Indonesian Journal of Pharmacy

VOL 36 (1) 2025: 20–45 | REVIEW ARTICLE

Potential of Macroalgae for Anti Alopecia: A Systematic Review

Lilies Wahyu Ariani[1,2], Abdul Karim Zulkarnain[3*], Triana Hertiani [4] and Arief Nurrochmad[5]

1. Doctoral Program of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
2. Department of Pharmaceutics, Faculty of Pharmacy, Sekolah Tinggi Ilmu Farmasi Semarang Yayasan Pharmasi, Semarang, 50193, Indonesia
3. Laboratory of Physical Pharmacy, Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada Yogyakarta, Skip Utara 55281 Yogyakarta.
4. Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
5. Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia, 55281

Article Info

Submitted: 22-01-2024
Revised: 30-08-2024
Accepted: 02-09-2024

*Corresponding author
Abdul Karim Z

Email:
akarimzk08@gmail.com

ABSTRACT

Alopecia, commonly referred to as baldness, is a condition in which hair loss exceeds hair growth. The most prevalent types of alopecia are androgenetic alopecia (AGA) and alopecia areata (AA). Macroalgae are known to contain secondary metabolites with significant ecological potential that can be harnessed for various applications. The main types of macroalgae include red algae (Rhodophyta), green algae (Chlorophyta), and brown algae (Phaeophyta). Among the bioactive components found in macroalgae, one of the notable benefits is their potential as anti-alopecia agents. This review article aims to summarize the mechanisms by which macroalgae and their active compounds contribute to alopecia treatment by stimulating hair follicle growth. The review employs a literature study approach, analyzing secondary data from several articles sourced from online databases such as PubMed, ScienceDirect, and Google Scholar, using the keywords "algae for androgenetic alopecia" and "algae for alopecia." The review presents findings from 18 articles on various algae species that exhibit potential as alternative treatments for alopecia, each with distinct mechanisms of action. This research aims to contribute to the development of herbal medicinal products derived from macroalgae for the treatment of alopecia.

Keywords: macroalgae, algae, androgenetic alopecia, alopecia areata, mechanism of action

INTRODUCTION

Algae represent a vast natural resource in the ocean (Xu et al., 2017) and are categorized as lower plants (Thallophyta), lacking true roots, stems, and leaves. Based on size, algae are divided into two categories: microalgae and macroalgae (Festi, 2022). Macroalgae are characterized by their macroscopic body form and size, consisting of fronds that similarly lack true roots, stems, and leaves (Festi, 2022). Marine algae are further classified into three major groups based on pigmentation and chemical composition: (1) brown algae (Phaeophyceae), (2) red algae (Rhodophyceae), and (3) green algae (Chlorophyceae). The composition of algae compounds is significantly influenced by environmental factors such as sunlight intensity, temperature, pH, salinity, and CO_2 levels (Zheng et al., 2023). Macroalgae are among the most extensively studied and exploited marine resources, due to the bioactivity of their components, which are rich in compounds exhibiting a variety of biological activities. These compounds are utilized across multiple sectors, including agriculture, horticulture, cosmetics, and the food industry (Ścieszka & Klewicka, 2019; André et al., 2021). Algae, particularly among aquatic flora, are known to contain high concentrations of polysaccharides, such as carrageenan, alginate, fucoidan, laminaran,

agarose, rhamnan, and ulvan, as well as bioactive polyphenolic compounds (Wang et al., 2017).

Hair loss, commonly referred to as alopecia or baldness, is a widespread clinical condition affecting millions of individuals globally and is often associated with significant emotional and psychological distress (Qi & Garza, 2014). While psychological and physical stress are among the primary causes of hair loss, various other factors also contribute. Numerous studies have been conducted to better understand the underlying causes and pathophysiology of hair loss and to explore potential treatments aimed at stimulating hair follicle growth (Pope, 2014). Hair loss can be influenced by a range of factors, including genetic predisposition (such as trichodystrophy and androgenetic alopecia), coexisting medical conditions, hormonal imbalances (e.g., thyroid disease and insulin resistance), immune system disorders (e.g., alopecia areata and lupus erythematosus), nutritional deficiencies, and environmental factors (e.g., drug use and ultraviolet (UV) radiation). In addition, mental health issues (e.g., stress and trichotillomania) and aging can contribute to hair loss. These adverse factors disrupt the hair growth cycle, reducing the activity of stem cells and diminishing the regenerative capacity of hair follicles (Gentile & Garcovich, 2019).

Alopecia is a prevalent clinical disorder that can significantly impact a person's quality of life, making it a considerable concern due to its effects on hair follicles. Typically, alopecia begins before the age of 30 and affects individuals of all genders. In individuals with alopecia, hair follicles shrink, eventually leading to the cessation of hair production. Consequently, patients may experience hair loss, resulting in either partial or total baldness. Hair loss is typically characterized by reduced hair density, thinning, or a combination of both, and it can be attributed to both hormonal and non-hormonal factors (Choi, 2020). The two most common types of alopecia are androgenetic alopecia (AGA) and alopecia areata (AA). AGA is primarily caused by increased sensitivity of scalp follicles to dihydrotestosterone (DHT), whereas AA is often triggered by an autoimmune reaction, which is one of its primary causes (Meidan & Touitou, 2001).

Many studies have been conducted to identify the underlying causes and pathophysiology of hair loss, with the goal of developing treatment methods to stimulate hair follicle growth (Pope, 2014). Hair growth is a cumulative process, driven by the coordinated proliferation and differentiation of cells within the hair follicle. Hair follicles consist of both epithelial and dermal components and function as mini-organs that produce hair shafts. These follicles undergo a regular cycle of regeneration, known as the hair cycle, which is characterized by successive growth phases. This cycle involves three key stages: the active growth phase (anagen), during which the previous hair sheds; the brief transition or regression phase (catagen); and the resting phase (telogen), which allows the follicle to prepare for new hair production in response to hormonal changes (Patel et al., 2015). The anagen phase, lasting between two and eight years, represents the active phase of hair growth. The catagen phase is a short regression period of about 2-3 weeks, during which the hair follicle shrinks. Telogen, the resting phase, lasts for approximately three months, ending with the shedding of the old hair and the emergence of new hair (Pope, 2014).

The causes of baldness remain poorly understood, though various treatments have been developed to address alopecia. According to the FDA, only two medications are approved for the treatment of alopecia: Minoxidil, which is applied topically, and Finasteride, which is taken orally (Lee et al., 2018). Minoxidil is metabolized by sulfotransferase in the scalp into minoxidil sulfate, which stimulates hair follicle cell growth and reduces hair loss. Finasteride, a 5α-reductase inhibitor, blocks the conversion of testosterone into dihydrotestosterone (DHT), a key factor in androgenetic alopecia (Park & Lee, 2021). Despite their efficacy, these treatments have notable drawbacks. Both drugs require long-term use, as their effects are not permanent, and they are associated with various side effects (Choi, 2020). Minoxidil can cause side effects such as facial hypertrichosis in 3-5% of women and contact dermatitis in approximately 6.5%. Finasteride, when taken systemically, has been linked to sexual dysfunction, mood disorders, and post-finasteride syndrome, which can include depression. Another option for treating alopecia is hair transplantation; however, it is often expensive, as most insurance plans do not cover the procedure. Additionally, hair transplantation carries risks, including bleeding and infection (Lee et al., 2018). This has led to a growing interest in alternative medicine, which is often associated with fewer side effects. Herbal plants are being explored for their therapeutic potential in treating various conditions, including alopecia (Ashique et al., 2020).

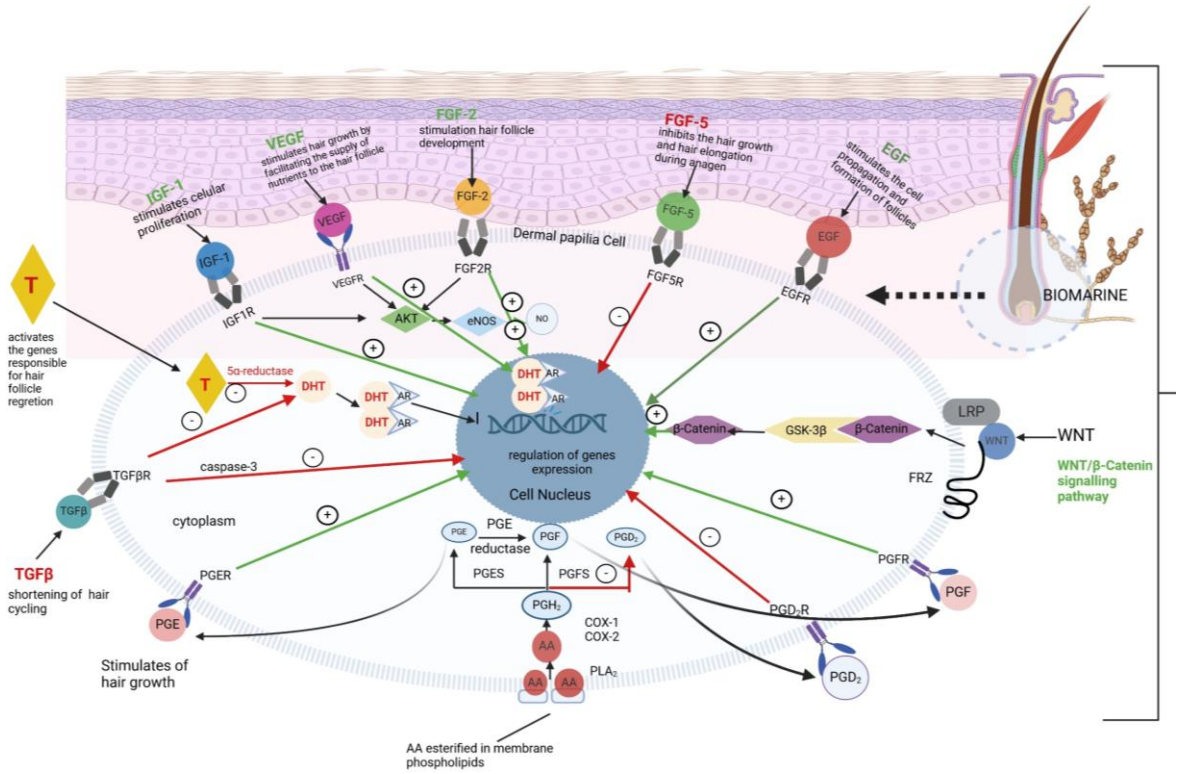

Figure 1. Flow diagram of obtaining inclusion articles that match the key

In light of this, and based on a review of several articles, this review aims to provide a comprehensive summary of the mechanisms through which bioactive compounds derived from macroalgae can be utilized in the treatment of hair loss. These compounds demonstrate promising effectiveness as anti-alopecia agents.

METHODOLOGY

The literature search was conducted using secondary data, which refers to data collected indirectly from sources rather than directly from participants. The data for this review was sourced from online databases, including Google Scholar, PubMed, and ScienceDirect, using the keywords "algae for androgenetic alopecia" and "algae for alopecia." Given the scarcity of research specifically discussing the anti-androgenetic and anti-alopecia properties of algae, the author limited the search to journals published within the last 15 years. A total of 18 relevant articles were identified and included in this review. These articles reported on 18 species of algae that are believed to possess anti-alopecia activity, each with different mechanisms of action. Additional articles were also referenced to supplement the review.

The selection criteria included articles that examined herbal plants derived from macroalgae used for the treatment of alopecia based on animal trials with biochemical analysis of their mechanism of action. In addition to macroalgae, microalgae in the treatment of alopecia were not included in the study.

RESULTS AND DISCUSSION

From the reviewed articles, 18 species of algae were identified, each containing different bioactive compounds, although some compounds belong to the same chemical group. These compounds exhibit anti-alopecia activity through various mechanisms of action, with some algae species sharing similar pathways. Several studies have explored the use of algae in treating alopecia, demonstrating their effectiveness in promoting hair growth through diverse mechanisms (Figure 1 and Table I).

Table I. Types of algae that have the potential to act as anti-alopecia

No	Species	Combined content	Mechanism	Results	Therapeutic effect	Reference
1	*Laminaria japonica and Undaria pinnatifida*	• nonacosan-10-ol • β-sitosterol	• Stimulates hair growth promoting genes such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1. • Suppresses the expression of transforming growth factor β1 which is the gene that causes hair loss	The results of the 14th day of treatment can increase the hair growth effect of the LU mixture which is the same as 3% minoxidil treatment. The LU mixture significantly (P<0.05) stimulated genes that promote hair growth, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1	alopecia	(Park, 2016)
2	*Ecklonia cava*	Dieckol (phlorotannin)	The bioactive compound Dieckol from E. cava can stimulate hair growth through DPC proliferation and/or inhibition of 5α-reductase activity	Enzymatic extract of E. cava at a concentration of 1 µg/mL can increase the length of hair fibers in the follicles by 12.4%	Androgenetic alopecia	(Kang, et al., 2012)
3	*Cistanche Tubulosa and Laminaria Japonica*	Fucoidan	Increases blood flow to the scalp, which helps normalize hair follicles and promotes hair growth by reducing scalp inflammation and dandruff.	Increased hair density and diameter after 16 weeks of treatment	alopecia	(Seok et al., 2015)
4	*Ecklonia cava (APD)*	phlorofurofucoeckol (phlorotannin)	Proliferation of hair dermal papilla cells (hDPC) with increased growth factors such as IGF-1 and VEGF and decreased oxidative stress	The increase in hDPC proliferation was 30.3% more than the negative control ($p < 0.001$). In addition, 0.1 µg/ml APD lengthened the hair shaft 30.8% longer than the negative control for 9 days ($p<0.05$). Insulin-like growth factor-1 (IGF-1) mRNA expression increased 3.2-fold in hDPCs after treatment with 6 µg/ml APD ($p<0.05$). Vascular endothelial growth factor (VEGF) mRNA expression also increased 2.0-fold with PPE 3 µg/ml ($p<0.05$). Treatment with 10 µg/ml APD reduced oxidative stress in hDPCs ($p<0.05$)	alopecia	(Shin et al., 2016)
5	*Polyphonia tomorrowii*	5-bromo-3,4-dihydroxybenzaldehyde (BDB)	Promotes hair growth by stimulating anagen signaling by activating the Wnt/β-catenin pathway and autophagy and inhibiting the TGF-β pathway in DPCs.	Treatment with BDB concentrations of 0.01, 0.1, and 1 µM increased hair fiber length in vibrissa follicles by 87.31% ± 17.7%, 98.29% ± 26.3%, and 175.7% ± 22 .44% ($p < 0.05$),	alopecia	(Kang et al., 2022)
6	*Tunic Ascidian (Halocynthia roretz)*	Glycosaminoglycans	The highest proliferative activity in follicular dermal papilla (HFDP) cells by inhibiting the production of dihydrotestosterone (DHT)	Increased proliferation of HFDP cells treated with Tunic ascidian 50 and 100 µg/mL (21% and 27%, respectively)	alopecia	(Neri, et al, 2022)

Table I. (7-10)

No	Species	Combined content	Mechanism	Results	Therapeutic effect	Reference
7	*Grateloupia elliptica*	Bromo- phenol	Dermal papilla proliferation, inhibition of 5α-reductase, increased production of PGE2, inhibitory effect on LPS-stimulated production of IL-12, IL-6 and TNF-α in bone marrow-derived dendritic cells stimulated by lipopolysaccharide (LPS) and inhibitory activity against Pityrosporum ovale causing dandruff	G. elliptica extract significantly increased dermal papilla cell proliferation by 169.5% at a concentration of 100 µg/ml G. elliptica extract can inhibit 5α-reductase activity by 48% at a concentration of 10 µg/ml. G. elliptica extract at 12.5, 25, and 50 µg/ml increased PGE2 production in a single dose G. elliptica extract inhibited IL-12 p40 production by 47.8% and at a concentration of 50 µg/ml. IL-6 production on LPS-with an inhibition value of 31.4%. G. elliptica extract showed an inhibitory zone diameter of 10 mm.	Alopecia and Androgenetic Alopecia	(Kang et al., 2012)
8	*Tetrathelmis tetrathele*	Flavonoids	Inhibits the production of inflammatory mediators, nitric oxide (NO), prostaglandin E2 (PGE2), proliferation of HaCaT and HFDPC cells, and inhibits 5α-reductase activity.	TTE inhibits the production of inflammatory mediators, nitric oxide (NO), and prostaglandin E2 (PGE2) without cytotoxicity in LPS-stimulated RAW 264.7 cells	alopecia	(Park et al., 2021)
9	Brown Algae Isolate 7-Floroeckol phloroglucinol	7-Phloroeckol, phloroglucinol	Stimulation of DPC and ORS cells and induction of IGF-1 in DPC	The proliferative activity of 7-floroeckol was increased by 116 and 126% in DPC. 132 and 126% in ORS. resulted in hair shaft elongation of 1.57 and 1.84 mm, compared to the control 0.96 mm at concentrations of 0.1 and 1 µM, respectively. Increased IGF-1 mRNA expression, 4.98 and 5.37 fold. induced an increase in IGF-1 secretion of 783 and 841 pg/ml	alopecia	(Bak et al., 2014)
10	Brown Alga Loliolida Isolate	Lolliolide	Increased expression levels of hair growth-related autocrine factors including VEGF, IGF-1, and KGF and induced hair DP cell growth through the AKT/β-catenin signaling pathway.	Increases HDP spheroid cell viability up to 100 µg/ml, and highest at a dose of 20 µg/ml. At a dose of 20 µg/ml, growth factor mRNA expression in HD spheroids increased. Loliolide activates the WNT/β-Catenin signaling pathway in HDP spheroids via AKT WNT/β-catenin signaling.	alopecia	(Lee, et al, 2019)

Table I. (11-12)

No	Species	Combined content	Mechanism	Results	Therapeutic effect	Reference
11	*Sargassum muticum*	apo-9′-fucoxanthinone	Increases dermal papilla cell (DPC) proliferation and reduces 5α-reductase activity as well as activation of Wnt/β-Catenin and VEGF-R2.	Increase in hair fiber length in vibrissa follicles treated with S. muticum extract (0.1, 1 μg/mL) 134.4, 133.0%: S. muticum extract inhibited 5α-reductase activity by 12.4, 18.8, 15.8 and 14.6% at concentrations of 0.1, 1, 10 and 100 μg/mL The solvent fraction of S. muticum extract significantly inhibited 5α-reductase activity by 44.8–82.6%. S. muticum extract increased DPC proliferation by 135.7% at a concentration of 10 μg/mL The solvent fraction, EtOAc fraction 40 μg/mL and hexane fraction 1 μg/mL significantly increased DPC proliferation by 135.6 and 125.7%, respectively. The EtOAc fraction of S. muticum extract can effectively promote the telogen to anagen transition in an in vivo model	alopecia	(Kang et al., 2016)
12	*Ishige sinicola*	octaflorethol A	DPC proliferation is followed by activation of the β catenin pathway, and inhibition of 5α-reductase induces DPC proliferation through cell cycle regulation and Wnt/β-catenin signaling.	The length of hair fibers from vibrissa follicles treated with 1 μg/mL of I. sinicola extract increased significantly compared with the control I. sinicola extract promotes telogen to anagen transition in C57BL/6 mice I. sinicola extract inhibited 5α-reductase activity by 16.3%, 39.8% and 41.3% at concentrations of 0.1, 1 and 10 μg/mL, respectively. Octaphlorethol A inhibited 5α-reductase activity by 29.1%, 27.5% and 20.9% at concentrations of 0.01, 0.1 and 1 μM, respectively Octaphlorethol A increased DPC proliferation by 103 and 110.5% at concentrations of 0.1 and 1 μM	Androgenetic alopecia	(Kang et al., 2013)

Table I. (13-14)

No	Species	Combined content	Mechanism	Results	Therapeutic effect	Reference
13	*Ecklonia cava*	Dioxinodehydroeckol	Induces increased IGF-1 expression in DPCs. Dioxinodehydroeckol, a component of E. cava, induces hair shaft elongation, increases DPC and ORS cell proliferation, and increases IGF-1 expression in DPCs.	At treatment concentrations of 0.01 and 0.1 lg/mL, proliferation increased in DPC by 130.6% and 138.6% and in ORS by 121.8% and 118.7% At concentrations of 0.01 and 0.1 lg/mL, elongation was seen (1.26 and 1.52 mm, respectively) Treatment with 0.1 lg/mL EAFE resulted in a significant increase in IGF-1 mRNA expression levels, which was 2.17-fold higher than control Hair follicles in the group treated with EAFE and minoxidil were in the anagen stage dioxinodehydroeckol at concentrations of 0.1 and 1 lmol/L produced hair shaft lengthening of 1.43 and 1.36 mm, respectively increased IGF-1 mRNA expression with 0.1 lmol/L dioxinodehydroeckol was 2.70-fold higher than control	alopecia	(Bak et al., 2013)
14	*Undariopsis peterseniana*	apo-9'-fucoxanthinone	Dermal papilla cell proliferation via activation of the Wnt/β-catenin and ERK pathways.	The length of hair fibers from vibrissa follicles treated with U. peterseniana extract (1 μg/mL) increased significantly after 7 days; the increase continued for 21 days. On day 21, U. peterseniana extract (1 and 10 μg/mL) increased hair fiber length by 206.5% and 165.6% respectively compared to the control. Specifically, 1 μg/mL U. peterseniana extract significantly increased hair fiber length compared with the positive control 10 μM minoxidil, whereas 100 μg/mL U. peterseniana extract did not affect hair fiber length. Mice given 10 μg/mL U. peterseniana extract showed larger gray/black skin areas compared to controls. These results indicate that U. peterseniana extract significantly induces the transition of the hair cycle from	alopecia	(Kang et al., 2017)

Table I. (15-16)

No	Species	Combined content	Mechanism	Results	Therapeutic effect	Reference
				The addition of U. peterseniana extract (0.1, 1, 10, and 100 μg/mL) to the reaction mixture inhibited 5α-reductase activity by 25.8%, 30.8% ($p < 0.05$), 41.9% ($p < 0.01$), and 22.5% respectively. U. peterseniana extract (1 and 10 μg/mL) significantly increased the proliferation of NIH3T3 fibroblasts compared with controls. U. peterseniana extract can act as a KATP channel opener which can be a supporting factor for hair growth. U. peterseniana extract (1 and 10 μg/mL) significantly increased dermal papilla cell proliferation by 112.4% ($p < 0.01$) and 146.2% ($p < 0.001$), respectively. U. peterseniana increases β-catenin levels in the nucleus through regulation of GSK-3β.		
15	*Sargassum glaucessscens*	Fucoidan	HFPDC proliferation correlated with IGF-1 and LEF-1 gene expression	Sargassum glaucescens fucoidan extract with a molecular weight higher than 1 KDa shows its ability to increase hair growth. Oligo-fucoidan is more effective in increasing hair follicle cell proliferation. The effect of fucoidan on HFPDC proliferation was correlated with IGF-1 and LEF-1 gene expression.	Androgenetic alopecia	(Huang et al., 2022)
16	*Padina arborescens*	1–O–myristoyl–2–O–oleoyl–3–O–(α– D–glucopyranosyl)–glycerol(MOGG)	Inhibition of 5α-reductase, proliferation of dermal papillae, opening of KATP channels and/or increased production of PGE2.	MOGG from P. arborescens extract has the potential to treat alopecia through inhibition of 5α-reductase, proliferation of dermal papillae, opening of KATP channels and/or increasing PGE2 production	Alopecia and Androgenetic Alopecia	(Kang et al., 2020)

Table I. (17-18)

No	Species	Combined content	Mechanism	Results	Therapeutic effect	Reference
17	*Grateloupia elliptica*	polyphenols	Inhibits the activity of 5α-reductase, which converts testosterone to dihydrotestosterone (DHT), and PGE 2 production in HaCaT cells resulting in an inhibitory effect on the production of IL-12, IL-6, and TNF-α in LPS-stimulated lipopolysaccharide (LPS) derived from the marrow bones stimulated by dendritic cells.	100 μg/ml G. elliptica extract was found to induce a greater increase in dermal papilla cell proliferation than 10 μM minoxidil G. elliptica extract inhibited 5α-reductase activity by 7.2%, 14.7% and 48.3% at concentrations of 0.1, 1 and 10 μg/ml G. elliptica extract at doses of 12.5, 25, and 50 μg/ml increased PGE2 G. elliptica extract and positive control zinc pyrithione showed inhibition zone diameters of 10 mm and 35 mm, while the inhibition zone was 0 mm in the negative control G. elliptica extract inhibited IL-12 p40 production by LPS-stimulated BMDCs with an inhibition value of 47.8% at a concentration of 50 μg/ml. In addition, G. elliptica extract showed a significant inhibitory effect on IL-6 production in LPS-stimulated DC with an inhibition value of 31.4%.	alopecia	(Kang, et al., 2012)
18	Isolated from Ishige okamurae	Diflorethohydroxycarmalo	Prostaglandin (PG) E2, those The biological effects and mechanisms of action of DPHC on prostaglandin synthesis in HaCaT human keratinocytes were examined	DPHC significantly and dose-dependently induced PGE2 synthesis by increasing the protein and COX-1 and COX-2 mRNA levels. Interestingly, DPHC-induced COX-1 expression precedes COX-2 expression. Also, while both rofecoxib and indomethacin inhibit PGE2 production, the latter appears to be more potent. From the results above, we can expect that DPHC has some beneficial effects through increasing PGE2 production	alopecia	(Kang et al., 2012)

In general, the mechanisms that stimulate hair growth involve key signaling pathways and growth factors such as Insulin-like Growth Factor 1 (IGF-1), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Fibroblast Growth Factor 2 (FGF-2), Endothelial Nitric Oxide Synthase (eNOS), and the Wnt/β-catenin pathway. These factors promote hair follicle growth and regeneration. Conversely, the mechanisms that inhibit hair growth typically involve 5α-reductase, which converts testosterone to dihydro-testosterone (DHT), as well as Transforming Growth Factor Beta (TGF-β) and Fibroblast Growth Factor 5 (FGF-5), both of which contribute to the suppression of hair follicle activity and regression.

Polysaccharides are the primary bioactive components in algae that influence mechanisms of hair growth. Among these, various other bioactive compounds are found in *Sargassum sp*., including phlorotannins, terpenoids, chromene, tetraprenyltoluquinol derivatives, fucoxanthin, fucoidan, alginate, phenolic acids, catechins, quercetin, fucosterol, stigmasterol, β-sitosterol, pheophytin A, and sulfoquinovosyldiacylglycerol. In addition, *Sargassum* contains alkaloids, flavonoids, steroids, meroditerpenoids, and gentisic acid, all of which are dominant bioactive compounds contributing to its potential therapeutic effects (Cahyaningrum et al,. 2016; Sinurat & Maulida, 2018; Rohimet al., 2019).

Polysaccharides are the primary bioactive components of algae that influence mechanisms of hair growth. Their diverse structures confer a wide range of physical and chemical properties, leading to various biological activities. Polysaccharides are polymers of monosaccharides connected by glycosidic bonds and can be classified into sulfated and non-sulfated types. Sulfated polysaccharides, which include fucoidans, agar, carrageenan, and ulvans, possess unique properties, while non-sulfated polysaccharides include alginates. The structural variations among these polysaccharides contribute to their distinct biological activities (Sinurat & Maulida, 2018). Among them, sulfated polysaccharides are particularly notable for their bioactivity. Their effectiveness is attributed to their physicochemical properties, including molecular weight, sulfate content ($-OSO_3H$), and polyphenol content (Ma et al., 2017).

Algal polysaccharides are primarily located in the cell walls of algae, with their quantity and chemical structure varying according to the species. Three main types of polysaccharides are identified based on the type of algae: fucan predominates in brown algae, sulfated rhamnans and ulvan are found in green algae, while red algae primarily contain galactans and carrageenan. The bioactivity of these polysaccharides is closely linked to their chemical properties, such as molecular size, the type and ratio of monosaccharide constituents, and the nature of their glycosidic linkages (Indahyani et al., 2019). In addition, the biological activity of these polysaccharides is influenced not only by the sulfation of the molecule but also by factors such as branch structure, molecular weight, and monosaccharide composition (He et al., 2016).

The bioactive components of algae that fall under the polysaccharide group (Table I) include *Cistanche tubulosa* and *Laminaria japonica* (both containing fucoidan), *Tunic Ascidian* (which contains glycosaminoglycans), and Sargassum *glaucescens* (also rich in fucoidan).

Fucoidan is a class of sulfated polysaccharides predominantly found in the cell walls of brown algae. It primarily consists of L-fucose sulfate, along with smaller quantities of other monosaccharides such as glucose, galactose, xylose, and uronic acid. The structure of fucoidan features O-sulfated L-fucopyranose residues linked through α-(1→2)-, α-(1→3)-, and/or α-(1→4)-glycosidic chains, resulting in a branched configuration. The average molecular weight of fucoidan is approximately 2000 Da, and it is soluble in water and acidic environments (Rupérez et al., 2002).

Glycosaminoglycans (GAGs) are long, unbranched polysaccharides characterized by repeating disaccharide units. Each disaccharide unit typically consists of one of two amino sugars: N-acetylglucosamine (GlcNAc) or N-acetylgalactosamine (GalNAc), in combination with a uronic acid, such as glucuronic acid or iduronic acid (Neri et al., 2022).

The following algae-derived compounds belong to the polyphenol group: *Saccharina japonica* and *Undaria pinnatifida* (LU): contain nonacosan-10-ol and β-sitosterol. *Ecklonia cava*: rich in phlorofurofucoeckol and phlorotannins. *Polysiphonia morrowii*: contains 5-bromo-3,4-dihydroxybenzaldehyde (BDB). *Grateloupia elliptica*: features bromophenols. Brown Algae Isolate 7: contains phloroeckol and phloroglucinol. *Ishige sinicola*: rich in octaphlorethol A. *Ecklonia cava*: also contains dioxinodehydroeckol. *Ishige okamurae*: includes diphlorethohydroxycarmalol. *Grateloupia elliptica*: contains additional polyphenols.

Brown algae (Phaeophyta) contain significantly higher levels of polyphenols compared to red and green algae. Among these, phlorotannins are the predominant polyphenolic compounds found in brown algae. Phlorotannins exist in various forms, with several derivative compounds, including fucol, phloroglucinol, ploretol, fucoploretol, diploretol, difucol, trifucol, triphloretol A, triplorethol B, fucoplorethol A, and fucophlorethol B, among others (Bare et al., 2022).

Phloroglucinol (PG), a polyphenolic compound, along with its derivatives eckol and triphloroethol-A, is a secondary metabolite commonly found in various microorganisms, particularly in brown and red algae (Park et al., 2011; Blackman & Rogers, 1988). The compound's structure is primarily characterized by a 1,3,5-trihydroxybenzene core, contributing to its wide range of bioactivities (Singh et al., 2009). In particular, 7-phloroeckol, a derivative of PG, has been reported to promote hair follicle elongation and upregulate the expression of hair growth-related genes (Bak et al., 2014).

5-bromo-3,4-dihydroxybenzaldehyde (BDB), isolated from the red algae *Polysiphonia morrowii*, is a halogenated compound, specifically a brominated phenol, characterized by hydroxylated and brominated benzene rings. Bromophenols are common metabolites found in marine organisms, particularly algae. These basic brominated phenols—such as 2-bromophenol, 4-bromophenol, 2,4-dibromophenol, 2,6-dibromophenol, and 2,4,6-tribromophenol—are present across green, brown, and red algae (Kang et al., 2022; Jacobtorweihen & Spiegler, 2023).

Nonacosan-10-ol is a long-chain fatty alcohol, specifically a nonacosane molecule substituted by a hydroxyl group at position 10. It functions as a plant metabolite and belongs to the class of very long-chain and secondary fatty alcohols. This compound is derived from nonacosane hydride. In addition, β-sitosterol is a phytosterol commonly found in plant fats and is a crucial precursor for the synthesis of steroids. Loliolide, on the other hand, is a monoterpene lactone, known for its bioactive properties, including antioxidant and anti-inflammatory activities.

Diphlorethohydroxycarmalol (DPHC) is a phlorotannin compound isolated from the brown algae Ishige okamurae (Kang et al., 2012). In addition to DPHC, algae also contain other bioactive compounds with antialopecia properties, namely compounds in the meroditerpenoid group (Brown Algae Loliolide Isolate) and fucoxanthin (Sargassum muticumAndUndariopsis peterseniana(apo-9′-fucoxanthinone)).
Meroditerpenoid compounds, such as those found in *Sargassum sp*., consist of a polyprenyl chain attached to a p-benzoquinone or hydroquinone core. Structural variations in these meroditerpenoids often occur in the terpene side chains, which may include functional groups like exocyclic double bonds, carboxylic acids, alcohols, or aldehydes (Brkljača & Urban, 2015).

Algae, specifically macroalgae, are a rich source of secondary metabolites that offer significant potential for various applications. These organisms produce structurally diverse bioactive compounds with a broad spectrum of biological activities (Lestari & Mita, 2013). Some extracts derived from algae have shown promising activity in stimulating hair growth. However, the precise mechanisms behind this activity are not yet fully understood (Huang et al., 2022).

Hair is a distinctive feature of mammals, playing a vital role in skin homeostasis by providing benefits such as thermoregulation, sebum production, and protection against ultraviolet (UV) radiation (Houschyar et al., 2020). To maintain tissue homeostasis, hair follicles go through a specific growth cycle with three distinct phases: (anagen, catagen, and telogen) to maintain tissue homeostasis(Choi, 2018).

The hair growth cycle is intricately regulated by several factors, including growth hormones and cytokines. These secreted proteins play a crucial role in the differentiation and proliferation of hair follicle stem cells (hfSCs), ultimately driving the telogen-anagen transition, which is critical for hair regeneration (Rishikaysh et al., 2014). Factors contributing to alopecia often include genetics, androgen levels, stress, and inflammation.

The increased expression of growth hormone-regulating factors such as insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), epidermal growth factor (EGF), keratinocyte growth factor (KGF), endothelial nitric oxide synthase (eNOS), Wnt/β-catenin signaling pathway, and vascular endothelial growth factor (VEGF) plays a vital role in maintaining the anagen phase of the hair growth cycle by promoting hair growth. Conversely, the decreased expression of factors like transforming growth factor beta (TGF-β), 5α-reductase, and dihydrotestosterone (DHT), known as suppressors of hair growth, leads to an increase in hair follicle apoptosis during the catagen phase (Danilenko et al., 2021).

This review identifies 19 species of algae with potential anti-alopecia properties, each demonstrating various mechanisms of action. Data on algae species hypothesized to exhibit anti-alopecia activity (Table I). The articles offer a comprehensive summary of the mechanisms of action for several algae species, including red, green, and brown algae, that have been studied for their efficacy in promoting hair growth and treating alopecia, particularly androgenetic alopecia (Figure 1).

Hair Morphology and Cycles

Hair is an elastic keratin thread that originates from the epidermis. The follicle, which encloses the hair root in a tube-like structure, consists of both an epithelial part derived from the epidermis and a connective tissue part from the dermis. At the lower end of the follicle, it expands to form the hair bulb, which connects to the hair papilla via connective tissue. One or more sebaceous glands, along with a tuft of smooth muscle, are associated with the hair follicle, collectively forming the pilosebaceous unit (Ayuningtyas, 2018).

Hair follicles are an integral part of the skin, serving to protect internal organs, regulate body temperature, and play a crucial role in hair production. The human scalp typically contains approximately 120,000 hair follicles (HF), which regulate the hair cycle and contribute to ongoing hair maintenance. Structurally, HF extends from the epidermis into the deeper layers of the dermis, forming a spherical structure at its base. This structure surrounds the dermal papilla (DP), composed of dermal papillary cells (DPC), connective tissue, and a capillary network (Choi, 2020). Hair follicles are associated with sebaceous glands, apocrine glands, and the arrector pili muscle (APM), forming pilosebaceous units. Recent studies have also shown that eccrine glands are integrated within the pilosebaceous unit (Poblet et al., 2016; Wall et al., 2022). Scalp hair follicles aggregate to form a combined pilosebaceous unit, consisting of one primary follicle and one or more secondary follicles, all associated with a single APM and sebaceous gland (Sinclair et al., 2015).

Dermal papilla cells (DPC), located at the base of the hair follicle, play a key role in the hair cycle by producing growth factors that interact with various hair follicle cells, including adjacent matrix cells, the dermal sheath, and stem cells (Stenn & Pope, 2001; Pope, 2014). DPCs, as specific mesenchymal components, periodically regulate the regeneration of hair follicles (HF). Surrounding the lower dermal papilla is a layer of hair matrix keratinocytes, which proliferate during the hair growth cycle to form hair fibers. In addition, hair follicle stem cells (HFSCs) reside in the bulge area of the follicle (Choi, 2020). Hair development is facilitated by a regulated cross-interaction between mesenchymal and epithelial cells within the HF, which are influenced by signals from both the epidermal and dermal compartments (Hardy, 1992).

Hair follicles are small structures in the skin where hair growth or loss occurs, driven by changes in the hair cycle (Pope, 2014). Hair follicles undergo a lifelong cyclical transformation, transitioning from the resting (telogen) phase to the growth (anagen) phase, during which follicular keratinocytes rapidly proliferate, leading to hair lengthening and thickening. This is followed by a regression (catagen) phase, resulting in hair follicle involution (Chase, 1954; Hardy, 1992). Dermal papilla cells (DPCs) are specialized fibroblasts that play a crucial role in regulating the hair cycle through the secretion of diffusible proteins, such as insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), Wnt signaling/β-catenin, and transforming growth factor-β (TGF-β) (Herman & Herman, 2016). These growth factors perform distinct functions in hair growth regulation, with TGF-β and fibroblast growth factor-5 (FGF-5) acting as negative regulators, while VEGF and FGF-7 serve as positive regulators (Houschyar et al., 2020). Moreover, TGF-, FGF, and VEGF are closely related to autophagy (Suzuki et al., 2010) (Belleudi, et al., 2014) (Spengler et al., 2020). Autophagy is an evolutionarily conserved lysosomal degradation system in eukaryotes that is important for maintaining cellular homeostasis (Komatsu et al., 2007) (Ryter et al., 2013). Inhibition of autophagy has been reported to be associated with hair follicle regression (Parodi et al., 2018).

The regulation of the hair cycle involves numerous endocrine, autocrine, and paracrine signaling pathways, many of which are not fully understood and interact in complex ways. Notably, the Wnt signaling pathway deserves special attention, though the specific roles of its members remain to be fully elucidated. Beta-catenin, a core component of the Wnt pathway, plays a critical role in the differentiation of stem cells into follicular keratinocytes (Huelsken et al., 2001). The transition from the anagen (growth) to telogen (resting) phase is induced by transient β-catenin signaling

(Celso & Prowse, 2004; Van Mater et al., 2003) and is influenced by the cyclic expression of Bone Morphogenetic Proteins (BMPs), specifically BMP2 and BMP4, which are produced by dermal fibroblasts and subcutaneous adipocytes (Plikus et al., 2009). Additional regulators include fibroblast growth factors (FGF 7 and 10), BMP inhibitors (such as transforming growth factor β2 [TGF-β2] and noggin), and Wnt7b (Plikus et al., 2009; Greco et al., 2009; Oshimori, 2012; Hsu & Li, 2014; Kandyba, 2014). Furthermore, adipocyte precursor cells express platelet-derived growth factor (PDGF)α, which activates PDGF receptors in the dermal papilla (DP), leading to the activation of hair germ cells (Festa et al., 2011).

Perifollicular vascularization has been observed to increase during the anagen phase and decrease during the catagen phase, correlating with the over- and under-expression of vascular endothelial growth factor (VEGF) ORS mRNA (Yano et al., 2001). Hepatocyte growth factor (HGF), also known as a spreading factor, has been shown to stimulate hair follicle growth *in vitro* (Jindo et al., 1995; Jindo et al.,1998). In addition, insulin-like growth factor (IGF-1) has been identified as a significant regulator of hair follicles (Trueb, 2018; Weger & Schlake, 2005).

Role of Wnt/β-Catenin Signaling in Hair Growth

Among the various signaling pathways involved in hair follicle (HF) development and growth, Wnt/β-catenin signaling in dermal papilla (DP) cells plays a crucial role in the interaction between DP and epithelial cells in the HF. Wnt signaling is essential for the growth, regeneration, and development of hair follicles, as well as the regulation of cellular proliferation (Wu et al., 2020; Kang et al., 2022).

In the Wnt/β-catenin signaling pathway, secreted proteins bind to Frizzled receptors—a family of G protein-coupled receptors— (Choi, 2020) and lipoprotein receptor-related protein (LRP; a receptor tyrosine kinase) co-receptors on the cell surface. This binding inhibits the activity of glycogen synthase kinase-3β (GSK-3β), an enzyme that regulates phosphorylation (Choi, 2020), resulting in increased levels of free β-catenin within the cells (Van Mater et al., 2003). Following Wnt signaling activation, β-catenin is translocated to the nucleus, where it interacts with the transcriptional regulator T cell lymphoid enhancer factor-1 (TCF/LEF-1) to activate target gene expression (Aoki et al., 1999). The degradation of cytoplasmic β-catenin is regulated by GSK-3β, which plays a critical role in reducing the proliferation of hair follicle progenitor cells responsible for hair shaft production and in rapidly inducing the catagen phase. Therefore, inhibition of GSK-3β may promote hair growth by stabilizing β-catenin (Herman & Herman, 2016).

Some algae have been found to promote hair growth by increasing β-catenin levels, making them a potential alternative therapeutic option for alopecia (Herman & Herman, 2016). For instance, *Ishige sinicola* extract, which contains octaphlorethol A, has demonstrated the ability to combat alopecia by stimulating dermal papilla cell (DPC) proliferation through activation of the β-catenin pathway and inhibition of 5α-reductase (Kang et al., 2013). In addition, red algae containing 5-bromo-3,4-dihydroxybenzaldehyde (BDB) have been shown to enhance the length of hair fibers in mouse vibrissa follicles and increase DPC proliferation by modulating cell cycle-related proteins. BDB activates the Wnt/β-catenin pathway by phosphorylating GSK-3β and β-catenin, thereby inhibiting the TGF-β pathway, which promotes the transition to the catagen phase (Kang et al., 2022).

Loliolide, a monoterpenoid compound derived from brown algae, has been studied for its effects on hair growth in human dermal papilla (DP) cells treated with a concentration of 20 μg/mL for 48 hours (Choi, 2020). This compound regulates hair growth and hair loss by inducing AKT phosphorylation, which leads to the stabilization of β-catenin. This, in turn, promotes the proliferation and expression of hair growth regulatory genes in keratinocytes (Lee et al., 2019).

The main component of brown algae (*Sargassum muticum*), apo-9'-fucoxanthinone, has been shown to promote hair growth by stimulating dermal papilla cell (DPC) proliferation via activation of the Wnt/β-catenin signaling pathway and the VEGF-R2 pathway (Kang et al., 2016). In a study on *Undariopsis peterseniana*, a 21-day treatment with this brown algae significantly increased hair fiber length. In addition, *U. peterseniana* extract markedly accelerated the initiation of the anagen phase in vivo. The extract also increased ERK phosphorylation and elevated levels of Wnt/β-catenin signaling proteins, such as glycogen synthase kinase-3β (GSK-3β) and β-catenin (Kang et al., 2017).

Grateloupia elliptica (red algae) has been reported to promote the proliferation of dermal papilla cells (DPCs), which play a crucial role in regulating the hair cycle. Treatment of isolated rat

vibrissa follicles with *G. elliptica* extract resulted in a significant increase in hair fiber length. In addition, the extract accelerated the telogen-to-anagen transition in C57BL/6 mice. To explore the molecular mechanism underlying this effect, the activation of Wnt/β-catenin signaling known to regulate hair follicle development, differentiation, and hair growth—was investigated. The results showed that *G. elliptica* extract activates Wnt/β-catenin signaling by increasing β-catenin levels and phosphorylated GSK3β (Kang et al., 2012).

Hair follicle morphogenesis and development rely on multiple signaling pathways. Among these, the Wnt/β-catenin signaling pathway is regarded as a key regulator, as the loss of β-catenin function an essential signal transducer within this pathway prevents placode formation and the subsequent generation of hair follicles during embryogenesis (Zhang et al., 2016).

The Role of 5α-reductase Signaling in Hair Growth

The dermal papilla serves as the central hub for maintaining and regulating hair growth, and it is a primary target of androgens, which can induce hair follicle miniaturization and alterations in the hair cycle. In androgenetic alopecia (AGA), the anagen phase shortens with each cycle, while the telogen phase either remains constant or lengthens. Although the precise mechanisms behind these changes are still unclear, androgens particularly dihydrotestosterone (DHT) are known to play a critical role in the development of AGA in men. DHT is synthesized from testosterone by the enzyme 5-α-reductase, which exists in two forms: type I and type II. These lipophilic enzymes are predominantly found in intracellular membranes. Type I 5-α-reductase is primarily located in sebaceous glands, epidermal and follicular keratinocytes, dermal papillae, sweat glands, and the liver, while type II 5-α-reductase is found in genital skin, the liver, and the prostate. In AGA, hair loss occurs when the 5-AR (5-α-reductase) enzyme converts testosterone into DHT, which then binds to receptors in hair follicles, leading to hair loss and, eventually, baldness (Lolli et al., 2017).

Some species of algae have been shown to promote hair growth by inhibiting the synthesis of dihydrotestosterone (DHT) through the suppression of 5α-reductase activity. For instance, the green algae *Ecklonia cava* has been observed to increase hair fiber length after topical application of a 0.5% enzymatic extract of *E. cava* to the backs of C57BL/6 mice. Dieckol, a compound extracted from *E. cava*, stimulates hair growth by promoting dermal papilla cell (DPC) proliferation and/or inhibiting 5α-reductase, resulting in a 12.4% increase in hair follicle length at a concentration of 1 μg/mL (Kang et al., 2012). In addition, the microalga *Tetrathelmis tetrathele* (TTE) has been found to inhibit the production of inflammatory mediators such as nitric oxide (NO) while promoting the proliferation of HaCaT keratinocytes and human follicle dermal papilla cells (HFDPC). TTE also exhibits inhibitory effects on 5α-reductase activity (Park & Lee, 2021). *Padina arborescens* extract, which contains the compound –O–myristoyl–2–O–oleoyl–3–O–(α–D–glucopyranosyl)–glycerol (MOGG), inhibits 5α-reductase activity by preventing the conversion of testosterone to DHT, thereby stimulating dermal papilla cell proliferation, opening KATP channels, and/or increasing the production of prostaglandin E2 (PGE2) (Kang et al., 2020). Research has further shown that catechols present in flavonoids effectively inhibit type I 5α-reductase, and several polyphenolic compounds are more effective inhibitors of this enzyme than those targeting type II (Hiipakka et al., 2002). Moreover, extracts from *Ascidian tunicates* demonstrate the highest proliferative activity in human follicle dermal papilla (HFDP) cells, significantly inhibiting DHT production and enhancing HFDP cell proliferation by 21% and 27% at concentrations of 50 and 100 μg/mL, respectively, which suggests a potential for increased hair growth (Neri et al., 2022). Lastly, *Grateloupia elliptica* promotes hair growth by enhancing dermal papilla cell proliferation, inhibiting 5α-reductase activity, increasing PGE2 production, reducing lipopolysaccharide (LPS)-stimulated production of pro-inflammatory cytokines IL-12, IL-6, and TNF-α, and exhibiting antifungal activity against *Pityrosporum ovale*, a known cause of dandruff (Kang et al., 2012).

Role of IGF Signaling in Hair Growth

The production of insulin-like growth factor 1 (IGF-1) in dermal papilla cells plays a crucial role in promoting hair growth by regulating cell proliferation and migration during hair follicle (HF) development (Herman & Herman, 2016). IGF-1's proliferative effects on the skin are significant and may be implicated in the development of heart failure. Given the presence of IGF-1 receptors on keratinocytes, it is hypothesized that IGF-1 produced by dermal papilla cells may stimulate keratinocyte proliferation within the hair follicles, thereby enhancing hair growth (Ahn et al., 2012).

Furthermore, IGF-1 activates cells within the hair root, extending the anagen (growth) phase and delaying the catagen and telogen phases of the hair growth cycle (Herman & Herman, 2016).

Hair follicle (HF) growth and dormancy are closely linked to IGF activity in dermal papilla (DP) cells, which is influenced by dihydrotestosterone (DHT). Among the insulin-like growth factors, IGF-1 has a more pronounced effect on hair growth compared to IGF-2. IGF-1 signaling regulates the hair growth cycle and hair shaft differentiation, potentially exerting an anti-apoptotic effect during the catagen phase. Both IGF-1 and IGF-2 help prevent hair follicles from entering the catagen phase. Notably, IGF-1 significantly accelerates linear hair growth and prolongs the overall anagen phase. The hair growth-promoting effects of IGF-1 are associated with the upregulation of platelet-derived growth factors A (PDGF-A) and B (PDGF-B), as well as IGF-1's anti-apoptotic properties (Ahn et al., 2012).

In his research, *Ecklonia cava*, a species of brown algae, was found to contain various bioactive compounds, including carotenoids, fucoidan, and phlorotannin. Polyphenols extracted from *E. cava* (ECP) have been shown to enhance fibroblast survival. Human dermal papilla cells (hDPCs), which possess fibroblast-like properties of mesenchymal origin, demonstrated a 30.3% increase in proliferation following treatment with 10 μg/mL of purified polyphenols from *E. cava* (PPE) compared to the negative control ($p < 0.001$). Moreover, treatment with 0.1 μg/mL of APD resulted in a 30.8% elongation of human hair shafts over a 9-day period compared to the negative control ($p < 0.05$). Insulin-like growth factor 1 (IGF-1) mRNA expression increased 3.2-fold in hDPCs after treatment with 6 μg/mL of APD ($p< 0.05$), while vascular endothelial growth factor (VEGF) mRNA expression was elevated 2.0-fold after treatment with 3 μg/mL of PPE ($p< 0.05$). In addition, treatment with 10 μg/mL of APD significantly reduced oxidative stress in hDPCs ($p < 0.05$).

7-Phloroeckol, a phloroglucinol derivative isolated from marine brown algae, exhibits antioxidative, anti-inflammatory, and matrix metalloproteinase (MMP) inhibitory activities. In this study, 7-phloroeckol promoted the proliferation of dermal papilla cells (DPCs) and outer root sheath (ORS) cells. Hair shaft growth was assessed using a hair follicle organ culture system, where 7-phloroeckol was shown to enhance hair shaft elongation in human hair follicle cultures. In addition, 7-phloroeckol induced insulin-like growth factor 1 (IGF-1) mRNA expression in DPCs and increased IGF-1 protein concentration in conditioned medium. The results indicate that 7-phloroeckol significantly promotes hair growth, with DPC proliferation increasing by 116% and 126%, and ORS cell proliferation by 132% and 126%. Furthermore, hair shaft length increased to 1.57 mm and 1.84 mm compared to the control length of 0.96 mm at concentrations of 0.1 μM and 1 μM, respectively. IGF-1 mRNA expression was elevated 4.98- and 5.37-fold, corresponding to an increase in IGF-1 secretion to 783 and 841 pg/mL, respectively.

Role of Vascular Endothelial Growth Factor (VEGF) in Hair Growth

Vascular endothelial growth factor (VEGF) is a growth factor that promotes vasculogenesis and angiogenesis, stimulating hair growth by enhancing nutrient supply to hair follicles and increasing the diameter of the follicle base (Gnann et al., 2013). Transgenic overexpression of VEGF in keratinocytes of the outer root sheath of hair follicles significantly induces perifollicular vascularization, leading to accelerated hair regrowth following hair removal and an increase in both hair follicle and hair shaft size (Yano et al., 2001). VEGF is secreted by dermal papilla cells (DPCs) and contributes to hair growth by promoting the formation of new blood vessels around the follicles (Miele et al., 2000; Ozeki & Tabata, 2003).

Certain algae stimulate hair growth by affecting the anagen phase, during which vascular endothelial growth factor (VEGF) expression is elevated, while it is reduced during the catagen and telogen phases (Lachgar et al., 1998). Research conducted by Park (2016) demonstrated increased expression of insulin-like growth factor 1 (IGF-1) in mice treated with a *Saccharina japonica* and *Undaria pinnatifida* mixture (LU), as well as elevated VEGF expression in mice treated with 3% minoxidil. Polymerase chain reaction (PCR) data revealed similar patterns of upregulation or downregulation for both LU and minoxidil treatments. Mice treated with the LU mixture exhibited enhanced hair regrowth, along with an increase in the size and number of follicles. Hematoxylin and eosin (H&E) staining confirmed increased hair growth following treatment with the LU and 3% minoxidil mixture. The LU mixture was found to have hair growth effects comparable to minoxidil, with hair growth on day 14 matching

that observed in the 3% minoxidil group. The LU mixture significantly ($p < 0.05$) upregulated genes associated with hair growth, such as VEGF and IGF-1, compared to minoxidil and negative controls. In addition, the LU mixture inhibited the expression of transforming growth factor-β1 (TGF-β1), a gene associated with hair loss. Histological analysis revealed that the induction of anagen-stage hair follicles occurred more rapidly in the LU and minoxidil-treated groups than in the control group. Similarly, *Polysiphonia morrowii* promotes hair growth through a comparable mechanism to LU, stimulating anagen signaling by activating the Wnt/β-catenin pathway and autophagy, while inhibiting the TGF-β pathway in dermal papilla cells (DPCs) (Kang et al., 2022).

Treatment with 10 μg/mL of purified polyphenols from *Ecklonia cava* (PPE) increased human dermal papilla cell (hDPC) proliferation by 30.3% compared to the negative control ($p < 0.001$). In addition, 0.1 μg/mL of *E. cava* PPE resulted in a 30.8% elongation of human hair shafts over a 9-day period compared to the negative control ($p < 0.05$). Insulin-like growth factor-1 (IGF-1) mRNA expression in hDPCs increased 3.2-fold following treatment with 6 μg/mL of APD ($p < 0.05$), while vascular endothelial growth factor (VEGF) mRNA expression increased 2.0-fold after treatment with 3 μg/mL of PPE ($p < 0.05$). Furthermore, treatment with 10 μg/mL of APD significantly reduced oxidative stress in hDPCs ($p < 0.05$) (Shin et al., 2016).

Loliolide, a common monoterpenoid compound found in brown algae, has been shown to affect hair growth in dermal papilla (DP) cells, which are key regulators of hair growth and loss. In this study, a three-dimensional (3D) DP spheroid model, which mimics the *in vivo* hair follicle system, was used. Biochemical tests demonstrated that low doses of loliolide increased both the viability and size of 3D DP spheroids in a dose-dependent manner. These findings were correlated with elevated expression levels of hair growth-related autocrine factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and keratinocyte growth factor (KGF). Immunoblotting and luciferase-reporter assays further revealed that loliolide induced AKT phosphorylation, leading to the stabilization of β-catenin, which is critical for the hair-inductive properties of DP cells. Loliolide also significantly enhanced the proliferation and expression of hair growth regulatory genes in keratinocytes. These results suggest that loliolide may promote the hair growth-inductive capacity of DP cells via the AKT/β-catenin signaling pathway (Lee et al., 2019).

Role of Transforming growth factor β (TGF-β) in Hair Growth

The transforming growth factor-beta (TGF-β) pathway plays a crucial role in the progression of the hair cycle, particularly in the transition from the anagen phase to the catagen phase (Foitzik et al., 2000). 5-Bromo-3,4-dihydroxybenzaldehyde (BDB) has been shown to inhibit the effects of TGF-β1 on dermal papilla cells (DPCs), thereby preventing the transition to the catagen phase and prolonging the duration of hair growth. In this study, BDB, derived from red algae, promoted hair growth by increasing hair fiber length in vibrissa follicles cultured ex vivo. BDB enhanced the proliferation of DPCs, which are key regulators of hair growth, by modulating cell cycle-related proteins and maintaining the anagen phase. This effect was achieved through activation of the Wnt/β-catenin signaling pathway, stimulation of autophagy, and inhibition of the TGF-β pathway (Kang et al., 2022).

The TGF-β pathway inhibits both hair growth and epithelial cell proliferation (Foitzik et al., 2000; Inui et al., 2002). Injection of TGF-β1 into mice accelerates the progression to the catagen phase (Foitzik et al., 2000). Androgens stimulate the transcription of TGF-β1 mRNA in dermal papilla cells (DPCs) and inhibit the growth of keratinocytes co-cultured with androgen-treated DPCs (Inui et al., 2002). 5-Bromo-3,4-dihydroxybenzaldehyde (BDB) was found to inhibit the TGF-β1-induced increase in phospho-Smad2 levels, suggesting that BDB may offer a protective effect against TGF-β1-induced keratinocyte apoptosis and subsequent hair loss.

Role of Epidermal growth factor (EGF) in Hair Growth

Epidermal growth factor (EGF) is a key growth factor that stimulates hair growth. It is expressed in the outer root sheath of hair follicles, promoting cell proliferation and follicle formation (Hansen et al., 1997). The role of EGF in hair growth follows a two-step process: (1) EGF is activated in the hair follicle a few days after birth, facilitating proper follicle growth and hair fiber production, and then deactivated when the follicle enters the catagen phase; (2) EGF is reactivated during the anagen phase, promoting follicular keratinocyte migration and hair growth, and deactivated again in the next catagen phase (Zhang et al., 2016). In

both phases, EGF binds to the EGFR/ErbB2 receptor heterodimer. The dimerization of EGFR at the plasma membrane induces tyrosine kinase activation and trans-autophosphorylation. Tyrosine phosphorylation sites in the active EGFR form a complex network with other signaling molecules, allowing for precise regulation of the hair cycle. EGF promotes the proliferation and migration of outer root sheath (ORS) cells and upregulates the expression of several follicle-regulatory genes through the Wnt/β-catenin signaling pathway (Mak & Chan, 2003). Some algae utilize this pathway as a mechanism to promote hair growth.

Role of Endothelial Nitric Oxide Synthase (eNOS) in Hair Growth

Endothelial nitric oxide synthase (eNOS) is expressed in follicular papilla cells and plays a key role in regulating hair follicle growth and the hair growth cycle. In contrast, inducible nitric oxide synthase (iNOS) expression tends to increase in the peripheral tissue of hair follicles under inflammatory conditions. Therefore, reduced iNOS expression suggests a role in promoting hair growth by mitigating inflammation. Certain macroalgae, particularly those containing flavonoid compounds, influence this pathway. Macroalgae rich in polyphenols, especially flavonoids, exhibit strong anti-inflammatory properties by inducing eNOS and inhibiting cyclooxygenase (COX) activity (Sun et al., 2022).

Nitric oxide (NO) mediates various physiological effects, ranging from stimulating cell proliferation to inducing apoptosis or necrosis in mice (Wolf et al., 2003). NO plays a critical role in several regulatory processes within the skin, including angiogenesis, cell proliferation, and differentiation. Human hair follicles, particularly the dermal papilla region, are surrounded by a dense network of capillaries, with vascular expansion closely linked to the hair cycle phases. Increased vascularization of hair follicles enhances hair growth and increases both follicle number and hair size (Yano et al., 2001). Dermal papilla cells have been identified as a source of several factors that regulate blood supply during different phases of the hair cycle, such as vascular endothelial growth factor (VEGF), which induces low levels of NO through eNOS expression in endothelial cells, resulting in vasodilation (Blume-peytavi et al., 1998; Yano et al., 2001).

Currently, little is known about the expression of nitric oxide synthase (NOS) and the potential role of nitric oxide (NO) in human hair follicles, particularly regarding its regulatory function in the physiological hair cycle or its involvement in androgen-dependent hair disorders. NADPH-diaphorase staining, which indicates NOS activity, has only been detected in specialized keratinocytes forming the outer root sheath of murine hair follicles. However, further analysis using antibodies against neuronal NOS (nNOS) showed no immunoreactivity, suggesting that the NADPH-diaphorase histochemical assay may be detecting other NOS isoforms besides the neuronal variant (Dippel et al., 1994).

In vitro studies of human dermal papilla cells (DPCs) demonstrate spontaneous nitric oxide (NO) production, which is further enhanced by stimulation with lipopolysaccharides (LPS) and androgens. The constitutive and inducible NO synthesis observed in these cells is linked to the expression of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS). Based on these findings, it has been hypothesized that androgen-dependent NO production by human DPCs represents a significant signaling pathway in human hair follicles (Wolf et al., 2003).

Role of Fibroblast Growth Factor (FGF) in Hair Growth

Fibroblast growth factors (FGFs) play a crucial role in human hair follicle development, as well as in epidermal differentiation and proliferation (Danilenko, M., Ring, D., & Pierce, F., 1996). Various members of the FGF family, including FGF-1, FGF-2, and FGF-7, are expressed throughout the hair growth cycle. Keratinocyte growth factor (KGF), also known as FGF-7, is synthesized by skin fibroblasts and has been shown to be vital for the development of human hair follicles and epidermal differentiation and proliferation (Lee et al., 2018). FGF-7 is localized in dermal papilla cells (DPCs), where it instructs hair germ cells to proliferate, initiating a new hair growth cycle (Greco et al., 2009).

Loliolide, an isolate from brown algae, has shown a significant effect on hair growth in dermal papilla (DP) cells, which are the main regulators of hair growth and loss. This study utilized a three-dimensional (3D) DP spheroid model that mimics the *in vivo* hair follicle system. Loliolide increased the expression of hair growth-related autocrine factors, including g VEGF, IGF-1 and KGF and

stimulated DP cell growth via the AKT/β-catenin signaling pathway. Results showed that loliolide enhanced the viability of HDP spheroid cells up to 100 μg/ml, with the highest viability observed at 20 μg/ml. At this dose, mRNA expression of growth factors in HDP spheroids also increased (Lee et al., 2019). Loliolide induced AKT phosphorylation, leading to β-catenin stabilization, which is crucial for the hair-inductive properties of DP cells. Additionally, loliolide upregulated the expression of DP signature genes, including ALP, BMP2, VCAN, and HEY1.

FGF signal transduction requires the involvement of heparin or heparan sulfate proteoglycans (HSPG) to activate receptor tyrosine kinases, specifically the FGF receptor (FGFR), leading to diverse cellular responses induced by this large family of growth factors (Eswarakumar et al., 2005). The binding of FGF and HSPG to the extracellular ligand domain of FGFR triggers receptor dimerization, followed by activation and autophosphorylation of several tyrosine residues in the receptor's cytoplasmic domain.

The Role of Prostaglandin D2 in Hair Growth

Dihydrotestosterone (DHT) and prostaglandin D2 (PGD2) are key factors contributing to alopecia and inducing the miniaturization of hair follicles (Vasserot et al., 2019). PGD2 levels are elevated in patients with alopecia, and it reduces wound-induced hair follicle neogenesis (WIHN) (Garza et al., 2012; Nelson et al., 2013). PGD2 is known to inhibit hair growth via its receptor, Gpr44 (Nelson et al., 2013).

Macrophages are inflammatory and immune effector cells that play a central role in inflammatory reactions, activated by various stimuli, including bacterial lipopolysaccharide (LPS) (Marks-Konczalik et al., 1994; Joung et al., 2015). LPS, a major component of gram-negative *Escherichia coli* cell walls, stimulates the production of various inflammatory mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2) (Kaplanski et al., 2003; Liu et al., 2014; Mittal et al., 2014; Piercing, 1990). Local inflammation around hair follicles is associated with the autoimmune condition alopecia areata, characterized by isolated patches of hair loss on the scalp and potentially leading to total scalp hair loss (Chen et al., 2019).

Prostaglandins (PGs) are members of the eicosanoid family, known for their role in a variety of normal and pathophysiological responses, including vascular contraction and relaxation, renal filtration, angiogenesis, increased proliferation, and immune suppression (Harris et al., 2002; Flowers, 2006). Among them, PGE2 is the most abundant prostaglandin in the human body, synthesized from arachidonic acid through the action of the enzyme cyclooxygenase (COX). PGE2 plays a diverse role, exerting homeostatic, cytoprotective, inflammatory, and, in some instances, anti-inflammatory effects (Giuliano & Warner, 2002; Ricciotti & FitzGerald, 2011).

Recent studies have established a link between hair regrowth and PGE2. Specifically, PGE2 has demonstrated moderate growth-stimulating effects on early anagen hair follicles in mice, while the PG analogue latanoprost has been shown to stimulate eyelash growth in humans (Johnstone & Albert, 2002; Sasaki et al., 2005). In individuals with androgenetic alopecia (AGA), prostaglandin D2 synthase (PTGDS) levels are elevated at both the mRNA and protein levels in bald scalps compared to hairy scalps. The enzyme activity of PTGDS produces increased levels of prostaglandin D2 (PGD2) in bald areas. During the normal turnover of mouse hair follicles, levels of Ptgds and PGD2 rise immediately before the regression phase, suggesting an inhibitory effect on hair growth. Experimental results indicate that PGD2 inhibits hair growth in follicle-explored human hair and when applied topically to mice. This inhibitory effect on hair growth necessitates the activation of the PGD2 receptor, GPR44 (a heterotrimeric guanine nucleotide-coupled receptor), but not PGD2 receptor 1 (PTGDR). Additionally, in transgenic K14-Ptgs2 mice, which express prostaglandin-endoperoxide synthase 2 in the skin, there is a notable increase in PGD2 levels, leading to the development of alopecia, follicle miniaturization, and sebaceous gland hyperplasia characteristics commonly associated with human AGA. These findings position GPR44 as a potential target for therapeutic interventions (Garza et al., 2012).

Prostaglandin E2 (PGE2), the most abundant prostaglandin in the human body, is synthesized from arachidonic acid through the action of the enzyme cyclooxygenase (COX). PGE2 plays diverse roles, exerting homeostatic, cytoprotective, inflammatory, and, in some cases, anti-inflammatory effects. Notably, it has also been implicated in hair growth regulation. Diphlorethohydroxycarmalol (DPHC), a phlorotannin compound isolated from the brown algae *Ishige okamurae*, exhibits various biological activities both *in vitro* and *in vivo*. This study

investigates the biological effects and mechanisms of action of DPHC on prostaglandin synthesis in HaCaT human keratinocytes. The results demonstrate that DPHC significantly and dose-dependently induces PGE2 synthesis in these cells by increasing the protein and mRNA levels of both COX-1 and COX-2. Notably, DPHC-induced COX-1 expression occurs prior to that of COX-2.

TTE macroalgae demonstrated the ability to inhibit the production of inflammatory mediators, including nitric oxide (NO) and prostaglandin E2 (PGE2), without exhibiting cytotoxicity on LPS-stimulated 264.7 crude cells. Furthermore, TTE promoted the proliferation of HaCaT and HFDPC cells. These results indicate that TTE possesses anti-inflammatory activity, enhances the growth of HaCaT and HFDPC cells, and inhibits 5α-reductase activity (Park et al., 2021).

Padina arborescens and 1–O–myristoyl–2–O–oleoyl–3–O–(α–D–glucopyranosyl)–glycerol (MOGG), the active component, demonstrate potential in treating alopecia. This is achieved through the inhibition of 5α-reductase, promotion of dermal papillae proliferation, opening of KATP channels, and/or increased production of prostaglandin E2 (PGE2) (Kang et al., 2020).

G. elliptica extract increased PGE2 production in HaCaT cells in a dose-dependent manner. In addition, the extract exhibited a significant inhibitory effect on the production of pro-inflammatory cytokines, including IL-12, IL-6, and TNF-α, in lipopolysaccharide (LPS)-stimulated bone marrow-derived dendritic cells (Kang et al., 2012).

CONCLUSIONS

Research findings on biomarine algae with anti-alopecia properties are promising, indicating their potential for development into herbal medicinal products. Consequently, further innovation is warranted to explore the potential of macroalgae as anti-alopecia agents, particularly through the formulation of suitable dosage forms. This includes optimizing transfollicular delivery of pharmacologically active molecules to enhance drug release at the target location of hair growth follicles. By employing appropriate topical dosage forms on hair follicles, we can minimize hepatic metabolism and systemic toxicity.

ACKNOWLEDGMENTS

We would like to express our gratitude to the Education Financial Services Center (Puslapdik) and the Education Fund Management Institute (LPDP) for their financial support.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

REFERENCE

Ahn, S. Y., Pi, L. Q., Hwang, S. T., & Lee, W. S. (2012). Effect of IGF-I on hair growth is related to the anti-apoptotic effect of IGF-I and up-regulation of PDGF-A and PDGF-B. *Annals of Dermatology*, *24*(1), 26–31. https://doi.org/10.5021/ad.2012.24.1.26

André, R., Pacheco, R., Bourbon, M., & Serralheiro, M. L. (2021). Brown algae potential as a functional food against hypercholesterolemia: Review. *Foods*, *10*(2). https://doi.org/10.3390/foods10020234

Aoki, M., Hecht, A., Kruse, U., Kemler, R., & Vogt, P. K. (1999). Nuclear endpoint of Wnt signaling: Neoplastic transformation induced by transactivating lymphoid-enhancing factor 1. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(1), 139–144. https://doi.org/10.1073/pnas.96.1.139

Ashique, S., Sandhu, N. K., Haque, S. N., & Koley, K. (2020). A systemic review on topical marketed formulations, natural products, and oral supplements to prevent androgenic alopecia: A Review. *Natural Products and Bioprospecting*, *10*(6), 345–365. https://doi.org/10.1007/s13659-020-00267-9

Ayuningtyas, D. dan Linawati, M. (2018). Peranan follicular unit grafting dalam mengatasi alopecia (The role of follicular unit grafting in treatment alopecia). Jurnal Medika Udayana, 2(8), 1-13.

Bak, S. S., Ahn, B. N., Kim, J. A., Shin, S. H., Kim, J. C., Kim, M. K., Sung, Y. K., & Kim, S. K. (2013). *Ecklonia cava* promotes hair growth. 904–910. https://doi.org/10.1111/ced.12120

Bak, S. S., Sung, Y. K., & Kim, S. K. (2014). 7-Phloroeckol promotes hair growth on human follicles *in vitro*. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *387*(8), 789–793. https://doi.org/10.1007/s00210-014-0986-0

Bare, Y., Sari, D. R. T., Mogi, M. C., & Nurak, M. M. D. (2022). Senyawa fucodiphlorethol dan phloroglucinol alga coklat sebagai inhibitor

lipase secara in silico. (Fucodiphlorethol and phloroglucinol compounds of brown algae as Lipase Inhibitors in silico). *Florea: Jurnal Biologi Dan Pembelajarannya*, *9*(1), 53–59.

Belleudi, F., Purpura, V., Caputo, S., & Torrisi, M. R. (2014). FGF7/KGF regulates autophagy in keratinocytes: A novel dual role in the induction of both assembly and turnover of autophagosomes. *Autophagy*, *10*(5), 803–821. https://doi.org/10.4161/auto.28145

Blackman, J., & Rogers, G. I. (1988). Phloroglucinol derivatives from three australian marine algae of the genus zonaria. Journal of Natural Products, *5*(1), 158–160.

Brkljača, R., & Urban, S. (2015). Chemical profiling (HPLC-NMR & HPLC-MS), isolation, and identification of bioactive meroditerpenoids from the southern australian marine brown alga Sargassum paradoxum. *Marine Drugs*, *13*(1), 102–127. https://doi.org/10.3390/md13010102

Cahyaningrum, K., Husni, A., & Budhiyanti, S. A. (2016). Aktivitas antioksidan ekstrak rumput laut cokelat (Sargassum polycystum) (Antioxidant activity of brown seaweed (Sargassum polycystum) extracts). *Agritech*, *36*(4), 137–144.

Chase, B. (1954). Growth of the hair. *American Physiological Society*, *34*.

Chen, Q., Sun, T., Wang, J., Jia, J., Yi, Y. H., Chen, Y. X., Miao, Y., & Hu, Z. Q. (2019). Hydroxytyrosol prevents dermal papilla cells inflammation under oxidative stress by inducing autophagy. *Journal of Biochemical and Molecular Toxicology*, *33*(9), 1–9. https://doi.org/10.1002/jbt.22377

Choi, B. Y. (2018). Hair-growth potential of ginseng and its major metabolites: A review on its molecular mechanismsHair-growth potential of ginseng and its major metabolites: A review on its molecular mechanismsHair-growth potential of ginseng and its major metabolites: A r. *International Journal of Molecular Sciences*, *19*(9). https://doi.org/10.3390/ijms19092703

Choi, B. Y. (2020). Targeting wnt/β-catenin pathway for developing therapies for hair loss. In *International Journal of Molecular Sciences* (Vol. 21, Issue 14, pp. 1–16). https://doi.org/10.3390/ijms21144915

Celso, C. L., Prowse, D. M., & Watt, F.M., (2004). Transient Activation of Wnt Catenin Signaling.pdf.crdownload. *The Company of Biologists*, 1787–1799. https://doi.org/10.1242/dev.01052

Danilenko, M., Ring, D., Pierce, F. (1996). Growth factors and cytokines in insights from and the potentials. *Molecular Medicine Today*, *2*(11), 460–467.

Dippel, E., Mayer, B., Schönfelder, G., Czarnetzki, B. M., & Paus, R. (1994). Distribution of constitutive nitric oxide synthase immunoreactivity and NADPH-diaphorase activity in murine telogen and anagen skin. *Journal of Investigative Dermatology*, *103*(1), 112–115. https://doi.org/10.1111/1523-1747.ep12391865

Eswarakumar, V. P., Lax, I., & Schlessinger, J. (2005). Cellular signaling by fibroblast growth factor receptors. *Cytokine and Growth Factor Reviews*, *16*(2 SPEC. ISS.), 139–149. https://doi.org/10.1016/j.cytogfr.2005.01.001

Festa E, Fretz J, Berry R, Schmidt, B., Rodeheffer, M., Horowitz, M., Horsley, V. (2011). Adipocyte lineage cells contribute to the skin stem cell niche to drive hair cycling. *Cell*, *146*(5), 761–71. https://doi.org/10.1016/j.cell.2011.07.019. Adipocyte

Festi, Jumiati & Aba, L. (2022). Identifikasi jenis-jenis makroalga di perairan pantai sombano kabupaten wakatobi. (Identification of macroalgae types in the coastal waters of sombano, wakatobi regency). *Jurnal Penelitian Biologi Dan Kependidikan*, *1*(1), 11–24.

Flower, R. J. (2006). Prostaglandins, bioassay and inflammation. *British Journal of Pharmacology*, *147*(SUPPL. 1), 182–192. https://doi.org/10.1038/sj.bjp.0706506

Foitzik, K., Lindner, G., Mueller-Roever, S., Maurer, M., Botchkareva, N., Botchkarev, V., Handjiski, B., Metz, M., Hibino, T., Soma, T., Paolo Dotto, G., & Paus, R. (2000). Control of murine hair follicle regression (catagen) by TGF-β1 *in vivo* . *The FASEB Journal*, *14*(5), 752–760. https://doi.org/10.1096/fasebj.14.5.752

Garza, L. A., Liu, Y., Yang, Z., Alagesan, B., Lawson, J. A., Scott, M., Loy, D. E., Zhao, T., Blatt, H. B., Stanton, D. C., Carrasco, L., Ahluwalia, G., Fischer, S. M., Fitzgerald, G. A., & Cotsarelis, G. (2012). Prostaglandin D2 inhibits hair growth and is elevated in bald scalp of men with androgenetic alopecia. *4*(126), 1–21. https://doi.org/10.1126/scitranslmed.300

3122.Prostaglandin

Gentile, P., & Garcovich, S. (2019). Advances in regenerative stem cell therapy in androgenic alopecia and hair loss: Wnt pathway, growth-factor, and mesenchymal stem cell signaling impact analysis on cell growth and hair follicle development. *Cells*, *8*(5). https://doi.org/10.3390/cells8050466

Giuliano, F., & Warner, T. D. (2002). Origins of prostaglandin E2: Involvements of cyclooxygenase (COX)-1 and COX-2 in human and rat systems. *Journal of Pharmacology and Experimental Therapeutics*, *303*(3), 1001–1006. https://doi.org/10.1124/jpet.102.041244

Gnann, L. A., Castro, R. F., Azzalis, L. A., Feder, D., Perazzo, F. F., Pereira, E. C., Rosa, P. C. P., Junqueira, V. B. C., Rocha, K. C., Machado, C. D. A., Paschoal, F. C., de Abreu, L. C., Valenti, V. E., & Fonseca, F. L. A. (2013). Hematological and hepatic effects of vascular epidermal growth factor (VEGF) used to stimulate hair growth in an animal model. *BMC Dermatology*, *13*, 2–6. https://doi.org/10.1186/1471-5945-13-15

Greco V, Chen T, Rendl M, Schober, M., Pasolli, A.H., Stokes, N., Cruz-Racelis, D.J., & Fuchs E., (2009). A two-step mechanism for stem cell activation during hair regeneration. *Cell Stem Cell*, *4*(2), 155–69. https://doi.org/10.1016/j.stem.2008.12.009.A

Hansen, L. A., Alexander, N., Hogan, M. E., Sundberg, J. P., Dlugosz, A., Threadgill, D. W., Magnuson, T., & Yuspa, S. H. (1997). Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development. *American Journal of Pathology*, *150*(6), 1959–1975.

Hardy, M. H. (1992). The secret life of the hair follicle. *Trends in Genetics*, *8*(2), 55–61. https://doi.org/10.1016/0168-9525(92)90350-D

Harris, S. G., Padilla, J., Koumas, L., Ray, D., & Phipps, R. P. (2002). Prostaglandins as modulators of immunity. *Trends in Immunology*, *23*(3), 144–150. https://doi.org/10.1016/S1471-4906(01)02154-8

He, J., Xu, Y., Chen, H., & Sun, P. (2016). Extraction, structural characterization, and potential antioxidant activity of the polysaccharides from four seaweeds. *International Journal of Molecular Sciences*, *17*(12). https://doi.org/10.3390/ijms17121988

Herman, A., & Herman, A. P. (2016). Mechanism of action of herbs and their active constituents used in hair loss treatment. *Fitoterapia*, *114*, 18–25. https://doi.org/10.1016/j.fitote.2016.08.008

Hiipakka, R. A., Zhang, H. Z., Dai, W., Dai, Q., & Liao, S. (2002). Structure-activity relationships for inhibition of human 5α-reductases by polyphenols. *Biochemical Pharmacology*, *63*(6), 1165–1176. https://doi.org/10.1016/S0006-2952(02)00848-1

Houschyar, K. S., Borrelli, M. R., Tapking, C., Popp, D., Puladi, B., Ooms, M., Chelliah, M. P., Rein, S., Pförringer, D., Thor, D., Reumuth, G., Wallner, C., Branski, L. K., Siemers, F., Grieb, G., Lehnhardt, M., Yazdi, A. S., Maan, Z. N., & Duscher, D. (2020). Molecular mechanisms of hair growth and regeneration: Current understanding and novel paradigms. *Dermatology*, *236*(4), 271–280. https://doi.org/10.1159/000506155

Hsu YC, Li L, Fuchs E (2014). Emerging interactions between skin stem cells and their niches. *Nat Med*, *20*(8), 847–56. https://doi.org/10.1038/nm.3643.Emerging

Huang. C-Yu, Huang. C-Yen, Yang. C, L. ., & Chang.J. (2022). Hair growth-promoting effects of Sargassum glaucescens oligosaccharides extracts. *Journal of the Taiwan Institute of Chemical Engineers*, *134*, 104307. https://doi.org/10.1016/j.jtice.2022.104307

Huelsken, J., Vogel, R., Erdmann, B., Cotsarelis, G., & Birchmeier, W. (2001). β-Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin. *Cell*, *105*(4), 533–545. https://doi.org/10.1016/S0092-8674(01)00336-1

Indahyani, D. E., Praharani, D., Barid, I., Handayani, A. T. W., (2019). Aktivitas Antioksidan dan total polisakarida ekstrak rumput laut merah, hijau dan coklat dari pantai jangkar situbondo (Antioxidant activity and total polysaccharide of red, green and brown seaweed from jangkar situbondo coastal). *Stomatognatic (J.K.G Unej)*, *16*(2), 64–69.

Inui, S.; Fukuzato, Y.; Nakajima, T.; Yoshikawa, K.; Itami, S. (2002). Androgen-inducible TGF-β1 from balding dermal papilla.pdf. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol*, *16*, 1967–1969.

https://doi.org/10.1096/fj.02-0043fje

Jacobtorweihen, J., & Spiegler, V. (2023). Phylogenetic distribution of bromophenols in marine algae and the generation of a comprehensive bromophenol database. In *Phytochemistry Reviews* (Vol. 22, Issue 3). Springer Netherlands. https://doi.org/10.1007/s11101-022-09847-8

Jindo, T., Tsuboi, R., Imai, R., Takamori, K., Rubin, J. S., & Ogawa, H. (1995). The effect of hepatocyte growth factor/scatter factor on human hair follicle growth. *Journal of Dermatological Science*, *10*(3), 229–232. https://doi.org/10.1016/0923-1811(95)00429-V

Jindo, T., Tsuboi, R., Takamori, K., & Ogawa, H. (1998). Local injection of hepatocyte growth factor/scatter factor (HGF/SF) alters cyclic growth of murine hair follicles. *Journal of Investigative Dermatology*, *110*(4), 338–342. https://doi.org/10.1046/j.1523-1747.1998.00144.x

Johnstone, M. A., & Albert, D. M. (2002). Prostaglandin-induced hair growth. *Survey of Ophthalmology*, *47*(4 SUPPL. 1). https://doi.org/10.1016/S0039-6257(02)00307-7

Joung, E.J., Lee, B., Gwon, W.G., Shin, T., Jung, B.M., Yoon, N.Y., Choi, Jae-Sue, oh, C.W, Kim, Hyeung-Rak., (2015). Sargaquinoic acid attenuates inflammatory responses by regulating NF-kB and Nrf2 pathways in lipopolysaccharide-stimulated RAW 264.7 cells. *Int. Immunopharmacol*, *29*, 693–700.

Kang, Jung-II, Kim, J., Kim, Sang-Cheol., Han, Sang-Chul., Lee, Ji-Hyeok., Lee, J., Noh, E., Jeon, You-Jin., Yoo, Eun-Sook., & Kang, Hee-Kyoung., (2020). The Effect of Glucopyranosyldiacylglycerol from padina.pdf. *Kor. J. Pharmacogn.*, *51*, 41–48.

Kandyba E, K. K. (2014). Wnt7b is an important intrinsic regulator of hair follicle stem cell homeostasis and hair follicle cycling. *Stem Cells*, *32*(4), 886–901. https://doi.org/10.1002/stem.1599.Wnt7b

Kang. Jung Il, Kim. Sang Cheol, K. M. K., & Boo. Hye Jin, Jeon. You Jin, Koh. Sang Young, Yoo. Eun Sook, Kang. Sung Myung, K. H. K. (2012). Effect of dieckol, a component of ecklonia cava, on the promotion of hair growth. *International Journal of Molecular Sciences*, *13*(5), 6407–6423. https://doi.org/10.3390/ijms13056407

Kang, G. J., Han, S. C., Koh, Y. S., Kang, H. K., Jeon, Y. J., & Yoo, E. S. (2012). Diphlorethohydroxycarmalol, isolated from Ishige okamurae, increases prostaglandin E2 through the expression of cyclooxygenase-1 and -2 in HaCaT human keratinocytes. *Biomolecules and Therapeutics*, *20*(6), 520–525. https://doi.org/10.4062/biomolther.2012.20.6.520

Kang, J. Il, Choi, Y. K., Koh, Y. S., Hyun, J. W., Han, S. C., Nam, H., Lee, G., Kang, J. H., Yoo, E. S., & Kang, H. K. (2022). 5-Bromo-3,4-dihydroxybenzaldehyde promotes hair growth through activation of Wnt/β-Catenin and autophagy pathways and inhibition of TGF-β pathways in dermal papilla cells. *Molecules*, *27*(7), 2176. https://doi.org/10.3390/molecules27072176

Kang, J. Il, Kim, J., Kim, S. C., Han, S. C., Lee, J. H., Lee, J., Noh, E., Jeon, Y. J., Yoo, E. S., & Kang, H. K. (2020). The effect of Glucopyranosyldiacylglycerol from Padina arborescens on the prevention of hair-loss. *Korean Journal of Pharmacognosy*, *51*(1), 41–48.

Kang, J. Il, Kim, M. K., Lee, J. H., Jeon, Y. J., Hwang, E. K., Koh, Y. S., Hyun, J. W., Kwon, S. Y., Yoo, E. S., & Kang, H. K. (2017). Undariopsis peterseniana promotes hair growth by the activation of Wnt/β-catenin and ERK pathways. *Marine Drugs*, *15*(5). https://doi.org/10.3390/md15050130

Kang, J., Kim, E., Kim, M., Jeon, Y., & Kang, S. (2013). The promoting efect of *Ishige sinicola* on hair growth. 1783–1799. https://doi.org/10.3390/md11061783

Kang, J., Kim, S. C., Han, S. C., Hong, H. J., Jeon, Y. J., Kim, B., Koh, Y. S., Yoo, E. S., & Kang, H. K. (2012). Hair-loss preventing effect of Grateloupia elliptica. *Biomolecules and Therapeutics*, *20*(1), 118–120. https://doi.org/10.4062/biomolther.2012.20.1.118

Kang, J., Kim, S., Kim, M., Boo, H., & Jeon, Y. (2012). Effect of Dieckol , a Component of *Ecklonia cava* , on the promotion of hair growth. Int. J. Mol. Sci, 13, 6407–6423. https://doi.org/10.3390/ijms13056407

Kang, J., Yoo, E., Hyun, J., Koh, Y., Lee, H., Ko, M., Ko, C., & Kang, H. (2016). Promotion effect of Apo-9 ′ -fucoxanthinone from *Sargassum muticum* on hair growth via the activation of

Wnt / β -Catenin *and VEGF-R2*. Biol. Pharm. Bull, *39*(8), 1273–1283.

Kaplanski, G., Marin, V., Montero-Julian, F., Mantovani, A., & Farnarier, C. (2003). IL-6: A regulator of the transition from neutrophil to monocyte recruitment during inflammation. *Trends in Immunology*, *24*(1), 25–29. https://doi.org/10.1016/S1471-4906(02)00013-3

Komatsu, M., Waguri, S., Koike, M., Sou, Y. shin, Ueno, T., Hara, T., Mizushima, N., Iwata, J. ichi, Ezaki, J., Murata, S., Hamazaki, J., Nishito, Y., Iemura, S. ichiro, Natsume, T., Yanagawa, T., Uwayama, J., Warabi, E., Yoshida, H., Ishii, T., & Tanaka, K (2007). Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice. *Cell*, *131*(6), 1149–1163. https://doi.org/10.1016/j.cell.2007.10.035

Kozlowska, U., Blume-peytavi, U.V.K., Kodelja, V., Sommer, C., Goerdt, S., Majewski, S., & Jablonska, S. C E., (1998). Expression of vascular endothelial growth factor (VEGF) in various compartments of the human hair follicle. Archives of Dermatological Research, 290, 661–668.

Lachgar, S., Charveron, M., Gall, Y., & Bonafe, J. L. (1998). Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. *British Journal of Dermatology*, *138*(3), 407–411. https://doi.org/10.1046/j.1365-2133.1998.02115.x

Lee, S.W., Juhasz, M., Mobasher, P., Chloe Ekelem, C. and Mesinkovska, N. A. (2018). A systematic review of topical finasteride in the treatment of androgenetic alopecia in men and women. *J Drugs Dermatol*, *17*(1), 457–463.

Lee. Y.R, Bae. S, Kim. J.Y, Lee. J, Cho. D-Hyun, Kim. Hee-sik, An. In-sook, A. S. (2019). Monoterpenoid loliolide regulates hair follicle inductivity of human dermal papilla cells by activating the AKT/ β -Catenin signaling pathway. J. Microbiol. Biotechnol. 29(11), 1830–1840. https://doi.org/10.4014/jmb.1908.08018

Lestari, I. L., & Mita, S. R. (2013). Review: Potensi Alga Laut dan Kandungan Senyawa Biologisnya Sebagai Bahan Baku Kosmeseutikal. Review: Potential of marine algae and their biological compound content as cosmetic raw materials), *Farmaka*, *14*(1), 114–126.

Liu, Z., Tang, L., Zou, P., Zhang, Y., Wang, Z., Fang, Q., Jiang, L., Chen, G., Xu, Z., Zhang, H., & Liang, G. (2014). Synthesis and biological evaluation of allylated and prenylated mono-carbonyl analogs of curcumin as anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *74*, 671–682. https://doi.org/10.1016/j.ejmech.2013.10.061

Lolli, F., Pallotti, F., Rossi, A., Fortuna, M. C., Caro, G., Lenzi, A., Sansone, A., & Lombardo, F. (2017). Androgenetic alopecia: a review. *Endocrine*, *57*(1), 9–17. https://doi.org/10.1007/s12020-017-1280-y

Ma, X. T., Sun, X. Y., Yu, K., Gui, B. S., Gui, Q., & Ouyang, J. M. (2017). Effect of content of sulfate groups in seaweed polysaccharides on antioxidant activity and repair effect of subcellular organelles in injured HK-2 cells. *Oxidative Medicine and Cellular Longevity*, *2017*. https://doi.org/10.1155/2017/2542950

Mak, K. K. L., & Chan, S. Y. (2003). Epidermal growth factor as a biologic switch in hair growth cycle. *Journal of Biological Chemistry*, *278*(28), 26120–26126. https://doi.org/10.1074/jbc.M212082200

Marks-Konczalik, J., Chu, S. C., & Moss, J. (1998). Cytokine-mediated transcriptional induction of the human inducible nitric oxide synthase gene requires both activator protein 1 and nuclear factor κB-binding sites. *Journal of Biological Chemistry*, *273*(35), 22201–22208. https://doi.org/10.1074/jbc.273.35.22201

Meidan, V. M., & Touitou, E. (2001). Treatments for androgenetic alopecia and alopecia areata: Current options and future prospects. *Drugs*, *61*(1), 53–69. https://doi.org/10.2165/00003495-200161010-00006

Miele, C., Rochford, J. J., Filippa, N., Giorgetti-Peraldi, S., & Van Obberghen, E. (2000). Insulin and insulin-like growth factor-I induce vascular endothelial growth factor mRNA expression via different signaling pathways. *Journal of Biological Chemistry*, *275*(28), 21695–21702. https://doi.org/10.1074/jbc.M000805200

Mittal, M., Siddiqui, M. R., Tran, K., Reddy, S. P., & Malik, A. B. (2014). Reactive oxygen species in inflammation and tissue injury. *Antioxidants and Redox Signaling*, *20*(7), 1126–1167.

https://doi.org/10.1089/ars.2012.5149

Nelson, A.M.; Loy, D.E.; Lawson, J.A.; Katseff, A.S.; Fitzgerald, G.A.; Garza, L. . (2013). Prostaglandin D2 inhibits wound-induced hair follicle neogenesis through the receptor, Gpr44. *J. Investig. Dermatol*, *133*, 881–889. https://doi.org/10.1038/jid.2012.398.Prostaglandin

Neri, T.A, Palmos, G. N., Park, S.Y., Jung. T.S, & Choi, B. D. (2022). Hair growth-promoting activities of glycosaminoglycans extracted from the tunics of ascidian (Halocynthia roretzi). *Polymers*, 14, 1096. https://doi.org/10.3390/ polym14061096

Oshimori N, F. E. (2012). Paracrin TGFb signaling counterbalance BMP mediated repression in hair folicle SC activation. *Cell Stem Cell*, *10*(1), 63–75.

Ozeki, M., & Tabata, Y. (2003). *In vivo* promoted growth of mice hair follicles by the controlled release of growth factors. *Biomaterials*, *24*(13), 2387–2394. https://doi.org/10.1016/S0142-9612(03)00045-0

Park. Ki Soo, P. D. H. (2016). Comparison of Saccharina japonica–Undaria pinnatifida Mixture and Minoxidil on Hair Growth Promoting Effect in Mice. Archives of plastic surgery, 43(6)

Park, S. H., Lee, K. D., Ahn, G., Park, H. J., Choi, K. S., Chun, J., & Shim, S. Y. (2021). Microalgae, Tetraselmis tetrathele has alopecia prevention and scalp improvement. *Microbiology and Biotechnology Letters*, *49*(4), 528–533. https://doi.org/10.48022/mbl.2104.04007

Park, S. J., Ahn, G., Lee, N. H., Park, J. W., Jeon, Y. J., & Jee, Y. (2011). Phloroglucinol (PG) purified from Ecklonia cava attenuates radiation-induced apoptosis in blood lymphocytes and splenocytes. *Food and Chemical Toxicology*, *49*(9), 2236–2242. https://doi.org/10.1016/j.fct.2011.06.021

Park, S., & Lee, J. (2021). Modulation of hair growth promoting effect by natural products. *Pharmaceutics*, *13*(12), 1–24. https://doi.org/10.3390/pharmaceutics13122163

Parodi, C., Hardman, J. A., Allavena, G., Marotta, R., Catelani, T., Bertolini, M., Paus, R., & Grimaldi, B. (2018). Autophagy is essential for maintaining the growth of a human (mini-)organ: Evidence from scalp hair follicle organ culture. *PLoS Biology*, *16*(3), e2002864. https://doi.org/10.1371/journal.pbio.2002864

Patel, S., Sharma, V., Chauhan, N., Thakur, M., & Dixit, V. K. (2015). Hair Growth: Focus on herbal therapeutic agent. *Current Drug Discovery Technologies*, *12*(1), 21–42. https://doi.org/10.2174/1570163812666150610115055

Paus R, C. G. (2014). The biology of hair follicles. *The New England Journal of Medicine*, *341*(7), 491–497.

Pierce, G. F. (1990). Macrophages: important physiologic and pathologic sources of polypeptide growth factors. *American Journal of Respiratory Cell and Molecular Biology*, *2*(3), 233–234. https://doi.org/10.1165/ajrcmb/2.3.233

Plikus, M. V, Mayer, J., Cruz, D. De, Baker, R. E., Maini, P. K., Maxson, R., & Chuong, C. (2009). Cyclic dermal BMP signaling regulates stem cell activation during hair regeneration. *Nature*, *451*(7176), 340–344. https://doi.org/10.1038/nature06457.Cyclic

Poblet, E., Jiménez-Acosta, F., Hardman, J. A., Escario, E., & Paus, R. (2016). Is the eccrine gland an integral, functionally important component of the human scalp pilosebaceous unit? *Experimental Dermatology*, *25*(2), 149–150. https://doi.org/10.1111/exd.12889

Qi, J., & Garza, L. A. (2014). An Overview of alopecias. *Cold Spring Harbor Perspectives in Medicine*, *4*(3), 1–14.s

Ricciotti, E. and FitzGerald, G. A. (2011). Prostaglandins and Inflammation.pdf. *Arterioscler Thromb Vasc Biol*, *31*(5), 986–1000. https://doi.org/10.1161/ATVBAHA.110.207449

Rishikaysh, P., Dev, K., Diaz, D., Shaikh Qureshi, W. M., Filip, S., & Mokry, J. (2014). Signaling involved in hair follicle morphogenesis and development. *International Journal of Molecular Sciences*, *15*(1), 1647–1670. https://doi.org/10.3390/ijms15011647

Rohim, A., Yunianta., & Estiasih, T. (2019). Senyawa-senyawa bioaktif pada rumput laut cokelat Sargassum Sp. : Ulasan Ilmiah. (Bioactive Compounds on Sargassum sp. Brown Seaweed: A Review). *Jurnal Teknologi Pertanian*, *20*(2), 115–126. https://doi.org/10.21776/ub.jtp.2019.020.

02.5

Rupérez, P., Ahrazem, O., & Leal, J. A. (2002). Potential antioxidant capacity of sulfated polysaccharides from the edible marine brown seaweed Fucus vesiculosus. *Journal of Agricultural and Food Chemistry*, *50*(4), 840–845. https://doi.org/10.1021/jf010908o

Ryter, S. W., Cloonan, S. M., & Choi, A. M. K. (2013). Autophagy: A critical regulator of cellular metabolism and homeostasis. *Molecules and Cells*, *36*(1), 7–16. https://doi.org/10.1007/s10059-013-0140-8

Sasaki, S., Hozumi, Y., & Kondo, S. (2005). Influence of prostaglandin F2α and its analogues on hair regrowth and follicular melanogenesis in a murine model. *Experimental Dermatology*, *14*(5), 323–328. https://doi.org/10.1111/j.0906-6705.2005.00270.x

Ścieszka, S., & Klewicka, E. (2019). Algae in food: a general review. *Critical Reviews in Food Science and Nutrition*, *59*(21), 3538–3547. https://doi.org/10.1080/10408398.2018.1496319

Seok, J., Kim, T. S., Kwon, H. J., Lee, S. P., Kang, M. H., Kim, B. J., & Kim, M. N. (2015). Efficacy of Cistanche Tubulosa and Laminaria Japonica Extracts (MK-R7) Supplement in preventing patterned hair loss and promoting scalp health. Clin Nutr Res, 4, 124–131. http://dx.doi.org/10.7762/cnr.2015.4.2.124

Shin, H., Cho, A., Kim, D. Y., Munkhbayer, S., & Choi, S. (2016). Enhancement of hman hair growth using Ecklonia cava polyphenols. Ann Dermatol , *28*(1), 15–21. http://dx.doi.org/10.5021/ad.2016.28.1.15

Sinclair, R., Torkamani, N., & Jones, L. (2015). Androgenetic alopecia: New insights into the pathogenesis and mechanism of hair loss. *F1000 Research*, *4*, 1–9. https://doi.org/10.12688/f1000research.6401.1

Singh, I. P., Sidana, J., Bansal, P., & Foley, W. J. (2009). Phloroglucinol compounds of therapeutic interest: Global patent and technology status. *Expert Opinion on Therapeutic Patents*, *19*(6), 847–866. https://doi.org/10.1517/13543770902916614

Sinurat, E., & Maulida, N. N. (2018). Effect of fucoidan hydrolysis on its activity as an antioxidant. *Jurnal Pascapanen Dan Bioteknologi Kelautan Dan Perikanan*, *13*(2), 123–130.

Spengler, K., Kryeziu, N., Große, S., Mosig, A. S., & Heller, R. (2020). VEGF triggers transient induction of autophagy in endothelial cells via AMPKα1. *Cells*, *9*(3). https://doi.org/10.3390/cells9030687

Stenn, K. S., & Paus, R. (2001). Controls of hair follicle cycling. *Physiological Reviews*, *81*(1), 449–494. https://doi.org/10.1152/physrev.2001.81.1.449

Sun, M., Deng, Y., Cao, X., Xiao, L., Ding, Q., Luo, F., Huang, P., Gao, Y., Liu, M., & Zhao, H. (2022). Effects of natural polyphenols on skin and hair health: A Review. *Molecules*, *27*(22), 7832. https://doi.org/10.3390/molecules27227832

Suzuki, H. I., Kiyono, K., & Miyazono, K. (2010). Regulation of autophagy by transforming growth factor-β (TGFβ) signaling. *Autophagy*, 645–647.

Trüeb, R. M. (2018). Further clinical evidence for the effect of IGF-1 on hair growth and alopecia. *Skin Appendage Disorders*, *4*(2), 90–95. https://doi.org/10.1159/000479333

Van Mater, D., Kolligs, F. T., Dlugosz, A. A., & Fearon, E. R. (2003). Transient activation of β-catenin signaling in cutaneous keratinocytes is sufficient to trigger the active growth phase of the hair cycle in mice. *Genes and Development*, *17*(10), 1219–1224. https://doi.org/10.1101/gad.1076103

Vane, J. R., Mitchell, J. A., Appleton, I., Tomlinson, A., Bishop-Bailey, D., Croxtall, J., & Willoughby, D. A. (1994). Inducible isoforms of cyclooxygenase and nitric-oxide synthase in inflammation. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(6), 2046–2050. https://doi.org/10.1073/pnas.91.6.2046

Vasserot, A. P., Geyfman, M., & Poloso, N. J. (2019). Androgenetic alopecia: combing the hair follicle signaling pathways for new therapeutic targets and more effective treatment options. *Expert Opinion on Therapeutic Targets*, *23*(9), 755–771. https://doi.org/10.1080/14728222.2019.1659779

Wall, D., Meah, N., Fagan, N., York, K., & Sinclair, R.

(2022). Advances in hair growth. *Faculty Reviews*, *11*. https://doi.org/10.12703/r/11-1

Wang. H.M, L. X.-C., Jong, L. D., & Shu, C. J. (2017). Potential biomedical applications of marine algae. *Bioresource Technology*, *244*(1), 1407–1415. https://doi.org/10.1016/j.biortech.2017.05.198

Weger, N., & Schlake, T. (2005). IGF-I signalling controls the hair growth cycle and the differentiation of hair shafts. *Journal of Investigative Dermatology*, *125*(5), 873–882. https://doi.org/10.1111/j.0022-202X.2005.23946.x

Wolf, R., Schönfelder, G., Paul, M., & Blume-Peytavi, U. (2003). Nitric oxide in the human hair follicle: Constitutive and dihydrotestosterone-induced nitric oxide synthase expression and NO production in dermal papilla cells. *Journal of Molecular Medicine*, *81*(2), 110–117. https://doi.org/10.1007/s00109-002-0402-y

Wu, Z., Zhu, Y., Liu, H., Liu, G., & Li, F. (2020). Wnt10b promotes hair follicles growth and dermal papilla cells proliferation via Wnt/β-Catenin signaling pathway in Rex rabbits. *Bioscience Reports*, *40*(2), 1–10. https://doi.org/10.1042/BSR20191248

Xu, S. Y., Huang, X., & Cheong, K. L. (2017). Recent advances in marine algae polysaccharides: Isolation, structure, and activities. *Marine Drugs*, *15*(12), 1–16. https://doi.org/10.3390/md15120388

Yano, K., Brown, L. F., & Detmar, M. (2001). Control of hair growth and follicle size by VEGF-mediated angiogenesis. *Journal of Clinical Investigation*, *107*(4), 409–417. https://doi.org/10.1172/JCI11317

Zachary, I. (2001). Signaling mechanisms mediating vascular protective actions of vascular endothelial growth factor. Vascular Surgery, 280, 1375–1386. https://doi.org/10.1177/153857449803200307

Zhang, H., Nan, W., Wang, S., Zhang, T., Si, H., Yang, F., & Li, G. (2016). Epidermal growth factor promotes proliferation and migration of follicular outer root sheath cells via Wnt/β-Catenin signaling. *Cellular Physiology and Biochemistry*, *39*(1), 360–370. https://doi.org/10.1159/000445630

Zheng.L, Liu. Y, T. S., Zhang, W., & Cheong, K. L. (2023). Preparation methods, biological activities, and potential applications of marine algae oligosaccharides: a review. *Food Science and Human Wellness*, *12*(2), 359–370. https://doi.org/10.1016/j.fshw.2022.07.038