A study on the efficacy of 2% and 5% topical minoxidil solution on Adrenergic Alopecia

By

Tanjina Pioush Bhuiyan
18346030

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
April 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Tanjina Pioush Bhuiyan
18346030

Approval

The project titled “A study on the efficacy of 2% and 5% topical minoxidil solution on Adrenergic Alopecia” submitted by Tanjina Pioush Bhuiyan (18346030) of Summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on April, 2023.

Supervised by:

_____

Dr. Mesbah Talukder
Professor, School of Pharmacy
Brac University

Approved By:

Assistant Dean & Program Director

_____

Dr. Hasina Yasmin
Assistant Dean and Program Director
School of Pharmacy
Brac University

Dean

_____

Dr. Eva Rahman Kabir
Dean, School of Pharmacy
Brac University

Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

Minoxidil, mostly used as a vasodilator was first introduced as an oral drug used to treat high blood pressure. Then gradually minoxidil showed hair darkening of fine body hair as a side effect. This specific side effect led to the development of topical minoxidil. Topical minoxidil is mainly produced as a 2% solution to treat female adrenergic alopecia and a 5% solution for male adrenergic alopecia. But the changes disappeared after stopping its use for a month. Minoxidil is mainly potassium channel opener so it assumes that it causes hyperpolarization and again it's a vasodilator. The mechanism it mainly widening blood vessels and opening potassium channels so it allows more oxygen and nutrients to the hair which causes regrowth of hair. This article will show a complete review of the pharmacokinetics, pharmacodynamics, and mechanism of action, side effects, and clinical efficacy of topical minoxidil.

Keywords: Topical minoxidil; Adrenergic alopecia; Hyperpolarization; Vasodilator; Dihydrotestosterone; AR Gene.

Dedication

Dedicated to my faculty members, family, and friends

Acknowledgement

I would like to begin by expressing my gratitude towards Almighty Allah for providing me with the strength during this whole period; I am indebted and would like to express my sincere gratefulness and gratitude towards Dr. Mesbah Talukder, Professor, School of Pharmacy, BRAC University for being a constant guiding spirit throughout my study and for being so supportive, kind and motivating throughout the journey.

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List of Acronyms

TM	Topical Minoxidil
FPHL	Female pattern hair loss
AGA	Androgenetic Alopecia
MPHL	Male pattern hair loss
ATP	Adenosine triphosphate
DHT	Dihydrotestosterone
AR	Androgen Receptor
FDA	Food and Drug administration
AAP	American Academy of Pediatrics

Glossary

Male pattern hair loss	“M” shape pattern hair loss caused by hormone, aging
Female pattern hair loss	Crown shape pattern hair loss cause by hormone and genetics.
Topical Minoxidil	Stimulate hair growth in baldness
Dihydrotestosterone	A hormone made from testosterone
AR Gene	It provide instruction for androgen receptor protein
5a-reductase	Converts testosterone to dihydrotestosterone

Chapter 1

Introduction

Hair is one of the most attractive and effective parts of the body for human appearance. Hair is mainly a subordinate of the epidermis. It consists of two main parts: one is follicle and another one is the hair shaft. The main purpose of the follicle is to maintain the formation of hair. On the other hand, the hair shaft mainly made of a cortex and cuticle cells, and sometimes a medulla for some specific types of hairs (Sinclair et al., 2007).

Hair loss or baldness at an early age may affect self-esteem. Nowadays baldness or losing hair in men and women is very common. Most common type of alopecia is adrenergic alopecia (AGA). This type of alopecia is very common in case of both men and women. But it is mainly known as male-pattern baldness. Again, it is specified by an "M" shape. The pattern of losing is different in men and women. In men, hair thins near the crown and leads to partial or complete baldness. On the other hand, in the case of women, the hair all over the head becomes thinner. In the case of women, it rarely leads to total baldness.

The age factor of adrenergic alopecia has been listed in numerous study populations. A study was conducted in Australia between 1390 men ages 40 and 69 to determine the reason and risk factors for male adrenergic alopecia. The risk of full baldness increases with age from 40-55 and almost 31% had shown the result. Again, among 1390 men almost 53% who are between 65-69 years also showed the risk of full baldness. Among 25% of men between the ages of 40-55 and 31% of men between the ages of 65-69 receding frontal hairline. On the other hand, a survey conducted in the USA reported a reason for moderate or severe male adrenergic alopecia of 53% in the age group between 40-4 years. The number of incidences and risk of male

adrenergic alopecia with growing age had also been reported in the Korean population survey. According to a Singapore survey, the prevalence of Male adrenergic alopecia in that country males was reported 63% with aging, almost 32% at the age of 17-26 years, finally 100% after 80 years (Cranwell, W et al., 2015).

Genetic and environmental factors play a role in causing adrenergic alopecia. Mostly, genetic factors are established by the research as almost 80% of patients have a previous history like their father or grandfather has this alopecia. Although risk factors may contribute to this condition, most of these remain unknown. A study was conducted on the fifty-four father-son relationships and found that almost 81.5% of balding sons had fathers who had significant balding (Cranwell, W et al., 2015).

A hormone called androgens is responsible for adrenergic alopecia in both males and females. Dihydrotestosterone (DHT) particularly an androgen is mainly responsible for this specific alopecia. Dihydrotestosterone (DHT). Androgens are important hormones for both, males and females. In the case of men, it is important for male sexual development before birth and during puberty. On the other hand, in both males and females, it has some other functions too like hair growth and sex drive. In women, the amount of androgen is less than in men so that is the reason the case of adrenergic alopecia is high in men. When hair growth begins under the skin and takes a shape then it is called follicles. The growing period for a single strand of hair is normally 2 to 6 years and then it goes on a resting period for several months and then finally falls out. The cycle starts over again when a new follicle begins growing new hair. If the amount of androgen is in Increased levels in hair follicles its cycle decreases and hair becomes shorter and thinner. Additionally, the growth of shedding hair can be delayed or replaced.

Again, according to some researchers, several genes like AR play a role in adrenergic alopecia. Androgen receptor which is a protein made by this AR gene. Androgen receptors is a protein

receptor that allows the body to respond appropriately to dihydrotestosterone and other androgens. According to some studies, AR gene variation increased the activity of androgen receptors in hair follicles.

Some researchers believe that and continue to search for the relation between androgenetic alopecia and various medical conditions for example coronary heart disease and prostate cancer in men and in the case of women polycystic ovary syndrome. According to some researchers, some of these medical conditions may be incorporated with increased androgen levels that lead to androgen-related hair loss (Suchonwanit et al., 2019).

For this androgen-related hair loss researcher believes in minoxidil for treatment. Especially, to control this condition topical minoxidil is widely used in the form of solution and ointment (Suchonwanit et al., 2019). It is widely used in both male and female baldness and is found highly effective. But in the case of men, the efficacy of this drug is high.

A group of dermatologists conducted an observational study to confirm the effectiveness of minoxidil. They studied 984 men for 1 year who had male pattern hair loss. The target of the research was to confirm the effectiveness of 5% topical minoxidil against balding and generate new hair and fight against side effects. In this 1year time period, patients applied 1ml of 5% topical minoxidil solution twice a day to their area of hair loss on the scalp. During the study time period, lost hair were collected by patients their lost hair in hair washing and sent them to the laboratory after every 3 months.

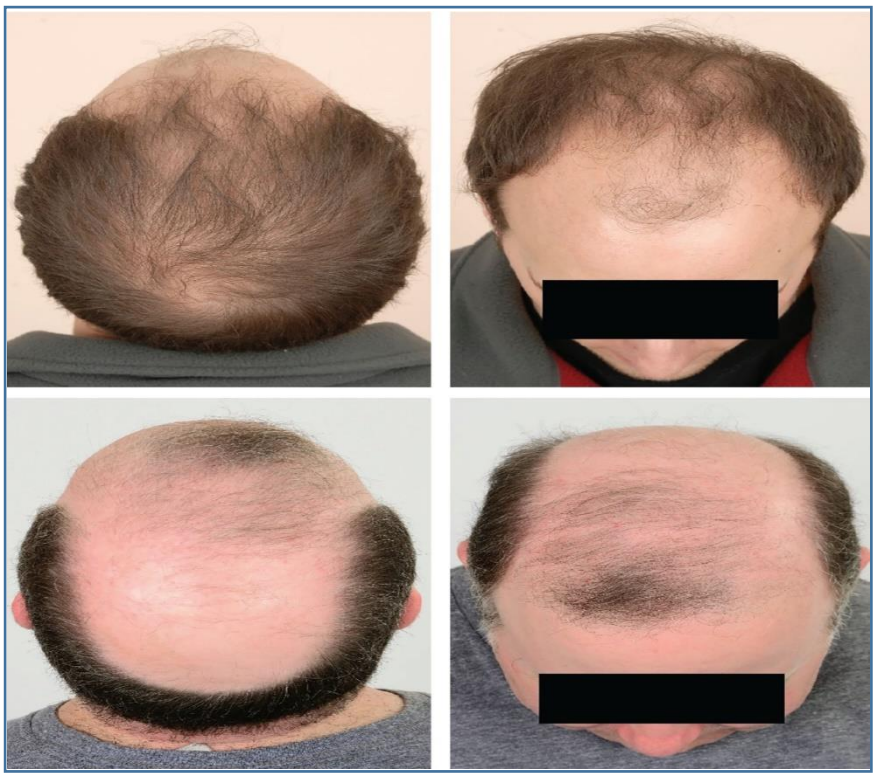

Figure 1 A patient with M shape male pattern baldness (Suchonwanit et al., 2019)

After 1 year of studies:

The dermatologist reported among 62% of patient's hair loss areas become smaller but it was not changed in 35.1% and larger in 2.9% of patients. In minoxidil effectiveness evolution it was found that it stimulated new hair growth, the researcher found that 5% topical minoxidil solution worked very effectively in the case of 15.9% of patients, it was effective for 47.8%, and moderately effective for 20.6% but unfortunately, it not effective in 15.7% of patients. The number of hair loss during washing had a mean of 69.7 at the beginning of the study, in the middle of the study the ratio became 33.8% at the end of the study-a measure of the effectiveness of 5% topical minoxidil in stopping hair loss in the patients who are participated in the study. The mean score of patient satisfaction marked on a scale of 10 increased from 2.9

to 4.4 at the end of the study. The score of patient satisfaction were lower than the estimated expectation of the investigators: the investigators rated the efficacy of treatment as good or very good which is 25% more often than the patients. Mostly dermatologic side effects, were reported by 3.9% of patients in the whole study. But none of the side effects was classified as alarming (Ishrs et al., 2012)

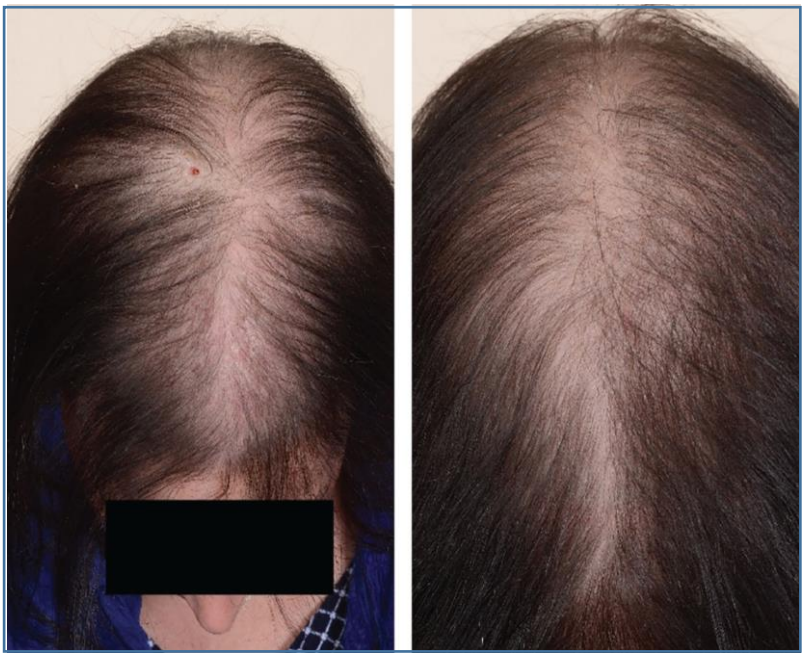

Figure 2 A patient with female pattern hair loss (FPHL) (McCoy et al., 2016).

Topical minoxidil solution is the only type of medication that is approved by the US FDA to treat female pattern hair loss. About 40% of women re-growing of hair is effectively shown by 5% topical minoxidil. For this reason, more than cases of FPHL cases remain untreated. In the past, researchers claim that patients who did not non-response to 5% minoxidil have low metabolism of minoxidil in hair follicles. It was examined by the researcher that if the dose was increased to low metabolizers would increase the number of responders with less increasing incidence of adverse reaction, according to medical study, the researcher claims that female pattern hair loss (FPHL) subjects that were identified as non-responders to 5%

topical minoxidil. The female alopecic patients were treated for 12 weeks with 15% topical minoxidil solution. At the end of 12 weeks, 60% of female patients achieved a clinically significant response. Which was counted based on target area hair counts that greater than 13.7% from baseline as well as noticeable improvement in global photographic study. None of the female patients go through significant hemodynamic changes or any other adverse effects. For better learning, this is the first study which explain the potentially beneficial effect of a higher dosage topical minoxidil in female pattern hair loss (FPHL) patients who failed to respond to the treatment of 5% minoxidil solution. (McCoy et al., 2016).

In the case of both male and female pattern hair loss 5% topical minoxid show various kinds of side effects. The most alarming side effects are burning sensation, redness and stinging in the application site. This medicine is absorbed by the skin and causes side effects as it can get incorporated with blood. If a patients suffer from unwanted facial hair, body hair, irregular heartbeat, weight gain, fainting, chest pain, tiredness, difficulty breathing then the patient should immediately stop using the drug and a consult the doctor

Chapter 2

Methodology

This study was conducted by reviewing PubMed, Elsevier, ResearchGate, Nature (1990-2020) for relevant articles. For searching the relevant article or information used keywords like alopecia, adrenergic alopecia, doses, side effects, case history of patient. This paper discusses the doses and impacts of topical minoxidil and its side effects. It also contains how useful the drug is in the serious condition and success of this drug. The information from these articles were retrieved manually. The sources of the information of this paper were cited using the software: Mendeley.

Chapter 3

Background

Minoxidil was first used to treat severe and refractory hypertension as an oral medication in the 1970s. (Suchonwanit et al.,2019) Coincidentally, physicians observed hair growth and then considered hypertrichosis in balding patients, which mainly the first led to the development of topical minoxidil solution for treatment of androgenetic alopecia (AGA), first it use in males and then in females. The 2% topical minoxidil solution was first introduced commercially to the market in 1986 then 1993 5% solution in 1993 was introduced (Suchonwanit et al., 2019).

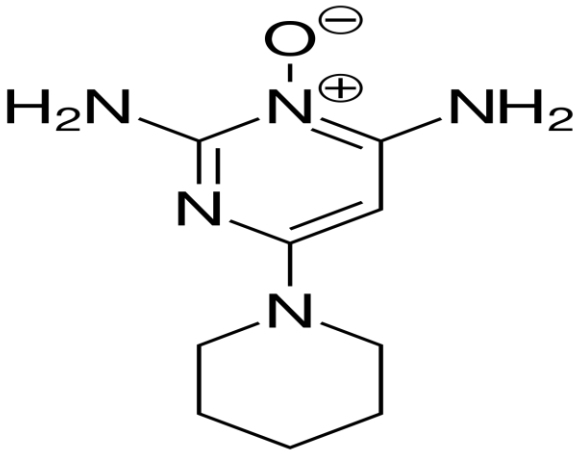

Figure 3. A Chemical Structure of Minoxidil (Suchonwanit et al., 2019).

Because of its global acceptance for almost more than 30 years, the mechanism of minoxidil in hair regrowth effects remains unknown. It has been aimed to review and update critical clinical information on topical minoxidil, such as pharmacology, mechanism of action, clinical efficacy, and adverse effects (Suchonwanit et al., 2019).

Chapter 4

Pharmacodynamics

4.1Mechanisms of action

The mechanism of action of topical minoxidil stimulates hair regrowth, whether orally or topically, remains unknown. A number of different type of possible mechanisms have been proposed, and these are discussed further below. Importantly, minoxidil promotes regrowth in such disparate 'diseases' as alopecia areata and alopecia androgenetic, implying that it acts on the hair follicles per se or that it may be indicative of a more widespread mechanism as it has a direct effect on cellular function. There are not any evidence of a systemic androgen effect following the use of topical minoxidil (Weiss et al. 1984). Clearly, more research is needed to determine the mechanism of minoxidil by which it stimulates hair growth (Clissold & Heel et al., 1987).

A drug may cause an increase in the upright regrowth of hair, an increasing diameter of the hair follicle, an alteration in the hair growth cycle by either shortening the telogen phase or increasing the anagen phase, or this drug may act through a combination of these effects in order to achieve its desired result of stimulating hair growth. Minoxidil may improve hair diameter in addition to acting primarily on the hair cycle, according to the research that is currently available.

Minoxidil is a topical hair regrowth stimulant. Its mechanism of action is not well understood but is found that scalp sulfotransferase converts minoxidil into its active form of minoxidil, minoxidil sulfate. Individual differences in sulfotransferase activity may explain the variance in minoxidil's effectiveness (Badri T, Nessel TA, Kumar D D et al., 2023).

Minoxidil works by shortening the length of the telogen phase, which stimulates dormant hair follicles to transfer into the anagen phase earlier than normal. During the beginning of minoxidil treatment, telogen effluvium may be brought on by a reduction in the length of the telogen phase. In addition to this, minoxidil lengthens the time spent in the anagen phase. Last but not least, the clinical effects of minoxidil include increased hair length as well as diameter (Badri T, Nessel TA, Kumar D D et al., 2023).

After around eight weeks of therapy with minoxidil, the drug will begin to show some effects, while the drug's full effects won't be seen for another four months. Minoxidil seems to have an vast effect on the vascular smooth muscles potassium channels as well as hair follicles, which may result some side effects (Badri T, Nessel TA, Kumar D D et al., 2023).

The microcirculation activation close to the hair follicles by generating arteriolar vasodilation results in an increase in hair growth.

- the activation of vascular endothelial growth factor (VEGF) expression leads to an increase in the vascularization that covered the hair follicles, which in turn contributes to the growth of hair.

- Prostaglandin-endoperoxide synthase, the enzyme responsible for stimulating hair growth, has its activity increased.

- Suppression of the effects of androgen on the androgen-sensitive hair follicles

- Direct stimulation of the hair follicles: Topical minoxidil solution contain an epidermal growth factor on matrix cells that delay hair follicles aging and extend the anagen phase by activating the beta-catenin pathway.

- Minoxidil has been shown to have anti-fibrotic qualities as a result of its influence on collagen synthesis.

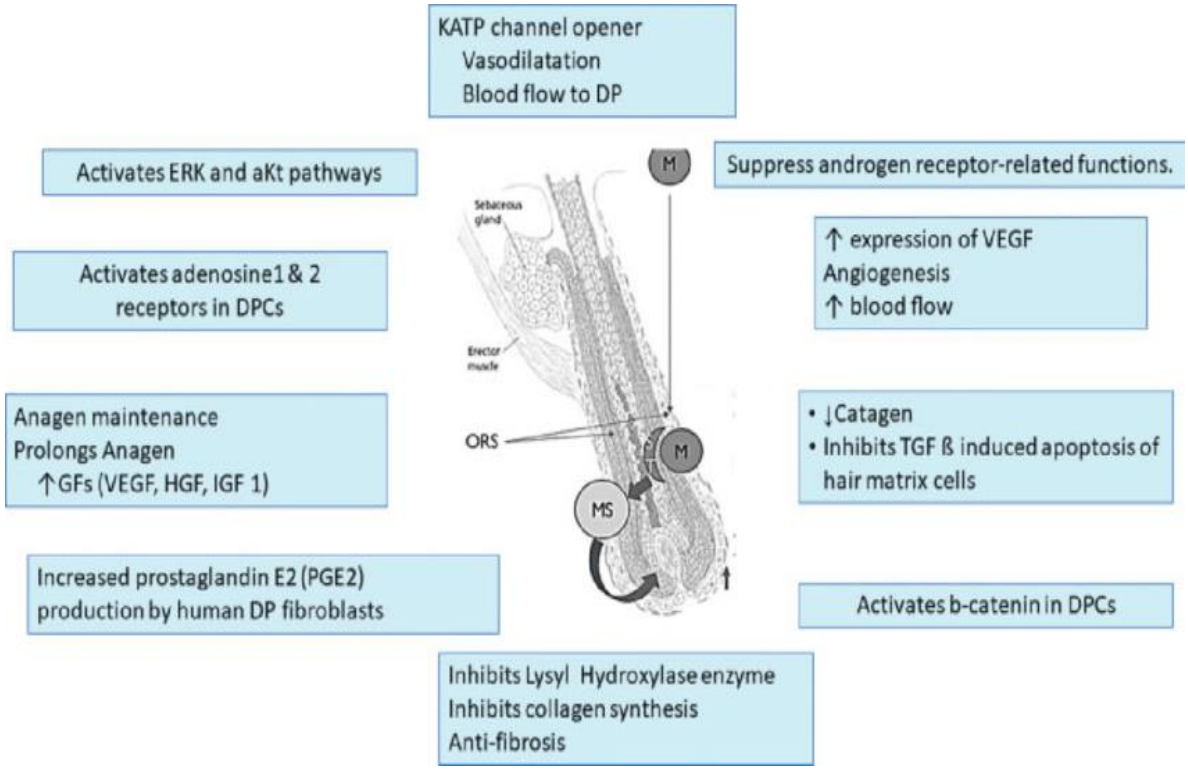

Figure 4. Mechanism of action topical minoxidil (Sattur & Sattur et al., 2021)

4.2 Effects on Epidermal Cells

Several studies have been done to see if minoxidil has any effect on the growth and shape of epidermal cells grown in a lab. Cohen and his colleagues showed in 1984 that minute effects on blood flow to the skin Since other vasodilators like diazoxide have been shown to sometimes cause hypertrichosis (Burton et al. 1975), it has been suggested that localized hair growth may be linked to vasodilation in the cutaneous circulation of the scalp and direct stimulation of the microcirculation around the hair follicle. To test this theory, Wester et al. (1984) used noninvasive methods (laser/Doppler velocimetry and photo pulse plethysmography) to measure blood flow to the scalp during a double-blind, placebo-controlled comparison of different strengths (1, 3, and 5%) of topical minoxidil lotion in 16 balding people. When compared to vehicles alone, all three strengths of minoxidil lotion increased blood flow to the

skin. These results, which are at best only semi-quantitative, showed a dose-response relationship. The 5% lotion changed blood flow the most. On day 2, after a second application, it increased blood flow by three times, and this effect lasted for about an hour. After the first hour, there was no big difference between the blood flow of the different treatments and the placebo (Clissold & Heel et al., 1987).

4.3 Local Irritation

There is some evidence that scalp irritation by chemicals or ultraviolet light stimulates hair growth (for a review see Mitchell & Krull 1984). Hence, it has been postulated that propylene glycol in the vehicle of topical minoxidil lotion may be necessary for stimulating hair growth with this formulation (Castillo et al. 1985). These authors found that propylene glycol does produce contact sensitisation in alopecia androgenetica patients and that minoxidil appears to exacerbate this reaction. According to the fact that minoxidil causes hypertrichosis when delivered orally in the absence of propylene glycol, it seems highly improbable that sensitization is the primary mechanism of action of minoxidil (Clissold & Heel et al., 1987).

4.4 Effects on Immune Function

As noted by Mitchell and Krull (1984) there is accumulating evidence, albeit for the most part circumstantial, that alopecia areata has an autoimmune aetiology. Again, prolong support for this comes from a preliminary study reported by Galbraith et al. (1984) in which inosine pranobex (inosip1ex, methisoprino1), an immunostimulant, was successfully used to treat a small number of patients with alopecia. Minoxidil has been shown to have an immunosuppressive effect on Balb/c murine T (but not B) lymphocytes (Cohen et al., 1982). There is also some preliminary evidence that the application of topical minoxidil 3% lotion may cause changes in lymphocyte function in patients with alopecia areata (Hordinsky et al.

1985). Furthermore, histopathological studies showed a positive correlation between minoxidil treatment and subsequent disappearance of perifollicular lymphocytic infiltration at sites of alopecia areata (Weiss et al. 1984). For patients treated with topical minoxidil 5%, enhanced T lymphocyte blastogenesis pretreatment seemed to be a predictor for hair growth (FiedlerWeiss & Buys 1986). The relationship of these changes to the mechanism of action of minoxidil remains unclear at present (Clissold & Heel et al., 1987).

4.5 Effect on Epithelial Cells:

In newborn mouse epithelial cells, minoxidil produces direct effects that can be described as both mitogenic and morphological. Culture of cells showed a substantial dose-dependent second peak of DNA synthesis 8 to 10 days after when the culture was first started when minoxidil was present. This peak was proportional to the amount of minoxidil present. Minoxidil was shown to increase the amount of time human epidermal cells could survive in culture, as discovered by Baden and Kubilus (1983). The findings of this experiment were consistent with there being a delay in the onset of senescence in the epidermal matrix cells, which would result in an increase in the amount of time that the cells had to cycle. Although the aging of cells in culture and the transition of anagen to telogen hairs are two separate processes, it is probable that the same signal is what kick-starts both of them. This is discussed more in the article Topical Minoxidil: A Preliminary Review. Minoxidil has the capacity to either impede response to such a signal or suppress the signal itself (Baden & Kubilus et al., 1983).

As the work has been divided into a total of 3 segments. First of all, the first 6 data set was selected and the algorithm has implemented over them. Then the data were visually analyzed and figure out the distribution of values was. The following metrics were used to determine the

performance of the model and then the time taken to build the model, Kappa statistics, mean absolute Error, Root Mean Squared Error, Relative Absolute Error, and Prediction accuracy.

Chapter 5

Pharmacokinetics

5.1 Absorption

The gastrointestinal tract has a high capacity for the oral absorption of minoxidil (GIT). During an hour after oral administration of minoxidil, plasma concentrations of the medication reach their highest point. On the other hand, absorption rate of 2% topical minoxidil solution in a normal intact scalp is 1.4%, whereas the absorption rate of 3% topical minoxidil solution in the normal intact scalp is 1.2%. When using a topical treatment, the concentration of serum is often lower than 5 ng/mL but it may even be not findable in some cases. Just seven out of 12 Androgenetic alopecia (AGA) patients in a research using a minoxidil solution at a concentration of 3% were able to have their minoxidil levels in their serum detected, and then the concentration of the solution ranged from 0.4 to 7.5 ng/mL. According to Franz's hypothesis that two applications of topical minoxidil at a 5% concentration across the entire scalp could be comparable to a 5.4 mg oral dose (Gupta et al., 2022).

Minoxidil, on the other hand in topical treatment, is poorly absorbed, with not more than 3% of a radiolabeled dosage recovered from the urine. There does not appear to be any significant metabolism of minoxidil in the skin. After receiving a topical dose of minoxidil, the medication's disposition follows a zero-order process that is reportedly rate regulated by cellular drug absorption. It was found that the skin serves as storage for minoxidil; however, it is unknown whether the rate-limiting step in the minoxidil elimination from the body occurs due to the minoxidil penetration either drug vehicles into the skin or diffusion through the skin or sometimes a combination of the two processes. By systematically removing the topical minoxidil from the applied dosing area at specified times throughout the dosing interval. The

purpose of this study is to evaluate the percutaneous absorption of topical minoxidil from drug vehicles into skin. This evaluation was meant to determine whether or not minoxidil is absorbed into skin from drug vehicles. It would be possible to analyze the absorption of topical minoxidil from the vehicle separately from the drug's diffusion through the skin in this way. In order to evaluate the formulation elements for an improved medicine, it would be helpful to differentiate between these procedures (Ferry et al., 1990)

5.2 Distribution and metabolism

Minoxidil must be metabolized properly since the sulfated metabolite of minoxidil is responsible for the drug's pharmacological activity. The bulk of minoxidil that has been taken orally is metabolized in the liver through the processes of glucuronidation, hydroxylation, and sulfation. The medication has a weak affinity for the plasma protein and is incapable of penetrating the blood-brain barrier. In the treatment with topical minoxidil, follicular sulfotransferase is an essential component (Gupta et al., 2022).

5.3 Excretion

Oral minoxidil has an elimination half-life of three to four hours, and the kidneys primarily remove it from the body within twelve to twenty hours in the urine. After discontinuing topical treatment, approximately 95% of the minoxidil that was absorbed into the system is removed within four days (Gupta et al., 2022)

Chapter 6:

Contradiction

Those who have a previous history of an adverse reaction to minoxidil should not use the medication. The use of topical minoxidil solution in animals has been linked to the development of heart abnormalities. Some lesions are typical of other medicines that have the potential to produce rapid heartbeats and/or low blood pressure (e.g., isoproterenol, hydralazine). Those who already have reduced renal function, as well as patients who have uremic syndrome, connective tissue disease, congestive heart failure, or minoxidil-induced fluid retention, are more likely to experience these side effects (Rossi et al., 2012).

A specialized treatment environment is required for patients who are suffering from cardiac disease, cardiac tamponade, cerebrovascular illness, coronary artery disease, angina orthostatic hypotension, acute myocardial infarction pericardial effusion, and peripheral edema (Rossi et al., 2012).

Minoxidil, when taken systemically, is a powerful vasodilator that has the potential to cause hypotension as well as reflex tachycardia. This drug may cause serious problems. Those who have a cardiac disease such as coronary artery disease, angina or recent or acute myocardial infarction, or cerebrovascular disease should not use minoxidil since it causes a reflex increase in heart rate and falls in blood pressure, which can make the condition of a patient worse. Because of the potential for reflex tachycardia and an increase in the severity of angina, minoxidil should be avoided as much as possible in patients who suffer from coronary insufficiency, which includes angina. It is possible for minoxidil to cause pericardial effusion, which could potentially lead to cardiac tamponade in rare cases. Patients with hypertension do not respond effectively to maximum therapeutic doses of a loop diuretic, in conjunction with

two other antihypertensive medicines, should be given oral minoxidil as a last resort treatment for hypertension. Topical minoxidil solution has been proven to generate multiple various types of myocardial lesions in animals use in experiments, in addition to other harmful cardiac consequences. This was discovered through the use of animal testing. In order to prevent reflex tachycardia and increased myocardial strain, topical minoxidil must be given under close monitoring, and it is typically combined with therapeutic doses of a beta-blocker. This is the only way the medication can be given. Minoxidil is frequently administered in conjunction with a diuretic and that one works preferably within the ascending limb of the loop of Henle to avoid the buildup of fluid and the development of peripheral edema. First administering minoxidil to a patients with malignant hypertension, in that case the use of minoxidil requires a specialized care in case of setting the hospitalization to avoid rapid or large orthostatic reductions in blood pressure. This is to protect the patient from potentially life-threatening low blood pressure. Although while minoxidil does not directly cause orthostatic hypotension, the administration of the medication to patients who are also on guanethidine can result in significant orthostatic effects. It is recommended that guanethidine be stopped taking well before minoxidil treatment is started whenever it is possible. If this is not the case, minoxidil treatment should be initiated within hospital, and the patient should stay in hospital until the danger of vast orthostatic effects is reduced to an acceptable level and the patient become able to stay away from activities that cause orthostatic hypotension. Insufficiency of the heart and lungs, high blood pressure in the lungs, kidney disease, kidney failure, and kidney impairment (Rossi et al., 2012).

Minoxidil is considered to be contraindicated in patients who have reexisting pulmonary hypertension, renal disease, chronic congestive heart failure that is not secondary to hypertension. This is due to the fact that minoxidil can cause an increase in pulmonary artery pressure and that become detrimental to the patients. The use of topical minoxidil has been

linked to the development of adverse effect in some patients so that it is possible that people with renal impairment are at an increased risk for developing these conditions. Minoxidil is safe to use even in patients with renal impairment because the kidneys are responsible for the elimination of approximately only 10% of the active medication in its unaltered form. Nonetheless, there is that renal elimination will be decreased, and a dosage adjustment might be required. Minoxidil should not be used in patients whose creatinine clearance is less than 10 milliliters per minute (CrCl) (Rossi et al., 2012).

6.1 Breast-feeding

The manufacturer recommends that minoxidil not be given to women who are nursing their young children. According to the American Academy of Pediatrics (AAP) minoxidil is considered to be compatible with breastfeeding; but, other researchers are less comfortable of using this potent antihypertensive agent in nursing mothers. The drug minoxidil was found to be promptly eliminated into the mother's breast milk from one case study of a breastfeeding mother report who took minoxidil 5 mg of orally twice a day. Following a period of two months, the physicians found no reports of any adverse effects in the nursing infant. It is uncertain what the effects of extended exposure are while a woman is breastfeeding. Enalapril, hydrochlorothiazide, methyldopa, and propranolol are some examples of other antihypertensive that have more recorded data in this population are classified as usually compatible with breast-feeding by the American Academy of Pediatrics (AAP). These antihypertensive may be used as a possible alternative for some patients. The American Academy of Pediatrics (AAP) also classified these types of antihypertensive as usually compatible with breastfeeding. It is currently unknown whether or not topically applied minoxidil makes its way into breast milk. Think about the benefits of breastfeeding, the potential dangers of exposing the infant to drugs, and the possibility of the ailment going

untreated or just being treated improperly. Healthcare practitioners are strongly encouraged to notify the Food and Drug Administration (FDA) of any harmful effects that may occur in a breast-feeding newborn as a result of a mother's use of a medicine in their own treatment of the infant. (Rossi et al., 2012).

6.2 Skin abrasion

It is quite improbable that topically applied minoxidil would cause systemic effects, but this does not mean that they cannot happen if the medication is used in excess. Abrasions or irritations of the skin, such as those caused by psoriasis, sunburn, might increase the amount of minoxidil that is absorbed into the body when it is topically applied (Rossi et al., 2012).

6.3 Geriatric

There have been no variations in the reported clinical experience between the reactions of patients who are younger adults and those who are older adults. The selection of a systemic dose for a geriatric should be done with caution, and should typically begin with low dose. The reason behind this are elderly patients are more likely to have lower hepatic, cardiac and renal function, as well as concurrent diseases or other drug therapies. It is not necessary for senior patients to take any additional safety precautions when using topical minoxidil; nevertheless, patients who experience lightheadedness or fainting should stop using topical minoxidil. The Omnibus Budget Reconciliation Act (OBRA) is a federal law that governs how residents of long-term care homes are allowed to utilize their medications (LTCFs). Antihypertensive regimens should be customized, as recommended by the OBRA, in order to obtain the desired outcome while simultaneously reducing unwanted effects. Some side effects like postural hypotension, dizziness weariness, and risk of falling are all potential side effects of antihypertensive medication use. There is a lot of different drugs that interact and that can make

the effects of antihypertensives even stronger. Specific medications must be weaned off gradually in order to prevent the unpleasant side effects that can be brought on by suddenly stopping treatment (Rossi et al., 2012).

Chapter7

Side Effects

The topical minoxidil solution is presently accessible without a prescription and has a good safety profile. The losing of hair due to using minoxidil is a typical adverse effect. It is thought that this "shedding" occurs because hairs in the telogen phase are stimulated to shed early, after which they typically enter a new, healthier anagen phase. Consistent use over time is necessary for optimal results. Some individuals, as is the case with prolonged exposure to any drug, may develop contact dermatitis to a particular chemical in the formulation. Although topical minoxidil solution has a positive safety profile, pruritus and scaling of the scalp are the most often reported adverse effects. These symptoms may be the result of an aggravation of seborrheic dermatitis or another skin condition. Fortunately, topical minoxidil solution mostly causes dermatological side effects that are localized to the scalp. Minoxidil used topically does not cause hypotension. Although the medicine is neither teratogenic nor mutagenic, it should nonetheless be used with caution during pregnancy and breastfeeding. In the literature, congenital anomalies appear seldom. The medicine can be stopped throughout pregnancy and breastfeeding because AGA is a benign condition. In order for the patient to continue taking topical minoxidil for the treatment of their alopecia, it is important to distinguish between these situations so that the right course of action may be taken. An allergic reaction to minoxidil on the skin is possible. Because this adverse effect only manifests itself superficially as modest erythema, light scaling, and scalp itch clinical investigations tend to downplay its significance. 5.7% of patients utilizing the 5% formulation and 1.9% of patients using the 2% formulation experienced application site responses during clinical trials. With greater propylene glycol (50%) in the 5% minoxidil formulation than in the 2% minoxidil formulation (30%), more occurrences of itching, erythema, and dryness were reported. Patients who used a vehicle

containing 50% propylene glycol reported an incidence of adverse events comparable to those who used a formulation containing 5% minoxidil, indicating that the difference is not attributable to the minoxidil content. Epicutaneous tests (Sid APA patch testing and patch by patch with excipients and/or minoxidil) demonstrate that these symptoms, sometimes referred to as irritation symptoms, are indeed allergic reactions. Some sources blame propylene glycol for sensitization, while others point to minoxidil as the active principle or butylene glycol. Propylene glycol can be substituted by butylene glycol, glycerin, or polysorbate in allergic patients. In addition to topical corticosteroids, a number of symptomatic therapies may temporarily alleviate pruritus. However, the only surefire way to cure allergic contact dermatitis is to eliminate the patient's exposure to the allergens that are triggering the reaction. Unfortunately, individuals who test positive for a minoxidil allergy cannot benefit from topical minoxidil treatments for their alopecia. The patient may be able to continue treatment with a different topical minoxidil solution if the particular contact is identified. Topical minoxidil usage has been linked to hypertrichosis outside of the scalp. A 5% solution is more likely to have this impact than a 2% one. The pollution causes it to spread to the temples, forehead, and cheeks. Patients need to be educated on this matter. Affected regions further from the face occur less frequently. Systemic adoption is likely, however it has not been shown. Tosti found that after using topical minoxidil 5%, 9% of women and 1% of males experienced extensive hypertrichosis throughout the face, upper and lower arts. After stopping treatment, this adverse effect goes away. The reason is unknown but is more prevalent in females. The use of medications might cause those with fair or white hair to take on a yellow or green hue. The lotion's base determines the extent of these results. The cardiovascular system is safe to use minoxidil. Only one occurrence of a heart attack following the use of minoxidil 1% has been reported in the scientific literature. The authors claim that higher permeability of young people is responsible for enhanced systemic absorption of medicines. (Rossi et al., 2012).

Chapter 8

Discussion

It is not known how minoxidil works to stimulate hair growth; the mechanism behind this process is not known. It is regarded to be hypertrichosis without virilism because endocrine problems have not been found to explain the aberrant growth that has been observed. Minoxidil, which is a vasodilator, has been hypothesized by Burton and Marshall 2 to work by facilitating an increase in the volume of blood flows to the follicles of hair. In 1979, two researcher Ebling and Rook 7 found that chronic cutaneous hyperernia could lead to excessive hair growth in some individuals. It is possible that the clinical response of the body in androgenic alopecia is connected with the topical absorption of minoxidil, the reflection can be seen in the blood level. Those individuals who were being treated for androgenic alopecia (AGA) with 1% topical minoxidil solution had unmeasurable levels of minoxidil in their bloodstream and did not observed any regrowth. Three patients that saw hair regrowth used the 5% topical minoxidil solution, and their blood levels were measured two hours after the topical application to be 0.5, 2.1, and 4.5 ng/ml respectively. A minoxidil blood level that is 4 ng/ml is roughly when 6% of the mean minoxidil blood level that is present 2 hours after the oral administration of a 5 nag pill. (Five milligrams per day is the minimum dosage that should be taken for the treatment of hypertension.) Those with androgenic alopecia (AGA) had the highest minoxidil blood levels and gave the best clinical responses to treatment. Because the medicine was gradually applied to the scalp, the absorbed minoxidil levels that were measured in the blood must have been the result of topical absorption. This may be an essential factor in evaluating how well the treatment works for androgenic alopecia. In patients with alopecia areata, the clinical response was unclear, and the correlation between the topical minoxidil blood levels was also unclear. From a survey of four patients' blood levels were lower than 2

rig/m1; 2 of these patients did not show any reaction, while the other two patients displayed values like growth. 1 patient blood level of minoxidil was higher than 4 ng/ml, although that patient had a modest response to the clinical study, with only barely noticeable callus-like growth. The outcomes in the study were unable to be compared to those obtained by Weiss et al. and by Fenton and Wilkinson, 9 who reported positive results with 1% topical minoxidil in alopecia areata. The manner in which minoxidil was applied in Weiss and colleagues' research is one of the key distinguishing characteristics of t own investigation in comparison to that one. They applied it to the scalp using a glass rod, but in the research, filtered applicator tip was provided by the producer of the minoxidil. Minoxidil blood level were not recorded by the other researcher; as a result, there is no evidence with regard to changes in drug delivery between the research and the studies that were cited. Regarding the phase of the trial known as the double-blind phase, during which patients were only allowed to use the 1%, 5%, or vehicle solutions, roughly forty percent of the patients who had alopecia areata and were participating in the study did experience hair growth. The regrowth appeared as terminal hairs isolated patches and followed by the typical pattern of hair regrowth seen in the patients. At the beginning of the research project, the hypothesis was that hair regrowth might be attributable to topical minoxidil, and the initial response to this hypothesis was encouraging. On the other hand, it was discovered that the patient who had the best hair growth at 6 months, the only one who had been utilizing the vehicle. The other patients who experienced regrowth of patchy patches did not maintain this growth and, after a period of 12 months, their appearance was virtually identical to how it was before therapy. Minoxidil did not produce any discernible or long-lasting growth response in any of the patients who suffered from alopecia areata. This is essential for researchers to examine apparent hair growth in alopecia areata with caution in order to avoid misleading spontaneous patchy regrowth. For the whole course of the study, which lasted for a whole year, there was no discernible change in blood pressure. This outcome

was not surprising given that the oral administration of minoxidil did not result in a reduction in blood pressure in patients who have normotension. All of the patients were able to successfully complete the topical treatment without any complications. There is reason to assume that using topical minoxidil might be effective in androgenetic alopecia treatment. The effectiveness of this medication might be enhanced by raising its rate of local absorption, which could be accomplished, among other things, through the employment of various alternative vehicles. If future studies will conducted with bigger patient populations that will provide more remarks about the topical minoxidil effectiveness in patients with androgenetic alopecia. The study will have better clarity of the significance of bloodstream minoxidil level with the therapy of topical minoxidil(Vanderveen et al., 1984).

Chapter 9

Conclusions

At the beginning of the 1980s, topical minoxidil discovered as a treatment for androgenetic alopecia ushered in a new age in hair research. This discovery guide to the awareness that losing hair may be curable, which then bring a new era in hair research. The results of a series of research conducted by Buhl and others on cultured vibrissae follicles as well as on the stump tailed macaque lend credence to the theory that response of hair follicles to minoxidil is somehow mediated by its sulfated metabolite, which acts as a potassium channel opener. Despite this, there are contradictions in the data that have not yet been resolved, thus it is necessary to approach this theory as one that has not yet been confirmed. Cultured cells have been shown to exhibit a wide range of reactions when exposed to minoxidil. Some of these effects, such as vascular endothelial growth factor (VEGF) stimulation and synthesis of prostaglandin and the impact on cell proliferation and senescence, may have some bearing on the process of hair development. Others of the impacts, like how it affects the body's ability to produce collagen, are more challenging to describe. When taken in isolation, the findings of investigations conducted using cell cultures require a cautious approach to their interpretation. To begin, it is unknown how the complexity of hair growth is related to the behavior of a single cell type when that cell type is cultivated in a petri dish. Then, minoxidil concentrations that were employed to treat the hair follicles were frequently higher than those that the exposing of hair follicles expected in vivo. The levels of the blood of individuals who take oral minoxidil are in the high nanomolar to the low micromolar range is 20 to 2000 ng mL, whereas the blood levels of individuals who apply minoxidil topically are even lower (2 ng mL). Finally, the population of target cells in the hair follicle that minoxidil is intended to affect is uncertain. In spite of this, the vascular endothelial growth factor (VEGF) stimulation and synthesis of

prostaglandin synthesis in dermal papilla cells offer an appealing and reasonable starting point for future research by minoxidil, which is supported by evidence from other sources. Further information regarding the signaling mechanisms has been needed that are responsible for these effects. Whether KATP channels are involved in the hair growth regulation or androgenetic alopecia development. It was answered that is it necessary to use minoxidil. Although the effectiveness of minoxidil in treating androgenetic alopecia (AGA) has shown in clinical trials, but still there a prevalent inclination to downplay the value of this treatment. To this day, it is the only medical treatment that has been shown to be effective in topically use, and it is also an approved treatment for female pattern hair loss. Minoxidil has an effect on the life cycle of hair, causing an early end to the telogen phase and presumably extending the anagen phase. If a greater grasp of how minoxidil produces these effects have been obtained, It will be easy to develop more effective therapies for hair loss and also deeper comprehension of the systems that are responsible for managing the hair cycle (Boden et al., 1985).

References

Boden, W. E., Korr, K. S., & Bough, E. W. (1985). Nifedipine-lnduced Hypotension and Myocardial Ischemia in Refractory Angina Pectoris. JAMA: The Journal of the American Medical Association, 253(8), 1131–1135. https://doi.org/10.1001/jama.1985.03350320055016

Clissold, S. P., & Heel, R. C. (1987). Topical Minoxidil: A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy in Alopecia Areata and Alopecia Androgenetica. *Drugs*, *33*(2), 107–122. https://doi.org/10.2165/00003495-198733020-00002

Ferry, J. J., Shepard, J. H., & Szpunar, G. J. (1990). Relationship between contact time of applied dose and percutaneous absorption of minoxidil from a topical solution. *Journal of Pharmaceutical Sciences*, *79*(6), 483–486. https://doi.org/10.1002/jps.2600790605

Gupta, A. K., Talukder, M., Venkataraman, M., & Bamimore, M. A. (2022). Minoxidil: a comprehensive review. *Journal of Dermatological Treatment*, *33*(4), 1896–1906. https://doi.org/10.1080/09546634.2021.1945527

McCoy, J., Goren, A., Kovacevic, M., & Shapiro, J. (2016). Minoxidil dose response study in female pattern hair loss patients determined to be non-responders to 5% topical minoxidil. *Journal of Biological Regulators and Homeostatic Agents*, *30*(4), 1153–1155. https://doi.org/10.1016/j.jid.2017.02.867

Rossi, A., Cantisani, C., Melis, L., Iorio, A., Scali, E., & Calvieri, S. (2012). Minoxidil Use in Dermatology, Side Effects and Recent Patents. *Recent Patents on Inflammation & Allergy Drug Discovery*, *6*(2), 130–136. https://doi.org/10.2174/187221312800166859

Sattur, S. S., & Sattur, I. S. (2021). Pharmacological Management of Pattern Hair Loss. *Indian Journal of Plastic Surgery*, *54*(4), 422–434. https://doi.org/10.1055/s-0041-1739254

Sinclair, R. D. (2007). Healthy hair: What is it? *Journal of Investigative Dermatology Symposium Proceedings*, *12*(2), 2–5. https://doi.org/10.1038/sj.jidsymp.5650046

Suchonwanit, P., Thammarucha, S., & Leerunyakul, K. (2019). Minoxidil and its use in hair disorders: A review. *Drug Design, Development and Therapy*, *13*, 2777–2786. https://doi.org/10.2147/DDDT.S214907

Vanderveen, E. E., Ellis, C. N., Kang, S., Case, P., Headington, J. T., Voorhees, J. J., & Swanson, N. A. (1984). Topical minoxidil for hair regrowth. *Journal of the American Academy of Dermatology*, *11*(3), 416–421. https://doi.org/10.1016/S0190-9622(84)70183-6

Cranwell W, Sinclair R. Male Androgenetic Alopecia. In: Endotext. MDText.com, Inc., South Dartmouth (MA); 2000. PMID: 25905192

Jimenez-Cauhe J, Saceda-Corralo D, Rodrigues-Barata R, Hermosa-Gelbard A, Moreno-Arrones OM, Fernandez-Nieto D, Vaño-Galvan S. Effectiveness and safety of low-dose oral minoxidil in male androgenetic alopecia. J Am Acad Dermatol. 2019 Aug;81(2):648-649.

Hunter N, Sayed K, Hay RA, Allam R, Hussein N. Comparing the Efficacy of Mesotherapy to Topical Minoxidil in the Treatment of Female Pattern Hair Loss Using Ultrasound Biomicroscopy: A Randomized Controlled Trial. Acta Dermatovenerol Croat. 2019 Mar;27(1):1-7.

Ahluwalia J, Fabi SG. The psychological and aesthetic impact of age-related hair changes in females. J Cosmet Dermatol. 2019 Aug;18(4):1161-1169

Badri T, Nessel TA, Kumar D D. Minoxidil. [Updated 2023 Feb 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482378/