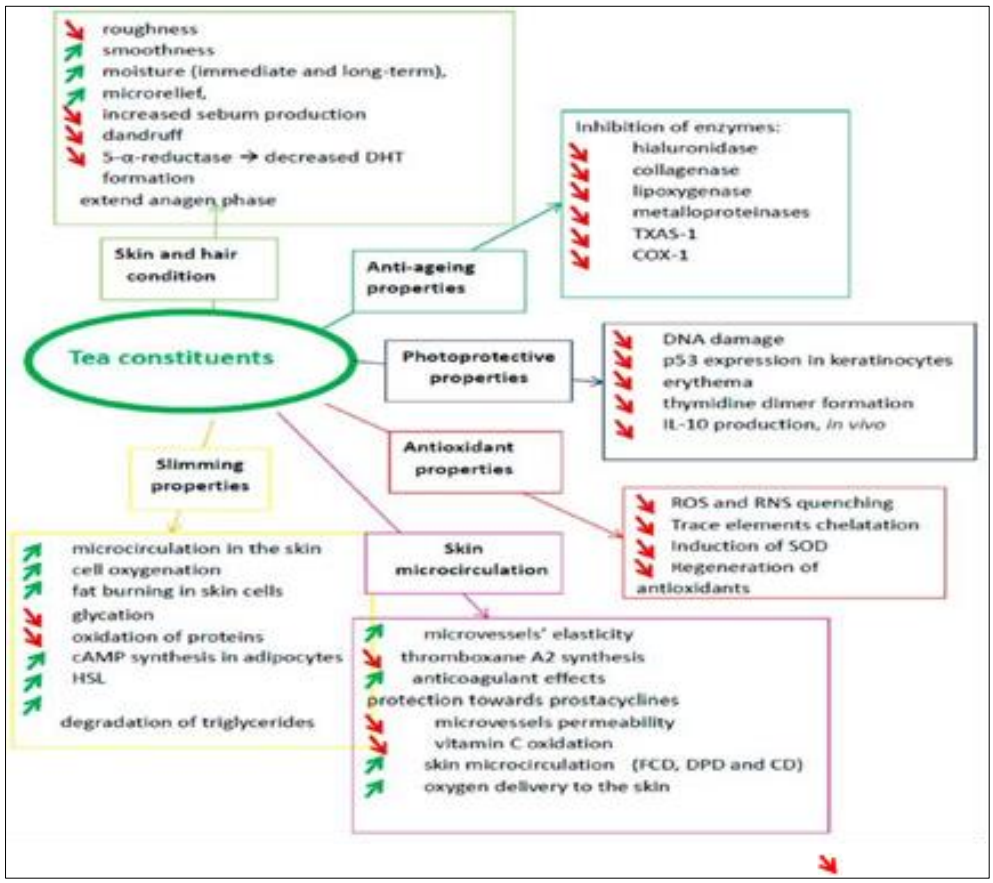

Fig 8: The main dermatologic properties of catechins (stimulation, inhibition) [34]

Flavonoids

Camellia sinensis is rich in flavonol glycosides, which contain myricetin glycosides, quercetin glycosides, and behenyl glycosides [51].

Phenolic acids

The amounts of phenolic acids in *Camellia sinensis* are relatively low, and include substances such as gallic acid, chlorogenic acid, caffeic acid, p-coumaric acid, ellagic acid, and quinic acid (Figure 9) [51].

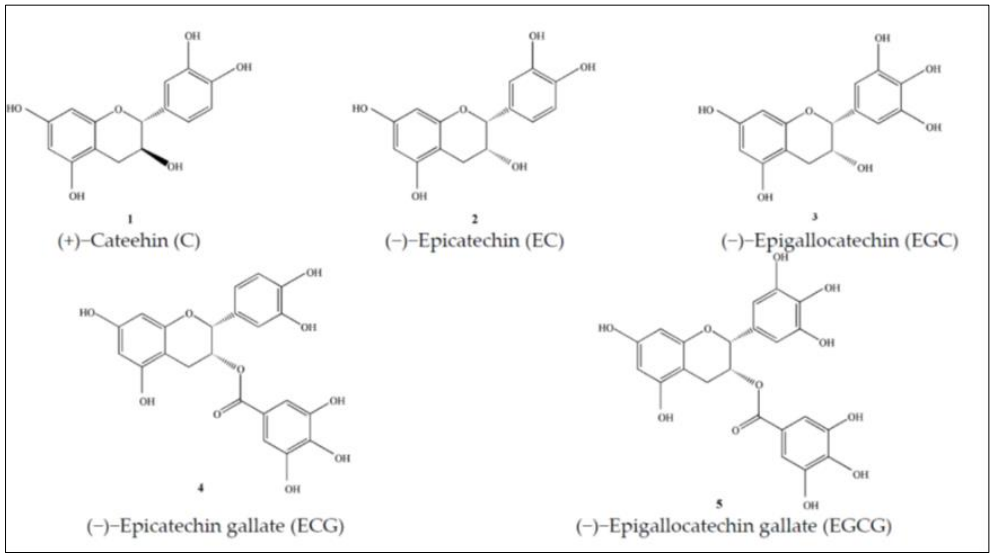

Fig 9: Phytochemical structures of green tea phenolic acids [51]

Hair Growth and regrowth enhancement function of *Camellia sinensis* extract

Various dietary ingredients, including polyunsaturated fatty acids, flavonoids, and tea catechin gallate inhibit 5α-Reductase *in vitro* and *in vivo* (Figure7) [53]. Kwon *et al*. [18] investigated hair growth *in vitro*, and *in vivo* by EGCG. In the *in vivo* study, scalp tissue samples obtained from the occipital scalp areas of 5 healthy male volunteers (20-31 years). The samples containing more than 100 hair follicles dissected into individual hair follicle under a stereo disc microscope. Then the dermal papillae cells (Figure 3) separated from the hair follicles. A total of 30 anagen hair follicles from 3 different

volunteers cultured under each growth condition, respectively. Briefly, based on the isolation, and culture method of Randall *et al.*, (1991), DPCs were cultured in Dulbecco's modified eagle's medium and 10% fetal bovine serum. In an *in vivo* study, researchers daily applied 10% EGCG extract in ethanol applied to two occipital scalp areas of three volunteers, and then the treated areas removed about 1-1.5 cm. After four days, participants experienced a significant increase in hair growth activity. The hair follicles samples carefully divided into hair follicles. DPCs were selectively dissected under a stereomicroscope and separated into single cells for western blot analysis. EGCG found to induce considerable human hair follicle elongation ex vivo. EGCG at 0.1- or 1-mM increased hair follicle length by 123.0% and 121.6%, compared to the vehicle-treated control group, respectively. They deduced that EGCG induced hair re-growth by dual proliferation and anti-apoptosis activity on DPC [20]. In another study performed by Adele Esfandiari and A Paul Kelly [54], they investigated the effects of green tea polyphenol ingredients on hair loss in rodents. In this experimental study, they randomly divided 60 female Balb/black mice with spontaneous head, neck, and back areas hair loss into two equal groups: A (experimental) and B (control).

Group A received a 50% fraction of dehydrated polyphenol extract in their drinking water for six months. Group B received regular drinking water. The results of this study exhibited that 33% of the mice in the first experimental group that received the polyphenol extract in their drinking water had significant hair re-growth within six months of treatment. No hair growth observed in mice control group that received normal water [54]. Liao S, Hiipakka RA., [1] indicated that steroid 5α-reductase isozymes are selectively inhibited by tea epicatechin-3-gallate and epigallocatechin-3-gallate, and green tea catechins, (-) epigallocatechin-3-gallate and (-) epicatechin- 3-gallates are potent inhibitors of 5α-reductase type 1(5-AR-1). Their results suggested some green tea gallates could modulate androgen action in target organs [1]. Liao S [1] studied the androgens' pharmacological effects and epigallocatechin gallate. Modulation of androgen function and EGCG administration may help treat hormone-related abnormalities such as benign prostatic hyperplasia, alopecia, acne, androgen-dependent and -independent prostate cancer [16]. Kim YY, *et al.* [16] examined the topical use of EGCG on mice testosterone-induced hair loss. Their results indicated that testosterone injection in mice causes hair loss primarily through apoptosis of hair follicles, rather than via the androgen metabolic pathway. It also observed that topical EGCG reduces testosterone-induced hair loss apoptosis in hair follicles. In addition, to the topical effects research of green tea on preventing hair loss and promoting hair growth, some studies also investigated the oral effects of green tea on hair loss. The results of the green tea supplement survey, and other compounds showed that a new green tea dietary supplement, cholecalciferol, ω3 and ω6, melatonin, antioxidants, and 5-ARIs plant may be a beneficial supplement for preventing AGA [22]. Zhang H, *et al.* [55] found that concentrations of 0.5–25 μM of EGCG resulted in a significant enhancement of mink hair growth. The potential for growth enhancement exhibited by EGCG appears to be related to the heightened proliferation of DPCs and outer ORSCs via the activation of Shh and AKT signaling pathways [56]. Epigallocatechin is a DHT inhibitor, which prevents IGF-1 levels from being depressed. IGF-1 prevents hair follicles from transitioning from anagen-to-catagen while influencing the telogen to anagen transition [55].

Table 5: Researches on green tea (*Camellia sinensis)*, and hair growth from 1995 to 2023

Study	Journal	Results	Reference
Selective inhibition of steroid 5-AR isozymes by tea epicatechin-3-gallate & epigallocatechin-3-gallate	Biochem Biophys Res Commun	The green tea catechins, (-) epigallocatechin-3-gallate and (-) epicatechin-3-gallate are potent 5-AR-1. These results exhibited that specific green tea gallates could modulate androgen activity in target organs.	[1]
Medicinal action of androgens and green tea EGCG	HKMJ	Modulation of androgen function and administration of EGCG may help treat hormone-related abnormalities such as benign prostatic hyperplasia, alopecia, acne, androgen-dependent prostate cancer.	[23]
Human hair growth enhancement *in vitro* by green tea (EGCG)	Phytomedicine	The results indicated that EGCG stimulated promoting hair growth via dual proliferation and anti-apoptosis effects on DPCs.	[18]
Topical application of EGCG on testosterone-induced hair loss in a mouse	Experimental dermatology	The results revealed that testosterone injection in mice causes hair loss and topical EGCG reduces testosterone-induced hair loss,and apoptosis in hair follicles.	[23]
Physical Stability, Safety, and Hair Growth Activity from Microemulsion Containing White Tea Extract Compared to Green Tea	The 2nd Korean ASEAN Symposium on Indonesian Natural Products 2014	Both green tea and white tea microemulsion are physically stable,, and the formulation did not cause any irritation, and microemulsion with green tea extract of 7.5% has a better ability to trigger hair growth than white tea.	[33]
EGCG-Mediated Alteration of the MicroRNA Expression Profile in 5αDihydrotestosterone Treated Human DPCs	Ann Dermatol	EGCG improves the harmfull effects of DHT by modulation the microRNA expression in DPCs.	[56]

Table 5: Cont.

Study	Journal	Results	References
Efficacy & Safety of a New Nutritional Supplement in AGA	J Clin Aesthet Dermatol	A new dietary supplement containing green tea, cholecalciferol, omega 3 and 6 fatty acids, melatonin, antioxidants, and the herbal 5-ARI may have a therapeutic effects in controlling AGA.	[22]
EGCG Promotes the Growth of Mink Hair Follicles Through Sonic Hedgehog and Protein Kinase B Signaling Pathways	Front. Pharmacol.	EGCG enhances the growth of mink hair follicles at concentrations of 0.5–2.5 μM. The potential for growth enhancement exhibited by EGCG appears to be related to the heightened proliferation of DPCs and outer ORSCs via the activation of Shh and AKT signaling pathways.	[57]
A Multimodal Hair-Loss Treatment Strategy Using a	Case Rep Dermatol	Epigallocatechin, one of the main active ingredients in green tea, is a DHT inhibitor that prevents decreasing IGF-1 levels. IGF-1 prevents the transition of	[15]

New Topical Phytoactive Formulation	Med	hair follicles from anagen to catagen phase and, at the same time, promotes from telogen to anagen phase.	
Herbal alternatives in androgenetic alopecia	J Cosmet Dermatol.	To overcome these side effects, herbal therapy may be a potential alternative. Saw palmetto, green tea, pumpkin seeds, and licorice have been reported to 5-ARIs, while rosemary improves scalp blood circulation, and grape seed induces the proliferation of hair follicle cells.	[8]
Hair Growth Promoting Activity of Green Tea Leaves Ethanolic Extract	Trad. Med. J	Concentrations of 1% and 4% of green tea ethanol extracts indicated the effect of strengthening and stimulating hair growth in a rabbit model. The results offered that the concentration of 4% is higher than that containing flavonoid and showed the best hair growth stimulating promotion.	[58]

Conclusion

EGCG and the group of catechins in green tea play a key role in inhibiting 5AR and blocking AGA, while improving hair regrowth by stimulating DPC in hair follicles. This study suggests that the active green tea polyphenol compounds may help reduce hair loss, and increase hair regrowth through a dual mechanism of inhibiting the DHT enzyme, as well as an anti-apoptotic effect on DPCs. Further investigation into using herbal anti-hair loss medication with a combination of green tea extract with two or more effective herbs could open new horizons in dermatological science. More research on the topical effects of green tea in preventing hair loss and increasing hair growth is necessary in the future.

Acknowledgment

I am sincerely grateful to my Dear brother Dr. Meiam Nasiri, the CEO of Dr. Akhavi Laboratory Co., for his kind support of this research.

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