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Nothopanax scutellarium: Natural Hair Growth Plant

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ABSTRACT

Hair plays an important role in supporting appearance and self confidence, but problems with hair loss and slow hair growth still often occur; Mangkokan leaves (*Nothopanax scutellarium*) are known to contain flavonoids such as quercetin which can stimulate hair growth through various mechanisms, and nanoemulsion formulations have been shown to increase the absorption of these active compounds, so this study aims to examine the effectiveness of mangkokan leaves on hair growth through a systematic review based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines with a literature search until November 16, 2024 in the Emerald Publishing, SpringerLink, EBSCO, Cochrane, ProQuest, Science Direct, Scopus, and PubMed databases, of the 68 articles found, only 5 studies met the inclusion criteria after screening, and the results showed that the formulation of mangkokan leaves in the form of ethosomal gel or phytosome lotion at a concentration of 25% was most effective in stimulating hair growth with a mechanism involving the activation of endothelial nitric oxide synthase (eNOS) to increase blood supply to follicles, regulation of nitric oxide (NO) balance and decreased inflammation by quercetin, inhibition of the enzyme 5-alpha reductase to reduce dihydrotestosterone (DHT) levels, as well as increasing the expression of growth factors such as insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF), which overall support the extension of the anagen phase (active hair growth phase) and improve hair health, so that mangkokan leaves have high potential as an active ingredient in hair care products, although further research is still needed to ensure their long-term safety and effectiveness.

INTRODUCTION

Hair is an important component of human appearance, which not only functions as a protector of the scalp, but also influences a person's self-confidence (Heroweti et al., 2023). However, various hair health problems, such as hair loss, baldness, and slow hair growth, are challenges that are often faced by people. This condition can be caused by various factors, including genetics, stress, excessive use of chemical products, and unhealthy lifestyles (Almohanna et al., 2019; Gokce et al., 2022). Therefore, solutions to improve hair health, especially in terms of stimulating hair growth, continue to be a focus of research in the pharmaceutical and cosmetic fields. The use of natural ingredients for hair care has become a popular choice because it is considered safer, environmentally friendly, and has a lower risk of side effects compared to synthetic ingredients (Sang et al., 2023).

One of the plants that has great potential in hair care is *Nothopanax scutellarium* or known as mangkokan leaves (Darmadi & Sepriyani, 2020; Nurhayati, 2019). This plant has long been used

in traditional medicine in various regions in Indonesia as a natural remedy to treat hair loss and stimulate hair growth (Nurhayati, 2019). Mangkokan leaves are known to contain bioactive compounds such as flavonoids which are believed to contribute to its pharmacological activity, including hair growth stimulating effects(Ijeise et al., 2023; Kurniawan & Humaedi, 2021).

The potential of *Nothopanax scutellarium* as a natural hair growth plant has attracted the attention of researchers to develop innovative natural ingredient-based formulations. With the advancement of formulation technology, such as nanoemulsion, the efficacy of active compounds in mangkokan leaves can be increased through increased bioavailability and absorption (Kumar et al., 2019; Preeti et al., 2023). This article aims to explore further the available literature regarding the active compounds, mechanism of action, and effectiveness of *Nothopanax scutellarium* as an active ingredient in hair care products.

METHODS

This systematic review adheres to the specifications set out by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Haddaway et al., 2022). Emerald Publishing, SpringerLink, EBSCO, Cochrane, ProQuest, Science Direct, Scopus, PubMed databases were searched comprehensively up to November 16 for relevant articles evaluating the utilization of *Nothopanax scutellarium* for hair growth. The search strategy used to locate articles involved specific search phrases and related tags to identify relevant articles. The search terms included "hair growth" AND "*Nothopanax scutellarium*". Results were reviewed from abstracts and titles discussing *Nothopanax scutellarium* for hair growth and studies that met the following inclusion criteria: (i) no duplication; (ii) original research; (iii) studies published after 2017. Data extracted from the articles included information on authors, year of publication, title, plant part studied, isolation method, compounds contained in the isolate, concentration of the isolate, preparation used to utilize *Nothopanax scutellarium*, bioavailability, mechanism of action and results of the study (**Figure 1**).

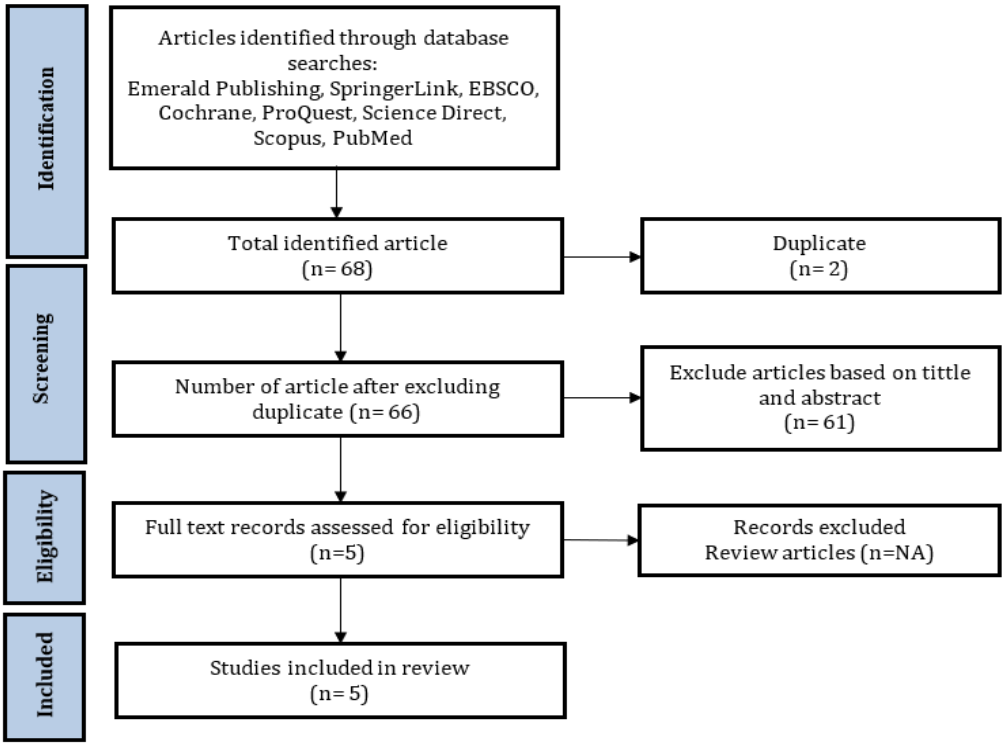

Figure 1. PRISMA flow diagram of a systematic review of the literature to examine the use of Nothopanax scutellarium for hair growth.

Table 1. Overall summary of the studies included in the systematic review

Plant parts, Isolation methods	Isolate concentration	Dosage form	Comparative control	Types of test animals	Research result	Reference (author, year)
Leaf, Maceration	-	Hair tonic	Minoxidil	Male rabbit	• Formula A (25% ethanol extract) showed better hair growth. • The positive control (minoxidil) showed the best overall results, with hair length measured on day 22 reaching 18.58 mm. • Hair length of Formula A, B, and C on day 22 was 16.19 mm, 14.60 mm, and 18.58 mm.	Aini, 2017
Leaf, Maceration	4,79%	Hair tonic	Minoxidil	Male New Zealand strain rabbit	• Formula II (0.5% fraction) showed effective hair growth. • Formula III (1% fraction) had the fastest hair growth activity with a hair length of 28.25. • Significant results were observed at the end of the 3rd week.	Rifkia et al., 2017
Leaf, Maceration	5,83%	Ethosomal gel	Minoxidil	Male New Zealand strain rabbit	• 1% ethosomal gel showed the best hair growth activity. • Average hair length peaked at 24.39 mm at week IV. • Positive control (minoxidil gel) also showed significant growth.	Jufri et al., 2017
Leaf, Maceration	-	Hair tonic	Minoxidil	Male rabbit	• The most effective formula is A with a concentration ethanol extract of 25%. • Hair length measured on day 22 showed significant growth. • Formula A produced a hair length of 16.19 mm on day 22. • Positive control (minoxidil) showed a hair length of 18.58 mm on day 22.	Yasir, 2019
Leaf, Microwave-Assisted Extraction (MAE)	-	Lotion	Minoxidil	Male New Zealand strain rabbit	• Hair growth activity was evaluated weekly, significant improvement was observed. • Formula 3 (30% ethanol extract) induced the highest hair growth rate weekly. • Formula 3 showed the highest efficacy for hair growth of 1.72±0.19 cm at week 4.	Rahmi et al., 2021

RESULT AND DISCUSSION

There were 68 articles identified using the original literature search strategy. Articles were screened and 2 duplicate articles were found. The remaining 66 articles were re-screened for their titles and abstracts, after which 61 articles were further removed due to inappropriateness. No articles were excluded on final review. This systematic analysis considered a total of 5

articles that met the inclusion criteria according to the PRISMA diagram. Figure 1 shows the study selection process, according to the PRISMA guidelines. A summary of the studies included in the systematic review can be seen in **Table 1**.

Active compound of *Nothopanax scutellarium*

Nothopanax scutellarium, or known as mangkokan leaves, contains various active compounds that have the potential to provide pharmacological benefits, especially in supporting hair growth. The main components in these leaves include flavonoid groups such as daidzein, genistein, isorhamnetin, kaempferol, and quercetin, as well as vitamins A, B1, and C (**Figure 2, Table 2**). Flavonoids, as secondary metabolites, have significant biological activities, including as antioxidants, antimicrobials, and antivirals (Jufri et al., 2017; Rahmi et al., 2021; Yasir, 2019). The antioxidant activity of flavonoids is known to ward off free radicals that damage hair follicles, prolong the anagen phase, and support hair regeneration through cellular protection (Banjarnahor & Artanti, 2014; Xu et al., 2024).

Quercetin (QCT), as the main flavonoid in mangkokan leaves, shows great potential in preventing hair loss and improving scalp health. Studies have shown that QCT can improve blood circulation in the scalp, reduce inflammation, and optimize hair follicle nutrition, all of which play a role in promoting healthy hair growth. However, challenges in the formulation of this active compound are seen in the development of phytosomes, where increasing lipid content in the matrix can form lipid crystals that reduce the ability to bind with QCT, so optimization is needed to ensure the stability and efficacy of this compound In addition to flavonoids, vitamins contained in mangkokan leaves have the function of supporting hair growth. Vitamin A helps regulate sebum production which maintains scalp moisture, while vitamin B1 supports energy metabolism needed for follicle cell regeneration. Vitamin C, with strong antioxidant properties, protects hair follicles from oxidative damage caused by free radicals (Bassino et al., 2020; Jafar et al., 2017; Yasir, 2019). The combined biological activities of flavonoids and vitamins provide great potential in the development of pharmaceutical and cosmetic applications of mangkokan leaf extract.

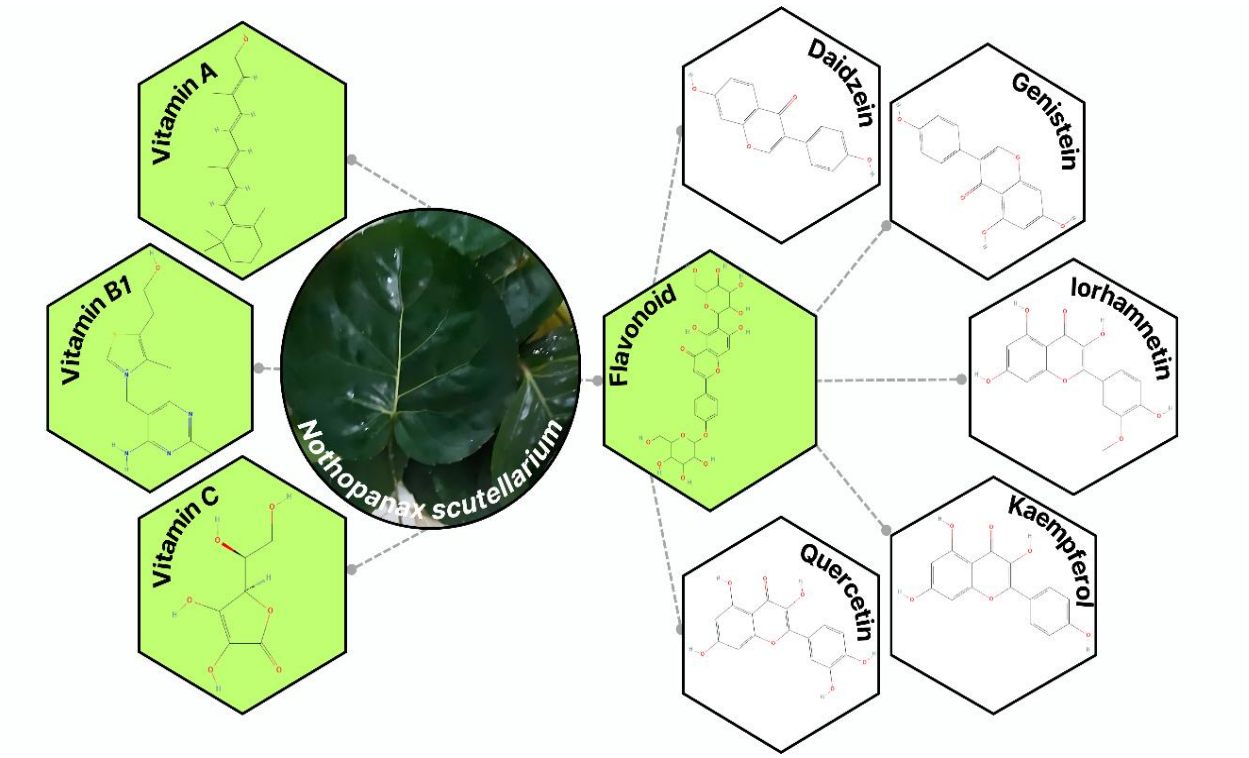

Figure 2. Active compounds in *Nothopanax scutellarium*

Table 2. Summary of studies on active compounds in systematic reviews

Reference (author, year)	Compound
(Aini, 2017)	Flavonoids, vitamins A, B1 and C
(Rifkia et al., 2017)	Daidzein, genistein, isorhamnetin, kaempferol, and quercetin
(Jufri et al., 2017)	Quercetin
(Yasir, 2019)	Flavonoids
(Rahmi et al., 2021)	Quercetin

Effectiveness of *Nothopanax scutellarium* in growing hair

The effectiveness of mangkokan leaves (*Nothopanax scutellarium*) in stimulating hair growth shows varying results, but overall provides a positive picture of the potential of this natural ingredient as an alternative therapy for hair care. Mangkokan leaves, which have been used traditionally for various health purposes, are now gaining attention in scientific research, especially in the field of hair growth. Based on research conducted by Aini (2017), hair tonic containing ethanol extract of mangkokan leaves with a concentration of 25% showed better results in stimulating hair growth compared to higher concentrations. Formula A (25%) showed better hair growth than formulas B and C, although the hair length measured on day 22 was 16.19 mm for Formula A, compared to 14.60 mm in Formula B, and 18.58 mm in Formula C. The positive control containing minoxidil still showed a more significant increase in hair length, with hair length on day 22 reaching 18.58 mm. Although the 25% concentration gave the best results, hair weight did not show a significant difference between the 25% formula and the positive control. This finding suggests that although higher concentrations may not always be more effective, a formula with a concentration of 25% is sufficient to provide optimal results in terms of hair growth (Aini, 2017; Arif et al., 2023; Heroweti et al., 2023).

Research by Rifkia et al.(Rifkia et al., 2017) revealed that the ethyl acetate fraction of mangkokan leaves, especially at a concentration of 1%, showed a better ability to stimulate hair growth at a higher rate compared to the positive control. Formula II (0.5% fraction) also showed effective hair growth, while Formula III (1% fraction) had the fastest hair growth activity, with hair length reaching 28.25 mm at the end of the study. Significant results were observed at the end of the 3rd week, showing that mangkokan leaves can accelerate hair growth in a relatively short time (Rifkia et al., 2017; Saputri & Al-bari, 2022).

Furthermore, research by Jufri *et al*. (Jufri et al., 2017) showed that mangkokan leaf extract formulated in the form of 1% ethosomal gel resulted in a significant increase in hair thickness, with an average hair length peaking at 24.39 mm in week IV. This result is most likely influenced by the vasodilating effect derived from flavonoids contained in mangkokan leaves, which can increase blood flow to hair follicles and increase the supply of nutrients and oxygen needed for hair growth. However, 1% ethosomal gel did not show better results compared to the positive control containing minoxidil. This study shows that although the ethosomal gel formula can increase hair thickness, its effectiveness in overall hair growth still needs to be improved (Jufri et al., 2017; Saputri & Al-bari, 2022).

Research by Yasir (2019) provides further insight into formula stability in the development of mangkokan leaf based preparations. This study found that a concentration of 25% in the hair tonic formula provided a better increase in hair length compared to higher concentrations, such as 35% and 45%. Formula A with a concentration of 25% produced a hair length of 16.19 mm on the 22nd day, while the positive control (minoxidil) showed a hair length of 18.58 mm on the same day. This is due to the instability of the formula at higher concentrations, which causes the active substance to not be perfectly dispersed. The 25% formula showed better stability, allowing the active substance to work optimally until the end of the study. These findings emphasize the importance of formula stability in the development of mangkokan leaf-based products for hair care (Arif et al., 2023; Yasir, 2019).

Meanwhile, research by Rahmi *et al*. (2021) revealed that the extraction technology used to process mangkokan leaves can affect its effectiveness in stimulating hair growth. In this study, mangkokan leaves were extracted using 1-butyl-3-methylimidazolium tetrafluoroborate solvent and processed using microwave-assisted

extraction technology. As a result, the phytosome lotion formula containing mangkokan leaves showed higher activity compared to 2% minoxidil. Formula 3 (phytosome) with a concentration of 30% was shown to have the highest efficacy, with hair length reaching 1.72±0.19 cm in the 4th week. Hair growth activity was evaluated weekly, and significant improvements were observed, especially in formula 3 which induced the highest level of hair growth. This study shows that phytosome technology offers advantages in increasing the penetration of active ingredients into the skin and hair follicles, making it an excellent choice for the development of more effective hair care products (Almas et al., 2022; Rahmi et al., 2021).

Overall, mangkokan leaves showed significant potential in stimulating hair growth, with effectiveness influenced by the dosage form, concentration, and stability of the formula. Aini (2017) research showed that hair tonic with a concentration of 25% produced a hair length of 16.19 mm on the 22nd day, better than formula B (14.60 mm) and C (18.58 mm), although minoxidil (positive control) reached a length of 18.58 mm.

Research by Rifkia *et al*. (2017) revealed that 1% ethyl acetate fraction provided a hair length of 28.25 mm in the 3rd week, faster than the positive control. Research by Jufri *et al*. (Jufri et al., 2017) showed that 1% ethosomal gel achieved a hair length of 24.39 mm in the 4th week, although still lower than minoxidil. Yasir (2019) emphasized the importance of formula stability, with 25% hair tonic producing a hair length of 16.19 mm, while minoxidil reached 18.58 mm. Research by Rahmi *et al*. (2021) indicated that phytosome technology with a concentration of 30% produced a hair length of 1.72±0.19 cm in the 4th week, higher than minoxidil.

Thus, mangkokan leaves showed optimal results at a concentration of 25% for hair tonic and 30% for the phytosome formula. The selection of the right dosage form, such as phytosome or ethosomal, affects its effectiveness, with phytosome technology providing better results in penetration and stability of active ingredients, supporting the development of more effective mangkokan leaf-based products for hair growth.

Mechanism of action of *Nothopanax scutellarium* in hair growth

Hair growth is the result of a complex process involving multiple molecules and molecular pathways that interact to support cellular activity in the hair follicle (Wang et al., 2022). One of the important pathways involved is the activation of Endothelial Nitric Oxide Synthase (eNOS), which plays a role in the synthesis of Nitric Oxide (NO). NO is a signaling molecule that functions as a vasodilator, thereby increasing blood flow to the hair follicles. This allows for optimal oxygen and nutrient supply to support metabolic activity in the hair follicles that will stimulate hair growth (SHG)(Förstermann et al., 2013; Förstermann & Sessa, 2012; Nauli, 2022). On the other hand, flavonoids such as QCT are able to inhibit the expression of Inducible Nitric Oxide Synthase (iNOS), thereby reducing the excess production of NO which is often associated with inflammatory responses. Thus, flavonoids help maintain the NO balance that supports a physiological environment conducive to hair growth (**Figure 3**) (Hämäläinen et al., 2007; Kim et al., 1999; Rifkia et al., 2017)

In addition, QCT has the ability to inhibit 5-alpha reductase type I (5ARI), an enzyme that plays a role in the conversion of testosterone (TT) to dihydrotestosterone (DHT). DHT is known to be a major factor in hair loss, especially in androgenic alopecia. By inhibiting DHT production, flavonoids help protect hair follicles from damage caused by this hormone, allowing the anagen phase (AP) or hair growth phase to last longer (Figure 3) (Azizi et al., 2024; Boam, 2015; Hiipakka et al., 2002; Shafqat et al., 2021).

Growth factors such as Insulin-Like Growth Factor-1 (IGF-1), Vascular Endothelial Growth Factor (VEGF), Keratinocyte Growth Factor (KGF), and Hepatocyte Growth Factor (HGF) also play a key role in stimulating hair follicle cell proliferation and differentiation (Lee et al., 2018; Lin et al., 2015; Rifkia et al., 2017). IGF-1 increases metabolic activity in dermal papilla cells (DPCs), while VEGF supports angiogenesis (Ag), which is the formation of new blood vessels, which is essential for blood supply to hair follicles. KGF and HGF contribute to keratinocyte proliferation (PK) to support healthy hair growth. Flavonoids can modulate this pathway by increasing the expression of these growth factors, so that hair follicles from the telogen phase are accelerated to the anagen

phase transition (APT) (Figure 3) (Lee et al., 2018; Yano et al., 2001).

In addition, the anti-inflammatory properties of flavonoids, especially QCT, play a role in treating hair disorders such as alopecia areata (Her *et al*., 2022; Serafini *et al*., 2010; Li *et al*., 2016; Wikramanayake *et al*., 2012). QCT can regulate nuclear factor-kappa B (NF-κB), which is a major mediator of inflammation (Chen et al., 2022; Liao et al., 2021). Suppression of NF-κB activity reduces the expression of proinflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-1 (IL-1), thereby creating a more supportive environment for stimulating hair growth (**Figure 3, Table 3**) (Arlıer et al., 2018; Guo et al., 2024; Rahmi et al., 2021). The hat may help protect hair follicles from damage caused by chronic inflammation or cellular stress, which are often major factors in hair disorders such as alopecia areata.

These overall molecular pathways suggest that hair growth involves a complex interplay of signaling molecules, enzymes, growth factors, and inflammatory mediators. Flavonoids, through their anti-inflammatory, anti-androgenic, and growth factor modulating properties, and minoxidil, through its vasodilatory and prostaglandin stimulating mechanisms, may complement each other in supporting hair regeneration and growth. The combination of these molecular approaches provides a strong scientific basis for the development of novel natural-based therapies, such as mangkokan leaf extract, in effectively promoting hair growth.

Table 3. Summary of active mechanisms of action in systematic reviews

Reference (author, year)	Mechanism of Action
Aini, 2017	-
Rifkia et al., 2017	↑IGF-1, ↑VEGF, ↑KGF, ↑HGF, ↑eNOS, ↓iNOS, ↓NO, ↓5-alfa reduktase, ↓DHT.
Jufri et al., 2017	-
Yasir, 2019	-
Rahmi et al., 2021	↓NF-κB, ↓TNF-α, ↓IL-1

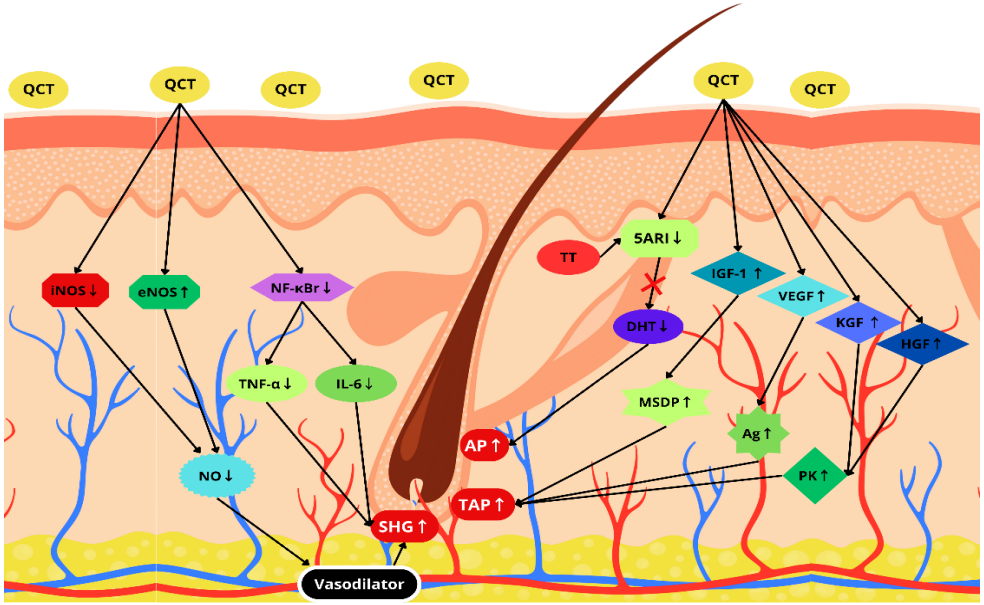

Figure 3. Mechanism of Action of *Nothopanax scutellarium* in Hair Growth

CONCLUSIONS

Mangkokan leaves (*Nothopanax scutellarium*) show significant potential in promoting hair growth due to their flavonoid content, particularly quercetin. The effectiveness of this extract is further enhanced when formulated into stable delivery systems such as ethosomal gel and phytosome lotion. The findings suggest that a 25% concentration is the most effective formulation for hair growth stimulation. Further studies are recommended to explore its long-term safety and efficacy in hair care applications.

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AUTHORS' CONTRIBUTIONS

All authors actively contributed to the preparation of this article.

CONFLICT OF INTERESTS

The author declares that he has no conflict of interest regarding this publication.

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