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# Ginseng in Hair Growth and Viability

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## Abstract

The hair follicle is the unique organ that has the capacity of undergoing cyclic transformations following periods of growth (anagen), regression (catagen), and rest (telogen) regenerating itself to restart the cycle. The dynamic capacity of hair to growth and rest enables mammals to control hair growth and length in different body side and to change their coats. Unlike what is observed in many animals in which the pelage synchronously passes from one phase of the cycle to other all stages of growth cycle are simultaneously found in the human pelage, the growth pattern is a mosaic where the hair cycling staging of one hair root is completely independent of it nearest hair follicle, meaning that each follicular unit (FU) can contain follicles in different stages at any given time. A variety of factors, such as nutritional status, hormones, exposure to radiations, chemotherapy or radiotherapy, environmental pollution or drugs may affect hair growth, and affects the number of hairs, this progressive hair loss has a cosmetic and social impact that often significantly affects social and psychological well-being of the patient that suffers from this hair loss. Although a number of therapies, such as finasteride and minoxidil, are approved medications, a wide variety of classes of phytochemicals and natural products, including those present in ginseng are being testing. The purpose of this chapter is to focus on study the potential of ginseng and its metabolites in hair loss.

**Keywords:** Ginseng, Hair, Hair Follicle, Hair growth, Hair Viability

## 1. Introduction

### 1.1 Hair structure

Hair is made of several proteins, the principal protein that compound the fibrous structure of the hair is keratin, in addition to keratin, which has a high content of the amino acid cysteine, the hair also contains water, lipids, minerals, and the pigment melanin.

The hair shaft (the visible fiber that is growth above the skin), is a fiber with a variety of color depending of the melanin content that pigmented the keratin fiber. The dermal element in the hair follicle is the dermal papilla, which is majorly former by fibroblast cells, this dermal element controls the hair cycle.

The fiber of the hair, the hair shaft, grows from the hair follicle which is a tubular structure that forms a bulb around the matrix of the hair bulb, specialized dermal

stem cell and different types of keratinocytes, from this hair bulb that form the dermal papilla the hair shaft growth by division of proliferative cells, thus cells goes to a process of differentiated, keratinized, and pigmented in the hair follicle to form the hair shaft in a cycling manner. The diameter of the hair shaft is directly related to the size of the papilla, and allows us to define the miniaturized hairs and normal hair.

The hair structure is composed by concentric layers that forms the hair follicle, the medulla which is the center is includes the cortex and outwards the cuticle of the cortex, and is surrounded by the inner and outer root sheath, and all the mini-organ is surrounded by connective tissue.

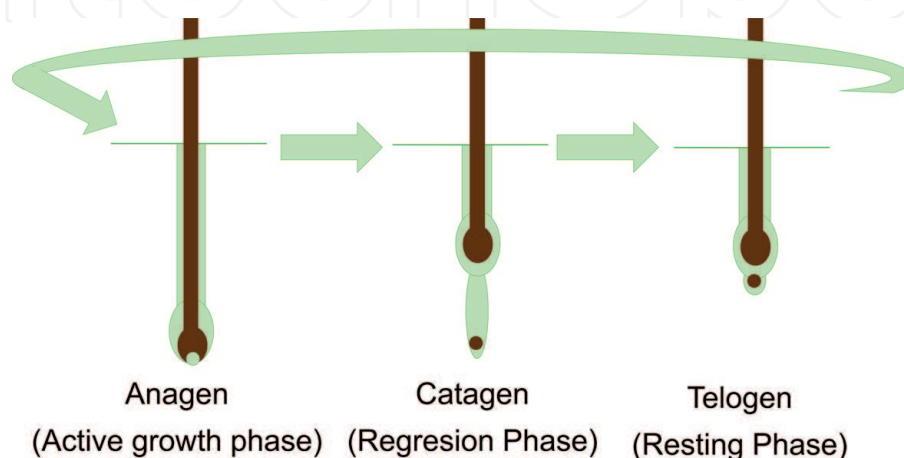
## 1.2 Hair function

The functional aspect of hair is not only to protect from radiation, heat or cold and any extern agent but also contribute to the appearance and personality. The loss of the hair contributes to psychological, social and psychosocial problems, generating a cosmetic and social impact in our society.

## 1.3 Hair cycle

The hair follicle has the unique capacity of undergoing periods of growth (anagen), regression (catagen), and rest (telogen and exogen) before regenerating itself to restart the cycle [1–4] (**Figure 1**). This dynamic cycling capacity enables mammals to change their coats, and for hair length to be controlled on different body sites [5].

Unlike what is observed in many animals in which the pelage synchronously passes from one phase of the cycle to other all stages of growth cycle are simultaneously found in the human, the growth pattern is a mosaic where the hair cycling staging of one hair root is completely independent of it nearest hair follicle, meaning that each follicular unit (FU) can contain follicles in different stages at any given time. In healthy individuals, 80–90% of follicles are in the anagen phase, 1–2% in the catagen phase, and 10–15% in the telogen phase [6]. The hair grows around one centimeter a month, and has a variable growth speed being faster in the summer than in winter. The growth phase, or anagen phase, lasts an average of 3–5 years. This normal hair-growth cycle can be modified or by internal or external factors such as hormones, stress, sun, disease, exposure to environmental pollution, drugs and smoking. This changes in the growth cycle and quality of hair can leads to hair loss by a shortening of the anagen phase, a premature ingression of the catagen phase, the prolongation of the telogen phase or a loss of the hair



**Figure 1.** Hair cycle stages scheme, phase of growth (anagen), regression (catagen), and rest (telogen) before regenerating itself to restart the cycle.

follicle function [6, 7]. Common hair loss is medically named as alopecia, and can be suffered by men and women.

#### **1.4 Hair loss**

Research has shown that in hair loss, the percentage of telogen follicles is increased, while the percentage of anagen and catagen follicles is reduced. A healthy individual loses approximately 100–150 hairs per day [6]. Cell-signaling pathways in hair follicular cells resulting in the induction of apoptosis, changes in usual pattern of hair cycling, inducing the hair follicle to turn into regression or resting phase and thinning or fracture of the hair shaft leads to progressive hair loss and alopecia [7].

Hair loss is a universal problem for numerous people in the world, is a disorder in which the hair falls out from skin areas such as scalp, the body and face. Multiple factors contribute to hair loss including genetics, hormones, nutritional status, and environmental exposure (exposure to radiations, environmental toxicants...), medications and nutrition.

Androgenic alopecia can be suffered by women and men and the androgen hormones are the most important of the factors that cause the hair loss characterized by a miniaturized of the hair follicles that leads to hair loss in the frontal to parietal area.

Other forms of hair loss are for example caused by immunogenic hair loss, like alopecia areata, this is characterized by a spot of hair loss all around the scalp. The approved therapies such as finasteride and minoxidil, are the traditional medication used for this hair loss diseases, a few others are in progress, like a wide variety of diverse phytochemicals, including those present in ginseng, the ginsenosides which have demonstrated hair growth-promoting effects in a large number of preclinical studies [7].

Androgenic baldness (androgenic alopecia) and circular/spot baldness (alopecia areata) are the most common forms of hair loss. The first is characterized by high sensitivity of the hair follicles to DH, while the second is induced by an autoimmune reaction [8, 9]. Hair also possesses its own immune system, the failure of which can lead to spot baldness (alopecia areata).

Alopecia is extended all round the world, reaching nowadays approximately to 10 million patients suffering from alopecia. Considering the pathological background of alopecia and its impact on an individual's health and social value, there is now a growing interest in the development of novel therapeutics for its medical management [7].

#### **1.5 Conventional treatment for hair loss**

Given the negative psychosocial impact of hair loss, patients follow different therapies, conventional treatments such as the two medications approved by the United States Food and Drug Administration (US-FDA): Minoxidil and Finasteride, for the treatment of alopecia.

Finasteride has a potent effect against androgens, being non-steroidal, it has shown to prevent male and female hair loss through the inhibition of type II 5 $\alpha$ -reductase, which affects androgen metabolism avoiding the conversion of free testosterone into 5 $\alpha$ -dihydrotestosterone, playing an important role in the pathogenesis of androgenetic alopecia in men and women [10].

The effect of minoxidil as hair growth stimulating has been known over last decades, since it was introduced in the early 1970 as a treatment for hypertension. But yet the basic mechanism of action on the hair follicle is not clearly understood [11, 12].

These drugs work improving the quality of the hair follicles and reducing the hair loss but exhibit certain adverse effects, such as allergic contact dermatitis, erythema, and itching, and also stop recommended guideline of minoxidil leads to recurrence

of alopecia and a prolonged use of finasteride causes male sexual dysfunction and appears as a major cause of infertility and teratogenicity in females.

Patient that do not see significant hair restoration with conventional therapies or suffer side effects often change from these conventional treatments to alternative medicine trying new treatments from the vast resources of natural products, in an attempt to find safe, natural and efficacious therapies to restore the hair.

## 2. Natural products

Natural products as it is known in the market “Dietary supplements” includes diverse subgroups like vitamins, probiotics, minerals, herbs, extracts, gels that do not require Food and Drug Administration (FDA) approval [13].

To treat hair loss are available treatments using amino acids, caffeine, capsaicin, curcumin, garlic gel, onion gel and extract, cinnamon, *Aloe Vera* gel, marine proteins, melatonin, procyanidin, pumpkin seed oil, rosemary oil, saw palmetto, vitamin B7 (biotin), vitamin D, vitamin E, zinc and Ginseng [9, 13].

## 3. Ginseng

Ginseng is an ancient herbal remedy that was recorded in The Herbal Classic of the Divine Plowman, the oldest comprehensive Materia Medica, which was scripted approximately 2000 years ago [9].

Among different species which are known as ginseng, *Panax ginseng* (Korean or Asian red ginseng) is the most frequently used one. The Ginseng is widely appreciated because it promotes health effect improving the immune response, the cardiovascular system, helping with sexual dysfunctions, preventing cancer, inhibiting tumor cell proliferation among others. In Dermatologic diseases, cancer is being investigate for its therapeutic effects in skin wound reparation, reducing immune response in dermatitis, reduces and prevent skin damage due to photo aging and cold hypersensitivity, improves hair growth reducing hair loss in alopecia [14].

Nowadays has gained fame as one of the most popular herbs originating from Eastern Countries, because contemporary science has revealed that ginseng contains a wide variety of bioactive constituents, especially a group of saponin compounds collectively known as ginsenosides, which have been proposed to account for most of the diverse biological activities, including the hair-growth potential of ginseng [9]. Ginsenosides can be classified, depending on the number of hydroxyl groups available for glycosylation via dehydration reactions, as protopanaxadiol (PPD) and protopanaxatriol (PPT). Common PPD-type ginsenosides include ginsenosides Rb1, Rb2, Rc, Rd., Rg3, F2, Rh2, compound K (cK), and PPD, whereas PPT-type ginsenosides include Re, Rf, Rg1, Rg2, F1, Rh1, and PPT [9] and malony ginsenosides mRb1, mRb2 and mRbc [15]. Ginseng extract or its specific ginsenosides have been tested for their potential to promote hair growth.

### 3.1 Ginseng biochemical effects on hair growth promotion

The major bioactive constituents of ginseng are ginsenosides and there has been evidences suggesting that promote hair growth by enhancing proliferation of dermal papilla and preventing hair loss via modulation of various cell-signaling pathways [9, 16, 17].



The role of 5 $\alpha$ -reductase enzyme in the hair-loss process has been well-documented [18], affects androgen metabolism, and it is the pathway how drugs approved are used nowadays.

Novel therapeutics ways for the management of hair loss and alopecia improving hair-follicle proliferation and reducing hair-loss need new targets (Figure 2). These targets include, matrix metalloproteinases (MMPs), extracellular signal-regulated protein kinase (ERK), and Janus-activated kinase (JAK), the activation of the proliferation by WNT/Dickkopf homolog 1 (DKK1), sonic hedgehog (Shh), vascular endothelial growth factor (VEGF), apoptosis inhibition by transforming growth factor-beta (TGF- $\beta$ ).

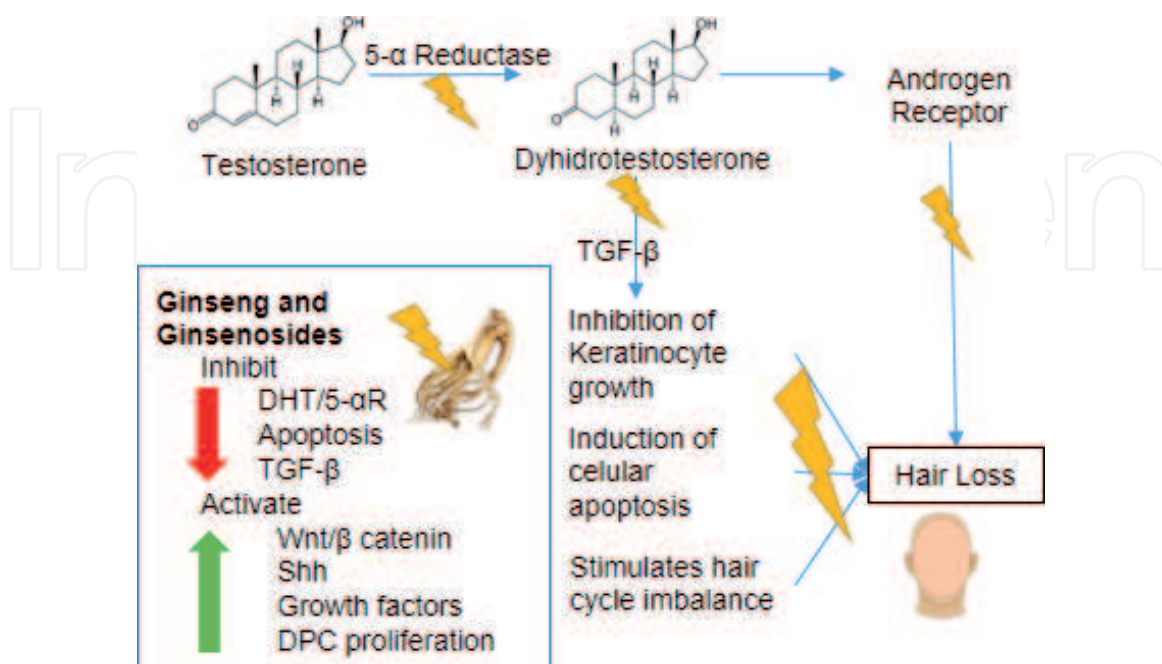
### 3.1.1 Photo aging prevention

Photo aging is skin damage induced by radiation exposure (Sun exposure) characterized by different inflammatory responses to ultraviolet radiation (UVR). Excessive UV irradiation is known to cause skin photo damage by release of oxidative species which leads to skin inflammation, and keratinocyte cell death producing photo aging and carcinogenesis.

There are evidences that suggest that misbalances in the hair-growth cycle, affecting keratinocyte and dermal papilla growth [19] is cause by UVR exposure not only producing the damage of the hair shaft as an extracellular tissue, as it is clearly evident but also alters the molecular growth [19].

The Reactive Oxidative Species (ROS) accumulation and activation of matrix metalloproteinase (MMPs), a tissue-degrading enzymes, produced by UV irradiation compromises dermal and epidermal structural integrity [9].

The inhibitory effect of ginsenosides on UVB-induced activation of MMP2 suggests the potential of these ginseng saponins in hair-growth regulation [9]. Ginsenosides Rb2 [20] and 20 (S) PPD, have been reported to reduce the formation of ROS and MMP-2 secretion in cultured human keratinocytes (HaCaT) cells after exposure to UVB radiation. Ginsenoside Rg3 20 (S), reduced ROS generation in



**Figure 2.**  
 The effect of the 5 $\alpha$ -reductase enzyme, dihydrotestosterone, and the growth factor TGF- $\beta$  on hair loss and the potential targets of ginseng in hair growth and loss.

HaCaT cells and human dermal fibroblasts without affecting cell viability. The 20 (S) Rg3 also attenuated UVB-induced MMP-2 levels in HaCaT cells [21]. Ginsenoside Rh2 reduced UVB radiation-induced expression and activity of MMP-2 in HaCaT cells, but UVB-induced ROS formation was only suppressed by 20 (S)-Rh2 [22].

Ginsenosides extracts from the Ginseng radix have shown attenuates radiation-induced cell death in the skin, improving hair growth. Ki67 positive number of cells and Bcl2 protein expression, an antiapoptotic protein, are induced by Total-root saponins and ginsenoside Rb1 diminishing apoptotic cells in UVB-exposed human keratinocytes [9, 23]. Ginsenoside F1, an enzymatically modified derivative of ginsenoside Rg1, by maintaining a constant level of the antiapoptotic protein Bcl-2 expression in UVB-irradiated HaCaT cells, protect keratinocytes from radiation-induced apoptosis [9, 24].

### 3.1.2 Ginsenosides reduces skin aging

Skin aging is a multifactorial process consisting of two distinct and independent mechanisms: intrinsic and extrinsic aging.

Ginsenosides, extracted from Ginseng have been tested in several studies in antiaging [25, 26]. This antiaging effects, of ginseng extract and ginsenosides is produced by maintaining skin structural integrity and regulating hair-growth by stimulating wound healing cells, collagen and hyaluronic acid.

Lee et al incubates fibroblasts, which are key wound-healing cells, with *Panax ginseng*, and found that *P. ginseng* stimulated human dermal fibroblast proliferation and collagen synthesis [27]. Human dermal fibroblast have different functions and are classified as key wound-healing cells because their function includes the production of collagen, growth factors, antioxidants and a balance of matrix-producing proteins and protease enzymes. In the Human fibroblast *P. ginseng* root extract activates human collagen A2 promotes and induces type-1 pro-collagen via phosphorylation of Smad2 [28].

Wrinkle formation, is associated as marker of dermal aging and present a reduced level of hyaluronan in the dermis [29]. On HaCaT cell treated with major ginseng metabolite (compound K, 20-O-beta-D-glucopyranosyl-20(S)-protopanaxadiol) were report that hyaluronan synthase2 (HAS2) gene is one of the most significantly induced genes [30] and also was tested that topical application of compound K on mouse skin and shows elevated the expression of hyaluronan synthase-2 [30]. The hyaluronan synthase-2 is an enzyme essential to hyaluronan synthesis, hyaluronan is a major component of most extracellular matrices that has a structural role in tissues architectures and regulates cell adhesion, migration and differentiation.

These antiaging effects of ginseng extracts through Src kinase-dependent activation of ERK and AKT/PKB kinases in the dermis and papillary dermis result in improved skin health, thereby ensuring hair-follicle health and a regular hair cycle [9, 30].

### 3.1.3 Ginseng on androgen alopecia

The exposure to androgens is the major triggers for hair loss is which in most cases is genetically predetermined in androgenic alopecia patients [9, 31, 32].

The androgen that mainly plays a role in altering hair cycling is 5 $\alpha$ -dihydrotestosterone (DHT), which is a metabolite of testosterone. The conversion of testosterone to DHT is mediated by the 5 $\alpha$ -reductase (5 $\alpha$ R) enzyme in each follicle [33, 34] (**Figure 2**). Treatment with 5 $\alpha$ -reductase inhibitors, e.g., finasteride, prevents the development of alopecia and increases scalp-hair growth [9].

Topical application of ginseng extract or ginsenosides was reported to enhance hair growth. Rhizomes of *P. ginseng* (red ginseng) containing a considerable amount of ginsenoside Ro, Ro is the predominant ginsenoside in the rhizome showed greater dose-dependent inhibitory effects against testosterone 5 $\alpha$ -reductase (5 $\alpha$ R) [35]. Ginsenoside Rg3 (a unique ginsenoside in red ginseng) and Rd. also exhibited similar inhibitory effects against 5 $\alpha$ R [36]. Another variety of ginseng, the *Parribacus japonicas* rhizome extract that contains a larger quantity of ginsenoside Ro also inhibited 5 $\alpha$ R enzyme activity. Topical administration of red-ginseng rhizome extracts and ginsenoside Ro onto shaved skin of C57BL/6 mice abrogated testosterone-mediated suppression of hair regrowth [36].

Major components of hair regenerative capacity such as linoleic acid (LA) and  $\beta$ -sitosterol (SITOS) were significantly restored with Red Ginseng Oil (RGO) after testosterone (TES)-induced delay of anagen entry in C57BL/6 mice, also RGO and its major components reduced the protein level of TGF- $\beta$  and enhanced the expression of anti-apoptotic protein Bcl-2, suggesting that RGO is a potent novel therapeutic natural product for treatment of androgenic alopecia [37].

Red Ginseng Extract (RGE) and ginsenosides protect hair matrix keratinocyte proliferation against dihydrotestosterone (DHT)-induced suppression and affects the expression of androgen receptor.

Moreover, RGE, ginsenoside-Rb1, and ginsenoside-Rg3 at lower levels that have been shown to inhibit 5 $\alpha$ -reductase [35] inhibit the DHT-induced suppression of hair matrix keratinocyte proliferation and the DHT-induced upregulation of the mRNA expression of androgen receptor in hDPCs [16]. DHT is the product of testosterone and does not require the activity of 5 $\alpha$ -reductase to affect hair follicles, and the inhibitory effect of DHT on hair growth is mediated by the androgen receptor in DPCs [38]. These results suggest that red ginseng may promote hair growth in humans through the regulation of androgen receptor signaling [16].

#### *3.1.4 Effects of ginsenosides on chemotherapy*

Majeed et al. review the recent perspectives of ginseng phytochemicals as therapeutics in oncology and explain the chemotherapeutic effect of ginsenoside as result of its appetites, ant proliferative, anti-angiogenic, anti-inflammatory and anti-oxidant properties [39]. The anticancer effect of ginseng was proven in various types of cancer: breast, lung, liver, colon and skin cancer. It increases the mitochondrial accumulation of apoptosis protein and down regulate the expression of anti-apoptotic protein, reducing cancer development. It also aids in the reduction of alopecia, fatigue and nausea, the known side effects of chemotherapeutic drugs [39].

Alopecia induced by chemotherapy is one of the most distressing side effects for patients undergoing chemotherapy. One drug used as chemotherapy is Cyclophosphamide (CP), also known as cytophosphane. Cyclophosphamide metabolite, 4-hydroperoxycyclophosphamide (4-HC) inhibited human hair growth, induced premature catagen development, and inhibited proliferation and stimulated apoptosis of hair matrix keratinocytes inducing the side effect of alopecia. In human hair follicle organ culture model pre-treatment with Korean Red Ginseng (KRG) before cyclophosphamide metabolite Dong In Keum et al shows that KRG suppress 4-HC-induced inhibition of matrix keratinocyte proliferation and stimulation of matrix keratinocyte apoptosis, playing a protective effect on 4-HC-induced hair growth inhibition and premature catagen development. Moreover, KRG restored 4-HC-induced p53 and Bax/Bcl2 expression [17].



### 3.1.5 Activation of dermal papillary cell proliferation

Different intracellular signaling pathways are involving and plays a critical role in stimulating hair growth by promoting dermal papillary-cell proliferation.

Hair growth is promote by Ginsenoside Rg3 upregulating Vascular Endothelial Growth Factor (VEGF) expression [36]. VEGF is a signaling protein which is released from the epithelium and increases the angiogenesis of the hair follicle [9, 40–42]. Was also demonstrate by Shin et al. that Rg3 increased the proliferation of human dermal papillary cells, associating this proliferation with an upregulation of mRNA expression of VEGF also stimulated stem cells by upregulating factor-activating CD34 and CD8 [36] and promoted hair growth even more than minoxidil in mouse [43] it was conclude that Rg3 might increase hair growth through stimulation of hair follicle stem cells [36].

RGE and ginsenoside-Rb1 enhanced the proliferation of hair matrix keratinocytes, human hair-follicle dermal papillary cells (hDPCs). Treated hair with RGE or ginsenoside-Rb1 exhibited substantial cell proliferation and the associated phosphorylation of ERK and AKT [16], it was recently demonstrated that ERK activation plays an important role in the proliferation of hDPCs [42] and AKT mediates critical signals for cell survival and also regulates the survival of DPCs as an antiapoptotic molecule [9, 16, 44] proliferation and the prolongation of the survival in the hDPCs by red ginseng may be mediated by the ERK and AKT signaling pathway [9, 16].

Human DPC treatment with Gintonin-enriched fraction (GEF) stimulated vascular endothelial growth factor release. Topical application of GEF and minoxidil promoted hair growth in a dose-dependent manner. Histological analysis showed that GEF and minoxidil increased the number of hair follicles and hair weight [45].

The Bcl-2 family proteins is notable for their regulation of apoptosis machinery, a form of programmed cell death, the member of this family either acts as antiapoptotic or pro apoptotic in nature. During the hair cycle, the dermal papillary cells (DPC) is the only region where Bcl-2 is expressed consistently and is considered to resist apoptosis [9, 46–48]. In mice Fructus *Panax ginseng* extract (FPG) increases the expression of Bcl-2 and decreases Bax expression, a pro apoptotic species, in cultured DPCs [49]. Parks et all concluded that FPG extract improves the cell proliferation of human DPCs through anti apoptotic activation. Topical administration of FPG extract might have hair regeneration activity for the treatment of hair loss [49].

### 3.1.6 Modulation of Wnt/Dickkopf homolog 1 (DKK1), sonic hedgehog (Shh), JAK-STAT3 and TGF- $\beta$ signaling by ginseng

Shh/Gli and Wnt/ $\beta$  path way and related proteins (Shh (Sonic hedgehog,) Smoothened (Smo),  $\beta$ -catenin, Cyclin D1 Cyclin E and Gli1 (glioma-associated oncogene homolog)) are associated to hair regeneration, promoting telogen-to-anagen transition, hair follicle formation and growth. [50–56].

Wingless-type integration-site (WNT) signaling plays a key role in hair-follicle development. Activation of WNT signaling is necessary for initiation of follicular develop, the blockade of WNT signaling by overexpression of the WNT inhibitor, Dickkopf Homolog 1 (DKK1), prevents hair-follicle formation in mice [50] and inhibited hair growth [9, 50].

$\beta$ -catenin signaling is essential for epithelial stem-cell fate since keratinocytes adopt an epidermal fate in the absence of  $\beta$ -catenin [51], and this signaling pathway is related to WNT [52] affecting hair follicle placodes formation, when  $\beta$ -catenin is mutated during embryogenesis, formation of placodes that generate hair follicles is blocked [53].

The role of TGF- $\beta$  in hair loss has been documented through the study revealing that treatment with a TGF- $\beta$  antagonist can promote hair growth via preventing catagen progression [57]. Also through the activation of TGF- $\beta$  and brain-derived

neurotrophic factor (BDNF), it was describe that it was enhanced the transition from the anagen to the catagen phase [58].

Since TGF- $\beta$ 1 induces catagen in hair follicles and it is closely related to alopecia progression it can be say that acts as a pathogenic mediator of androgenic alopecia [57, 59] and red ginseng extract can delay the catagen phase and holds the potential to promote hair growth, thought downregulation or inhibition of the TGF- $\beta$  pathway.

On Young Go Kim investigation was concluded that on ultraviolet B (UVB)-irradiated skin aging in mice, oral administration of Red Ginseng extract protects from skin damage induced by ultraviolet B (UVB)-irradiation, increases of skin thickness and pigmentation, reduction of skin elasticity, inhibited the increases of epidermis and corium thickness. The administration of Red Ginseng extract exert the protective action on UVB-radiation skin aging inhibiting the increase of skin TGF-beta1 content induced by UVB irradiation [60].

Furthermore on Zheng Li the hair-growth-promoting effects of Protopanaxatol type ginsenoside Re were associated with the downregulation of TGF- $\beta$ -pathway-related genes, which are involved in the control of hair-growth phase-transition-related signaling pathways [61]. On their study shows that topical administration of ginsenoside Re on to the back skin of nude mice for up to 45 days significantly increased hair-shaft length and hair existent time, and stimulated hair-shaft elongation in the ex vivo cultures of hair follicles isolated from C57BL/6 mouse [61].

The hyper activation of the c-Jun-N-terminal kinase (JNK) pathway in associate with an activation of TGF- $\beta$ -induced hair loss. Korean red ginseng has been attributed to exert protective effects on TGF- $\beta$ -induced hair loss by the inhibition of JNK on radiation-induced apoptosis of HaCaT cells [62].

By promoting telogen-to-anagen transition of follicular cells and epidermal growth, Shh/Gli regulates hair-follicle development, growth and cycling [54, 55]. Shh<sup>-/-</sup> mice develop have abnormal hair follicular cells in the dermal papillae and blocking Shh activity mice diminished hair growth, this results indicates the importance of Shh signaling in hair-growth promotion [56].

Androgenetic alopecia is related to testosterone (TES)-induced delay of anagen phase and hair loss. In C57BL/6 mice Red-ginseng oil (RGO) reversed testosterone-induced suppression of hair regeneration through early inducing anagen phase by up-regulating the expression of Shh/Gliand Wnt/ $\beta$  pathway-related proteins, Shh, Smoothened (Smo),  $\beta$ -catenin, Cyclin D1 Cyclin E and Gli1. Additionally, RGO reduced the protein level of TGF- $\beta$  but enhanced the expression of anti-apoptotic protein Bcl-2 [37] suggesting that RGO is a potent therapeutic natural product for treatment of androgenic alopecia possibly through hair re-growth activity [37].

The signaling pathway and anagen induction effect of ginsenoside F2 were investigated and compared with finasteride on the effect of hair growth induction in Heon-Sub Shin at all paper [43] where MTT assay results indicated cell proliferation in human DPC increased a 30% with ginsenoside F2 treatment compared to finasteride [43]. Studding the expression of  $\beta$ -catenin and its transcriptional coactivator Lef-1, the Ginsenoside F2 compared to finasteride group, increased the expressions while decreased the expression of DKK-1. Tissue histological analysis shows that administration of ginsenoside F2 promoted hair growth as compared to finasteride, increase in the number of hair follicles, thickness of the epidermis, and follicles of the anagen phase [43]. Heon-Sub Shin conclude that ginsenoside F2 might be a potential new therapeutic compound for anagen induction and hair growth through the Wnt signal pathway [43]. In another study by Matsuda et al., ginsenosides Rg3 and Rb1 [63] extracted from red ginseng stimulates hair growth activity in an organ culture of mouse vibrissa follicles. No detailed explanations are given in this paper about the mechanism of hair growth, but the results presented by Matsuda et al. [63] indicated that Ginseng Radix possesses hair growth promoting activity.

*Panax ginseng* (PG) has diverse pharmacological effects such as anti-aging and anti-inflammation it exert this effects thought stimulating the proliferation and inhibiting the apoptosis [64]. PG extract treatment affected the expression of apoptosis-related genes in HFs, Bcl-2 and Bax, through this regulation reversed the effect of DKK-1 on ex vivo human hair organ culture, antagonizes DKK-1-induced catagen-like changes [9, 64].

Growth factors and cytokines have been proved to influence hair follicle development or cycling [65] overexpression and/or secretion of Cytokines, such as interleukins (ILs) and interferons (IFN), cause skin inflammation, TGF beta 1 partially inhibited hair growth and EGF, TNF alpha and IL-1 beta completely abrogated it [66] There is an aberrant expression pattern of cytokines in alopecia areata hair follicles.

The presence of CD8<sup>+</sup> T cells and NKG2D<sup>+</sup> cells around the peri-bulbar area of the affected hair follicles [67] and upregulation of several ILs, such as IL-2, IL-7, IL-15, and IL-21, and IFN- $\gamma$  leads to immune activation area where're main suppressed natural killer (NK) cells [68] and is defined as immune-tolerated area. Loss of immune tolerance [68] or immune activation [67], leads to hair-follicle dystrophy and acceleration of the catagen phase [9] by the activation of a cytotoxic cluster of differentiation 8-positive (CD8<sup>+</sup>) and NK group 2D-positive (NKG2D<sup>+</sup>) T cells. In alopecia Areata (AA) are found more CD57 – CD16<sup>+</sup> NK cells and there is a association between NK cells and the collapse of HF-IP (immune privilege) while normal human scalp skin—that indeed there is no sign of an NK attack on normal anagen VI HFs [69].

Phosphorylate Stat3 in the Janus Kinase (JAK)/Signal transducer and activator of transcription-3 (STAT3) pathway regulate the activation of CD8<sup>+</sup> and the NKG2D<sup>+</sup> CD8<sup>+</sup> T cells [70]. The inhibition of the upstream pathway JAK appears as a plausible target for developing a therapy for hair loss [67]. In fact, a number of JAK inhibitors, such as tofacitinib, ruxolitinib, baricitinib, CTP-543, PF-06651600 and PF-06700841 are in the progress of developing a therapy for alopecia [71, 72] more often in alopecia areata a common form of non-scarring hair loss that usually starts abruptly with a very high psychological impact [73], it is a T-cell-mediated disease which produces circular patches of non-scarring hair loss and nail dystrophy [72].

Ginsenoside Rk1 inhibited the lipopolysaccharide- stimulated phosphorylation of JAK2 and STAT3 in murine macrophage cells [74] and Ginsenoside 20(S)-Rh2 exerts anti-cancer activity through targeting IL-6-induced JAK2/STAT3 [75]. Topical application of ginsenoside F2 by inhibiting the production of IL-17 and ROS, ameliorated dermal inflammation skin [69]. In the pathogenesis of alopecia areata is believed to be an imbalance of inflammatory cytokines IL-17. Monoclonal antibodies against IL-17A leads to hair regrowth in human volunteers [76]. Treatment with *Panax ginseng* saponins diminished the proliferation and differentiation of Th17 cells and decreased IL-17 expression [77]. This regulating IL-17 secretion ginsenosides may enhance hair growth in alopecia areata [69, 77]. It would be interesting to investigate whether ginsenoside Rk1 or other ginsenosides can target JAK/STAT3 signaling in dermal papilla and diminish activation of inflammation and immune cells.

#### 4. Conclusion

Ginseng may be a multipurpose natural medicine with an extended history of medical application throughout the globe, particularly in Eastern countries.

The beneficial effects of Ginseng cover a good spectrum from immune to cardiovascular, cancer and sexual diseases. New advances in the science leads elucidate new pharmacological activity of the ginseng and its ginsenosides. There are some studies of the use of Ginseng in dermatology investigating its effects from molecular to physiological in a skin cancer, dermatitis, alopecia wound

injury and of course hair loss because also ginseng and its ginsenosides regulate the expression and activity of major proteins involved in hair-cycling phases, so the medical use of ginseng is not only restricted to the improvement of general wellness, but also extended to the treatment of organ-specific pathological conditions, like hair.

Ginseng and its metabolites are associated with the induction of anagen phase preventing hair loss and promoting hair growth although further studies should be done to elucidate and clarify the mechanisms by which ginseng and its metabolites regulate human hair health.

### **Conflict of interest**

The authors declare no conflict of interest.

### **Acronyms and Abbreviations**

AA	Alopecia Areata
AGA	Androgenetic Alopecia
FU	Follicular Unit
US-FDA	United States Food and Drug Administration
DKK1	Dickkopf homolog 1
Shh	sonic hedgehog
VEGF	vascular endothelial growth factor
TGF- $\beta$	transforming growth factor-beta
MMPs	matrix metalloproteinase
ERK	extracellular signal-regulated protein kinase
JAK	Janus-activated kinase
PPD	protopanaxadiol
PPT	protopanaxatriol
cK	compound K
UVR	ultraviolet radiation
ROS	reactive oxygen species
LA	linoleic acid
SITOS	$\beta$ -sitosterol
TES	testosterone
HHDPCs	human hair-follicle dermal papillary cells
RGE	red-ginseng extract
HFDPs	hair follicle dermal papilla cells
GEF	Gintonin-enriched fraction
KRG	Korean Red Ginseng
DPCs	Dermal papillary cells
NKG2D+	NK group 2D-positive
ULBP3	UL16-binding protein 3
Shh/Gli	glioma-associated oncogene homolog
CD8+	cluster of differentiation 8-positive
ILs	interleukins
IFN	interferons
ORS	outer root sheath
STAT3	Signal transducer and activator of transcription-3
WNT	Wingless-type integration-site
GEF	Gintonin-enriched fraction



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