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UNVEILING THE POWER OF SILVER SULFADIAZINE AND CURCUMIN IN TOPICAL THERAPY FOR WOUND HEALING.

Christina Viju John, Sakshi Hemant Shinde, Bhavesh Girish Sakpal, Ashlesha Gopinath Munde, Ritesh Vijay Jadhav
Assistant Professor, Final Year B.Pharm student,
TMV's Lokmanya Tilak Institute of Pharmacy, Kharghar

Dr. Shrutika Patil
principal
TMV's Lokmanya Tilak Institute of Pharmacy, Kharghar.

Abstract:

The review explores the therapeutic potential of silver sulfadiazine (SSD) and curcumin in wound healing. It provides an overview of the wound healing process, which includes four phases—haemostasis, inflammation, proliferation, and remodelling—and highlights various factors that can impair healing, such as aging, infections, diabetes, and nutritional deficiencies. Silver sulfadiazine is recognized for its broad-spectrum antimicrobial properties, especially in treating burn wounds and preventing infections, while curcumin, derived from turmeric, is known for its anti-inflammatory, antioxidant, and antimicrobial benefits. The review examines the mechanisms by which SSD and curcumin individually promote healing and prevent infection, focusing on their ability to manage inflammation and enhance tissue regeneration. Additionally, it suggests that combining these two agents could provide synergistic effects, potentially accelerating recovery, reducing infection risk, and improving overall wound outcomes. Advances in drug delivery technologies, particularly nanotechnology, are also discussed as a means to improve curcumin's bioavailability and enhance the therapeutic impact of both agents. The review concludes by stressing the need for further clinical research to validate the efficacy and safety of these topical therapies in wound care.

Index terms: Wound healing, Silver sulfadiazine, Tissue regeneration, Nanotechnology

1. INTRODUCTION:

The wound is defined as the disruption of the anatomic and cellular continuity of tissue caused by chemical, physical, thermal, microbial, or immunological injury to the tissue [1]. Wounds can arise from pathological processes that begin externally or internally within the involved organ. They can have an accidental or intentional aetiology or they can be the result of a disease process.[5] Proper healing of wounds is essential for the restoration of disrupted anatomical stability, to shorten healing time, to decrease the risk of infection, and to restore functional status to the skin.[2]. Wound healing is a process of replacement of dead tissue with healthy functional tissue. Both surfaces should be close enough to each other for an effective process of tissue bridging among them.[1].The wound healing process is usually characterized as four sequential but overlapping phases: haemostasis (0–several hours after injury), inflammation (1–3 days), proliferation (4–

21 days) and remodelling (21 days–1 year). [2]. Unbalancing one or more of these phases could lead to two distinct damaging outcomes: either chronic wound development or the formation of a hypertrophic scar/keloid. [3]. Wounds that exhibit impaired healing, including delayed acute wounds and chronic wounds, generally have failed to progress through the normal stages of healing. [4]. Wounds that repair themselves and that proceed normally by following a timely and orderly healing pathway, with the end result of both functional and anatomical restoration, are classified as acute wounds. The time course of healing usually ranges from 5 to 10 days, or within 30 days. Chronic wounds are those that fail to progress through the normal stages of healing and they cannot be repaired in an orderly and timely manner. [5].

1.1 Factors affecting wound healing: [5] [6]

Impaired wound healing can result from a number of circumstances. Following are some factors affecting wound healing:

1.Age: Aging slows down re-epithelialization, angiogenesis, and collagen deposition, weakens wounds, and slows tissue repair by increasing platelet aggregation, extending inflammation, delaying immunological responses, and reducing macrophage function.

2.Oxygenation: Oxygen plays a key role in wound healing by supporting collagen formation, angiogenesis, and cell metabolism. Extended hypoxia and infections decrease the healing process, and antibiotic-resistant bacterial biofilms make treatment more difficult. Efficient wound healing depends on maintaining appropriate oxygen levels and controlling infections.

3.Stress: Stress can lead to anxiety and depression, which impair immunological and endocrine function and encourage harmful habits including substance abuse, poor sleep, and bad diet. All of these things work against the body's ability to mend itself.

4.Infections: By eliminating microorganisms, inflammation aids in the healing process. If this process is not completed, it can slow down the healing process, raise pro-inflammatory cytokines, and damage tissue, which can result in chronic wounds and antibiotic-resistant biofilms like those produced by Staphylococcus aureus.

5.Diabetes: Diabetes causes chronic inflammation and interferes with leukocyte activity, which hinders wound healing. Additionally, it produces a hypoxic environment that delays reepithelialization and matrix remodelling by impeding angiogenesis and influencing keratinocyte and fibroblast activity.

6.Obesity: Obesity impedes the healing of wounds, resulting in hematoma, oedema, seroma, pressure and venous ulcers, and local infections.

7.Nutrition: Proteins, carbs, fatty acids, vitamins, and minerals are all necessary for wound healing. Because malnutrition reduces angiogenesis and prolongs inflammation, it can postpone healing. Omega-3 fatty acids, vitamin A, vitamin C, iron, and proteins like arginine and zinc are important nutrients that are necessary for a number of healing processes.

8.Alcohol: Chronic and acute alcohol intake might hinder wound healing by decreasing immune function and raising infection risk. Pro-inflammatory cytokines and neutrophil recruitment are first decreased by alcohol, but they are later increased. Moreover, it interferes with angiogenesis, leading to decreased collagen synthesis, oxidative stress, and hypoxia.

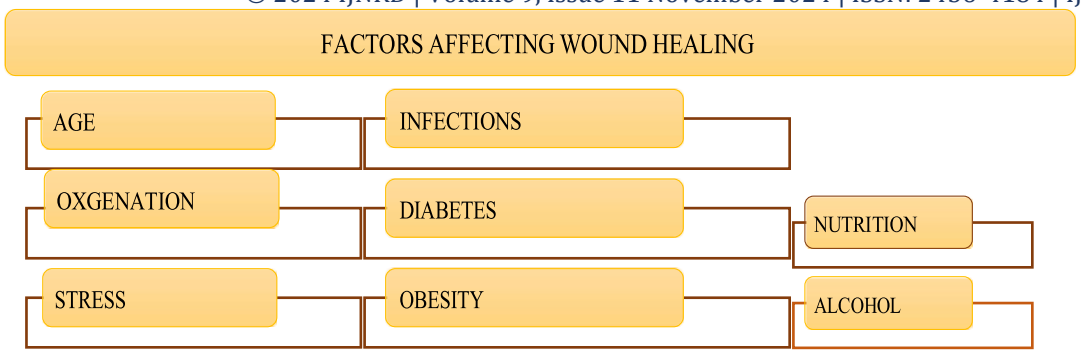

Fig 1: FACTORS AFFECTING WOUND HEALING

Wounds must be treated quickly to produce the best functional and aesthetic outcomes. Periodically reducing bacterial infection and eliminating soluble debris would be the ideal topical therapy, provided that it does not negatively affect cellular processes that are essential to the wound healing process.[11].Antibacterial topical treatment can change the wound environment by promoting epithelialization or decreasing fibroplasia.[7] Therapeutics applied topically are promising because they limit systemic side effects and produce local effects, but they are also hindered by the proteolytic wound environment, which lowers drug absorption.[8].

Turmeric is derived from the rhizome of the Zingiberaceae plant, *Curcuma longa linn. (Curcuma domestic Valeton*).[12]. The active ingredients in turmeric, known as curcuminoids, may be responsible for its therapeutic properties. Curcuminoids are the conjugate name for curcumin, desmethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). Because of its many benefits, including anti-inflammatory, anti-mutagenic, antibacterial, and antioxidant qualities, curcumin has long been utilized as a medicinal herb.[9]. Curcumin has been shown to boost the healing of cattle wounds. Myofibroblasts, fibroblasts, and macrophages are among the cells whose re-epithelialization and migration are enhanced by curcumin.[7].

Fig 2: PHARMACOLOGICAL ACTIVITY OF CURCUMIN

In medicine, silver salts and their complexes were extensively employed as antibacterial agents. Components of silver are resistant to both Gram-positive and Gram-negative bacteria. It was said that in order to combine the antibacterial activity of wound dressings with their biocompatibility, the concentration of silver components should be optimized. Silver Sulfadiazine (SilvadeneR, FlamazineR), [(4-aminophenyl) sulfonyl] (pyrimidin-2-yl) azanido silver(I)] is a famous broad-spectrum antibiotic ointment that works well against a variety of bacteria and yeasts. It is applied to burnt skin areas to prevent and treat skin infections.[13] As a cream, silver sulfadiazine has been used to inhibit wound infection. To assess the impact of SSD concentration on an actual wound healing process model, in vivo research is still necessary.[10].

FIG 2: PHARMACOLOGICAL ACTIVITY OF CURCUMIN

1.2 OBJECTIVES OF THE REVIEW:

1.Understand wound healing and how it helps to repair damaged skin.

2. Examine both acute and chronic wound types and how they develop via the stages of haemostasis, inflammation, proliferation, and remodelling.

3. Determine which variables—such as age, oxygenation, stress, infections, diabetes, obesity, diet, and alcohol—have an effect on wound healing and how they alter the processes that repair damaged tissue.

4. Analyse curcumin's effects on re-epithelialization and collagen deposition as well as its antiinflammatory, antioxidant, and antibacterial qualities in relation to wound healing.

5. Verify silver sulfadiazine (SSD) in wound care, focusing on infection prevention and antibacterial activity to maximize healing conditions.

6. Investigate how the anti-inflammatory and antibacterial properties of curcumin and SSD together may improve wound healing.

7. Examine the studies on topical therapies' efficacy in wound healing, with a focus on SSD and curcumin, and pinpoint areas that require more investigation.

These goals provide a framework for evaluating how curcumin and silver sulfadiazine affect wound healing and infection control. [11]

They work together to provide a synergistic impact that promotes wound healing. When combined, their qualities may promote healing, lower infection rates, and enhance wound care

results overall. This strategy is a potential development in topical treatments for a variety of wound types. The review looks at both chemicals' modes of action, therapeutic uses, and the possible advantages of combining them to improve healing results. Combining these two substances could provide a fresh method for enhancing wound care, speeding up the healing process, and lowering risks.

2. MECHANISM OF WOUND HEALING –

2.1.1 First phase - Haemostasis:

Blood and lymphatic fluid are released as a result of the first injury. The initial reparative coagulum is also formed during this process. The extrinsic and intrinsic clotting processes are both triggered. Thrombocytes are responsible for the

intrinsic mechanism, while wounded tissues are responsible for the extrinsic mechanism. Platelets stick to injured endothelium after vasoconstriction and release adenosine diphosphate (ADP), which encourages thrombocyte clumping and seals the lesion. After the brief vasoconstriction is over, the arteries widen, allowing more thrombocytes and other blood cells to enter.

The onset of the inflammatory phase can be considered at this point. Once more demonstrating the overlapping nature of the healing phases, the inflammatory phase begins during the haemostasis phase, despite the fact that some people refer to it as a distinct phase. To speed up the healing process, these thrombocytes and the white blood cells they have recruited release a variety of substances. Platelet-derived growth factor (PDGF), platelet factor IV, and transforming growth factor (TGF) are released by alpha-granules. Inflammation, collagen synthesis and breakdown, myoblastic formation from fibroblasts that have undergone transformation, the development of new blood vessels, and reepithelialisation have all begun.

Cytokines and growth factors, such as VEGF, which stimulates the creation of blood vessels, and interleukins, which control inflammation, are the main drivers of the inflammatory process. FGF-2 promotes reepithelialisation as well as angiogenesis. This reaction is aided by vasoactive amines generated by thrombocytes, such as serotonin and histamine. While fibrin, which is made from fibrinogen, gives inflammation structural support, PDGF and TGF-β3 promote fibroblast activity, which results in the synthesis of collagen. Following an injury, this procedure starts right away and may continue for a few days.

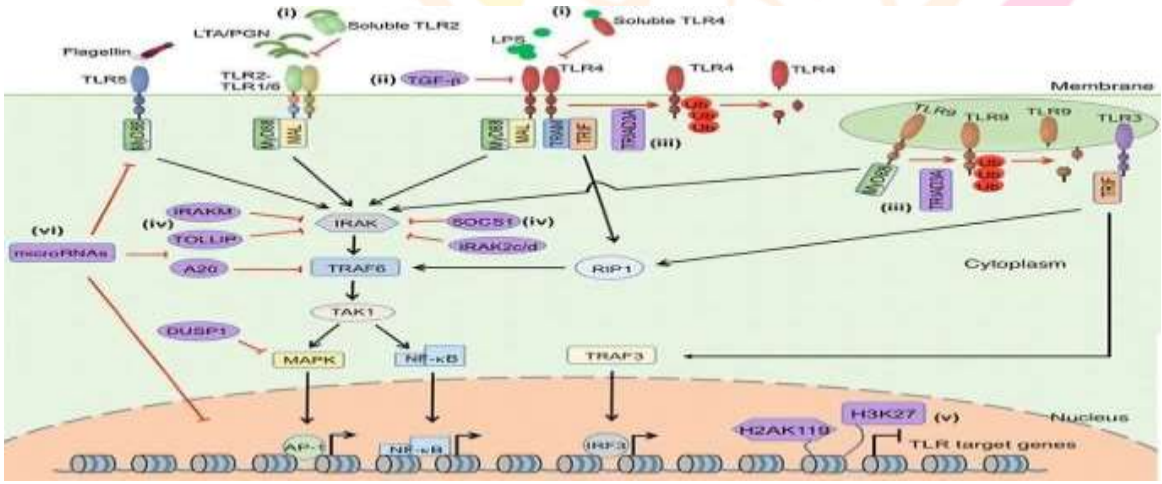

Fig. 4. Mechanism of Wound healing [14]

2.1.2 Second phase - Inflammation:

The haemostasis phase can be divided into two parts: the early phase is bleeding and haemostasis, and the late phase is coagulation. Although the inflammatory phase begins during the haemostasis phase, the inflow of polymorphonuclear leukocytes (PMNs) dominates the early part of the inflammatory phase, whereas monocytes and macrophages dominate the later part.

PMNs engorging the wound is the next stage of the healing process, which begins within the first 6 to 8 hours. PMN migrate from nearby blood vessels and extrude themselves from them with the help of TGF-13. By removing debris from the wound, these cells purify it. Within 24 to 48 hours, the PMNs reach their peak numbers, and by hour 72, they start to depart. FGF, TGF-13 and TGF-a, PDGF, and plasma-activated complements C3a and C5a (anaphylactic toxins) are among the other chemotactic agents produced. They are either buried in the scab or eschar or sequestered by macrophages.

Monocytes leave the arteries and transform into macrophages as the process goes on. By days three and four, these macrophages aid in wound cleaning and the production of growth factors that stimulate fibroblast activity, smooth muscle cell proliferation, endothelial cell multiplication, and the formation of new blood vessels. Additionally, they release important substances that affect wound healing, such as PDGF, TNF, IL-1, and TGFs.

2.1.3 Third phase - Proliferation

This phase consists of different subphases. These subphases do not happen in discrete time frames but constitute an overall and ongoing process. The subphases are fibroplasia, matrix deposition, angiogenesis, and reepithelialisation.

Fibroblasts have moved into the wound on days 5-7, forming new collagen of kinds I and III. Type III collagen predominates during the early stages of normal wound healing, although type I collagen eventually takes its place. All forms of collagen start with tropocollagen, which undergoes hydroxylation of proline and lysine in the rough endoplasmic reticulum of the cell. Three tropocollagen strands can form a triple left-handed triple helix, known as procollagen, thanks to the formation of disulphide bonds. True collagen fibrils are produced when peptidases in the cell wall cleave terminal peptide chains in the procollagen as it is released into the extracellular space.

Fibroblasts create fibronectin and GAGs, which are infused into the wound. Heparan sulphate, hyaluronic acid, chondroitin sulphate, and keratan sulphate are examples of these GAGs. GAGs known as proteoglycans aid in matrix deposition by being covalently bound to a protein core. The result of parent vessel offshoots is angiogenesis. The breakdown of the basement membrane and extracellular matrix, followed by endothelial cell migration, mitosis, and maturation, is necessary for the creation of new vasculature. Angiogenesis is thought to be modulated by vascular endothelial growth factor and basic FGF.

Cell migration from the adnexal structures and wound periphery results in reepithelization. Within 24 hours, the cells begin to spread, marking the beginning of this process. Peripheral cell division takes place between 48-72 hrs , producing a thin layer of epithelial cells that fills the incision. In this area of wound healing, epidermal growth factors are thought to be crucial. Up to four weeks may pass during this series of subphases in the clean, uncontaminated wound.

2.1.4 Fourth Phase - Remodelling and Maturation

Beyond the third week, the wound experiences ongoing changes, referred to as remodelling, which may continue for years beyond the original damage. The amount of collagen in the wound remains unchanged as a result of the equilibrium-producing manner in which collagen is broken down and deposited. In a typical wound healing process, the amount of collagen deposited peaks three weeks after the lesion has formed. Myofibroblasts, which are specialised fibroblasts that resemble contractile smooth muscle cells, proliferate and contribute to the continuous process of wound contraction. Compared to primary healing, wound contraction happens more frequently during secondary healing. By the 12th week, the wound has reached its maximum tensile strength, and the final scar has only 80% of the original skin's tensile strength, which it replaced[16]

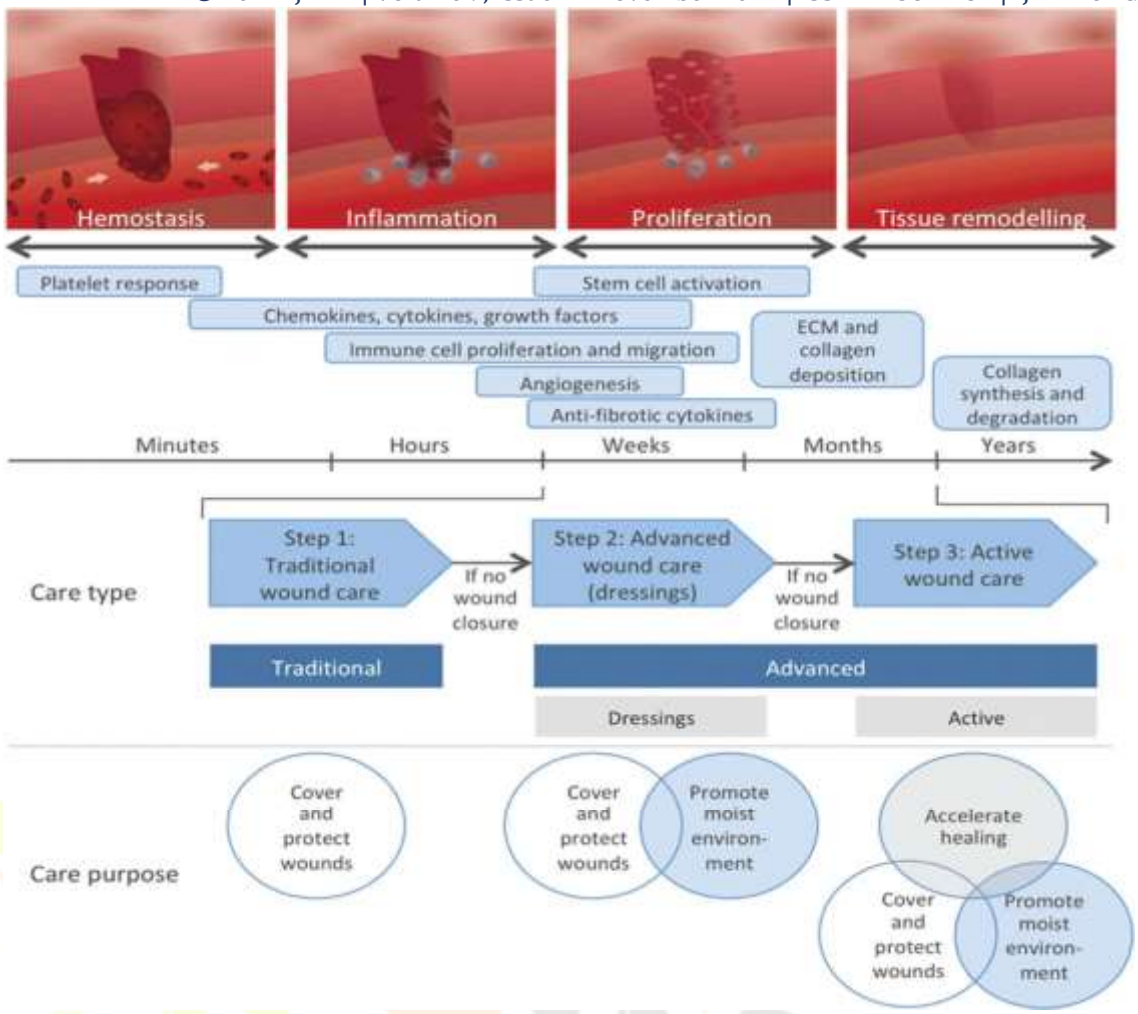

Fig 5. Overlapping phases involving distinct cells and effector mechanisms that all are required for efficient wound healing. [15]

2.2 Role of Topical Agents in wound healing

Topical agents play a significant role in wound healing by providing a conducive environment for tissue repair and protecting the wound from infection. Here's a breakdown of the key roles topical agents play in wound healing:

1. **Balance of Moisture**- Sustaining ideal moisture levels is essential for the healing of wounds. Topical medications including alginates, hydrocolloids, and hydrogels aid in moisture retention, resulting in a moist wound environment that speeds up healing, lessens discomfort, and stops tissue dryness. These substances aid in the removal of dead tissue from the wound through autolytic debridement. [17]

2. **Prevention of Infections** - By preventing bacterial development, topical antimicrobial medicines such polyhexamethylene biguanide (PHMB), honey, iodine, and silver-based dressings are frequently used to prevent illness. Burns, diabetic ulcers, surgical wounds, and other chronic or infection-prone wounds require these medications more than others.[18]

3. **Inflammation Reduction** - To lessen excessive inflammation, topical anti-inflammatory medications such corticosteroids or non-steroidal anti-inflammatory medicines (NSAIDs) might be used. In order to prevent persistent wounds and encourage effective healing, inflammation must be reduced. [19]

4. **Cellular Activity Promotion** - Some topical medications encourage the synthesis of collagen and cellular activity, both of which are necessary for tissue regeneration. Growth factors such as fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) are examples. These substances promote keratinocytes and fibroblasts, hastening the healing process of wounds. [20]

5. **Debridement** - Collagenase and other topical enzymatic debrides aid in the breakdown of necrotic tissue, making it easier for the body to eliminate dead tissue. This encourages the development of healthy granulation tissue, which is necessary for the closure of wounds.[21]

6. **Pain Control** - Localised pain relief by topical analgesics, like lidocaine or benzocaine, can help patients feel less uncomfortable, particularly in burns or wounds from surgery. [22]

7. **Reduction of Scars** - After healing, several topical treatments are used to lessen hypertrophic scars or keloids, such as silicone gel sheets or allantoin-containing lotions. By gradually softening, erasing, and flattening scars, they enhance their appearance. [23]

8. **Properties of Antioxidants** - Antioxidants found in some substances, such as vitamin E, honey, and *aloe vera*, aid in the neutralisation of free radicals, lowering oxidative stress in the wound and accelerating healing. [24]

3.SILVER SULPHADIAZINE:

As general antibacterial agents, silver and silver compounds have long been utilised. Most people agree that silver, in its typical ionic (active) form (Ag+), is a safe, all-purpose antibacterial. This topical antibacterial agent combines the pharmacodynamic effects of sulfadiazine and silver [25].

3.1 Chemical structure -

When sulphadiazine, a weak acid, combines with silver nitrate to form the complex silver salt, silver sulphadiazine (SSD), a non-ionized, water-insoluble, fluffy white powder, is created. Silver [(4-aminophenyl) sulfonyl] (pyrimidine2-yl) azanide (C10H9 AgN4 O2 S) is its chemical structure. From a structural perspective, it is a polymer in which every silver ion is tetracoordinate and encircled by three distinct deprotonated sulpha molecules, each of which binds three distinct silver ions.

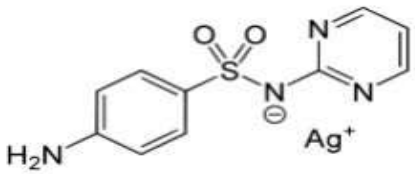

Fig 6: Chemical structure of silver sulphadiazine [26]

3.2 Mechanism of action:

Silver sulfadiazine is an antibiotic that contains sulphonamides, but unlike other sulpha medications, it does not prevent the formation of folic acid.[5] The silver ions are what give it its antibacterial properties. As a result, there is little eschar penetration and the silver ions only function superficially.[6] Although silver sulfadiazine's precise mode of action is currently unknown, it is hypothesised that the drug increases cell wall permeability by preventing the replication of deoxyribonucleic acids, altering the lipid cell membrane directly, and/or generating free radicals.[27]

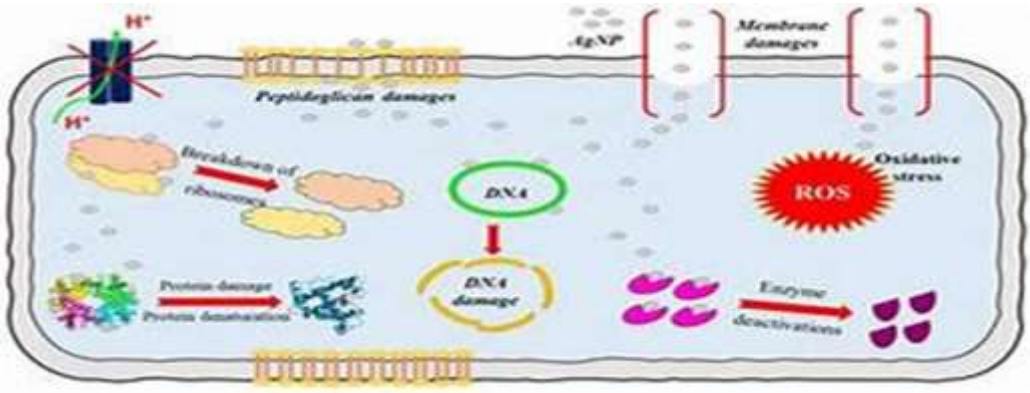

Fig 7: Mechanism of silver sulphadiazine

3.3 Properties:

a) Antimicrobial Activity

Broad-spectrum antimicrobial activity: SSD exhibits strong bactericidal properties against a variety of pathogens, including some fungi and both Gram-positive and Gram-negative bacteria. It works very well against *Candida species*, *Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa.*

b) Properties that Reduce Inflammation

By preventing bacterial colonization, SSD lowers the inflammatory response at the wound site, hence preventing chronic inflammation that may impede recovery.Additionally, it inhibits the synthesis of pro-inflammatory cytokines, which facilitates a more regulated healing environment.

c) Diabetes mellitus

Hyperglycemia is a hallmark of diabetes mellitus, a disorder of aberrant metabolism linked to a significant risk of certain long-term consequences. According to studies, AgNPs can regulate blood sugar by blocking important enzymes linked to diabetes and the breakdown of carbohydrates. AgNPs' potential for managing diabetes was highlighted by Kanmani et al., who demonstrated that they exhibit antidiabetic effects by significantly suppressing α-amylase (78.84%) and α-glucosidase (58.86%) at a concentration of 100 µg/ml. Additionally, it has been demonstrated that AgNPs exhibit strong hypoglycemic action that is very dose-dependent. Their anti-diabetic action is enhanced by their increased surface area and decreased NP size. Diabetic wounds are challenging to heal because of increased blood glucose, local hypoxia, compromised immunosuppression, and other reasons. AgNP-containing dressings can lessen the formation of scars and hasten wound healing. This has to do with AgNPs' antibacterial qualities as well as their anti-inflammatory and high surface volume ratio, which improve wound site penetration. A novel kind of AgNPs composite hydrogel was made by Kong et al. The novel dressing made of polymer materials may enhance the microenvironment, encourage wound healing, and reduce discomfort. Because of the dual mode of action that the metal covered by plant components provides, Khalil et al. thought that the biosynthesis of AgNPs had better free radical scavenging activity in wound healing.

d) Cancer

Thapa et al. created AgNPs embedded graphene oxide with associated MTX (MTXGO/AgNPs) and discovered that folate receptor targeted cancer therapy may be employed with this combination approach. According to other research, AgNPs can also be utilized to treat drug-resistant cancers, like metastatic illness or prostate cancer (PCa) that is resistant to hormone therapy. Morais et al. discovered that synthetic AgNPs can treat castration-resistant prostate cancer by producing cytotoxicity through endocytosis. AgNPs demonstrated fresh promise in radiological anticancer therapy techniques, according to Morais et al. In NDDS, medication delivery in cancer treatment was discussed. Furthermore, Haque et al. discovered that AgNPs can be used to treat cancer as a non-invasive near-infrared imaging technique. According to this perspective, AgNPs have a great deal of promise for using novel approaches to cancer treatment. According to Mukherjee et al., biologically produced AgNPs' red fluorescence may be used as an imaging enhancer in cancer illness theranostics to locate medication molecules inside cancer cells.

e) Wound coating/dressing

AgNPs exhibit superior antimicrobial, anti-inflammatory, and drug-carrying properties. AgNPs are added to gels together with other composite materials to create novel bandages and wound dressing solutions. It can lessen inflammation, boost immunity, encourage wound healing, and inhibit the formation of microorganisms resistant to drugs. Researchers have created and marketed wound dressings based on AgNPs that can cover sizable burn areas and promote wound healing. Popescu et al. showed that composite hydrogels containing ibuprofen and AgNPs can enhance the processes of healing and proliferation, rearrange the ultimately injured tissue, and have an antimicrobial effect on wound dressings. Pegylated AgNPs are employed in cancer gene therapy as carriers of short interfering RNA that cause leukemic line cells to undergo apoptosis [28].

3.4 Side effects:

Although silver sulfadiazine is thought to be very safe, its use should be restricted. Reepithelization is slowed by this medicine, which should end as soon as healing is evident. Furthermore, a pseudoscalar will develop over the afflicted area with frequent use, making it impossible to properly diagnose the burn lesion. The removal of this approach necessitates mechanical debridement, which is frequently painful. The most frequent adverse effects are haematologic ones, which include leukopenia, haemolytic anaemia, aplastic anaemia, and agranulocytosis. During patient visits, practitioners should ask about anaemia and/or infection symptoms and adhere to laboratory screening guidelines.There have been reports of dermatologic responses, including as rash, pruritus, skin discolouration, skin photosensitivity, erythema multiforme, and Stevens-Johnson syndrome. Silver sulfadiazine should not be used by patients who have previously developed a rash in response to this medicine, as this could indicate an allergy. Although the possibility of a cross-reaction to silver sulfadiazine is uncertain for individuals with sulphonamide allergies, product labelling advises those patients to refrain from using the medication if they have experienced a severe reaction to sulphonamides in the past.[29]

3.5 Limitation:

The growth of resistant bacteria strains, the purported delay in wound healing, and the onset of systemic adverse effects are undesirable traits linked to the clinical use of SSD. In vitro investigations using different skin cell lines have demonstrated that delayed wound healing is the clinical manifestation of mild toxicity [25]. Although silver sulfadiazine is frequently used to treat wounds, there are certain crucial factors to take into account, including its possible adverse effects, resistance, and ongoing disputes:

3.6 Adverse Reactions:

a) **Skin Reactions**: Localised irritation, burning sensations, and allergic reactions are typical side effects. A rash or discolouration of the skin may appear in certain patients.
b) **Systemic Effects**: In rare cases, systemic absorption may take place, which could result in adverse effects such as kernicterus, a form of brain injury, and leukopenia, a decrease in white blood cell count, in neonates.
c) **Postponed Recovery**: Silver sulfadiazine may not always encourage healing as well as other cutting-edge treatments, especially when it comes to persistent wounds. [30]

3.7 Opposition:

a) **Bacterial Resistance**: The possible emergence of resistance to silver compounds is a cause for concern. Inappropriate or excessive usage of silver sulfadiazine can lead to wider antimicrobial resistance, even though resistance to the drug itself is less well-documented than with other antimicrobials.

b) **Ineffectiveness Against Biofilms:** Silver sulfadiazine might not work well against bacteria that produce biofilms, which are frequently present in chronic wounds and can seriously impede the healing process.

3.8 Disputes:

a) **Efficacy Debate**: Although silver sulfadiazine works well for burn wounds, there is disagreement about how well it works for other kinds of wounds, such as pressure sores or diabetic ulcers. Alternative therapies (such as honey or more recent dressings) might work better, according to some research.

b) **Use in Paediatric Patients**: Its use in newborns and young children is cautious due to concerns about their safety, especially with regard to systemic absorption and the possibility of kernicterus.
c) Cost vs. Benefit: There is constant debate on the cost-effectiveness of silver sulfadiazine in comparison to more recent wound care products, particularly in healthcare settings where resource efficiency is a goal.
d) Clinical and Regulatory Guidelines: There may be discrepancies in the recommendations made by various clinical guidelines on the use of silver sulfadiazine. [31]

4. CURCUMIN:

The subterranean stem or rhizome of a plant that resembles ginger is called curcumin. The plant is 60-90 cm tall, herbaceous, perineal, and has tufted leaves on short stems. Its yellow flowers, which range in length from 10 to 15 cm, bloom from the end of spring until the middle of the growing season. They are grouped together in dense spikes. This plant has no known fruits.[] Profile of the Plant Typical name The Indian saffron, or curcuma biological origin Turmeric is derived from the rhizome of the Zingiberaceae plant, *Curcuma longa linn. (curcuma domestic valeton).* Geographic origin In Cambodia, China, India, Nepal, Indonesia, Madagascar, Malaysia, the Philippines, and Vietnam, it is frequently found. The situation in India It is frequently found in Madras, West Bengal, Tamil Nadu, and Maharashtra. Zingiberaceae is the family. [32]

Fig 8: *Curcuma longa* (Turmeric) Plant

Protein (6.3%), fat (5.1%), minerals (3.5%), carbs (69.4%), and moisture (13.1%) are all present in turmeric. After rhizomes were steam-distilled, an essential oil (5.8%) was produced. It contained a-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpenes (53%)5. The yellow color is caused by curcumin (diferuloylmethane), which is composed of curcumin I (94%), curcumin II (6%), and curcumin III (0.3%).6. Curcumin derivatives dimethoxy and bisdemethoxycurcumin have also been identified7 (Figure 1). Roughley and Whiting9 identified the chemical structure of curcumin in 1973 after it was initially isolated8 in 1815. It is soluble in ethanol, alkali, ketone, acetic acid, and chloroform, and it melts at 176–177°C to form a reddish-brown salt with alkali. [33]

4.1 Chemistry and Applications of Curcumin

A seven-carbon chain including an α, β-unsaturated β-diketone moiety connects two aromatic rings to produce the structure of curcumin, which has the chemical formula $C_{21}H_{20}O_6$. It possesses a high dipole moment of 10.77 D, isomerism (with a more stable trans-form), and keto-enol tautomerism. Curcumin can be added to aqueous solutions using surfactants and micelles since it is lipophilic (log P = 3.2), meaning it is soluble in lipids but insoluble in water.

It has anti-inflammatory, antibacterial, and antioxidant properties; it reduces pro-inflammatory cytokines and reactive oxygen species by blocking pathways such as NFκB and COX-2. Curcumin has also demonstrated potential for enhancing insulin sensitivity and demonstrating antibacterial qualities, especially against gram-positive and gram-negative bacteria, including effects on the formation of biofilms. [34]

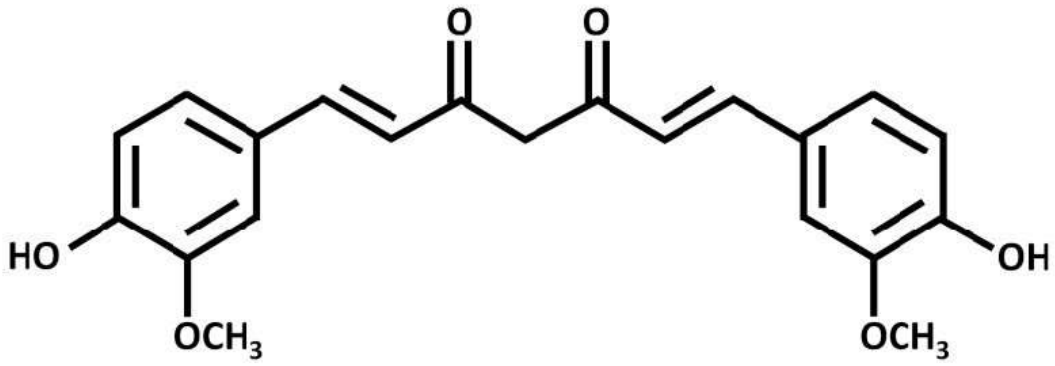

Fig :9 The chemical structure of curcumin

Inflammatory Disease	Viral activity	Cancer
• Rheumatoid • Arthritis • Inflammatory bowel • diseases • Ulcer • Alzheimer's • disease	• Hepatitis C • virus (HCV) • Herpes simplex • Virus (HSV1	• Lung cancer • Breast cancer • Ovarian cancer • Gastrointestinal cancer • Leukemia • Lymphoma

Fig 10: Therapeutic application of curcumin [35]

4.2 PHARMACOLOGICAL PROPERTIES OF *CURCUMA LONGA*

C. longa is said to have a variety of medicinal qualities. It has been observed that C. longa contains flavonoids, terpenoids, glycosides, and curcuminoids. Among curcuma longa's essential characteristics are:

a) **Effects on Inflammation**

By blocking a variety of inflammatory chemicals, including cytokines and enzymes like COX-2, curcumin demonstrates strong anti-inflammatory effects. Because of this, it is advantageous for ailments like inflammatory bowel disease and arthritis. [36]

b) Activity of Antioxidants

Curcumin, a potent antioxidant, can help prevent cellular damage and has implications for aging and a number of diseases by reducing oxidative stress and neutralizing free radicals. [37]

c) Properties of Antimicrobials

Turmeric may have antibacterial properties against fungus, viruses, and bacteria, according to studies. This characteristic could be helpful in the creation of natural preservatives and the management of infections. [38]

d) Properties Against Cancer

Preclinical research has indicated that curcumin may be able to stop the growth of cancer cells, trigger apoptosis, and stop them from spreading. It targets several signaling pathways that contribute to the development of cancer. [39]

e) Neuroprotective Effects

Studies show that curcumin may prevent oxidative damage and inflammation in the brain, hence protecting against neurodegenerative disorders such as Alzheimer's. It might improve cognitive performance as well. [40]

f) Advantages for the Heart

Curcumin promotes cardiovascular health by lowering cholesterol, reducing inflammation, and enhancing endothelial function. It might also aid in the prevention of atherosclerosis. [41]

g) Effects on Metabolism

By increasing insulin sensitivity and lowering blood sugar, curcumin may help control metabolic syndrome. Additionally, it may help with weight management. [42]

h) Effects on Gastroprotection

Digestive issues have long been treated with turmeric. Curcumin may improve gut health, lessen gastric ulcers, and shield the stomach lining. [43]

i) Pain Management

Curcumin is a potential supplementary treatment for chronic pain issues because of its antiinflammatory qualities, which also help to reduce pain.

j) Possible Side Effects of Antidepressants

According to certain research, curcumin may have antidepressant properties because of its impact on neurotransmitter levels and neuroinflammation. [44]

4.3 MECHANISM OF ACTION OF CURCUMIN:

4.3.1 Pro-inflammatory Cytokine Inhibition:

Curcumin efficiently suppresses the synthesis and function of important pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis
factoralpha (TNF-α). These cytokines play a crucial role in drawing immune cells to the site of injury and mediating the inflammatory response. [45]

4.3.2 Inflammatory Pathway Suppression:

Curcumin specifically targets the nuclear factor kappa B (NF-κB) pathway, although it also targets other signaling pathways implicated in inflammation. Curcumin lowers the production of inflammatory genes, which in turn lowers a variety of inflammatory mediators, by blocking NF-κB activation.

4.3.3 Inflammatory Enzyme Reduction

Enzymes that produce pro-inflammatory prostaglandins and leukotrienes, such as cyclooxygenase-2 (COX-2) and lipoxygenase, are inhibited by curcumin. Curcumin reduces pain, swelling, and redness in the afflicted area by inhibiting these enzymes. [46]

4.3.4 Enhancement of Anti-inflammatory Cytokines:

Curcumin may encourage the synthesis of anti-inflammatory cytokines like interleukin-10 (IL-10) in addition to blocking pro-inflammatory cytokines. Resolving inflammation and moving the healing process from the inflammatory to the proliferative phases are made easier by this change toward a more anti-inflammatory state.

4.3.5 Encouragement of Tissue Repair:

Curcumin promotes the best conditions for tissue repair by efficiently controlling inflammation. Inflammation reduction promotes fibroblast migration and proliferation, which raises collagen synthesis and improves re-epithelialization—two processes essential to successful wound healing. [47]

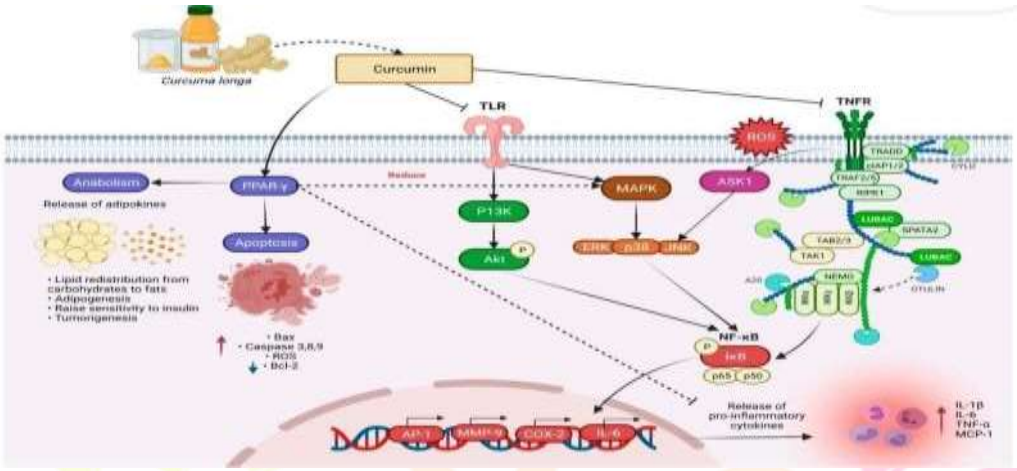

Fig 11: Mechanism of curcumin [48]

4.4 LIMITATIONS AND EFFICACY

4.4.1 Bioavailability: Curcumin's poor bioavailability is a significant challenge in clinical application, despite its benign nature making it a suitable therapeutic agent. The concentration of curcumin in plasma and target tissue is low because to its limited absorption, quick metabolism, and quick excretion. Numerous studies have recently developed strategies to boost curcumin's bioavailability. [49]

4.4.2 Stability: Due to curcumin's poor water solubility and low stability under physiological conditions, its therapeutic efficiency is restricted when supplied in conventional form, despite the possibility of wound healing effects. (50)

4.4.3 Topical use: It can cause skin irritation, such as redness or itching.

4.4.4 Allergic Reactions: Sensitive people may have hives or swelling.

4.4.5 Gastrointestinal Problems: Ingestion-related nausea or diarrhea.

4.4.6 Hormonal Effects: Possible impact on conditions where hormones are sensitive. [51]

5. SYNERGISTIC EFFECTS OF SILVER SULPHADIAZINE AND CURCUMIN:

The current extensive study digs into the potential of two medicines that show promise in improving wound healing outcomes: curcumin and silver sulfadiazine (SSD). Long regarded as the gold standard in the treatment of burn wounds, SSD is still prized for its broad-spectrum antibacterial action and capacity to create a healing environment. Curcumin, the primary active component in turmeric, has synergistic effects and can intensify the effects of other medications and substances. In fact, curcumin has been shown to have synergistic benefits when coupled with chemotherapy, anti-inflammatories, antibiotics, and several cytotoxic medications. [52]

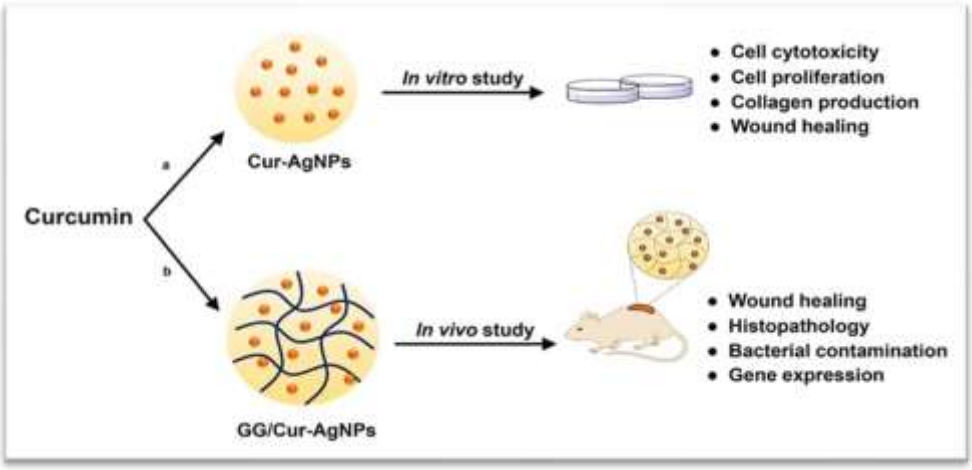

Fig 12: Overview of the study of enhanced wound healing using curcumin -silver nanoparticles [CurAgNPs] [53]

5.1 The effect of Cur-AgNPs in wound healing:

Cur-AgNPs were assessed for cytotoxicity on human dermal fibroblasts using an MTT assay. At concentrations lower than 0.200 nm., Cur-AgNPs exhibited no toxicity and more than 80% cell survival.
Over a period between 7 and 14 days, fibroblasts treated with 0.03 nm. and 0.06 nm. CurAgNPs revealed a significant increase in cell proliferation and collagen formation. After 7 days, 0.06 nm. significantly outperformed the effects of ascorbic cacid. [53]

After 7 days, collagen levels rose by 20% at 0.03 nm.; after 14 days, the two concentrations showed increase of 50% and 40%, respectively. Overall, Cur-AgNPs increase collagen production and fibroblast activity without being harmful, indicating a need for more research. (53]. The average healing time for wounds treated with 1% SSD was 30 days, but wounds treated with 1% SSD and curcumin took 33 days to recover. The control group took 38 days to heal, while curcumin alone demonstrated a 36-day healing duration. [54]

5.2 CURRENT RESEARCHES AND CLINICAL TRIALS:

5.2.1 Creation and Description of Wound Dressings Including Silver Sulphadiazine, Povidone Iodine, and Curcumin:

Because chitosan has antimicrobial qualities, the study used it as the basis material to integrate povidone-iodine, curcumin, and silver sulfadiazine to create an advanced wound dressing. Gelatine improved the swelling capacity, polyvinylpyrrolidone functioned as a plasticizer, and polyethylene glycol 6000 formed a film. The final dressing had a rough, porous texture and passed tests for viscosity, thickness, and medication content. The medication content stayed constant, according to stability tests, and the dressing delivered steady drug release for four hours. Excellent wound healing capability was shown by in vivo tests, indicating that such formulations may find widespread use in wound care procedures in the future. [55]

5.2.2 Topical administration of silver-curcumin on rabbit wound healing:

A study conducted on rabbits evaluated the impact of curcumin and silver sulfadiazine (1% SSD) on surgical wound healing. With the lowest edema, wound elevation, and colonization scores over a 42-day period, the wounds treated with 1% SSD alone demonstrated the best healing results. To a lesser degree, the combination of SSD and curcumin also enhanced healing. Histopathological findings showed that the SSD-treated wounds had more fibrous connective tissue and less reactive cells, indicating strong healing. 1% SSD was the most effective topical treatment for surgical wound care in this trial, despite curcumin's ability to speed up the healing process. [56]

5.2.3. Comparison of Traditional Herbal Ointment and Silver Sulfadiazine in Grade II Burn Wound Healing in Mice:

The study examined the effects of silver sulfadiazine (SSD) and a traditional ointment made of olive oil, sheep fat, honey wax, turmeric, salt, henna, yolk, and Saqqez on the healing of second-degree burn wounds in mice. When compared to the control group, the results over a 14-day period demonstrated that the ointment and SSD had comparable effects in lowering inflammation and accelerating wound healing. The ointment and SSD did not, however, significantly alter the healing process. Time was the main element determining the reduction in wound size, and although the traditional ointment aided in the healing process, it lacked the antibacterial action of SSD. Additionally, no discernible differences in wound size were seen between groups. Although the conventional ointment showed promise for healing overall, SSD continues to outperform it in terms of antibacterial activity.[57]

5.2.4. Acinetobacter baumannii photo disinfection effects of silver sulfadiazine nanoliposomes doped with curcumin: a mouse model:

The antibacterial activity of curcumin-doped photoexcited silver sulfadiazine nanoliposomes (AgSD-NLs@Cur) against *Acinetobacter baumannii* was assessed in a study. These nanoliposomes' analysis revealed low levels of hemolytic activity and cytotoxicity. A. baumannii's planktonic and biofilm forms, as well as its gene expression levels, were considerably decreased by antimicrobial photodynamic treatment (aPDT) employing AgSDNLs@Cur ($p < 0.05$). Histopathological analyses of infected burn wound sites treated with aPDT showed a considerable reduction in the bacterial load and notable epidermal growth. According to these results, photoexcited AgSD-NLs@Cur exhibits encouraging antibacterial activity against *A. baumannii*. [58]

5.2.5 An in vitro and in vivo investigation of curcumin nanoliposomes' effects on fibroblast cell survival and motility as well as the healing of burn wounds in mice:

One of turmeric's most potent ingredients is curcumin, also known as diferuloylmethane. This herbal substance has anti-inflammatory and beneficial effects on wound healing. This study's main goal was to assess how curcumin nanoliposomes affected the motility and survival of mouse fibroblast NIH 3T3 cells as well as the wound-healing properties of second-degree skin burns in BALB/c mice. Techniques: Four groups of twelve mature male BALB/c mice (n = 48) were created. Curcumin nanoliposome ointment was administered to group one, while silver sulfadiazine and placebo were administered to groups two and three, respectively, and no treatment was given to group four (sham). A metal instrument measuring one centimeter in diameter caused the burn wound. Treatment was given to the animals twice a day. Deep anesthesia, a wound biopsy, a microscopic examination, and the MTT assay were conducted
on days 4, 7, 10, and 14. Findings: Low-dose curcumin nanoliposomes enhanced cell proliferation and motility at 8, 12, and 24 hours in contrast to the control group, according to cellular tests conducted on mouse fibroblast NIH-3T3 cells. Mice given curcumin nanoliposomes on day 14 showed reduced inflammation in their tissue samples, but granulation tissue formation, fibroblast proliferation, epithelialization, and collagen fiber production all markedly increased in comparison to the control groups. In conclusion, our research shows that curcumin nanoliposomes have a beneficial impact on the inflammatory and proliferative stages of burn wound healing in mice as well as the motility process of mouse fibroblast NIH3T3 cells (in vitro). [59]

6.Challenges and Limitations:

Fig 13: Challenges and Limitations

Silver sulfadiazine and curcumin have a number of limitations and challenges when it comes to wound healing. In contrast to silver sulfadiazine, which is well-established but can induce skin irritation and cytotoxicity in fibroblasts and keratinocytes, curcumin exhibits uneven clinical efficacy and may cause gastrointestinal adverse effects. Silver sulfadiazine can make therapy with other topical medicines more difficult, while curcumin may alter drug metabolism. Both drugs may interact with pharmaceuticals. Patients with certain medical disorders should take precautions when using curcumin, and those with sulfa allergy or renal impairment should take precautions when using silver sulfadiazine. Ultimately, even though both substances have therapeutic potential, clinical practice requires a thorough evaluation of their safety and tolerability. [60], [61]

7.POTENTIAL FOR RESISTANCE AND TOXICITY:

7.1 Potential for microbial resistance

a) Curcumin's Antimicrobial Mechanisms -

Curcumin interferes with pathogens' energy metabolism, breaks down microbial cell membranes, and prevents the formation of nucleic acids. In contrast to traditional antibiotics, which frequently have a single target, its diverse modes of action lessen the possibility that microbes may acquire resistance.

b) Evidence of the Development of Resistance -

According to the most recent research conducted to 2023, there is little proof that bacteria rapidly grow resistant to curcumin. It is difficult for pathogens to adapt since it targets several cellular pathways. [62]

7.2 Toxicity Concerns

a) Effects on Cells and Cytotoxicity

Effects Dependent on Concentration: Curcumin is often non-toxic at therapeutic concentrations and even encourages cell migration and proliferation, which are crucial for wound healing. It can, however, cause cytotoxicity and apoptosis in some cell types when present in high doses.

b) Selective Toxicity

Curcumin has a degree of selectivity that is beneficial in therapeutic circumstances, since it tends to be more toxic to malignant cells than to normal ones.

c) Sensitivities and Allergic Reactions

Hypersensitivity, redness, itching, or swelling at the application site are symptoms of allergic reactions that some people may have to curcumin or its formulations.

d) Communication with Different Agents

Combination with Other Treatments: To avoid antagonistic effects or increased toxicity, it is important to assess how curcumin interacts with other wound care medicines, such as antibiotics and antiseptics. [63]

8.FUTURE DIRECTIONS AND EMERGING TRENDS:

CURCUMIN	SILVER SULFADIAZINE
Although curcumin and its derivatives have a lot of pharmacological potential, their low bioavailability, quick metabolism, instability, and poor water solubility limit their therapeutic effectiveness. To overcome these constraints and improve their efficacy, sophisticated distribution methods are required. [65]	Because of its low propensity to acquire resistance and the rise in antibiotic resistance, silver is attracting increasing study as a therapy. Silver nanoparticles (AgNPs) have uses in medicine administration, implant coatings, and wound care because they are efficient against a variety of microorganisms. AgNPs are useful in the prevention and treatment of infections, particularly biofilms, since they can damage bacterial cells, cause oxidative stress, and obstruct their communication. These days, they make up more than half of all consumer nanomaterial goods, including Acticoat for wound treatment, which has FDA approval.
1)NANOCRYSTALS: Nanocrystal techniques, such as high-pressure homogenization (HPH) with stabilizers like PVP, significantly enhance curcumin's solubility and bioavailability, increasing its dissolution rates and boosting solubility by more than five times compared to standard forms. [65]	
2) NANOCOMPOSITE HYDROGEL: Hydrogel-based delivery methods improve curcumin's (CUR) medicinal uses. In contrast to 50% for unmodified CUR, a new nanocomposite hydrogel including nano CUR and chitosan demonstrated enhanced stability, holding 100% of CUR after 5 hours. Additionally, it maintained antioxidant efficacy comparable to unmodified curcumin while permitting regulated release of nano-CUR, making it a successful delivery system for wound healing. [64]	Researchers are looking at environmentally sustainable ways to produce AgNPs and different ways to incorporate them into materials to improve their antibacterial qualities. All things considered, silver nanoparticles show promise in treating infections, particularly in the face of rising antibiotic resistance. [66]
3)NANO - FIBRE: CUR-loaded PCL/GT nanofibers showed potent antibacterial effects, releasing 60% of CUR in the first hour and effectively targeting MRSA (99.9%) and ESBL (85.14%), making them promising for antibacterial use. [64]	

4)FOAMS: For tissue repair, localized chemotherapy, and wound healing, silk fibroin scaffolds loaded with curcumin exhibited improved anticancer, antioxidant, and antimicrobial activities, as well as uniform pores, thermal stability, and slow CUR release. [64] 5) NANO VESICLE: Liposomes improve skin delivery and antioxidant action, especially hyalurosomes derived from sodium hyaluronate and curcumin. Studies conducted in vivo showed that mice had less oedema and inflammation, indicating that they could be used as skin treatments. [64]	

Rats surgical wound incisions were medicated with GG(guar gum) /Cur-AgNPs hydrogels to investigate their effects on in vivo incidental wounds. The hydrogels were then compared to commercial antibacterial gels, guar gum (GG), and Cur-AgNPs as which demonstrate more wound contraction. As a result, Te GG/Cur-AgNPs caused a >40% quicker wound.[53]

Conclusion:

Medical therapy has challenges because wound healing is a complicated process that involves haemostasis, inflammation, proliferation, and remodelling. SSD, a well-known burn treatment, is valued for its broad-spectrum antibacterial properties, while curcumin, a compound derived from turmeric, has anti-inflammatory, antioxidant, and antimicrobial properties, making it a potential option. Together, curcumin and SSD may accelerate wound healing, particularly in intricate situations where infection and inflammation management are critical. More research is required to optimize dosage, formulation, and application methods in order to balance efficacy and side effects. Advances in drug delivery technology, like nano formulations, have the potential to increase the stability and bioavailability of curcumin while increasing the efficacy of SSD. While SSD and curcumin combined show promise for better wound healing, clinical research is necessary to validate their effectiveness.

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