



Minoxidil: New Areas of Opportunity!

Luis Octavio Victoria García¹, Morelos Adolfo García Sánchez², Rafael Martínez Sanciprián³, Miranda Llama Luna⁴, Mariana Carolina Zúñiga García⁵, Luis Alberto González Valdez⁶, Marco Antonio Hernández Hernández⁷, Oscar Gregorio Ramírez Gamboa⁸, Karla Lizeth Martínez González⁹, Melba Michelle Romero Ovando¹⁰, Zarah Georgina Pérez Diosdado¹¹

1. Specialist in Surgery. Attached to the Department of Surgery General Hospital "Dr. Rubén Leñero" of the Ministry of Health of Mexico City. Graduated of the Universidad Anáhuac Mexico. Mexico City. Country Mexico
2. *Specialist in Surgery and with a subspecialty in Colon and Rectal Surgery attached to the Department of Surgery of the General Hospital of the Ministry of Health of Mexico City "Dr. Rubén Leñero". Graduated from the National Autonomous University of Mexico, Mexico City. Country Mexico. Correspondence: morelosadolfo@hotmail.com Tel 0155 55 53 41 12 58.
3. Specialist in Surgery. Attached to the Department of Surgery General Hospital "Dr. Rubén Leñero" of the Ministry of Health of Mexico City. Graduate of the Monterrey Institute of Technology. Mexico City. Country Mexico
4. Physician Attached to the Surgery Service. General Hospital "Dr. Rubén Leñero" of the Ministry of Health of Mexico City. Graduated of the Universidad Anáhuac Mexico. Mexico City. Country Mexico
5. Specialist in Surgery. Attached to the Surgery Service of the Regional Hospital of PEMEX "Dr. Alejandro Castanedo Kimball". Salamanca, Guanajuato. Graduated from the Michoacan University of San Nicolás de Hidalgo. State of Guanajuato. Mexico
6. Specialist in Surgery. Attached to the Surgery Service of the Regional Hospital of PEMEX "Dr. Alejandro Castanedo Kimball". Salamanca, Guanajuato. Graduated from the Autonomous University of Guadalajara. State of Guanajuato. Mexico
7. Specialist in Surgery. Attached to the Surgery Service of the Spanish Hospital of Mexico. Graduated from La Salle University. Mexico City. Mexico
8. Specialist in Surgery. Attached to the Department of Surgery General Hospital "Dr. Rubén Leñero" of the Ministry of Health of Mexico City. Graduated from the University of Guadalajara. Mexico City. Country Mexico
9. Physician Attached to the Surgery Service of the Old Civil Hospital of Guadalajara "Fray Antonio Alcalde". Graduated from the University of Guadalajara. State of Guadalajara. Mexico
10. Physician Attached to the Surgery Service General Hospital "Dr. Rubén Leñero" of the Ministry of Health of Mexico City. Graduated from the University of Health. Mexico City. Country Mexico
11. Physician Attached to the Surgery Service of the Satellite Corporate Hospital. State of Mexico. Graduated from the Universidad Anáhuac México. State of Mexico. Mexico

Abstract: Introduction: Minoxidil is a compound chemically synthesized in the laboratory, it underwent clinical trials in hypertensive patients in 1961. Objective: To carry out art history based on an exhaustive search of the national and international medical literature on its therapeutic use of minoxidil in humans. Discussion: the topical use of routine minoxidil for the treatment of multiple hair disorders. 2% and 5% minoxidil continue to be the approved treatments, with the most efficient being 5%, with an expected phase of loss, even under treatment. Another use that has been reported for minoxidil is that used together with phototherapy, it is the most common treatment for vitiligo; A novel

bioengineering approach to improve local delivery in the skin. The hydrogels are highly mechanically robust micro-needle patches with heights of 600 or 800 μm with sufficient mechanical strength to penetrate human skin. Minoxidil has been used in yellow nail syndrome, a rare disorder characterized by a triad of thickened yellow nails, primary lymphedema, and chronic respiratory manifestations. It has been determined as a treatment as an antihypertensive drug and has been studied since 2008, stating that minoxidil should be used together with β -blockers and diuretics. **Conclusions:** Minoxidil has demonstrated beneficial effects in androgenic alopecia, scarring and alopecia areata; however, it has been shown that there are other areas of therapeutic opportunities in other diseases, due to their already known pharmacological actions, evoking the option of new research protocols

Keywords: Minoxidil, High blood pressure, Alopecia, Vitiligo, Yellow nail syndrome, Skin, Hair.

INTRODUCTION

Minoxidil is a chemically synthesized compound in the laboratory, which has a molecular weight of 209.25 grams per mole. In its pure form, it is an odorless white crystalline powder. It has a melting point of 248 °C (478 °F) and a solubility of 220 milligrams per liter. When heated, it breaks down and emits toxic nitrogen oxide vapors. Its molecular formula is $\text{C}_4\text{H}_{13}\text{N}_3\text{O}$; Historically, its study began in the 1950s, where the Upjohn company developed minoxidil to try to treat stomach ulcers. However, tests on laboratory animals revealed that the drug did not cure or treat ulcers. [1, 2] Subsequently, a change in the line of research was carried out, it underwent clinical trials in hypertensive patients in 1961. DAMN-O was effective in lowering blood pressure, but it caused salt and water retention, resulting in edema and, due to a misunderstanding about discontinuation of treatment in such cases, led to heart failure in some patients, but toxicity is discovered in dogs that revealed hemorrhagic lesions in the right atrium, so DAMN-O was withdrawn from the study. [3, 4]

An intense search was made for isomers such as Minoxidil and by 1971 the Food and Drug Administration of the United States allowed a protocol in humans but only for 2 weeks, but hypertensive control was achieved so effectively that doctors extended the dosage longer, with the adverse effect of hypertrichosis after administration of more than 2 weeks. [5, 6] A study was published in patients with malignant or accelerated hypertension refractory to conventional drugs who were treated with minoxidil as the main antihypertensive agent, who had advanced renal disease, and all were candidates for nephrectomy to control blood pressure. Blood pressure was reduced to near-normal levels in all patients with diuretic and propranolol adjustments. [7] Minoxidil is almost completely absorbed into the gastrointestinal tract, peaking within an hour; its complete blood pressure response occurs in about 4 hours, and despite its half-life of about 4 hours, its antihypertensive effect can last up to 3 days, among other reasons due to its high affinity for the vascular smooth muscle of the vessel. Most of the drug is metabolized in the liver, so there is no need to adjust the dose in case of kidney failure. [8]

OBJETIVO

To carry out art history based on an exhaustive search of the national and international medical literature on the therapeutic use of minoxidil in humans, and to initiate its applicability in wound healing in experimental studies type I and according to the result of

a phase II. In addition, an analysis of the research of the national and international medical literature on what is described in relation to minoxidil is carried out.

DISCUSSION

Currently, the therapeutic efficacy of cytotoxic drugs encapsulated in nanoparticles is being developed, a strategy using nanoliposomes loaded with minoxidil, to be able to induce tumor vasodilation and improve the administration of pegylated liposomal doxorubicin applied in colorectal and pancreatic cancer, achieving a reduction in tumor cells. [9] Other advances in 3D and 2D tissue culture innovations, being high-research engineering applications such as hair follicle development, when dermal papilla cells and keratinocytes were grown together in 2D and 3D cultures, where arrays of polyethylene glycol diacrylate microwells were designed to be treated with minoxidil, The expressions of four capillary proteins were analyzed, demonstrating a significant increase in trichohyalin. [10]

The use of upadacitinib, a JAK1 inhibitor, in combination with oral minoxidil for the treatment of universal alopecia with Crohn's disease and atopic dermatitis. Alopecia universalis is the most widespread form of alopecia areata, a chronic autoimmune disease that often requires systemic therapy for hair regrowth; At 11 weeks, he achieved complete scalp, eyebrow, eyelash and beard regrowth with oral minoxidil, which was increased from 2.5 to 10 mg/day. [11] Topical use of routine minoxidil for the treatment of multiple hair disorders. 2% and 5% minoxidil remain the Food and Drug Administration's (FDA)-approved treatments, with the most efficient being 5%, with a 5% expected phase of hair loss, even under treatment. A temporary increase in hair loss occurs primarily during the first three months after initiation of minoxidil treatment. Human hair follicles continuously go through the "anagen-catagen-telogen" cycle, topical application of minoxidil can decrease the number of follicles in the catagen and telogen phases and reduce the average daily hair loss. [12]

On the other hand, short anagen hair syndrome is a rare congenital condition, treated with oral minoxidil 2.5 mg per month at low doses. [13] Insulin-like growth factor 1 (IGF-1), a multifunctional regulator of cell proliferation, plays a crucial role in modulating the hair cycle. It can stimulate the proliferation of hair follicle cells, participate in hair shaft differentiation, and inhibit the change from anagen to catagen phase. [14]

Testosterone-induced apoptosis and impairment of dermal papilla cell function, which alters epithelial-mesenchymal interactions and hinders hair follicle regeneration. Minoxidil and finasteride offer limited and temporary benefits. [15] The exact pathogenesis of androgen alopecia is complex and multifactorial. Genetic factors play a critical role, as the condition is known to be highly heritable. Androgens such as dihydrotestosterone have been shown to miniaturize hair follicles in predisposed individuals by binding to androgen follicular receptors and stress and lifestyle habits. [16]

Unlike male pattern baldness, women rarely experience complete baldness, but the psychosocial impact of thinning hair may be more significant and is associated with the various psychological impacts. [16, 17]

It should be mentioned that the effect of minoxidil is to act by accelerating blood flow around the hair follicles, improving the local supply of oxygen and nutrients, and thus promoting hair growth. Traditional formulas have a short residence time on the skin, are prone to cause allergic reactions, flaking. This highlights the urgent need to develop more

efficient and safer delivery systems to improve their therapeutic efficacy; therefore, delivery vehicles based on high molecular weight hyaluronic acid with excellent skin penetration and anti-inflammatory properties are used [18]

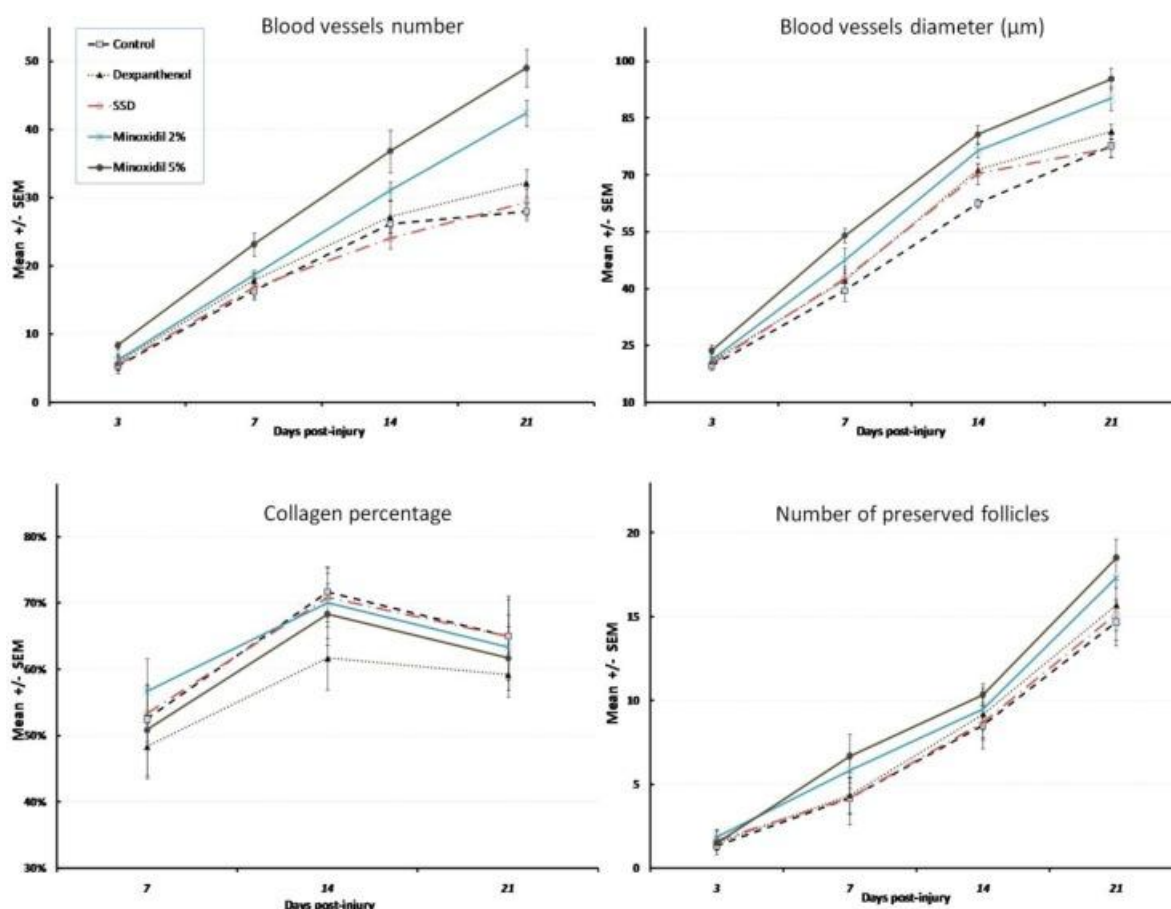


Figure 1: Histological evaluations in different treatment groups during the 21 days after the burn. Image extracted from the reference: Khazaeli P, Karamouzian M, Rohani S, Sadeghirad B, Ghalekhani N. Effects of minoxidil gel on burn wound healing in rats. Iran J Pharm Res. 2014 Winter;13(1):243-51. [19]

Another modality is the use of platelet-rich plasma therapy in androgenic alopecia therapy, which has not yet been approved by the Food and Drug Administration in the United States. That it has been purchased with topical minoxidil with a response rate of 46% to 68%, [20] however, it is a valuable therapeutic option, either as an adjuvant to topical minoxidil or as a second-line treatment. [21] On the other hand, low-dose oral minoxidil is an emerging option for the treatment of female pattern hair loss, generally well tolerated at doses below 1 mg/day. But the adverse effect of xerostomia has been reported to have developed dry mouth that progressively worsened and significantly affected speech and social interactions. [22] In addition, another drug has been documented to have been compared with minoxidil in the efficacy and safety of oral spironolactone for female pattern hair loss in premenopausal women, showing superiority in hair regrowth, in terms of clinically meaningful outcomes, over topical minoxidil for treatment alone, although the sample is insignificant. [23] Short anagen syndrome in pediatric patients is a rare condition characterized by a shortened anagen phase, resulting in the inability to develop long hair

on the scalp, and where low-dose oral minoxidil has recently become an effective treatment for a variety of pediatric hair disorders. [24, 25]

Telogen effluvium is an acute and diffuse hair loss due to an abnormal increase in telogen hair follicles in response to external or internal factors, substantial shedding causes great psychological stress in patients and there is no evidence-based treatment, however, the use of topical minoxidil 5%, with a very favorable response at 3 to 6 months and up to a follow-up of 24 months. [26] Chemotherapy-induced alopecia and radiation-induced alopecia, thinning, or hair loss due to cytotoxic chemotherapy and radiation therapy, respectively, are concerning adverse effects of cancer treatment. Topical and oral minoxidil in low doses has been confirmed to improve hair regrowth later in life. [27]

A protocol of testing treatments, when there are no clear Canadian guidelines on their management, is carried out in forty-five interventions. Seven interventions are recommended, including oral dutasteride; oral finasteride; topical finasteride; topical minoxidil; platelet-rich plasma; microneedling; and oral minoxidil. It is noted in the report that the use of minoxidil injection is not recommended. [28] Another way to administer it is by using needle-free "nebulized" jet injection, as this is an effective approach to improve drug deposition in the skin. Although it has been used in dermatology practice, optimal drug selection and device configuration have not yet been defined or standardized; Injection volume and operating pressure showed a positive correlation with minoxidil penetration, where the barrier properties of the skin, especially of the stratum corneum, limit the efficacy of treatment by preventing transport of the drug to the nest, methods of improved delivery that improve therapeutic efficiency are needed. Active technologies, such as microneedling, ablative lasers, and radiofrequency, improve drug absorption through physical disruption. [29] Exosomes (nanovesicles ranging from 30 to 150 nm in diameter) were applied with the procedure that was performed by intradermal injections into the treated areas of the scalp with a 1 cc syringe and 27-gauge needles. Injection sites were spaced approximately 0.5 to 1 cm apart; becoming alternatives to minoxidil and platelet-rich plasma. [30]

Another reported use for minoxidil is that used in conjunction with phototherapy, it is the most common treatment for vitiligo. The initial pigmentation appears in the perifollicular zone and finally fuses into a uniform pigmentation due to the migration of melanocytes from the hair follicles and manages to increase the pigmentation rate with a reduction in the score. [31] See Figure 2.

Microneedles can pierce the stratum corneum painlessly and increase the absorption of the drug through the skin. In addition, nitric oxide has been shown to improve blood flow to hair follicles and reduce inflammation. This effectively promoted the transition of hair follicles to the growth phase and stimulated angiogenesis around the follicles, offering a promising new direction for the clinical treatment of alopecia. [33] Low-level laser therapy is an innovative technology that can enhance the effects of minoxidil on hair growth. Evidence of the efficacy and safety of combined therapy and topical minoxidil compared to topical minoxidil alone for the treatment of androgenic alopecia, with combined therapy being far superior. [34] In radiation-induced alopecia following endovascular embolization procedure for cerebral arteriovenous fistula. There was a response with intramuscular injections of corticosteroids and topical minoxidil at 5%, which allowed complete hair regrowth after three months, after biopsy was taken where lymphocytic infiltration and increase in catagen and telogen follicles were described. [35]

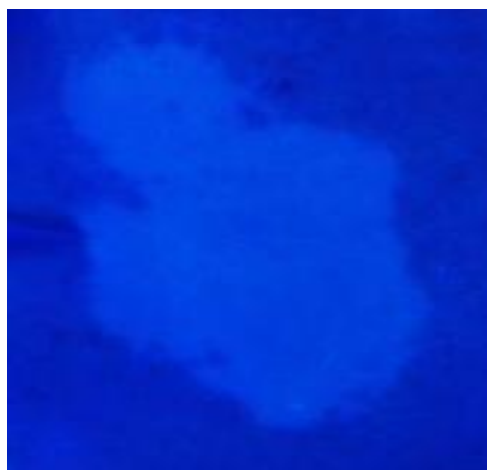


Figura 2: Wood's light phototomography in a patient with vitiligo showed a depigmented spot. Contributed by Dr. Daifallah Al Aboud.

Image taken from reference: Ahmed Jan N, Masood S. Vitiligo. [Updated August 7, 2023]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; January 2026-. Available in: <https://www.ncbi.nlm.nih.gov/books/NBK559149/> [32]

Although oral minoxidil in low doses has transformed the treatment of alopecia. However, its vasodilatory effects can lead to complications, such as the appearance of edema and, rarely, pericardial and pleural effusions that require hospitalization. [36] In this study, among cases of edema, 81.2% experienced no dose change or discontinuation of oral administration (55.6% reported tolerability of edema; 44.4% achieved resolution), 9.1% required dose adjustment with final resolution, and 9.1% discontinued due to edema intolerance without attempting dose adjustment. but no seriousness was reached. [37]

Minoxidil, a potent vasodilator commonly used for hypertension and androgenic alopecia, can exacerbate cardiovascular complications associated with pheochromocytoma due to its mechanisms of action and its effects are well established. [38] Low-dose oral minoxidil (≤ 5 mg daily) has become an effective off-label treatment for androgenetic alopecia, surpassing topical minoxidil in terms of adherence. However, the optimal dose has not yet been determined, and high doses may cause systemic adverse effects. In this study, the results showed an overall improvement in hair density of between 10% and 30% in most patients, although with variable responses. 17.5% of patients experienced significant improvements ($>50\%$), while another 17.5% improved $<10\%$. A quarter of patients (24.6%) developed adverse effects, such as hypertrichosis (17.5%) and tachycardia (3.5%). [39] An overdose of oral minoxidil that caused hypotension, dyspnea, edema, weight gain, and facial flushing should be considered. Since vital signs and results of laboratory and imaging tests were generally normal, no treatment was initiated. [38] Transient vision loss and achromatopsia have been reported as adverse effects of minoxidil [40] or is associated with fluid retention mentioned above, and in rare cases, pericardial effusion that may progress to cardiac tamponade. [41] Peripheral edema due to fluid retention and increased capillary hydrostatic pressure. While rare with topical formulations, systemic absorption is influenced by factors such as application site, concentration, and individual skin permeability, with a rare but clinically significant systemic side effect but with topical minoxidil. [42] Indeed, it is associated with a number of side effects, the most common of which is contact dermatitis, so a clear distinction must be made between allergic contact dermatitis and irritant contact dermatitis to minoxidil is essential for the treatment or not of androgenic alopecia. [43]

On the other hand, minoxidil has been experimented with in the study of the effects of common excipients on the permeability of six model drugs of moderate and deficient absorption in monolayer using it as a normalizing agent, the inclusion of minoxidil as a normalizing agent increased the number of excipient effects by increasing absorption. [44] However, it has been experimentally used documenting the use of minoxidil in chronic or acute anal fissure; this potential novel therapy remains poorly protocolized. Although the drug achieved intermediate rankings for cure 57.8% and recurrence 66.4%, its comparative performance was not statistically significant in most pairwise comparisons with confidence intervals were remarkably wide. [45]

Minoxidil is the only FDA-approved topical treatment for androgenic alopecia. However, its use is limited by its efficacy and tolerability. Here, we describe a novel bioengineering approach to improve local delivery in the skin. Highly mechanically robust microneedle patch hydrogels with heights of 600 or 800 μm with sufficient mechanical strength to penetrate human skin, exhibited an adjustable release of minoxidil for 6 weeks in vitro with induction of hair growth. [46] See Figure 3.

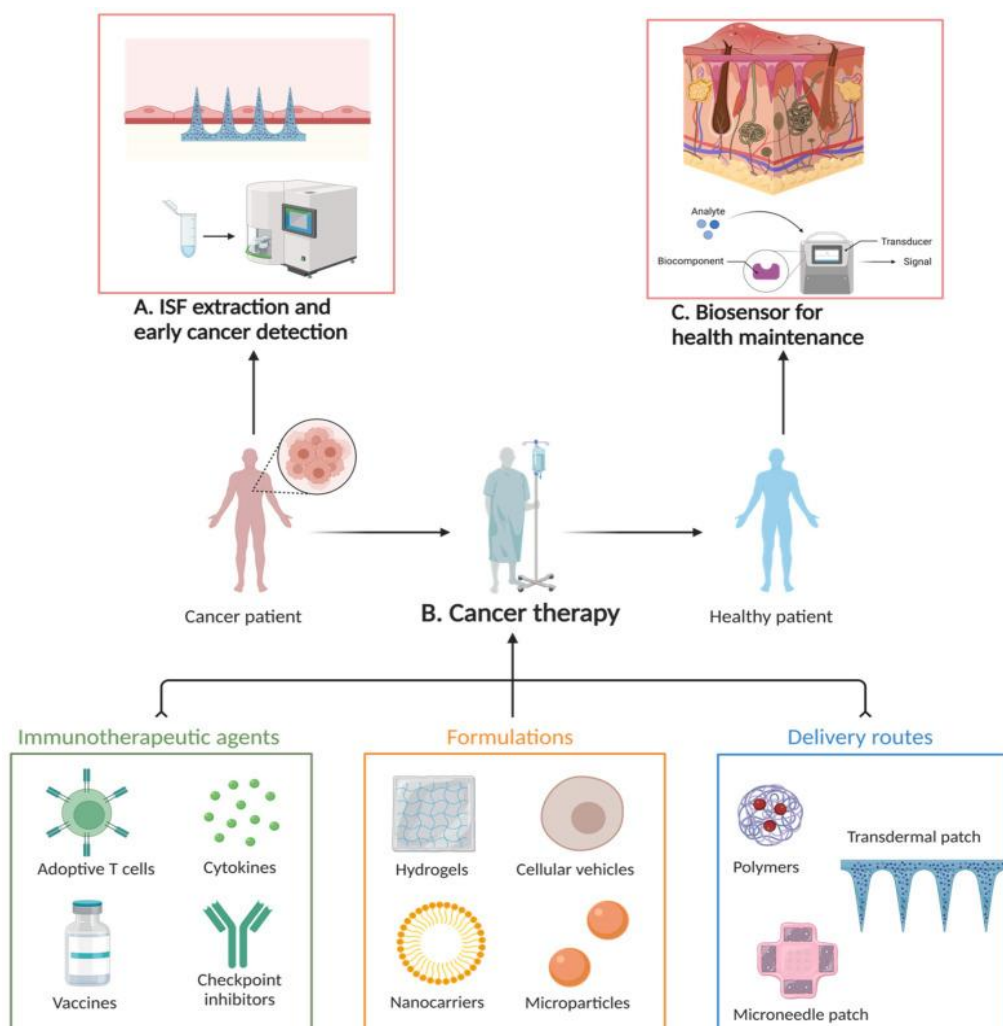


Figure 3

Schematic illustration of the potential applications of microneedles in cancer detection and treatment. (A) The microneedling device is used for the removal of interstitial fluid (LI), which can be used for early detection of cancer. LI contains

biomarkers that can indicate the presence of cancer in the body, making it a promising alternative to traditional blood tests for cancer screening. (B) Hydrogel microneedles can be used for localized delivery of cancer therapies. These microneedles can be loaded with adoptive T cells using microencapsulation, cytokines, vaccines, and checkpoint inhibitor drugs that act on cancer cells or specific regions of the body, allowing for precise and targeted treatment. (C) Microneedles can be used as biosensors to monitor the health of cancer patients during and after treatment. The figure was created with BioRender.com. Image taken from the reference: Li Y, Bi D, Hu Z, Yang Y, Liu Y, Leung WK. Hydrogel-Forming Microneedles with Applications in Oral Diseases Management. *Materials* (Basel). 2023 Jul 3;16(13):4805. doi: 10.3390/ma16134805. [47]

Minoxidil is a rare disorder characterized by a triad of thickened yellow nails, primary lymphedema and chronic respiratory manifestations, its underlying etiology is unclear, it is postulated that micro vasculopathy, lymphatic dysfunction and protein extravasation are involved; it is well that minoxidil has been tolerated and produced a visible improvement in nail changes being a promising new treatment. [48] In addition, it is used in 15q duplication syndrome (Dup15q), which is a neurogenetic disorder characterized by a high incidence of autism spectrum disorder and drug-resistant epilepsy, minoxidil, and which can suppress seizures by rebalancing extracellular K⁺. This pharmacological and molecular research further supports the role of extracellular K⁺ content in the convulsive activation of Dup15q and provides a potential target for therapeutic intervention. [49]

In the treatment as an antihypertensive medication it has been studied since 2008, issuing that minoxidil should be used together with β -blockers and diuretics. In fact, when combined with both classes, minoxidil achieved superior antihypertensive results compared to high-dose hydralazine, demonstrating that long-term treatment with minoxidil delayed renal deterioration in patients with malignant hypertension. [7, 50] However, its use has not been envisioned again in the operational area.

Minoxidil is an increasingly common treatment option for hair loss disorders, in androgenic alopecia, scarring and areata. There are several formulations of minoxidil, including topical, oral, and injectable. [51] Injectable application may offer certain advantages but may also come with potential risks and costs: it is clear that injections are significantly more expensive. 1.4% of topical minoxidil can be absorbed through the scalp. Oral minoxidil, usually 2.5 mg daily, has a bioavailability of 0.27 to 0.55%. In comparison, intradermal injection of minoxidil (0.5% dose) has a bioavailability of 100%. [52] It plays a crucial role in cell proliferation at an early stage. In animal studies, minoxidil increases cellular DNA synthesis and enhances cell proliferation to treat alopecia, proving a superior effect on hair growth [53]

CONCLUSIONS

Minoxidil has shown beneficial effects in androgenic alopecia, scarring and alopecia areata; however, it has been shown that there are other areas of therapeutic opportunities in other diseases, due to their already known pharmacological actions, evoking the option of new research protocols in terms of their applicability, such as surgical reconstructions with autologous grafts, acceleration in the healing process or even in reformatory or neoformative cell reproduction.

Conflict of Interest

The authors stated that they had no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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