

# “Antibacterial activity of medicinal plants and their role in wound healing”.

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## ABSTRACT

**Background:** The study of plant-based medications, or phytomedicine, involves a wide spectrum of biological activities. Due to the existence of secondary metabolites, herbal medicine has been used and practiced throughout history for the treatment of both acute and chronic conditions. Over the past century or so, numerous novel compounds with medicinal potential have been derived from plants. In the age of growing superinfections and the emergence of resistant strains, natural medicines are inspiring optimism.

**Main body of the abstract:** The review discusses the role of herbal medicine as antibacterial agents and their use in wound care and management of wounds and the critical role of secondary metabolites of herbal plants in fighting bacterial infections. Some medicinal plants such as Rosemary (*Rosmarinus officinalis*) also possess wide range of biological activities and can give a synergistic effect if combined with antibiotics. In addition, natural biopolymers play an important role in the management of wounds as well as the physiological processes of the skin (hemostasis, inflammation, proliferation, and remodelling).

**Method:** A narrative review of papers relevant to the use of phytomedicine in treating infections was conducted by using electronic databases PubMed, CrossREF, and Google Scholar. Short conclusion Phytomedicine is one of the top options for the treatment of chronic illnesses for millions of people around the world. To learn about the bioactive components of medicinal plants, their medical benefits, and their synergistic or additive effects to enhance the action of medications, substantial new studies are still needed.

**Keywords:** Phytomedicine, Secondary metabolites, Pathogens, Antibacterial

**Highlights:** • Phytomedicine involves a wide spectrum of biological activities. • Bioactive compounds extracted from plants are used for the treatment of both acute and chronic conditions. • Natural plant & secondary metabolites play a significant role in the treatment of bacterial infections. • Natural biopolymers are used in wound care and restoring physiological processes of the skin. • Substantial new studies are needed to learn about bioactive components medical benefits, and their synergistic or additive effects.

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## INTRODUCTION

An herbal remedy known as phytomedicine is utilized all over the world to treat or prevent physical and mental illnesses [1]. Herbal medicine or a phytopharmaceutical preparation is a type of medication that is made in a crude form solely from whole plants or specific plant parts [2]. Herbal medicine, which has a history spanning more than 3000 years and was enumerated in Sheng Nong's herbal book "The Devine Farmer's Classic of Herbalism" [3], is the foundation of traditional Chinese medicine (TCM). Herbal medicine is one of the most sought-after treatments by 3.5–4 billion people worldwide, mainly in Africa, India, and China, according to the World Health Organization (WHO) [4]. Products made from medicinal plants have greatly increased over the past 10 years, which has revolutionized and improved phytomedicine. There are about 35,000 plant species that are utilized as medicines, but only 20% of them go through the phytochemical analysis stage and only 10% make it to the biological screening stage, leaving the rest in need of further study [5]. As herbal medicine becomes more and more popular, it is important to maintain quality,

safety, and to prevent potential toxicity [6–8]. In addition to long-term boiled extract and cold infusion of plants, plants can be extracted using alcoholic, vinegar, and hot water as well as other solvents, times, and temperatures [1]. Due to the existence of secondary metabolites, which are abundant in bioactive substances, herbs are used to treat both acute and chronic illnesses, including depression, cardiovascular disease, inflammation, and others [9, 10]. Plant constitutes are used directly as therapeutic agents or as models for pharmacologically active compounds or as starting materials for the synthesis of drugs (**Table 1**) such as morphine which was produced from opium extracted from Papaver somniferum, digoxin from *Digitalis purpurea*, antimalarials such as quinine from *Cinchona* bark, and over 60% of cancer therapeutics are based on natural products such as paclitaxel from the Pacific yew tree [11–15]. Due to inadequate research methodologies, time-consuming, and expensive isolation techniques, there is little information available regarding the composition of the majority of herbal medications. As a result, this page discusses the crucial role of medicinal plant extract in

the battle against bacterial infections and the management of skin wounds and disorders such as atopic dermatitis (AD) and diabetic foot ulcers (DFUs). Additionally, extracellular matrix (ECM) and biopolymers derived from microorganisms, animals, and plants (cellulose, hyaluronic acid, collagen, alginate, and chitosan) all have bioactive qualities that make them useful in the treatment of wounds and the healing process.

## ANTIBACTERIAL ACTIVITIES OF MEDICINAL PLANTS

Globally high rates of morbidity and mortality are mostly caused by infectious diseases. Millions of people per year die as a result of the advent of bacterial strains that are resistant [81]. Antibiotic resistance in bacteria evolves through intrinsic or acquired resistance, by chromosomal mutation, or by horizontal gene transfer (HGT) [82, 83]. Several mechanisms can lead to the development of antibiotic resistance such as alteration in cell membrane permeability either by reducing antibiotic penetration or increasing its elimination by efflux pumps; moreover, bacteria can deactivate the antibiotic itself or modify the antibiotic targets, in addition to other alternative pathways which were described in literature and are illustrated in Fig.1[83–88].

The most harmful microorganisms for human health have been recognized by the World Health Organization (WHO) and are categorized into three priority groups: critical pathogens (*Acinetobacter*, *Enterobacteriaceae*, and *Pseudomonas*), high-priority pathogens (*Campylobacter*, *Enterococcus faecium*, *Helicobacter pylori*, *Nisseria gonorrhoeae*, *Staphylococcus aureus*, *Salmonella spp.*), and medium-priority pathogens (*Streptococcus pneumoniae*, *Shigella spp.*) [83, 89–91].

Pathogenic plant bacteria can cause diseases on susceptible plant hosts which starts usually with low numbers of pathogen cells and then colonize and multiply to large amounts in living plant tissue. This results in the alteration of plant's developmental system which eventually leads to reduction of plant growth and yield.

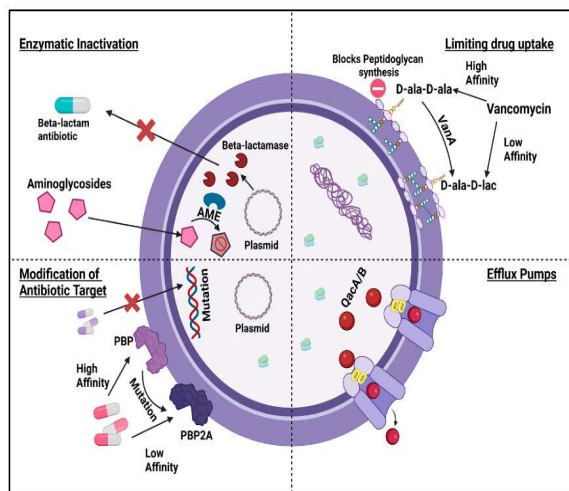


Fig:1 Resistance mechanisms of gram-positive bacteria.

Disease severity depends on the host genetic constitute, environmental conditions, and the pathogen [92]. Herbal plants produce unlimited wide variety of secondary metabolites which are mostly aromatic and phenol derivatives that gives them the ability to safeguard plants against pathogens [9, 93, 94].

Depicts four major resistance mechanisms discussed in the review, including beta-lactamase action, AMEs inactivating aminoglycosides, a mutation in the ribosomal binding site, PBP alteration, efflux pump, and cell wall modification. (Figure created using Biorender, <https://www.biorender.com/>).

Plants use oxygen for their growth and development but in stress like pathogen attack; the usage of oxygen causes the production of reactive oxygen species (ROS) in the plant and results in photo-oxidative damage [95–97]. In stress conditions plants induce excessive biochemical changes to activate defence pathways such as changing cell wall composition, detoxification of several ROS species, induction of enzymatic and nonenzymatic components, and alteration of pathogen activates. In addition, other parts of walnuts such as leaves are valuable products as well and their content was assessed spectrophotometrically by UPLC-PDA-MS/MS method. Several phenolic compounds were identified and expressed as total phenolic (TPC), proanthocyanidin (TPA) (Fig. 2), and total flavonoid contents (TFC) with quercetin 3-O-glucoside (Fig. 2) and quercetin pento-sides (Fig. 2) dominating.

Aqueous walnut leaf extracts antibacterial and antifungal activities were tested against Gram-negative bacteria (*E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), Gram-positive bacteria (*Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*), and fungus (*C. albicans*) [45-50]. Result showed highest susceptibility (at 10 mg/ml concentration) against *K. pneumoniae*, and *S. pyogenes*, less bactericidal activity against gram-positive and without any antifungal effect. These findings may be explained by the fact that gram-negative bacteria's cell walls contain lipopolysaccharide (LPS), which creates a hydrophilic environment and shields it from hydrophobic molecules. The aqueous and ethanol extracts of walnut leaves may contain more hydrophilic compounds as a result, leading to higher inhibitory activity against gram negative bacteria [90-95].

## MEDICINAL PLANTS AND WOUND HEALING

The epidermis, dermis, and hypodermis are the three layers of the skin, one of the biggest organs in the body. Additionally, it serves as the initial line of defence against aggressors like infections, chemicals, and physical contact. Due to the function of the epidermis, which blocks the entry or exit of water- or water-soluble substances, and the hypodermis, which blocks heat loss due to the poor thermal conductivity of fat, it also has the capacity to prevent water loss and preserve temperature [54–57]. In order to maintain skin hemostasis during inflammation, immune cells and nonimmune cells form a structure known as skin-associated lymphoid tissue (SALT). Additionally, the skin's microbiome, which includes bacteria, fungi, and viruses, is crucial for immune response, concluding that the skin serves as more than just a physical barrier [54, 58–59]. Over the years, natural product ingredients such polyphenols, fatty acids, probiotics, polysaccharides, and others have demonstrated their efficacy as immune system modulators. The secret to controlling or curing skin inflammatory problems may lie in using natural products [60–62]. Skin can react to infectious agents through innate and adaptive immune processes, just as other tissues like mucosal surfaces. To isolate the damaged area, stop bleeding, and initiate the coagulation cascade, a clot must first form in order for the wound healing process to begin. Then comes the inflammatory phase, where immune cells begin to infiltrate and high levels of pro-inflammatory mediators are discovered to stop pathogen entry and more serious problems. The next stage is the proliferative phase, which is characterized by a

significant growth of skin-resident cells including fibroblasts and high levels of angiogenesis. The remodelling phase, which may last for more than a year after the injury, is the longest and involves the skin regaining its natural structure. Any issue throughout these stages may hamper wound healing, which may then result in infections, excruciating pain, and occasionally neurological damage [63–66]. Several factors can cause impaired wound healing such as local factors that influence the characteristics of the wound like oxygenation and infections and systemic factors in which overall health or disease state affects the ability to heal like hormones and diabetes [67–70]. Impaired wound healing can result from a

variety of factors, including local ones that alter the characteristics of the wound, such oxygenation and infections, as well as systemic ones, like hormones and diabetes, that have an impact on overall health or disease states and the capacity to heal. Numerous abnormalities, including fibrosis, scarring, and nonhealing wounds like persistent ulcers, can result from aberrant wound repair [71,72]. New compounds with antioxidant, anti-inflammatory, and anticarcinogenic properties are being researched to prevent skin damage. Natural substances have been employed as anti-tumoural, analgesic, anti-inflammatory, and antioxidant agents [73, 74]. Table 1 lists the top plants for healing wounds.

**TABLE 1:** Most used medicinal plants in treating skin disorders.

Plant Names	Active Compounds	Therapeutic Uses
Aloe vera	Acemannan	Wound healing
<i>Achillea millefolium</i> L.	Flavonoids, monoterpenes, and sesquiterpenes	Skin inflammatory and wound healing
Boswellia sacra	Boswellic acids	Improvement of blood circulation, pain treatment, and rheumatoid arthritis
Cinnamomum cassia	Cinnamaldehyde	Analgesia and improvement of blood circulation
Ganoderma lucidum	Ganoderma lucidum polysaccharide	Cancer, diabetes, hepatitis, leukaemia, and ulcer
Polygonum cuspidatum	Emodin, polydatin, and resveratrol	Hepatitis, hyperlipidemia, jaundice, scald, skin burns, and suppurative dermatitis
Sanguisorba officinalis	Polysaccharides, tannins, triterpenoid glycosides, and triterpenoids	Burns, chronic intestinal infections, haemorrhoids, menorrhagia, and scalds
Zanthoxylum bungeanum	Afzelin, hyperoside quercitrin, and rutin	Skin wrinkles

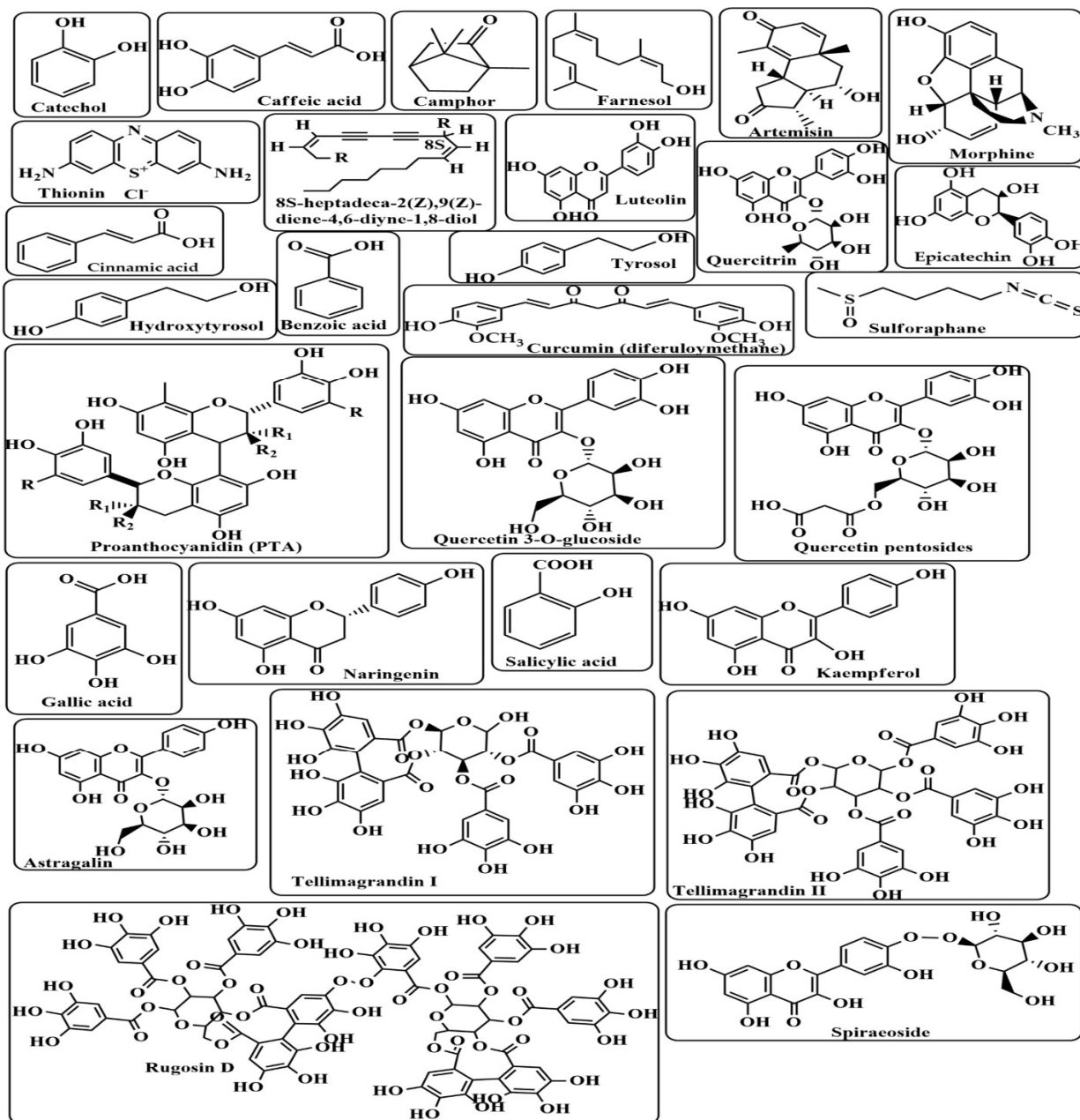


Fig. 2 Chemical structure of antimicrobial phytochemicals including catechol, caffeic acids, camphor, farnesol, artemisinin, morphine, thionins, 8S-heptadeca-2(Z),9(Z)-diene-4,6-diyne-1,8-diol, luteolin, quercetin, epicatechin, benzoic, cinnamic acids, tyrosol, hydroxytyrosol, sulphoraphane, proanthocyanidin (TPA), quercetin 3-O-glucoside, quercetin pentosides, gallic acid, naringenin, salicylic acid, kaempferol, astragalgin, tellimagrandin I, II, rugosin D, and spiraeoside.

## Rosemary (*Rosmarinus officinalis*, L.)

In addition to its use in food preservation to stop oxidation and microbial contamination, *Rosmarinus officinalis*, L., a member of the Lamiaceae family that originated in the Mediterranean, is renowned for its antioxidant, hepatoprotective, antiangiogenic, and potential treatment for Alzheimer's disease properties [90–92]. Numerous polyphenolic substances, including rosmarinic acid, hesperidin, carnosol, and carnosic acid, are found in rosemary (Fig. 3).

According to various studies [93–95], rosemary essential oil contains 1,8-cineole, camphor, and  $\alpha$ -pinene  $p$ -cymene-7-ol in addition to borneol (Fig. 3). Fresh or dried leaves, flowers, fruits, roots, stems, seeds, and bark can all be used to make

plant extracts, while dried samples were shown to contain higher quantities of flavonoids. Air, microwave, oven, and freeze drying are all acceptable drying techniques [96–98]. Antibacterial activity of rosemary *Rosmarinus officinalis* was found to have antibacterial properties in many research. In their research on the antibacterial properties of several natural extracts, including rosemary, [75] examined how long the shelf life of veal meatballs could be stored for. The results showed that all of the studied microorganisms were susceptible to rosemary extracts (oil extract, water miscible extract, oil, and water-miscible extract), with oil extract having the strongest inhibitory impact. The most vulnerable bacteria were *Brochothrix* spp., which might be a reference to the antibacterial action of nonpolar phenolic compounds against

gram-positive bacteria [62] reported that rosemary EOs prevented food-spoiling bacteria from growing. *Rosmarinus officinalis* and *Ocimum basilicum* essential oils have been shown to have antibacterial action against multidrug-resistant clinical isolates of *E. coli* by [93]. Since both EOs were effective against every clinical strain of *E. coli*, it can be inferred that they can be used to treat and prevent the emergence of resistance strains [85] found similar results, confirming rosemary essential oil's potent antibacterial action against *E. coli*. Carnosol, carnosic acid, rosmarinic acid, rosmanol, epirosmanol, isorosmanol, and rosmaridiphenol (Fig. 3) interact with the cell membrane and alter the production of nutrients, genetic material, and fatty acids to produce rosemary's inhibitory effects. Additionally, they affect electron transport, result in cellular component leakage, interact with proteins in the membrane, and cause a loss of membrane functionality [30, 31-33]. To increase the effectiveness of antibiotics against multi-drug-resistant bacteria like MRSA, [78] looked into the antibacterial activity and synergistic effect of rosmarinic acid (dimer of caffeic acid) with conventional antibiotics. The agar well diffusion method was used to assess the antibacterial activity of rosmarinic acid against microorganisms. In comparison to using an antibiotic alone, the results demonstrated that rosmarinic acid had a synergistic impact with the medications ofloxacin, amoxicillin, and vancomycin against *S. aureus*. However, only the vancomycin and rosmarinic acid combination was effective against MRSA. The activity of rosmarinic acid on surface proteins known as microbial surface components recognizing adhesive matrix molecules (MSCRAMM's) present in *S. aureus* and MRSA was suggested to be the mechanism of action. Pomegranate, rosemary, and antibiotic were combined and *P. aeruginosa* isolates with significant biofilm producers and antibiotic resistance were examined for the synergistic effects of the combination [101-103]. Pomegranate and rosemary plant extracts were the most successful at inhibiting biofilm by lowering swimming and twitching motility, which in turn decreased bacterial cells adhering to surfaces and quorum-sensing (QS) signals. The presence of polyphenol molecules such catechol, pyrogallol (Fig. 3), gallic, ellagic, rosmarinic acid, and benzoic acid may be referred to as these activities. There are, however, limited reports of plant extracts' antibacterial and antibiofilm activity. As a result, combining plant extracts with antibiotics may be able to prevent and get rid of microbial biofilms. Pomegranate and rosemary plant extracts combined with piperacillin, ceftazidime, imipenem, gentamycin, or levofloxacin had synergistic effects against a *P. aeruginosa* isolate and dramatically reduced biofilm mass after 24 h compared to the use of the plant extracts separately or together [102-105].

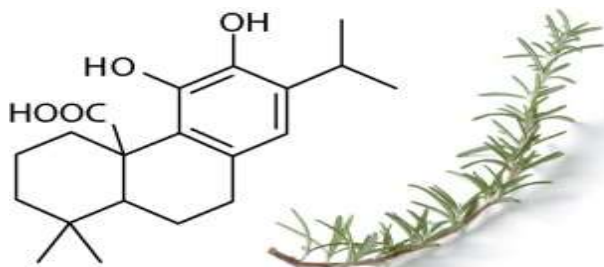


Fig:3 Rosmaridiphenol: A natural antioxidant found in rosemary.

To investigate the effects of medicinal plants and commercial antibiotics against bacterial pathogens, additional in-vitro and in-vivo investigations are required. In vitro tests using butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), two antioxidant food additives, and rosemary methanol

extract were also conducted by [13] to examine the antioxidant and antibacterial properties of the extract (Fig. 3). The outcomes demonstrated that rosemary extracts (rosmarinic acid, carnosic acid, and carnosol) increased the antioxidant activity of BHT and BHA as well as the antibacterial activity of BHA.

### TREATMENT OF SKIN DISORDERS

Diabetic foot ulcers (DFUs) Patients with uncontrolled diabetes mellitus frequently develop diabetic foot ulcers (DFUs), which can be brought on by poor glycemic management, peripheral vascular disease, neuropathy, or inadequate foot care [99]. According to the International Diabetes Foundation [59], there are 40–60 million persons worldwide with DFUs. DFUs can be treated using several methods, including as gene therapy, stem cells, skin substitutes, and antibiotics. Due to the high cost of local debridement (removal of nonviable wound tissue) and negative pressure therapy, antibiotic resistance as a result of prolonged use, the ineffectiveness of growth factors to inhibit bacterial growth, and the existence of stem cell and gene therapies in the experimental stage, nonsurgical treatments for DFUs must be quick and inexpensive [81]. Due to their anti-inflammatory qualities, several herbal extracts have been utilized as traditional treatments to treat wounds. [61] designed an experiment to explore the effects of five herbal extracts on wound healing, *Bauhinia purpurea* (inhibit inflammation, and act as analgesic and antipyretic) [60], *Paeoniae rubrae* (ameliorating inflammation by inhibiting glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ )) [55], *Angelica dahurica* (accelerate wound healing by regulating inflammation) [4], *Acorus calamus* L (promote collagen maturation) [15], and *Radix Angelicae biseratae* (inhibit inflammation and regulate immune system in osteoarthritis) [16].

In order to determine the mechanisms of action for wound healing, the mixture of herbal plants was identified by Ultra-High-Performance Liquid Chromatography (UHPLC) and Quadrupole Exactive-Mass Spectrometer (QE-MS) and tested in vivo on a rat model with diabetic ulcer wound utilizing transcriptomics and proteomics. The mixture speeds up the healing of wounds by encouraging angiogenesis and the growth of M2 macrophages, according to the results. Specific miRNAs and proteins were found to be crucial for controlling wound healing by transcriptomics and proteomics. Consequently, the herbal combination may offer a potential method to quicken the healing of diabetic wounds [51]. Atopic dermatitis (AD) Atopic dermatitis (AD), a chronic and relapsing inflammatory skin condition that affects children and is characterized by itchy, eczematous skin lesions, is another skin condition [50, 51]. Intense itching results in skin damage that compromises tissue repair and allows microorganisms to infiltrate the skin [9,10]. The absence of precise disease processes is a challenge for the development of successful AD therapeutics. Flavonoids, a type of secondary metabolite found in plants, exhibit a variety of antiallergic properties, including antioxidant, anti-inflammatory, antiangiogenic, antibacterial, and antiviral effects [11,12]. Quercetin inhibits the release of histamine, proinflammatory cytokines, and interleukin (IL)-4 and -13, among other antiallergic characteristics. Despite this, there have only been a few research on quercetin's effects on AD [99, 75]. Therefore, [16] studied the effect of quercetin on AD model of human keratinocyte and treated it with IL- 4, -13, and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) to mimic AD in -vitro. Result showed that quercetin accelerated wound healing by reducing AD-inducing agents IL-1 $\beta$ , IL-6, IL-8, thymic stromal lymphopoietin, phosphorylation of extracellular signal-regulated kinase 1/2/mitogen-activated protein kinase (ERK1/2 MAPK), and nuclear factor-kappa B (NF- $\kappa$ B), while

it upregulated the expression of IL-10, and antioxidant enzymes; glutathione peroxidase (GPx), superoxide dismutase-1 (SOD1), SOD2, and catalase (CAT), in addition to mRNA

expression of Twist and Snail. Therefore, quercetin may act as a potential therapy for AD symptoms.

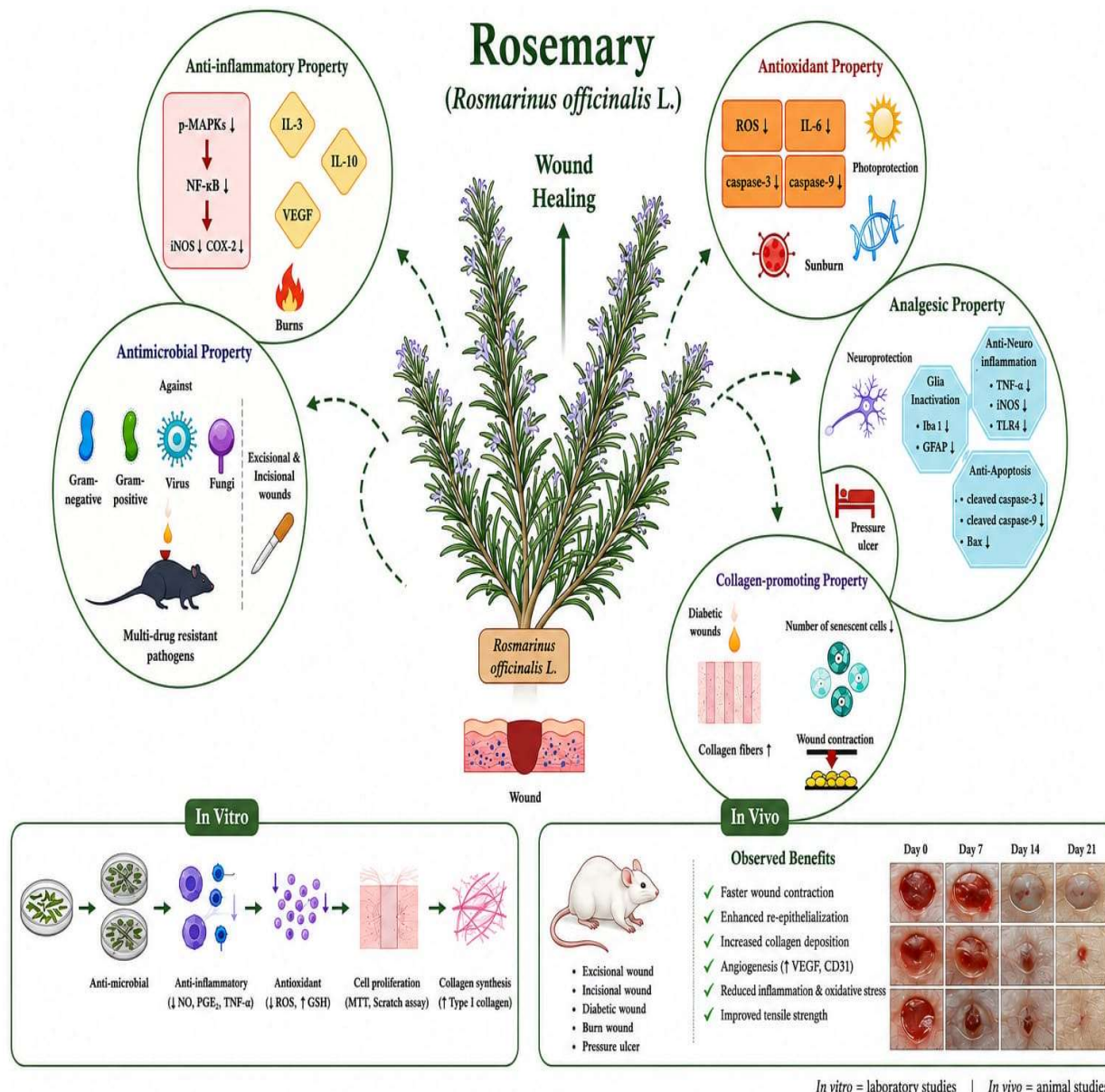


Fig:4 Rosemary-Based Wound Healing: From Cellular Responses to Tissue Regeneration.

**UV-IRRADIATED SKIN**

The metalloproteinases induced by ultraviolet may degrade collagen and thin the skin layer, leading to a loss of skin elasticity and wrinkle formation. Animal models and in vitro models suggested associated change in the UV-irradiated areas or cells following treatment with rosemary extracts. 4% and 10% rosemary hexane extract lipid nanocapsule-based mucoadhesive gels were previously tested in a UVB-irradiated rat model, showing improved skin contact, permeation, bioavailability, epidermal and dermal histological features[85-90]. while decreasing the level of inflammatory and wrinkling markers compared to controls. In a UV-Birradiated mouse model, the anti-wrinkle property and skin permeability of topically applied rosemary extract was enhanced by encapsulation of 20 mg rosemary extract in transferosomes [2]. More specifically, as the major antioxidative components of

rosemary extract, carnosol treatment has yielded some beneficial effects in UVB-induced inflammatory skin injuries, including a significant reduction in IgE and proinflammatory cytokines compared to untreated group exposed to UVB, which is in association with the inactivation of STAT3 [1], while CA displayed a protective effect in UVA-irradiated human skin fibroblasts [14]. When treating the human keratinocytes HaCaT (a spontaneously immortalized cell line) with a combination of rosemary extracts (especially diterpenes and citrus flavanone aglycones) after UVB radiation, some molecular events related to skin photodamage, such as intracellular ROS generation and DNA damage, were significantly attenuated [22]. The photoprotective potential of rosemary extracts has also been demonstrated in human studies [10-76]. However, data from patients is still lacking, and more clinical data is required draw a conclusion whether dietary polyphenols provide a skin photoprotective effect further than the daily consumption of topical sunscreens shown in Fig:4.

## CONCLUSIONS AND FUTURE RECOMMENDATIONS

The incidence of skin injuries continues to increase globally, leading to substantial annual financial costs. In response, we assessed Indonesia's pharmacopeia and traditional medicine for plants recognized for their medicinal properties. Each botanical investigated contains chemical compounds linked to various pharmacological effects, including antimicrobial, anti-inflammatory, and antioxidant properties [25-27].

In vitro and in vivo studies have demonstrated that medicinal plant extracts and their purified active components hold significant potential as wound-healing treatments due to their safety, diverse modes of action, and antibacterial activity. Novel wound-dressing formulations offer several advantages over standard dressings, addressing limitations of natural materials such as solubility and restricted activity at the wound site [85-90]. Further studies should focus on elucidating the mechanisms of action of the most promising natural substances, particularly their effects on cell surface receptors, to enhance their bioavailability and minimize adverse effects in wound healing. Extensive and inappropriate uses of antibiotics resulted in the development of antimicrobial resistance and the rise of bacterial strains that were resistant to multiple drugs (MDR) and multiple drugs extensively (XDR), which made the most powerful medications useless. Antimicrobial resistance is very concerning and urgent issue, and scientists are aware that the shelf life of antibiotics is finite. Natural product research is receiving a lot of interest internationally [12]. Today, millions of people around the world turn to phytomedicine as one of their top options for the treatment of chronic illnesses. Medicinal plant extracts are crucial in the fight against infectious diseases that pose a threat to public health globally. Alkaloids, phenolics, polyphenols, terpenoids, essential oils, lectins, polypeptides, and polyacetylenes are a few examples of antimicrobial phytochemicals that can be utilized as adjuvants or substitutes against bacterial infections. Natural anticarcinogenic, anti-inflammatory, and antioxidant substances can be employed to stop skin deterioration. Biopolymers derived from microorganisms, animals, and plants (cellulose, hyaluronic acid, collagen, alginate, and chitosan) and extracellular matrix (ECM) have bioactive properties that make them promising approaches for wound healing. These properties include antimicrobial, immune-modulatory, cell proliferative, and angiogenic effects.

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