Review Article

Advances in Nanoemulgel Formulation on Wound Healing: A Comparative Review of Efficacy and Regenerative Potential

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ABSTRACT

Nanoemulgel is a significant advancement in topical wound healing therapy over conventional gels, creams, emulsion, and antiseptic dressings. This review makes a strong evidence-based case for this claim across five distinct bio-active systems: curcumin, atorvastatin, thymoquinone, brucine, and combination of propolis-tea tree-jojoba oil. When compared to their traditional counterparts, nanoemulgel formulations demonstrated three-to sixfold increases in transdermal flow and permeability in all studied systems. This resulted from the addition of nanoscale oil droplets (90-190nm) in a gel matrix as opposed to the microscale droplets of traditional emulgels and plain gels. Even in the more hostile environment of diabetic's wounds, this delivery advantage was not coincidental; it contributed to consistently faster epithelization, stronger wound contraction, and performance that was or par with or better than the clinical gold standard, silver sulfadiazine, in many investigations. Most significantly, histological data from all the five systems showed that tissues treated with nanoemulgel did not just close but instead regenerated, resulting in minimal residual inflammation, organized collagen architecture, and most remarkably, regrowth of sebaceous gland and hair follicles, which are rarely observed conventional treatment. The contrast is further sharpened by the critical evaluation of povidone – iodine included, which reveals direct cytotoxicity to fibroblasts and keratinocytes at standard clinical concentrations and inconsistent antimicrobial benefit, undermining the very repair processes nanoemulgel is a superior mechanistically based platform for wound-healing therapeutics rather than an incremental variation of current dosage forms.

Keywords: Nanoemulgel, Wound healing, Tissue regeneration, Regenerative potential, Topical drug delivery, Re-epithelialization, Skin permeation.

INTRODUCTION

A novel drug delivery system (NDDS) can be defined as approach that combines innovative development, formulations, new technologies, novel methodologies for delivering pharmaceutical compound in the body as needed to safely achieve its desired safety effects.[1] The ability to maintain plasma drug levels in a limited therapeutic window for an extended period of time is the most advantageous feature of NDDS. This removes the negative "peaks and valleys" that occur when medication is taken on a regular basis.[2] Under order to protect delicate medications like peptides and nucleic acids from breakdown under harsh physiological conditions, NDDS employs innovative components like liposomes, polymeric nanoparticles, and hydrogels that react to stimuli.[3] Furthermore, NDDS can be designed to target specific cells or region, allowing the medication to reach its intended location without harming healthy tissues. This capability is particularly helpful for therapies that must pass through intricate cellular membrane or deal with medications that dissolve poorly in water. These innovative drug delivery systems are frequently quite complex, making it challenging to produce them on a large scale and ensure that every batch is identical.[4] Many innovative medication delivery methods, particularly nanocarrier, struggle to maintain long term chemical and physical stability during storage and transit. These issues, along with the high development costs, restricts their availability in comparison to more straightforward and affordable conventional dosage forms.[5]

Concerns about the long-term safety and biodistribution of new nanomaterials persist since NDDS interact at the molecular level in biological system. Therefore, to guarantee that the medicine and its carrier are safe for human use, regulatory agencies require through characterization and risk -based development strategies like Quality-by-Design.[6]

In various medical disciplines, novel drug delivery systems have brought about a significant transformation in the therapeutic realm by augmenting drug efficacy, diminishing adverse reaction, and enhancing patient compliance.[7] Within the field of oncology, specialized delivery vehicles like antibody – drug conjugates and nanoparticle carrier have facilitated the precise localization of chemotherapeutics agents to malignant cells, thereby reducing systemic toxicity and surmounting resistance to multiple drugs. In the domain of infectious diseases, nanoparticle-based platforms and inhalation therapies have streamlined the targeted conveyance of antimicrobial agent directly to sites of infection, such as the pulmonary system, thereby ameliorating treatment outcomes for ailments like tuberculosis and pneumonia.[8] The utilization of transdermal delivery mechanism has been notably advantageous in managing chronic conditions necessitating consistent drug plasma concentration, such as hormone replacement therapy, pain control, and smoking cessation, offering a non- invasive alternative to traditional oral or injectable routes.[9]

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Additionally, responsive systems that react to specific stimuli have been implemented in diabetes care through glucose -sensitive insulin delivery apparatuses that modulate dosages based on blood glucose levels, thus emulating natural insulin secretion patterns.[10] The field of gene and nucleic acid therapies has greatly profited from the progress in novel drug delivery systems, with lipid nanoparticles facilitating the secure and efficient transport of mRNA vaccines and CRISPR gene editing components. Furthermore, implantable drug delivery devices have supplied sustained release solutions for contraception, chronic pain management and neurological disorders, enhancing therapeutic consistency and the quality of life for patients.[11] These diverse application underscore the transformative capacity of novel drug delivery systems in contemporary medicines, holding the promise of more personalized, efficient and safer treatment modalities.[12]

WOUND

A wound may be defined as any disruption of the integrity of skin, mucous membrane or organ tissue.[13] The following shows the pictorial representation of wound;

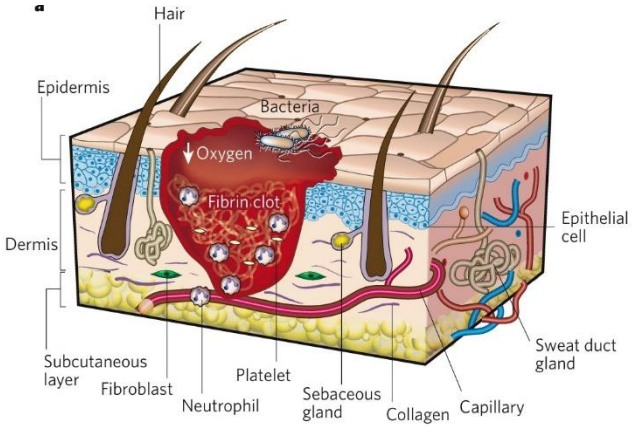


Figure 1: Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008 May 15;453(7193):314–321.

Depending on the type and length of the healing process, wounds can be categorized as either acute or chronic.[14] Depending on the size, depth, and the extent of the injury, acute wounds including trauma and surgical wounds often recover in two to three months.[15] Pressure, venous, and diabetic ulcers are examples of chronic wounds that either do not heal (non-healing chronic wounds), or take a very long time to heal (several months), which leads to the formation of scars, and bacteria and other external elements can cause infection.[16] Peripheral vascular disease, infection, and deepening wounds are frequently associated with poor clinical outcomes, all of which worsen chronic comorbidities.[17] Chronic wounds can result in a number of problems and higher medical expenses. This illustrates how wounds have wider systemic impacts on patient health outcomes.[18] The process of healing chronic wounds is complex and takes a longer period (12 weeks). This demonstrates the ongoing physiological strain that wounds put on the body's healing processes. Acute wounds heal more quickly than chronic wounds, which take longer to heal and have a more complicated healing process by nature.[19]

HEALING

The body regenerates dermal and epidermal tissue through the natural process of wound healing. Reconstructing the barrier between the human body and the external environment is a common, intricate, and well-organized physiological process that occurs after a skin tissue damage. Hemostasis (formation of fibrin plug), inflammation (swelling), proliferation (formation of new tissue and blood vessels), and remodeling of newly formed tissue and the four sequential and overlapping regeneration phases of this dynamic, interactive process that involves soluble mediators, different cell types (eg; blood cells, parenchymal cells), and extracellular matrix (ECM).[20]

STEPS; At the site of injury, platelets clump together and chemo attractants are produced, attracting important inflammatory cells. Inflammation then over takes over, with mast cells and neutrophils that have infiltrated the area generating pro-inflammatory cytokines and producing potent sanitizing effects. Neutrophil extracellular trap induction goes hand in hand with this, helping to capture and eliminate invasive microorganisms. Tissue – resident macrophages activate in response to pathogen and damage associated molecular patterns (PAMP's and DAMP's). Subsequently, fibronectin and other temporary extracellular matrix had potent sanitizing effects. This is followed by the induction of neutrophil extracellular traps, which aid in the capture and elimination of invasive microorganisms. Tissue-resident macrophages activate in response to molecular patterns linked to pathogens and damage. Later, the clot gives rise to a temporary matrix made of fibronectin and other temporary extracellular matrix constituents.[21]

Factors affecting healing

Hemostasis, inflammation, proliferation and remodeling are the four overlapping stages of the intricate and tightly controlled biological process that is wound healing. These phases must be properly coordinated in terms of duration, intensity, and sequencing for healing to be successful. Any kind of disruption can cause wound healing to be delayed or compromised, which frequently results in chronic wounds.[22]

Local and systemic factors have been used to broadly classify a number of elements that affect wound healing. Oxygenation, infection, foreign objects, vascular supply are examples of local variables. While hypoxia or inadequate perfusion considerably impedes healing, adequate oxygen is necessary for cellular metabolism, angiogenesis, collagen formation, and resistance to infection. Infection causes tissue damage and prolongs the inflammatory phase, which frequently results in chronic wounds that do not heal.[22,23]

Physiological disorders, illnesses, lifestyle choices, prescription drugs, and dietary status are all considered systemic variables. Due to altered inflammatory responses

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and decreased cellular activity, age related alterations are linked to delayed recovery. Sex hormones also impact; androgens often hinder healing while estrogen generally promotes it. Through processes including hypoxia, oxidative stress, poor angiogenesis, and immunological dysfunction, chronic diseases like diabetes significantly impede wound healing. Stress and obesity also have a role in changing immunological responses and raising the risk of problems.[24]

Smoking and alcohol use are examples of lifestyle choices that have a detrimental impact on healing because they lower oxygen delivery, weaken the immune system, and interfere with cellular functions. Medications that interfere with inflammation, cell proliferation and collagen formation, such as glucocorticoids, NSAIDS, and chemotherapeutic medicines can postpone healing.[25]

One important factor that Influencing wound healing is nutrition. To meet the metabolic demands of tissue regeneration, an adequate diet proteins, carbs, and lipid is required. Certain nutrients like glutamine and arginine promote the production of collagen and the immune system. Extracellular matrix production, antioxidant activity and cellular function all depend on Vitamin A, C, E as well as trace minerals like zinc, iron, and copper. Inadequate intake of nutrients might seriously hinder the healing process.[26]

TISSUE REGENERATION

Tissue types; In general, the four basic tissue types that make no the human body are muscle, nerve, connective, and epithelial tissue, each of which males a distinct contribution to overall physiological function. Closely spaced cells organized in continuous sheets with little extracellular material make up the epithelial tissue. Protection, absorption, filtration, and secretion are their main functions. This tissue creates glands, lines interior cavities, and covers body surfaces it is anchored to underlying tissues by a basement membrane. Interestingly, it does not have its own blood supply instead, it depends on diffusion from nearby connective tissue. The two types of epithelial tissue are glandular epithelium, which is specialized for secretion and covering and lining the epithelium. Epithelial cells can be arranged in one or more layers and have a variety of morphologies, including squamous, cuboidal, columnar and transitional, depending on their function.[27]

The body's most prevalent and extensively dispersed tissue type is connective tissue. It is made up of cells embedded in an extracellular matrix made up of fluid, pulverized material and protein fibers. Support, binding, protection, insulation, material transportation, energy storage and pathogen defence are just few of the many tasks this tissue completes. Connective tissue is typically well vascularized, in contrast to epithelial tissue. It can be found in a variety of forms, including cartilage, bone, blood, adipose tissue, dense connective tissue and loose connective tissue, each of which is tailored to a particular structural and functional function within the body.[28]

In addition to providing movement, regulating posture, and producing heat, muscle tissue is specialized for contraction. It is divided into three groups according to shape and function and is made up of long cells called muscle fibers. Conscious movement is made possible by skeletal muscle, which is voluntary and connected to the bones. Only the heart contains cardiac muscle, which is designed for constant, rhythmic contractions and is involuntary. Additionally, involuntary, smooth muscle is found in the walls of interior organs, where it helps with functions including blood vessel diameter regulation and peristalsis.[29]

The body uses nervous tissue specifically for coordination and communication. It is made up of neuroglial cells, which support shield, and nourish neurons, and neurons, which carry electrical impulses. Typically, neurons are made up of a cell body, signal -receiving stimuli, processing information, and producing suitable responses.[30]

REGENERATIVE PROPERTY

The capacity of cells and tissue to replace, repair, or restore lost or damaged structures in order to preserve normal function is known as the regenerative property of tissues. This process, which involves intricate interactions between cells, growth hormones, and the extracellular matrix (ECM), is a basic component of tissue homeostasis and wound healing. Tissue regeneration attempts to restore the damaged tissue's structural integrity as well as it's functional ability under normal physiological settings. For instance, deeper tissues frequently undergo repair with scar formation, showing weak regenerative potential, while the restoration of the epidermal layer following injury is very effective.[31]

Coordinated biological processes such cell division, migration, proliferation, and matrix remodeling - all of which are controlled by signaling molecules and interactions within the tissue microenvironment- lead to regeneration. By serving as a scaffold and regulating the availability and activity of growth factors essential for tissue healing, the extracellular matrix plays a critical function. Materials like collagen and fibrin matrices can assist and improve tissue regeneration by imitating the natural extracellular matrix (ECM) and promoting cell development and tissue formation, as advances in regenerative biology as shown.[32]

However, each tissue has varied capability for regeneration. Other tissues, such as muscle and particularly neurological tissue, display poor regeneration because some of their cells have low or no proliferative power, whereas epithelial tissues exhibit strong regenerative ability due to continual cell renewal. In certain situations, there may be insufficient healing or scar formation instead of actual regeneration.[33]

Furthermore, the regenerative process can be adversely affected by age, illnesses (such diabetes), inadequate blood supply, and compromised cellular signaling, which can result in chronic words or poor healing, tightly controlled process that is necessary to preserve tissue integrity.[34]

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NANOEMULGEL

Nanoemulgel is a topical drug delivery system in which a nanoemulsion is incorporated into a gel base to improve solubility, skin permeation, stability, and patient acceptability, especially for lipophilic drugs.[35]

Advantages[36]

- Better solubility and permeation of poorly water-soluble drugs.
- Improved stability compared with nanoemulsion alone, because the gel matrix reduces droplet mobility and helps limit phase separation.
- Longer residence time on sin due to higher viscosity and better spreadability.
- Reduced first pass metabolism and gastrointestinal degradation because it is usually used topically.
- Better patient compliance because it is noninvasive, nongreasy, and easy to apply.

Disadvantages[37]

- Formulation is more complex than simple gels or emulsions and needs careful selection of oil, surfactant, co-surfactant, and gelling agent.
- Surfactant and penetration enhancers may cause skin irritation if not chosen carefully.
- Physical and chemical stability still needs optimization; drop size, pH, viscosity, and phase behavior can change during storage.
- Scaleup and reproducibility can be difficult because nanosized systems are sensitive to preparation conditions.

WOUND HEALING AND REGENERATIVE POTENTIAL OF CURCUMIN NANOEMULGEL[38]

Curcumin is well known for its anti-inflammatory, antioxidant and anti-microbial effects, all of which are beneficial in tissue repair. However, its clinical utility in wound care has been limited by poor water solubility and penetration through the skin barrier. This is the reason for developing the nanoemulgel system, in this study they were specifically designed to overcome that limitation by encapsulating curcumin into the nanoscale oil droplets (around 50nm) and embedding them in a Carbopol based for practical topical use.

Wistar rats were used in the in vivo investigation, and four groups were compared: the untreated control, the regular curcumin gel, the curcumin nanoemulgel, and the standard antibacterial cream silver sulfadiazine. The percentage of the wound area that contracted during a 20 days period was used to track the wounds.

The outcomes showed a distinct order of therapeutic effectiveness. The group that was treated with nanoemulgel had the quickest epithelization, healing in about 10 days as opposed to 11 days for silver sulfadiazine and 14 days for traditional curcumin gel; the untreated group required 16 days. In terms of wound contraction, the emulgel and silver sulfadiazine groups demonstrated nearly total closure by day 20, the standard gel trailed behind. In the early stages of treatment, the nanoemulgel and silver sulfadiazine groups also showed less inflammatory exudated and produced granulation tissue earlier (by day 6) than the untreated and conventional-gel group (day 80).

These functional findings were confirmed by histopathological examination of the repaired tissue. The animals treated with the nanoemulgel had the greatest of granulomatous tissues, the fewest remaining inflammatory cells, and the highest degree of collagen fiber deposition of any group, according to hematoxylin-eosin and Van Gieson staining. Additionally, sections from the nanoemulgel and silver sulfadiazine groups showed a thicker epidermal layer, a well-formed papillary dermis, and regeneration of skin appendages (hair follicles and sebaceous glands) without noticeable inflammation. These findings point to more thorough structural and functional skin regeneration than just wound closure.

The better performance of the nanoemulgel is thought to be due to the increased skin penetration. The nanoemulgel demonstrated a roughly six-fold increase in drug flux and permeability coefficient when assessed for ex vivo permeability using Franz diffusion cells, with a shorter lag time before the onset of permeation and greater drug deposition within the skin itself. This is explained by the nanoemulsions tiny droplet size, its negative surface charge, and the surfactant tween 80, which is known to interfere with the stratum corneum's lipid structure and promote improved medication penetration.

In conclusion, the findings demonstrate the curcumin's encapsulation in a nanoemulsion-based gel not only improves its solubility but also dramatically alters biological performance at the wound site, leading to quicker contraction, re-epithelization, and histological evidence of more thorough tissue regeneration that is at least as good as a typical clinical wound treatment.

WOUND HEALING AND REGENERATIVE POTENTIAL OF ATORVASTATIN NANOEMULGEL[39]

Although the most well-known use of atorvastatin is as a lipid lowering medication, this work contributes to the mounting evidence that statins have pleiotropic effects that make them viable options for wound healing. These effects include regulating inflammation, apoptosis, and cell proliferation. A basic hydrogel, an emulgel and a nanoemulgel, then evaluated each system's effectiveness in a rat excisional wound model.

A nanoemulgel with a droplet size of about 148nm was found during formulation testing, which is much smaller than the emulgel microscale droplets (>3000nm) within a size range appropriate for enhanced skin engagement. It's interesting to note that in vitro raw drug release revealed that the basic hydrogel released atorvastatin is the quickest,

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followed by the nanoemulgel and emulgel. This was explained by the more complicated formulations higher viscosity and oil content slowing down the diffusion.

However, the ex vivo permeation results revealed a different picture, and release rate in and of itself does not control therapeutic delivery to the skin tissue, the nanoemulgel had the highest steady-state transdermal flux and enhancement ratio (almost three times that of a simple drug solution) and the shortest lag time before permeation started. The penetration through excised rat skin occurred in reverse order. They conclude that although the nanoemulgel released the drug more slowly, a higher proportion of the medication entered and passed through the skin more quickly. They explain this difference to the surfactant's impact on the fluidity of skin lipids and the larger surface area provided by nanoscale droplets. The benefits of permeation were seen in the functional healing outcomes. In a 21 day, in vivo research, wounds treated with nanoemulgel demonstrated the greatest area decrease between days 14 and 21 when compared to wounds treated with emulgel or pain gel. During the trial all three formulations were well tolerated and none of the treated animals showed signs of skin irritation.

The best indication of regenerative quality, as opposed to merely the rate at which a lesion closes, comes from histopathological findings, which supported macroscopic findings. At baseline, untreated wound tissue exhibited significant congestion, bleeding and inflammatory infiltration, along with a total absence of epithelium. After 21 days, pain-gel-treated wounds exhibited residual inflammatory cells and had not fully re-epithelialized, earning a "poor" healing score. With complete epithelialization, granulation tissue, and fibrous tissue, the emulgel treated wound healed more quickly and were placed in the "fair" category. The tissue sections of the nanoemulgel-treated skin group showed complete regeneration of the epithelium with an ordered skin architecture, normal – looking dermis and surprisingly – complete regeneration of the skin appendages (hair follicles and sebaceous glands), with only a faint trace of inflammation. This led to a "good" healing score, which was the best of all groups and indicates that the healing is of higher quality than scar repair and goes beyond surface closure.

All of the data show that the nanoemulgel formulation not only improves atorvastatin delivery kinetics in vitro but also modifies the biological nature of the healing product and produces a healing wound bed that resembles normal, intact skin with appendages rather than a healed defect because of its ability to promote wound healing without causing systemic side effects, atorvastatin nanoemulgel is an appealing topical administration strategy for statins.

WOUND HEALING AND REGENERATIVE POTENTIAL OF THYMOQUINONE NANOEMULGEL[40]

The main bioactive component of black seed (Nigella sativa), thymoquinone is well-known for its biological properties, such as antibacterial, anti-inflammatory, and anti-oxidant properties, which make it a viable option for wound treatment. However, its weak water solubility, poor skin penetration, and sensitivity to light degradation have limited its therapeutic applicability. In order to attain high drug loading the researchers were able to take advantage of the drug's inherent matching with its source material .They selected a formulation with a droplet size of approximately 94nm and a strongly negative zeta potential (which indicates good physical stability)to proceed into gel form after screening surfactant/co surfactant combinations and optimizing the ultrasonication process reduced eighteen candidate formulations to a few with droplet sizes below 100nm.The resulting nanoemulgel exhibited thixotropic flow behavior with pseudoplasticity and a pH that was comparable to the skin's natural acid mantle; that is it became less viscous during the shear of spreading and more viscous when at rest. This rheological profile is appropriate for topical application because it spreads easily but stays in place after applications.

Skin penetration was the formulation's biggest benefit, in an ex vivo study employing Franz diffusion cells, nanoemulgel demonstrated a five-fold increase in drug flux and permeability coefficient compared to traditional thymoquinone gel, along with a shorter permeation lag time and noticeably greater drug deposition in the skin. This is because the nanosized droplets higher surface area and negative surface charge, along with the co-surfactants in their formulation facilitate medication transport over the epidermal barrier.

This resulted in an in vivo healing trajectory that was significantly quicker in a 20 day research on wound healing in Wistar rats, the animals treated with the thymoquionone nanoemulgel required an average of 10.3 days to reach full epithelialization, whereas the untreated wounds took 16.6 days and the traditional thymoquinone gel took roughly 14.3 days. Surprisingly, the nanoemulgel healing duration was almost identical to the commercial silver sulfadiazine cream (about 11.7 days) a common clinical wound treatment. This puts a naturally occurring bioactive substance on par with a recognized pharmaceutical standard when administered correctly. Compared to the untreated or conventional -gel groups, the nanoemulgel and silver sulfadiazine groups also displayed early healing indicators such as reduced edema and the early development of granulation tissue.

The histological results at day 20 support the theory that there was both quicker closure and a higher quality regeneration as was also seen in the silver sulfadiazine group but not in the conventional gel group, the tissue from the nanoemulgel group displayed numerous collagen fibers, well-organized collagen fibers, thickened epidermal layer, well developed papillary dermis, and regenerated sebaceous glands and hair follicle. In contrast to traditional gel treated tissue, which showed signs of lingering inflammation, the inflammatory cells in the nanoemulgel and silver sulfadiazine groups were negligible. In contrast to

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the more chaotic scar-type tissue that results from incomplete or delayed healing, the existence of regenerated skin appendages is particularly significant since it signifies a return to the skin's original architecture.

Overall, the study indicates that thymoquinone delivered via nanoemulsion -based gel not only enhance as a lab -measured permeation parameter but also modifies the functional and structural outcome of the healing process itself, producing tissue that is more fully and normally regenerated at a rate comparable to a typical clinical wound care product.

WOUND HEALING AND REGENERATIVE POTENTIAL OF BRUCINE NANOEMULGEL IN DIABETIC WOUNDS[41]

This study takes on a more difficult healing model than the previous formulations discussed – diabetic wounds where chronic hyperglycemia disrupts nearly every stage of normal tissue repair, prolonging inflammation, impairing blood vessel formation, and delaying epithelial closure. The active compound brucine, an alkaloid from NUX VOMICA with recognized anti-inflammatory and anti-oxidant activity, but its poor solubility and known toxicity have historically restricted it to non-systemic, localized use encapsulating it in a nanoemulgel was intended to concentrate its benefits at the wound site while sidestepping the risks of broader systemic exposure.

Before any formulation work, the researchers used molecular docking to build a mechanistic case for brucine's relevance to wound repair. Brucine showed strong predicted binding affinity for fibroblast growth factor receptor (FGFR)and epidermal growth factor receptor (EGFR)-two proteins central to fibroblast activation /collagen synthesis and keratinocyte proliferation / re-epithelialization, respectively. It also showed moderate affinity for MMP-1(involved in extracellular matrix remodeling) IL-6 and IGF-1R, with weaker affinity for TNFα-and VEGF. Taken together, this docking profile suggested brucine's primary route of action in wound healing runs through fibroblast stimulation and tissue remodeling rather than direct anti-inflammatory or angiogenic effects, though these predictions weren't confirmed by direct protein expression or cytokine assays in this study.

From a formulation, the nanoemulgel produced a remarkably small particle size (about 125nm, as opposed to roughly 920nm for a plain drug-loaded gel and 168nm for a simpler emulgel) with a strongly negative zeta potential that indicated good colloidal stability. This was further supported by TEM imaging, which revealed uniform, well-defined spherical droplets. Ex vivo and In vitro testing revealed that the nanoemulgel provided about 1.8 times greater skin penetration than a plain gel, with more controlled release lasting up to 12 hours. This is a helpful feature for a topical product meant to sit on a wound and act gradually rather than dumping its payload quickly.

The in vivo findings, which were obtained over a 14-day period in Streptozotocin – induced diabetic rats, made a striking distinction between the treatment groups. By day 14, brucine nanoemulgel -treated wounds had closed around 80%of the time, compared to about 65% for normal povidone–iodine treatment and only 40% for diabetic controls who were left intermediate form, suggesting that than the nano-delivery system rather than merely the brucine was actually accelerating the healing process.

Untreated diabetic wounds showed high neutrophilic inflammatory infiltration, disordered architecture, and epidermal hyperplasia, all of which are indicative of the tissue's halted healing. Although some isolated ulceration and partially formed epidermis were still visible, the standard treatment group showed some actual repair activity, including the development of granulation tissue containing fibroblast and the production of new blood vessels. Only limited epithelial growth and mild scarring were observed in the simple gel and emulgel groups. The most ordered, well-formed epidermis and a markedly increased, well- organized collagen bundle formation were observed in the tissue treated with the nanoemulgel. These features can be attributed to more complete tissue regeneration rather than just quicker wound healing.

In the context of a diabetic wound model, where conventional treatments are frequently insufficient, the study presents two arguments for the overall regenerative value of brucine: computational support for a plausible mechanism involving fibroblast and keratinocyte growth-factor pathways, and experimental support for the enhanced delivery and healing efficacy of brucine in a nanoemulsion - based gel in vivo .This is still preclinical work; long -term toxicity and stability testing will be required before this can proceed toward clinical applications and no direct cytokine or protein expression data were gathered to validate the docking predictions.

WOUND HEALING AND REGENERATIVE POTENTIAL OF THE PROPOLIS-TEA TREE – JOJOBA OIL NANOEMULGEL[42]

This study takes a different approach than the single-drug formulations frequently found in this field. Instead of isolating a single active compound blends three naturally derived ingredients-propolis, tea tree oil, and jojoba oil -into a single nanoemulgel, hoping that their complementary and overlapping biological activities will result in synergistic wound-healing effect. Jojoba oil promotes collagen synthesis in fibroblasts and has anti-inflammatory while tea tree oil has broad antimicrobial action and antioxidant effects.

GC-MS analysis verified the phenolic and flavonoid content of the propolis after it was extracted using ethanolic maceration. After testing several loading concentrations, a loading of 5% propolis with the smallest particle size (approximately 188nm), lowest polydispersity, and best surface charge was chosen. The propolis was then mixed with the jojoba and tea tree oil base in an optimal 2:1 ratio.

In an albumin denaturation assay, the propolis nanoemulsion showed high concentration - dependent anti – inflammatory activity (similar in shape but not quite in magnitude to the reference drug diclofenac) and high

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antioxidant activity (nearly equal to ascorbic acid) in a DPPH free -radical scavenging assay. The propolis nanoemulsion decreased IL-1 levels by approximately 42% and nitric oxide production more than either an untreated control or a blank (propolis -free). The propolis nanoemulsion significantly reduced levels of BAX, a pro-apoptotic marker Bcl-2, as well as NF-κb, a crucial regulator of inflammatory gene expression. HO-1 and Nrf2, two essential components of the cell's own antioxidant defense system were both significantly increased concurrently. When considered collectively, these indicate that the formulation functions through a minimum of three converging channels: reducing inflammatory signaling, safeguarding mitochondrial apoptotic balance, and activating the cell's intrinsic antioxidant response. This is a more comprehensive αformulations.

Nanoemulsions in human dermal fibroblast cells challenged with an inflammatory stimulus .This suggests that the propolis component itself, rather than just the nanoemulsion delivery, the nanoemulgel worked better than a straight forward propolis gel once more, achieving approximately 14.6% skin penetration and 20.6% skin retention after 24 hours, whereas the plain gel only achieved approximately 1.6% and 7.1%, respectively the greater surface area of the nanoscale droplets and the Carbopol matrix's capacity to sustain contact time at the wound site are the cause of this.

There was an obvious functional advantage in vivo as a result of these cellular and delivery advantages. The propolis nanoemulgel group showed much faster wound closure in rats with excisional wounds starting on day 3 compared to untreated controls by day 14, the wounds were near completely closed matching or marginally better than a positive-control nanoemulgel (without propolis). This was corroborated at the tissue biochemical level: wound homogenates from the propolis -treated group had the lowest levels of TNF-α of all groups, the highest activity of superoxide dismutase, a crucial antioxidant lipid damage, this suggests that the antioxidant and anti-inflammatory effects seen in cell culture also occurred in the living wound environment.

This resulted in a better healed wound in terms of histology. On day 14, the untreated tissue continued to exhibit an incomplete or missing epithelial layer and prolonged inflammatory infiltration the group that did not include propolis in the nanoemulgel, on the other hand, demonstrated early and fully re -epithelialization, organized collagen fiber deposition (verified by Masson's trichrome staining ,where the propolis group was significantly better than the other's in terms of the area of collagen bundles at both day 7 and day 14),and regeneration of dermal appendage structures. All of these characteristics are consistent with a more mature, complete stage of tissue remodeling rather than merely surface closure.

Based on convergent action on inflammatory signaling, oxidative stress, and structural tissue regeneration, the study supports the idea that combining these three natural oils into a single nanoemulsion - based gel offers healing benefits that are likely to be greater than any one ingredient alone.

POVIDONE-IODINE AND WOUND HEALING: A CRITICAL LOOK AT THE EVIDENCE [43]

Although povidone-iodine, also known as betadine, is one of the most commonly used antiseptics in wound care, this review presents a more cautious than enthusiastic argument for it. The majority of the information presented here indicates the povidone-iodine is, at best, healing neutral and, at worst, actively cytotoxic to the exact cells that wound repair depends upon, rather than offering a mechanism of regeneration or stimulation of healing

The clearest aspect of the report is the in vitro picture, and it's not good. povidone -iodine is toxic to almost all cell types involved in tissue repair at doses far below what is employed clinically, according to the numerous studies that were mentioned.

Fibroblasts, the cells that lay down new collagen and rebuild tissue architecture, were totally destroyed at concentrations at or above the standard 10% clinical solution, with 0.05% being the only "safe" concentration for fibroblasts. Granulocytes were impacted at concentration above 0.05%, monocytes were toxic above the same threshold and completely toxic above 1%, and keratinocytes were killed 10%at concentrations above a mere 0.004%. Stated otherwise, this indicates that the povidone -iodine is killing the cell population that promote matrix remodeling, proliferation, and reepithelialization at the strength that is typically employed in practice. The nanoemulgel experiments you studied are attempting to speed up the same regenerative processes.

The in vivo results give this picture a hint of intricacy, but not in a reassuring way. Povidone -iodine- treated wounds too nearly 12 days to epithelialize, compared to roughly 7 days for untreated controls or those treated with silver sulfadiazine or mafenide acetate, according to one study that showed wound tensile strength at just 21%of saline-treated wounds by day 4 post surgery (through this difference vanished at later time). According to other research, povidone -iodine at higher concentration (5%) resulted in a detectable, prolonged stoppage of blood flow in granulation tissue, directly impeding the microcirculation that regenerating tissue depends on. However, this effect was either absent or less noticeable at 1% concentrations. The author concludes that any potential antibacterial benefit of povidone- iodine is simply offset by its cytotoxic cost to healing cells- a wash rather than a net positive – because other studies found no discernible difference in healing rates between treatment with saline and povidone -iodine

When it comes to infection control, which is the main justification for using an antiseptic in the first place, the situation is equally mixed rather than obviously beneficial , in acute surgical wounds, some studies have found that povidone -iodine lowers infection rates when compared to

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saline , while others have found no difference .The one study that specifically examined chronic wounds (pressure ulcers) found that povidone -iodine appears to be inferior to saline , with wounds treated with saline having lower bacterial counts after three weeks of treatment . Long -term povidone-iodine exposure has also been linked to renal failure, particularly in elderly individuals or those with preexisting kidney disease, diabetes, or heart failure who are at risk of systematic iodine toxicity.

As a conclusion povidone-iodine seems to be fairly safe for small, acute, short -term wound, but there is no solid evidence that it enhanced healing or regeneration; its safety in large or chronic wounds has not been thoroughly investigated.

WOUND HEALING AND TISSUE REGENERATION POTENTIAL OF THE TURMERIC BASED CREAM[44]

Qureshi et al.'s wound healing cream based on Curcuma longa (turmeric) provides a useful illustration of how regenerative qualities of curcumin might be incorporated into a stable topical delivery system. Turmeric powder was combined with coconut oil, beeswax, vitamin E oil, and tea tree oil in a lipid-based carrier made with a straightforward double boiler method. This formulation enhances the topical delivery of curcumin by combining it with occlusive/moisturizing carriers.

The rationale for formulation is based on curcumin's proven multi-phase impact on wound biology. The four traditional phases of healing (hemostasis, inflammation, proliferation, remodeling) are influenced by curcumin's support of collagen production, acceleration of epithelialization, and promotion of wound contraction. The formulation was created to address inflammation control and infection prevention concurrently with tissue regeneration by combining curcumin with vitamin E, an antioxidant linked to decreased oxidative stress at the wound site, and tea tree oil, valued for its antiseptic action.

The evidence supporting the regenerative and protective potential of the cream derived not from direct in vivo wound healing assays, but indirectly from physicochemical and antimicrobial testing. The pH (6.2-6.5) of the formulation was within the physiological pH range of skin and was therefore in line with the compatibility with the skin barrier during the proliferative and remodeling phases of repair. Agar well diffusion method was used for antimicrobial screening and inhibitory activity was observed against Staphylococcus aureus and Pseudomonas aeruginosa which are two organisms responsible for delayed wound healing and chronic wound infection, with efficacy comparable to a standard antiseptic. This is important as uncontrolled bacterial colonization is known to drive prolonged inflammation and impaired granulation tissue formation.

WOUND HEALING AND TISSUE REGENERATION POTENTIAL OF CURCUMA MANGGA CREAM[45]

One of the more mechanistically thorough analyses of a curcuminoid-based topical formulation that looks at the pro-regenerative and anti-inflammatory components of wound repair in a single oil-in-water cream system is offered by Srirod and Tewtrakul. The inclusion of a cell based functional assays (proliferation and scratch-wound migration on human dermal fibroblasts, HDF). In this work, in contrast to formulations based solely on physiochemical characterization, allowed to model two distinct cellular events driving tissue regeneration: fibroblast recruitment and wound bed closure.

Although not linearly, the formulation's regeneration activity was concentration dependent. At low concentration (1-3ug/ml), creams containing 2%.5%, 10% w/w C. Mangga extract all increased HDF viability above 100% of control, suggesting a proliferative rather than cytotoxic effect; at higher test concentrations (10-30 ug/ml), viability decreased toward or below baseline, suggesting a limited effective concentration window for regenerative benefit.

Since the resolution of inflammation is a prerequisite for the tissue to enter the proliferative phase, the scientists credit the formulation's anti-inflammatory action for this regenerative activity. The idea that the reduction of pro-inflammatory mediator output at the wound site can create a more permissive environment for the fibroblast-driven repair processes captured in the migration assay and that is supported by the cream's inhibition of nitric oxide production in LPS-stimulated RAW 264.7 macrophages, with the 10% w/w formulation showing IC50 values of 34.1-37.9 ug/ml, which is better than the 54.3 ug/ml for diclofenac gel.

This study's measurement of the wound healing bioactivity before and after an accelerated heating-cooling stability procedure six cycles of 45C/4C is important in evaluating formulation resilience. Following stability testing, the 5% cream's migration rates only slightly decreased from 80.1% to 75.2% at 36 hours. This was confirmed by HPLC data showing that, despite heat stress, the underlying curcuminoids-curcumin, desmethoxycurcumin and bisdemethoxycurcumin retained a relatively stable relative composition (10:75:15) with only a slight decrease in desmethoxycurcumin content.

LOW-CONCENTRATION POVIDONE-IODINE OINTMENT (LPIO): A REFORMULATION STRATEGY FOR TISSUE-COMPATIBLE ANTISEPSIS[46]

By evaluating whether reformulation of the antiseptic, rather than its discontinuation, could balance antibacterial action with tissue regeneration, Mitani et al. offer a mechanistic response to worries expressed over traditional povidone-iodine cytotoxicity. Their low-concentration povidone-iodine ointment was made in a hydrophobic white petrolatum-based carrier instead of the aqueous vehicles used in traditional povidone-iodine solutions, and it has an active iodine content of 1% w/w as opposed to 3%w/w standard concentration ointment, SPIO. The two factors-iodine concentration and base composition that have been linked to antiseptic-induced cytotoxicity and wound desiccation are immediately taken into consideration.

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LPIO consistently demonstrated superior outcomes to both SPIO and untreated controls in metrices directly related to tissue regeneration, not just infection management, in two full-thickness wound models involving hairless rats and rabbit ear lobes. In rat model, wounds treated with LPIO exhibited significantly smaller wound areas on day 14 compared with those treated with SPIO or the untreated control. Histopathological evaluation also revealed lower degrees of fibrin deposition, edema and cellular infiltration in the LPIO-treated wounds compared with the control group. These findings were interpreted as indicative of a more effectively resolving inflammatory phase rather than the persistence of chronically inflamed wound bed. Among the three groups, the SPIO-treated wound had the lowest histological healing ratings due to increased crust formation, hemorrhage and neutrophil infiltration.

A notable regenerative end point of study was the extent of re-epithelialization. In a rabbit model, the rate of re-epithelialization was92.8% for LPIO-treated wounds and 24.3% for SPIO-treated wounds. The authors explain this mechanistically by pointing out that while LPIO maintained a moist wound environment with no crust formation during treatment, SPIO-treated wounds developed a hard surface crust from day one, which they claim physically prevents keratinocyte migration across the wound bed. The effectiveness of epithelial migration is directly linked to moisture retention at the wound surface.

Furthermore, LPIO-treated rat wounds exhibited significantly greater numbers of PCNA-positive cells than both SPIO treated and untreated control wounds. Additionally, markers linked to basal keratinocyte turnover and proliferative phase keratinocyte activity were more strongly expressed in the regenerating epithelium of LPIO-treated wounds than in SPIO-treated tissue, while positive staining was primarily limited to the wound periphery rather than the actively healing center. Together, these indicators imply that the reformulated ointment was linked to an active proliferative response by some measures outperformed even the untreated control, in addition to having no negative effects on the regenerative cell populations.

Histological evidence of wound healing and tissue regeneration: curcumin powder versus essential oil

A complementary viewpoint to the physiochemical and cell culture- based evidence covered elsewhere in this review is provided by histopathological approach of Muhammad and Ghani, which directly investigates tissue level regeneration in a living wound model rather than assuming regenerative potential from formulation stability or in vitro assays. At four time points(days3,7,10 and 14), the authors examined the effects of topical curcumin powder and curcumin essential oil on incisional wounds made on the facial skin of New Zealand rabbits, monitoring histological indicators of healing such as inflammatory cell infiltration, granulation tissue formation, re-epithelialization, collagen remodeling and neovascularization.

Although the rate and extent of healing varied between the treatment groups, the temporal histological progression in both treatment groups closely matched the traditional phases of wound healing. On day three, granulation tissue with substantial inflammatory cell infiltration was seen in both the curcumin oil and powder groups. The powder rough also had clogged blood capillaries, which is a sign of an active inflammatory phase. By day seven, both groups had developed thin new epithelium with fibroblasts and early collagen fiber deposition, along with continuing vascular changes. By day 10, both treatment arms had finished re-epithelialization with visible blood vessels and maturing fibrous connective tissue, indicating a far quicker proliferative phase advancement than the untreated control, which at the same interval only displayed a thin covering.

By day 14, the two-curcumin preparation showed the most striking restorative difference with mature fibrous connective tissue with fibroblasts aligned along collagen fibers, numerous blood vessels, and numerous proliferating hair follicles, the essential oil group demonstrated what the authors called complete wound healing. These findings are consistent with a fully remodeled, functionally restored dermis. On day 14, the powder group likewise displayed full wound closure with dense, mature collagen fibers and new epithelial layers. Nevertheless, the author's overall evaluation favored the essential oil formulation since it was more successful in speeding up wound contraction and re-epithelialization throughout the investigation.

This is also statistically supported by the inflammatory cell count data. On day three, both curcumin treatments were linked to noticeably greater inflammatory cell numbers than the control. The scientists regarded this as evidence of an enhanced, more aggressive inflammatory response than facilitated a quicker transition into the proliferative phase rather than as a negative finding. A crucial mechanical distinction is made in the review. In this model, curcumin treatment appeared to increase the early inflammatory phase before causing a steeper subsequent decline in inflammatory cell number rather than completely decreasing inflammation. Both the histological picture and the essential oil group saw the fastest decline by day 14, falling to a mean of essentially the lowest levels.

By comparing different physical forms of curcumin delivery (essential oil versus crude powder), this study provides complementary evidence on how the delivery form may influence regenerative outcomes, independently of the specific cream or vehicle matrices investigated in the topical formulation studies discussed above. It therefore represents a valuable addition to a review of curcuminoid-based wound therapies. This suggests that the pace of granulation tissue maturation, collagen remodeling, remodeling and follicular regeneration may be more significantly impacted by the way curcumin is delivered in a bioactive form. This naturally complements the cream-based investigations adding a formulation science component. While this histology study discusses which

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physical form of curcumin (oil vs powder) gives the best results, the turmeric and C. Mangga creams deals with the stable delivery of curcuminoids via a lipid or emulsion carrier.

This study use a single wound model (facial incisional wounds in rabbits) without comparison to a non- curcumin topical vehicle control (such as a plain excipient base) is a limitation that should be emphasized for the critical discussion of the review. This means that the effect of the curcumin itself cannot be fully separated from potential occlusive or moisture retaining effects of the powder oi oil vehicle. This issue is also relevant to interpreting the cream – based curcuminoid studies covered elsewhere in this review.

CONCLUSION

The evidence in this analysis makes a strong case that nanoemulgel is a significant advancement over traditional gels, cream, hydrogel and antiseptic ointment that is compared to rather than a small improvement of current topical technology. After being reformulated as a nanoemulgel, every single active tested here- curcumin, atorvastatin, thymoquinone, brucine, and the propolis-tea tree, jojoba combination- performed better. Improvements were in comparison to a simple gel, cream and drug solutions, transdermal flux and permeability increased 3-6 times when droplet sizes dropped from the microscale of traditional emulgels (typically > 900-3000nm) to 90-190 nm. In this review none of the traditional formulations even approached that delivery improvement. Wounds treated with nanoemulgel typically epithelialized more quickly than their conventional – gel counterparts – roughly 10 days versus and 14 for curcumin and 10.3 days versus 13.34 for thymoquinone- and in a number of instances, they either matched or outperformed clinical gold standard silver sulfadiazine.In contrast to 65% for povidone iodine and 40% for untreated controls, brucine nanogel achieved over 80% closure on day 14 in the more challenging diabetic wound type. The tissue treated with nanoemulgel showed a thicker more ordered epidermis, denser, better-aligned collagen deposition, less residual inflammation, and -most glands. These characteristics are rarely attained with traditional gels and creams and the actively inhibited by fibroblasts, keratinocytes and monocytes at clinically used concentrations. To put it briefly, nanoemulgel formulations regenerate skin while conventional formulations heal wounds.

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