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A SYSTEMATIC REVIEW ON THE POTENTIAL ROLE OF SILDENAFIL AS A PRECURSOR FOR HAIR GROWTH: MECHANISMS, EFFICACY AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Aim and Objectives: This study systematically reviews the potential of sildenafil, a selective PDE5 inhibitor, as a therapeutic agent for hair growth. The objectives include evaluating its mechanisms of action, efficacy in preclinical and clinical studies, and its role in treating androgenetic alopecia (AGA). **Methodology:** A systematic review was conducted using PubMed to identify studies published between 2015 and 2023. Clinical trials, preclinical research, and in vitro studies were included, focusing on the effects of sildenafil on hair growth. Keywords such as "sildenafil," "hair growth," "PDE5 inhibitors," "vascular endothelial growth factor (VEGF)," and "androgenetic alopecia" guided the search. **Results:** Sildenafil enhances hair growth primarily by increasing cGMP levels, improving blood flow, and promoting angiogenesis through VEGF and PDGF upregulation. It also activates the ERK pathway, stimulating dermal papilla (DP) cell proliferation and prolonging the anagen phase. Preclinical studies showed increased follicle density and hair growth, while pilot clinical trials reported significant improvements in patients with AGA when sildenafil was applied topically or combined with minoxidil. **Conclusion:** Sildenafil demonstrates promising preclinical and clinical potential for hair restoration by improving follicular blood flow, promoting angiogenesis, and extending the anagen phase. However, larger randomized controlled trials are necessary to establish its efficacy, safety, and optimal dosing for clinical use.

KEYWORDS: Sildenafil, PDE5 inhibitors, hair growth, VEGF, androgenetic alopecia, dermal papilla cells, anagen phase.

INTRODUCTION

Hair follicle development and growth are complex processes regulated by coordinated interactions between mesenchymal and epithelial cells. Key players in this intricate cellular communication include dermal papilla (DP) and dermal sheath cells derived from the mesenchyme, along with epithelial-derived cells from the inner and outer root sheaths, the matrix, and the hair shaft.[1] The dermal papilla serves as a vital component for hair growth, supplying essential nutrients and growth factors that support follicle formation, sustain follicle growth, and regulate the hair cycle.[2] Given the demand for effective hair growth treatments, research on the cellular and molecular mechanisms involved in hair growth has expanded, revealing new therapeutic potentials in various drugs and compounds.

Sildenafil, a widely recognized selective inhibitor of phosphodiesterase-5 (PDE5), was initially developed as an anti-anginal medication due to its vasodilatory and antiplatelet properties, which help improve blood flow.[3,4,5] Its structural similarity to cyclic guanosine monophosphate (cGMP) allows sildenafil to bind competitively to the catalytic site of PDE-5, preventing cGMP degradation.[3] This inhibition of PDE5 increases intracellular cGMP levels, leading to smooth muscle relaxation and enhanced blood flow. These properties led to sildenafil's approval as a treatment for erectile dysfunction, where it facilitates penile blood flow through vasodilation and relaxation of smooth muscle in the corpus cavernosum.[6,7]

The role of sildenafil in promoting hair growth is a novel area of investigation, with one pilot study suggesting its potential influence on hair follicle activity. The study proposes that increased blood flow in the bald scalp might enhance microcirculation surrounding hair follicles, promoting follicle health, growth, and even hypertrichosis (excessive hair growth).[8,9,10,11] This emerging application of sildenafil leverages the drug's vasodilatory effects, hypothesizing that increased blood flow can address one of the primary challenges of hair loss: poor circulation in the scalp.

The mechanistic basis of sildenafil's influence on hair growth is also supported by evidence of PDE5 expression in human dermal papilla cells (hDPCs) and human hair follicles (hHFs). Sildenafil has been found to stimulate hDPC proliferation and up-regulate the mRNA expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), two key growth factors involved in hair growth processes.[12] Additionally, sildenafil's effect on the extracellular signal-regulated kinase (ERK) pathway is significant, as it induces phosphorylation of ERK, a process that advances the anagen (growth) phase of

hair by promoting perifollicular vessel formation and improving the delivery of nutrients to the follicle.[12]

The potential for sildenafil as a treatment for hair loss is particularly compelling in light of the limited effective options currently available for individuals experiencing hair loss or thinning. This review explores the pharmacological mechanisms by which sildenafil could stimulate hair growth and considers the therapeutic implications of these findings. By examining the molecular pathways influenced by sildenafil, this review aims to clarify its role as a possible precursor for hair growth and a prospective option in hair restoration therapies.

METHODOLOGY

This systematic review analyzes studies from PubMed specifically focusing on clinical trials, preclinical research, and in vitro studies published between 2015 and 2023. The primary keywords used for the search included "sildenafil," "hair growth," "PDE5 inhibitors," "vascular endothelial growth factor (VEGF)," and "androgenetic alopecia." Studies that explored the biological mechanisms, molecular interactions, and clinical applications of sildenafil in hair restoration were included. Articles were evaluated for methodological rigor, sample size, outcomes, and conclusions related to sildenafil's effects on hair follicles and scalp health.

Molecular Mechanisms of Hair Growth

Hair growth is a complex biological process involving multiple signalling pathways and cellular interactions between mesenchymal (dermal) and epithelial (epidermal) components of hair follicles. The hair follicle undergoes cyclical phases of growth (anagen), regression (catagen), and rest (telogen), with molecular signals regulating the transition between these phases.

1. Wnt/β-catenin Signalling Pathway

One of the most essential pathways in hair follicle development is the Wnt/β-catenin pathway. Activation of this pathway stabilizes β-catenin, which accumulates in the cytoplasm and translocates to the nucleus. It interacts with TCF/LEF transcription factors to activate genes that promote cell proliferation, survival, and differentiation, key factors for the initiation and maintenance of hair follicle growth during the anagen phase[13], MP (Bone Morphogenetic Protein) and Noggin Pathways:

BMPs inhibit hair follicle growth during the telogen phase, but the antagonist Noggin counteracts this effect to stimulate hair follicle regeneration. This balance is crucial for maintaining the hair cycle's proper timing and follicle maturation.[14]

2. Vascular Endothelial Growth Factor

VEGF is a key player in angiogenesis, promoting the formation of new blood vessels that supply oxygen and nutrients to the hair follicles, particularly during the anagen phase. Increased VEGF activity is linked to enhanced hair follicle survival and hair growth.[15]

3. PDGF (Plaved Growth Factor)

PDGF promotes the proliferation and migration of dermal cells, facilitating the transition from the telogen to the anagen phase. It is essential for follicle cycling and supporting dermal papilla cell functions.[16]

Influence of sildenafil on Hair Growth

Sildenafil is widely known as a PDE5 inhibitor used primarily to treat erectile dysfunction, but emerging studies suggest that it could also stimulate hair growth. Its role is thought to be mediated by its effects on blood flow and cellular signalling within hair follicles.

1. **PDE5 Inhibition and cGMP Signalling:** Sildenafil inhibits phosphodiesterase type 5 (PDE5), which is responsible for the breakdown of cyclic guanosine monophosphate (cGMP). cGMP is crucial for vasodilation and smooth muscle relaxation. Inhibition of PDE5 leads to increased levels of cGMP, promoting vasodilation in the microcirculation of the scalp, thus improving blood supply to hair follicles and stimulating growth.[17]

2. **VEGF and PDGF Expression:** Sildenafil has been shown to upregulate the expression of VEGF and PDGF in human dermal papilla cells (hDPCs), key growth factors for angiogenesis and dermal cell proliferation. This action potentially supports the transition of hair follicles from telogen (rest) to anagen (growth) by stimulating follicular regeneration.[18]

3. **Activation of ERK Pathway:** Sildenafil activate the extracellular signal-regulated kinase (ERK) pathway, a key signalling pathway involved in cellular proliferation and differentiation. ERK activation accelerates the anagen phase, enhancing follicle regeneration and hair growth.[19]

4. **Promotion of Dermal Papilla Proliferation:** Sildenafil has been shown to promote the proliferation of dermal papilla cells (DPCs), which play a central role in the regulation of the hair growth cycle. DPCs secrete signalling molecules that guide hair follicle development and are responsible for producing growth factors that influence hair shaft formation.[20]

Evidence from Studies

- **Preclinical Studies:** The studies have demonstrated that sildenafil can stimulate dermal papilla cell proliferation and increase the expression of growth factors such as VEGF and PDGF, which are crucial for hair follicle regeneration. Furthermore, animal models have shown enhanced hair growth with the topical application of sildenafil, possibly due to its vasodilatory effects.[21]
- **Clinical Studies:** Although limited, a pilot clinical study on shown promising results in individuals with androgenetic alopecia (AGA). Patients treated with topical sildenafil exhibited improved hair density and follicle regeneration, likely due to enhanced local circulation and upregulated VEGF production.[18]
- **Clinical Implications:** The findings suggest that sildenafil's effect onlation and growth factor expression could be beneficial in treating various forms of hair loss, particularly AGA, a condition characterized by progressive thinning and loss of hair. Although the evidence is still preliminary, sildenafil's potential as a topical treatment for hair loss warrants further investigation in larger clinical trials to establish its efficacy and optimal dosing regimen.[22]

Efficacy of Sildenafil in Hair Growth

The efficacy of sildenafil in promoting hair growth, while not yet fully substantiated, is supported by a growing body of evidence from preclinical studies, pilot trials, and molecular research. Sildenafil's potential benefits are hypothesized to arise from its vasodilatory effects, growth factor upregulation, and ability to stimulate dermal papilla cells, which are central to the regulation of hair follicle cycling and growth.

1. Vasodilation and Enhanced Blood Flow

Sildenafil is a potent phosphodiesterase-5 (PDE5) inhibitor, which results in elevated levels of cyclic guanosine monophosphate (cGMP). Increased cGMP leads to smooth muscle relaxation and vasodilation, significantly enhancing blood flow in the treated area [23]. In the context of hair growth, improved blood flow in the scalp could increase oxygen and nutrient

supply to hair follicles, addressing a known factor in hair loss: insufficient microcirculation. A study by Zhang et al. (2017) observed that increased blood flow stimulated perifollicular blood vessels, potentially enhancing hair follicle function and health, although more data are needed to confirm long-term efficacy in human scalp applications.[24]

2. Upregulation of Growth Factors: VEGF and PDGF

Sildenafil's ability to upregulate growth factors like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) has drawn particular interest. VEGF is crucial for angiogenesis, facilitating new blood vessel formation, which sustains hair follicles during the anagen (growth) phase. PDGF promotes dermal cell proliferation and migration, key processes in hair follicle cycling from the telogen (resting) phase to the anagen phase.[25] In a study by Kim et al. (2021), sildenafil was shown to increase VEGF and PDGF expression in human dermal papilla cells, with higher VEGF levels associated with improved follicular health and extended anagen phases in animal models.[25]

3. Impact on Dermal Papilla Cell Proliferation

The dermal papilla (DP) cells are a primary driver of hair follicle regeneration and cycling. DP cells secrete signalling molecules essential for initiating and sustaining the anagen phase. Sildenafil has been shown to stimulate DP cell proliferation, which may enhance hair follicle size and hair shaft formation. Zhang et al. (2019) observed that sildenafil-treated DP cells in vitro showed increased mitotic activity and produced higher levels of key signalling molecules compared to untreated controls.[26] The promotion of DP cell activity is particularly promising for androgenetic alopecia (AGA), where hair follicle miniaturization is a leading cause of hair thinning.

4. Activation of the ERK Pathway

Sildenafil has been shown to activate the extracellular signal-regulated kinase (ERK) pathway, which plays a critical role in cellular proliferation, differentiation, and survival.[27] ERK activation can stimulate dermal papilla cells and support perifollicular angiogenesis, improving nutrient delivery to the follicle. In research by Lee et al. (2020), sildenafil-induced ERK pathway activation promoted the anagen phase in mouse models, showing increased hair density and follicle size compared to controls.[27] These findings suggest that sildenafil could help maintain follicles in the active growth phase longer, a crucial factor in improving hair density.

5. Pilot Clinical Studies

While preclinical data are promising, clinical evidence remains limited but encouraging. A small-scale pilot study conducted by Vermeer et al. (2023) evaluated the effects of topical sildenafil on patients with androgenetic alopecia. Participants using a sildenafil-based topical solution for 16 weeks showed an increase in hair density and an improvement in scalp circulation, with some participants reporting subjective improvements in hair thickness.[28] However, this study emphasized the need for larger, more rigorous trials to confirm the efficacy and safety of sildenafil for hair restoration.

6. Comparative Efficacy with Established Treatments

Sildenafil's efficacy as a hair growth treatment has yet to be fully validated against established options like minoxidil and finasteride. Minoxidil, for example, is also a vasodilator and is FDA-approved for topical hair growth, but it operates through different mechanisms, including potassium channel opening. A study comparing sildenafil and minoxidil found that while both showed positive results in animal models, sildenafil required further testing to determine its long-term effects and any potential interactions with minoxidil or finasteride in combined therapy.[29]

Limitations and Considerations

- **Limited Human Trials**: Current evidence supporting sildenafil's efficacy in hair growth is mainly derived from preclinical studies, in vitro tests, and small pilot trials. Large-scale, randomized controlled trials (RCTs) are essential to establish sildenafil's therapeutic potential conclusively.
- **Topical Formulation Challenges**: Optimizing sildenafil's topical delivery and absorption in the scalp poses a challenge. Systemic absorption could lead to unwanted side effects, emphasizing the need for specially formulated topical solutions.[30]
- **Side Effect Profile**: Sildenafil's safety profile in oral use is well-known, but the risk of side effects from topical application, especially for those sensitive to PDE5 inhibitors, is still uncertain. More data are required to assess long-term safety and efficacy.[30]

Therapeutic implications of Sildenafil

1. Adjunctive Therapy with Minoxidil or Finasteride for Androgenetic Alopecia (AGA)

Sildenafil's vasodilatory effects make it a promising adjunctive therapy with existing treatments like minoxidil and finasteride, which have limited efficacy in some patients. Sildenafil's mechanism of action, distinct from both minoxidil and finasteride, targets the

vascularization aspect of hair follicle support. Garcia et al. (2022) found that in a group using a sildenafil-minoxidil combination, patients experienced a 30% increase in hair density compared to the minoxidil-only group, suggesting that sildenafil could improve outcomes by increasing scalp blood flow and enhancing minoxidil's effects on follicle stimulation (Garcia et al., 2022). This combinatorial approach is particularly relevant in AGA, where reduced scalp blood flow is believed to contribute to follicle miniaturization.[31]

2. VEGF-Mediated Angiogenesis and Follicle Survival

AGA's progressive nature leads to a miniaturization of hair follicles, which are deprived of essential nutrients due to reduced scalp vascularization. Sildenafil's ability to increase VEGF (vascular endothelial growth factor) levels has significant implications here. VEGF is a crucial growth factor for angiogenesis, and its upregulation improves the follicular microenvironment by enhancing blood vessel formation around hair follicles. Zhang et al. (2019) demonstrated in a preclinical model that sildenafil increased VEGF expression, which, in turn, led to prolonged follicular anagen (growth) phases and an increase in hair follicle density (Zhang et al., 2019). These findings suggest that sildenafil could be beneficial in restoring blood supply to aging or miniaturized hair follicles, enhancing their survival and growth.[26]

3. Wnt/β-catenin Pathway Activation and Follicular Regeneration

Hair follicle cycling relies heavily on the Wnt/β-catenin pathway, which plays a pivotal role in signalling hair growth. Many hair loss conditions, particularly AGA, involve an interruption in this cycle, where follicles remain in the telogen (resting) phase longer, reducing hair growth. Sildenafil's influence on the Wnt/β-catenin pathway suggests potential benefits for hair growth by shifting follicles back to the anagen (growth) phase. Kim et al. (2021) demonstrated that sildenafil activates Wnt/β-catenin signalling in dermal papilla cells in vitro, resulting in enhanced cellular proliferation and faster transition of follicles to the anagen phase (Kim et al., 2021). This activation could provide a critical mechanism for hair regrowth by reactivating dormant follicles.[25]

4. Localized Treatment with Topical Sildenafil for Reduced Systemic Effects

The side effects associated with oral sildenafil have limited its consideration as a systemic hair growth treatment. However, the development of topical formulations addresses this limitation by offering a localized approach. Lee et al. (2020) observed that topical sildenafil applied to the scalp led to improved blood flow and hair density in patients with AGA

without notable systemic side effects (Lee et al., 2020). This finding implies that sildenafil's therapeutic action can be harnessed locally, potentially making it a safer option for long-term use in hair regrowth.[32]

5. Therapeutic Synergy in Combined Treatment Regimens

Sildenafil's distinct mechanisms suggest a synergistic potential when combined with agents like minoxidil, which stimulates hair follicles directly, and finasteride, which reduces androgen effects on follicles. By targeting multiple pathways involved in hair growth — increased blood flow, follicle support via VEGF upregulation, and the activation of growth pathways like Wnt/β-catenin — combined treatments could yield more robust responses than single-agent therapies. A review by Patel and Singh (2023) recommended further studies on such regimens, noting that sildenafil's impact on hair density and thickness was enhanced in combination with other hair-promoting agents in pilot trials.[33]

6. Application in Non-AGA Conditions Involving Follicular Health

Beyond AGA, sildenafil's mechanisms could have applications in other hair loss conditions associated with poor follicular vascularization or microinflammation. Conditions like traction alopecia or even scarring alopecia might benefit from sildenafil's VEGF-mediated angiogenesis and anti-inflammatory effects, as suggested by the broader therapeutic uses of PDE5 inhibitors. Garcia et al. (2022) hypothesized that sildenafil's vascular benefits could be advantageous in improving follicle resilience in various alopecia's, though controlled studies are required to explore these applications further.[31]

CONCLUSION

The growing body of evidence suggests that sildenafil, primarily known for its vasodilatory effects in treating erectile dysfunction, holds promise as a potential therapeutic agent for hair growth. The drug's ability to inhibit phosphodiesterase type 5 (PDE5) and increase cyclic guanosine monophosphate (cGMP) levels offers significant vascular benefits, potentially enhancing blood flow to the scalp and promoting follicle health. Additionally, sildenafil's ability to upregulate key growth factors like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) further supports its role in stimulating hair growth.

Preclinical studies have demonstrated that sildenafil can increase hair follicle density, prolong the anagen phase of the hair cycle, and promote dermal papilla cell proliferation, all crucial elements for hair regeneration. While human clinical data remain limited, pilot studies show

promising results, particularly when sildenafil is used in combination with other treatments like minoxidil. However, the full therapeutic potential of sildenafil for hair restoration, especially as a standalone treatment, requires further investigation.

Despite the preliminary positive findings, there remain several challenges, including optimizing the delivery mechanisms of sildenafil to the scalp and establishing the most effective dosing regimen. Further clinical trials are needed to validate its long-term safety and efficacy, as well as to confirm its role as a viable adjunct to existing treatments for hair loss, such as minoxidil and finasteride.

Future Directions and Research Needs

The current evidence supporting sildenafil's role in hair growth is promising, but several key areas require further exploration. First, large-scale randomized controlled trials (RCTs) are essential to establish sildenafil's efficacy in diverse populations and to assess its long-term safety. These trials should focus on both the standalone effects of sildenafil as well as its potential synergistic effects when combined with other therapies for hair restoration, such as minoxidil and finasteride.

Additionally, the exact molecular mechanisms through which sildenafil influences hair growth need to be elucidated further. Research should aim to clarify whether sildenafil's effects are mediated primarily through vasodilation, enhanced nitric oxide (NO) production, or the activation of growth factors such as VEGF and PDGF. Understanding these pathways in greater depth will help optimize its therapeutic use and inform future clinical strategies.

Exploring sildenafil's safety and efficacy in different forms of alopecia, particularly androgenetic alopecia (AGA), will be crucial in determining its broader applicability. Special attention should also be given to optimizing the formulation of sildenafil for topical use, as well as investigating potential interactions with other commonly used treatments for hair loss. Finally, the development of novel, sildenafil-based formulations may improve patient adherence and minimize systemic side effects, advancing the potential for sildenafil to become a standard treatment option in the field of hair restoration.

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