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## Dermatological Health

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# Comparison of Traditional Dressing Change Techniques and Vacuum Sealing Drainage Techniques in the Treatment of Skin and Soft Tissue Injuries

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**Abstract:** *Objective:* To analyze the therapeutic effects of traditional dressing change techniques and vacuum sealing drainage (VSD) techniques on skin and soft tissue injuries. *Methods:* 60 patients with skin and soft tissue injuries admitted to the hospital from October 2021 to October 2023 were selected. They were randomly divided into an observation group (30 cases) receiving VSD treatment and a control group (30 cases) receiving the traditional dressing change technique. The total effective rate, treatment indicators, inflammatory factors, and complication rate were compared between the two groups. *Results:* The total effective rate of the observation group was higher than that of the control group, and the treatment indicators were better than those of the control group ( $P < 0.05$ ). Before treatment, the levels of inflammatory factors were similar between the two groups ( $P > 0.05$ ). After four weeks of treatment, the levels of inflammatory factors in the observation group were lower than those in the control group ( $P < 0.05$ ). The complication rate of the observation group was lower than that of the control group ( $P < 0.05$ ). *Conclusion:* In the treatment of skin and soft tissue injuries, VSD can improve the total effective rate, shorten the treatment cycle, alleviate the degree of inflammatory reaction, and reduce the risk of complications.

**Keywords:** Traditional dressing change technique; Vacuum sealing drainage technique; Skin and soft tissue injuries; Total effective rate; Complication rate

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## 1. Introduction

Soft tissue injury refers to a traumatic syndrome that occurs in skeletal muscles, skin surfaces, or soft tissue sites, with skin damage as the primary manifestation. It can lead to microcirculatory disorders in patients, causing local skin redness and swelling<sup>[1]</sup>. Minor injuries can heal spontaneously without special treatment,

while more severe skin and soft tissue injuries require standardized therapy and regular dressing changes to accelerate wound healing. Traditional dressing change techniques involve repeated debridement and timed replacement of dressings. Although the operation method is simple, the prolonged exposure time of the wound can easily lead to complications such as infection. Currently, vacuum sealing drainage (VSD) represents a novel dressing change technique for this condition. It can accelerate granulation growth, regulate blood circulation in the wound area, ensure wound cleanliness, and thus promote faster healing <sup>[2]</sup>. This technology addresses the limitations of traditional dressing change techniques, reducing wound complications while ensuring therapeutic efficacy, thereby offering more significant treatment advantages. Therefore, this study selected 60 patients with skin and soft tissue injuries to evaluate the application effects of traditional dressing change techniques and VSD technology.

## **2. Materials and methods**

### **2.1. General information**

Sixty patients with skin and soft tissue injuries, admitted between October 2021 and October 2023, were included in this study. They were randomly divided into the observation group and the control group using a random number table method, with 30 patients in each group. In the observation group, there were 19 male patients and 11 female patients, with ages ranging from 21 to 61 years old, and a mean age of  $39.65 \pm 4.18$  years. There were nine cases of blunt force crush injuries, 11 cases of traffic accidents, seven cases of mechanical entanglement injuries, and three cases attributed to other causes. In the control group, there were 20 male patients and 10 female patients, aged between 20 and 62 years old, with a mean age of  $39.97 \pm 4.25$  years. There were eight cases of blunt force crush injuries, 12 cases resulting from traffic accidents, six cases of mechanical entanglement injuries, and four cases due to other factors. A comparison of the baseline data between the two groups showed no statistically significant difference ( $P > 0.05$ ).

Patients were included in the study if they met the following criteria: the time from injury to the first debridement was less than 12 hours; they had a clear consciousness and were able to cooperate with dressing changes and treatment; their clinical data was essentially complete; and they were informed about the study and had provided consent.

Patients were excluded from the study if they had any of the following conditions: the presence of psychiatric disorders; comorbidities such as cardiovascular and cerebrovascular diseases; concurrent diseases like sepsis or septicemia; abnormal coagulation function; or allergies to the medications required for the study.

### **2.2. Methods**

The control group received traditional dressing change techniques: Before dressing change, the wound was disinfected with povidone-iodine (0.5%) and irrigated with sodium chloride injection (0.9%) to remove contaminants. The necrotic tissue at the wound edge was trimmed thoroughly. After achieving uniform and minor oozing of blood from the wound, it was covered with Vaseline gauze. If the dressing was contaminated, it was immediately replaced. The treatment cycle was four weeks.

The observation group was treated with VSD: Foreign bodies, exudate, bloody tissue, and necrotic tissue were removed from the wound surface. Foam dressings were selected rationally based on the area and characteristics of the wound. The foam dressing was appropriately drilled, and a drainage tube was inserted

into it, ensuring that both the end hole and side holes of the drainage tube were wrapped within the dressing. The wound surface was filled with the dressing, ensuring tight and gap-free contact. The wound edge and dressing were sutured to prevent the dressing from moving freely. A small amount of sterile gauze dipped in medical alcohol was used to clean and disinfect the skin around the wound, completely removing dirt and grease. The surrounding skin was dried with a dry gauze, and a complete layer of adhesive film (biologically semi-permeable) was applied over the wound. The negative pressure device and drainage tube were connected for 24-hour negative pressure drainage treatment with a negative pressure value of 50–60 kPa. If there was no fluid accumulation under the film and the dressing appeared collapsed, the negative pressure was considered effective. The duration of negative pressure treatment was 7–10 days. After the emergence of new granulation tissue on the wound surface, symptomatic treatments such as second-stage skin grafting were performed. The wound surface was then covered with a foam dressing, and negative pressure treatment was continued for another week. The skin grafting condition was evaluated, and if the wound healed well, ordinary dressings could be used during dressing changes.

### 2.3. Observation indices

- (1) Treatment indices: Treatment indicators were observed such as wound healing time, duration of antimicrobial therapy, number of dressing changes, wound area, pain score (using a visual analog scale ranging from 0 to 10, with higher scores indicating greater pain), and length of hospital stay.
- (2) Inflammatory factors: 3 ml of venous blood was collected and an automated cell counter was used to measure white blood cell count (WBC). Additionally, C-reactive protein (CRP) and procalcitonin (PCT) were measured using an automated biochemical analyzer.
- (3) Complication rates: The incidence of complications was monitored such as skin necrosis, incision infection, muscle atrophy, flap necrosis, bone blackening, and osteomyelitis.

### 2.4. Efficacy evaluation criteria

Cured: The wound is dry, with new granulation tissue, no infection, and complete wound healing or a reduction in size of more than 50%. Significant efficacy: The wound has minimal exudate, new granulation tissue, no infection, and a reduction in size ranging from 25% to 50%. No efficacy: The wound has excessive exudate, no new granulation tissue, and a reduction in size of less than 25%.

### 2.5. Statistical analysis

Data were processed using SPSS28.0 software. Measurement data were expressed as mean  $\pm$  standard deviation (SD) and compared using the *t*-test. Count data were expressed as frequencies and percentages [*n* (%)] and compared using the chi-square test ( $\chi^2$ ). Statistical significance was set at  $P < 0.05$ .

## 3. Results

### 3.1. Comparison of total effective rates between the two groups

As shown in **Table 1**, the total effective rate of the observation group was significantly higher than that of the control group ( $P < 0.05$ ).

**Table 1.** Comparison of total effective rates between the two groups [ $n$  (%)]

Group	$n$	Cured	Significant efficacy	No efficacy	Total effectiveness
Observation group	30	15 (50.00)	14 (46.67)	1 (3.33)	96.67 (29/30)
Control group	30	13 (43.33)	10 (33.33)	7 (23.33)	76.67 (23/30)
$\chi^2$	-	-	-	-	5.192
$P$	-	-	-	-	0.023

### 3.2. Comparison of treatment indicators between the two groups

Based on **Table 2**, all treatment indicators in the observation group were significantly better than those in the control group ( $P < 0.05$ ).

**Table 2.** Comparison of treatment indicators between the two groups [ $\pm s$ ]

Group	$n$	Wound healing time (d)	Antimicrobial treatment duration (d)	Number of dressing changes (times)	Wound area (cm <sup>2</sup> )	Pain score (points)	Hospitalization time (d)
Observation group	30	14.29 $\pm$ 2.61	5.78 $\pm$ 1.02	1.98 $\pm$ 0.63	10.11 $\pm$ 1.54	1.87 $\pm$ 0.43	18.31 $\pm$ 2.60
Control group	30	27.61 $\pm$ 3.99	11.26 $\pm$ 1.09	9.85 $\pm$ 1.27	14.69 $\pm$ 1.68	3.80 $\pm$ 0.56	27.19 $\pm$ 2.72
$t$	-	15.302	20.106	30.406	11.007	14.972	12.926
$P$	-	0.000	0.000	0.000	0.000	0.000	0.000

### 3.3. Comparison of inflammatory factors between the two groups

Before treatment, the levels of inflammatory factors were similar between the groups ( $P > 0.05$ ). After treatment, the levels of inflammatory factors in the observation group were significantly lower than those in the control group ( $P < 0.05$ ), as presented in **Table 3**.

**Table 3.** Comparison of inflammatory factors between the two groups (mean  $\pm$  SD)

Group	$n$	WBC ( $\times 10^9/L$ )		CRP (mg/L)		PCT (ng/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	16.79 $\pm$ 2.05	5.38 $\pm$ 0.47	61.59 $\pm$ 6.77	3.23 $\pm$ 0.42	1.38 $\pm$ 0.36	0.23 $\pm$ 0.05
Control group	30	16.82 $\pm$ 2.09	9.41 $\pm$ 0.52	61.52 $\pm$ 6.72	9.17 $\pm$ 1.55	1.41 $\pm$ 0.39	0.61 $\pm$ 0.09
$t$	-	0.056	31.491	0.040	20.260	0.310	20.216
$P$	-	0.955	0.000	0.968	0.000	0.758	0.000

### 3.4. Comparison of complication rates between two groups

According to **Table 4**, the complication rate in the observation group was significantly lower than that in the control group ( $P < 0.05$ ).

**Table 4.** Comparison of complication rates between two groups [*n* (%)]

Group	<i>n</i>	Skin necrosis	Incision infection	Muscle atrophy	Skin flap necrosis	Blackened bone	Osteomyelitis	Incidence rate
Observation group	30	0	0	1 (3.33)	1 (3.33)	0	0	6.67 (2/30)
Control group	30	1 (3.33)	1 (3.33)	2 (6.67)	2 (6.67)	1 (3.33)	1 (3.33)	26.67 (8/30)
$\chi^2$	-	-	-	-	-	-	-	4.320
<i>P</i>	-	-	-	-	-	-	-	0.038

## 4. Discussion

Soft tissue injury is a common condition in the locomotor system, often caused by external forces such as traffic accidents and mechanical injuries. It manifests as bleeding and severe pain in the affected area and can affect the blood circulation status of surrounding tissues, leading to serious complications. Compared with other soft tissues, skin tissue has a greater thickness, rich sebaceous glands, and hair follicles, but poor mobility. Due to its superficial location, skin is prone to severe injury under external forces and has a high infection rate [3]. Therefore, early treatment of skin and soft tissue injuries is necessary for thorough debridement, accelerated wound healing, and improved prognosis.

Conventional dressing change technique is a commonly used treatment for this condition, allowing regular debridement and dressing changes to promote good wound healing. However, this therapy has limitations, including a long treatment cycle, frequent dressing changes, and increased risk of complications such as infection and skin flap necrosis, which can cause significant physical and psychological stress to patients [4]. VSD, a novel treatment method, can thoroughly remove wound exudate, allowing harmful substances and necrotic tissue to be fully discharged. Simultaneously, it can isolate the wound from the external environment, preventing prolonged exposure to air and reducing infections. The highly permeable dressing used in VSD can regulate blood circulation around the skin, accelerating healing. Additionally, this technique does not require multiple dressing changes, causing minimal pain, and thus has a higher acceptance rate among patients [5].

The results showed that the total effective rate of the observation group was higher than that of the control group, and all treatment indicators were better in the observation group ( $P < 0.05$ ). This is because VSD, as an emerging treatment technology, combines the therapeutic effects of irrigation and sealing, providing continuous negative pressure suction therapy to the wound. Irrigation therapy prevents the dressing from drying out or blocking the wound tissue [6]. The purpose of sealing therapy is to completely seal the wound, isolating it from the external environment and preventing complications such as cross-infection. Negative pressure suction provides adequate and comprehensive drainage treatment to the wound, preventing the formation of necrotic tissue, avoiding bacterial accumulation on the wound surface, and reducing bleeding and fluid leakage [7]. Furthermore, negative pressure suction can accelerate granulation tissue growth, prevent tissue edema, regulate the microcirculation status around the wound, accelerate wound healing, and quickly reduce the wound area without requiring frequent dressing changes.

After treatment, the level of inflammatory factors in the observation group was lower than that in the control group ( $P < 0.05$ ). This is because this technology is simple, easy to implement, and can reduce the number of times the wound is exposed to air, preventing bacteria from colonizing the wound surface in large numbers. Therefore, it does not easily lead to significant inflammatory reactions [8]. Additionally, this



technology allows for standardized antibiotic treatment regimens tailored to the specific conditions of the wound, preventing antibiotic abuse and effectively controlling inflammatory responses.

The complication rate in the observation group was lower than that in the control group ( $P < 0.05$ ). This is because VSD treatment fully covers the wound with a dressing, uses a bio-semi-transparent membrane for strict sealing, and provides thorough irrigation and continuous drainage to maintain a moist environment in the wound. This preserves nutrients and active substances such as tissue proteinases, which dissolve necrotic tissue and prevent complications such as infection<sup>[9]</sup>. Negative pressure irrigation can drain wound secretions, remove necrotic tissue, maintain wound cleanliness, and promote rapid granulation tissue growth. Therefore, the incidence of skin necrosis and muscle atrophy is low. However, it is important to note that before VSD treatment, the wound should be thoroughly cleaned to ensure the dressing closely adheres to the wound, improving blood circulation and exerting the hemostatic effect of the dressing. Simultaneously, dynamic evaluation of the wound condition and reasonable adjustment of negative pressure are necessary to ensure efficacy<sup>[10]</sup>.

## 5. Conclusion

In summary, VSD demonstrates excellent efficacy in the treatment of skin and soft tissue injuries. It can shorten patients' recovery time, reduce inflammatory responses in the body, and actively prevent complications, exhibiting significant therapeutic advantages.

## Disclosure statement

The author declares no conflict of interest.

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# Evaluation of Antioxidant and Antibacterial Activities in Andaliman Fruit (*Zanthoxylum acanthopodium* DC.): An Approach to Bioactive Compound Analysis and Use of *In Vitro* Test Methods

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**Abstract:** Andaliman fruit extract has been shown to exhibit anti-inflammatory activity, immunostimulant effects, and anticancer activity. It contains antioxidant compounds, which can stimulate the immune system. The purpose of the study was to determine the antioxidant activity of andaliman fruit (*Zanthoxylum acanthopodium* DC.) using the DPPH method (2,2-diphenyl-1-picrylhydrazyl). The experimental research was conducted in January 2024. The sample used in this study was andaliman fruit (*Zanthoxylum acanthopodium* DC.) purchased from Onan Rungu village, Samosir Regency, North Sumatra Province. Ethanol extract of andaliman fruit showed significant antibacterial activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* at various concentrations, with the largest zone of inhibition at a concentration of 300 mg/mL. These results demonstrate the potential of andaliman as a source of natural antibacterial agents that can be used in the development of health products.

**Keywords:** Andaliman fruit extract; Antioxidant activity; Antibacterial properties; Natural health products; Experimental research

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## 1. Introduction

Andaliman (*Zanthoxylum acanthopodium* DC.), a member of the Rutaceae family, is a plant familiar to the Batak community and is considered a wild plant native to North Sumatra Province. The utilization of natural resources

is widespread, with approximately 80% of the global population—particularly in developing nations—relying on plants as medicinal resources to maintain their health, as documented by the World Health Organization (WHO) <sup>[1]</sup>. The antioxidant compounds present in spices including andaliman can stimulate the immune system and particularly demonstrate anticancer activity. Numerous studies focusing on medicinal plants have highlighted the substantial antioxidant content found in many of these plants <sup>[2]</sup>. The antioxidant properties of compounds are primarily attributed to phenol compounds, including flavonoids and phenolic acids. Compounds exhibiting antioxidant activity typically feature hydroxyl groups positioned in ortho and para positions relative to –OH and –OR groups <sup>[3]</sup>. The function is essential in neutralizing and eliminating free radicals in degenerative conditions. The digestive tract is particularly susceptible to bacterial infections, with common ailments such as cholera, diarrhea, and gastroenteritis affecting many individuals due to bacterial contamination in food and inadequate sanitation practices <sup>[4]</sup>.

Andaliman can also serve as a preservative, medicinal ingredient and supplement, and even as a vegetable pesticide <sup>[5]</sup>. Other research has indicated the antibacterial potential of andaliman extract against food-pathogenic bacteria such as *Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhimurium* <sup>[6,7]</sup>. Based on the information provided by relevant literature, this study aims to investigate the antioxidant activity of andaliman fruit (*Zanthoxylum acanthopodium* DC.) using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method, as well as evaluating its antibacterial properties through the minimum inhibitory concentration (MIC) method.

## 2. Research methods

The research methodology employed in this study is experimental research. The subsequent analysis of antioxidant activity used the DPPH free radical scavenging method. The study was conducted in January 2024. The equipment used included laboratory glassware, aluminum foil, and a laminar airflow cabinet (Astec HLF I200L), a rotary evaporator (Heidolph VV-300), and a UV-visible spectrophotometer (Shimadzu UV-1800).

The materials utilized in this study were Peridot leaves (*Saurauia vulcani*), ethyl acetate, distilled water, n-hexane, ethanol, methanol, DPPH, dimethyl sulfoxide (DMSO), nutrient agar (Oxoid), nutrient broth (Oxoid), *Staphylococcus aureus* ATCC 25923, and *Staphylococcus epidermidis* ATCC 12228. The sampling approach was purposive, without comparison with the same material from other regions. The andaliman fruit samples used in the study were obtained from Onan Rungu village, Samosir Regency, North Sumatra Province.

### 2.1. Preparation of extract

The andaliman fruit (*Zanthoxylum acanthopodium* DC.) was dried in a cabinet at a temperature of  $\pm 40^{\circ}\text{C}$  before pulverizing with a blender. The powder was weighed and stored in a plastic container to prevent the influence of moisture and other impurities.

Extraction was carried out by maceration using 96% ethanol solvent. First, 500 g of andaliman fruit powder with a suitable acceptable degree was poured into a vessel, mixed with 75 parts of 96% ethanol, then closed and left for five days, protected from light while stirring once a day. After five days, it was filtered, and the pulp was squeezed out. The dregs were washed with enough solvent, mixed, and filtered to obtain 100 parts. The macerate was collected into a closed vessel, and left protected from light for two days. The solvent was evaporated with a rotary evaporator at  $50^{\circ}\text{C}$ , and concentrated in a water bath until a thick extract was obtained (Directorate General of POM RI, 1979).

## 2.2. Antioxidant activity testing using DPPH method

The DPPH method measures the ability of the test sample to reduce the oxidation process of DPPH free radicals in methanol solution (resulting in a change in the color of DPPH from purple to yellow) with IC<sub>50</sub> value (concentration of the test sample that can reduce 50% free radicals) as a parameter to determine the antioxidant activity of the model.

For the preparation of blank solution, 5 ml DPPH 0.5 mM solution (200 ppm concentration) was pipetted and put into a 25 ml volumetric flask, and sufficed with methanol until the marked line (40 ppm concentration). The 40 ppm concentration of DPPH was homogenized and measured its absorption at a wavelength of 400–800 nm, which is the wavelength of visible light.

## 2.3. Preparation of standard solution

A total of 3 mg of andaliman ethanol extract was weighed and put into a 3 ml volumetric flask dissolved with methanol; then, the volume was filled with methanol until the marked line (concentration of 1000 ppm).

## 2.4. Preparation of quercetin standard solution

A total of 1 mg of quercetin powder was weighed, put into a 10 ml volumetric flask, dissolved with methanol, and then the volume was filled with methanol to the marked line (concentration 100 ppm).

The concentration was determined after several orientations. First, the standard liquid was pipetted as much as 0.125 ml, 0.25 ml, 0.5 ml, and 1 ml into a 10 ml volumetric flask; into each volumetric flask was added 1 ml of 0.5 mM DPPH solution (concentration 200 ppm), then methanol was added to the marked line. It was left to stand for 60 minutes, and then the absorbance was measured using a UV-visible spectrophotometer at the wavelength of maximum absorption obtained.

## 2.5. Preparation of quercetin test solution

The standard liquid was pipetted as much as 0.3125 ml, 0.625 ml, 1.25 ml, and 2.5 ml, and put into 25 ml volumetric flasks to obtain test solution concentrations of 1.25 ppm, 2.5 ppm, 5 ppm, and 10 ppm into each volumetric flask was added 5 ml of 0.5 mM DPPH solution (concentration 200 ppm), and methanol was added to the marked line. It was left to stand for 60 minutes, then the absorbance was measured using a UV-visible spectrophotometer at the wavelength obtained.

A total of 0.1 ml of the inoculum was put in a sterile petri dish, and 15 ml of nutrient agar medium was poured before placing at a temperature of 40–50°C. Petri dishes were shaken on a table surface so that the medium and bacterial suspensions were evenly mixed and allowed to solidify. Antibacterial activity was tested using the agar diffusion method using paper discs. Paper discs that had been dripped 0.1 ml with several concentrations of andaliman ethanol extract test solution were placed on top of the solid media that had been inoculated with bacteria and left for 15 minutes, then incubated in an incubator at  $36 \pm 1^\circ\text{C}$  for 18 hours, after which the diameter of the growth inhibition area (clear zone) around the disc was measured using a caliper.

## 3. Result and discussion

Phytochemical screening tests are carried out to determine and identify the components of bioactive compounds contained in andaliman fruit extract. Some components of active compounds identified include alkaloids, steroids/triterpenes, saponins, tannins, flavonoids, and glycosides. The screening results of andaliman fruit extract extracted

using ethyl acetate solvent can be seen in **Table 1**.

**Table 1.** Phytochemical screening test results of andaliman fruit extracts

Bioactive compounds	Andaliman fruit extract
Alkaloid	+
Flavonoid	+
Saponin	+
Tannin	+
Steroid/triterpenoid glycoside	-
	+

Description:

(+) = contains compounds

(-) = does not contain compounds

The screening test results revealed that the andaliman extract, when using ethyl acetate as the solvent, contained nearly all secondary metabolite compounds such as alkaloids, flavonoids, glycosides, saponins, and steroids, with the exception of tannins. However, in another study, the screening test results indicated that the andaliman extract, also prepared using ethyl acetate as the solvent, contained almost all secondary metabolite compounds including alkaloids, flavonoids, glycosides, tannins, and saponins, but did not contain steroids <sup>[8]</sup>. **Table 2** shows the absorbance results of ethanol extract of andaliman fruit, while **Tables 3** and **4** present the antibacterial activity test results of ethanol extract of andaliman fruit against *Staphylococcus aureus* and *Staphylococcus epidermidis*.

**Table 2.** Absorbance measurement results of ethanol extract of andaliman fruit

Concentration (ppm)	Absorbance	Percentage reduction
Blank	0.778	0
100 mg/mL	0.104	78.4441
50 mg/mL	0.114	74.448
25 mg/mL	0.433	47.1180
12.5 mg/mL	0.464	31.3801

**Table 3.** Antibacterial activity test results of ethanol extract of andaliman fruit against *Staphylococcus aureus*

Concentration (mg/mL)	P1	P2	P3	X	SEM
300	11.3	11.0	11.0	10.38	0.13
200	9.1	9.3	9.3	9.41	0.15
100	8.6	8.3	8.1	8.41	0.13
50	7.8	8.4	7.4	7.35	0.11
25	7.3	6.3	6.4	6.33	0.13
12.5	6.3	6.3	6.4	6.34	0.11
K-	6	6	6	6.00	0.00

**Table 4.** Results of antibacterial activity test of ethanol extract of andaliman fruit against *Staphylococcus epidermidis*

Concentration (mg/mL)	P1	P2	P3	X	SEM
300	13.3	13.4	10.3	10.46	0.20
200	9.2	6.2	9.3	8.34	0.32
100	8	8.4	8.2	8.38	0.32
50	7.2	7.4	8.3	7.25	0.53
25	6.6	6.4	6.5	6.46	0.33
12.5	6.9	6.2	6.6	6.22	0.04
6.25	6	6	6	6.00	0.00
K-	6	6	6	6.00	0.00

Antimicrobial compounds can cause damage to cell walls and cell membranes through the denaturation of proteins and fats that make up the cell membrane. Ethanol extract of andaliman fruit effectively inhibits the growth of Gram-positive bacteria *Staphylococcus aureus* and *Staphylococcus epidermidis*, this is likely due to antibacterial activity influenced by several factors, namely the concentration of the extract and the type of bacteria inhibited <sup>[7]</sup>. MIC is the minimum concentration of antimicrobial substances that can inhibit bacterial growth after 24 hours of incubation and no known bacterial colonies grow by observing the number of bacterial colonies. An inhibition zone diameter of 5 mm or less is categorized as weak, an inhibition zone diameter of 5–10 mm is categorized as moderate, an inhibition zone diameter of 10–20 mm is categorized as strong, and an inhibition zone of 20 mm or more is categorized as very strong. This study shows that the higher the concentration of extract, the greater the amount of antibacterial compounds released, thus facilitating the penetration of these compounds into cells; in other words, the higher the concentration of extracts and the length of contact time, the more active the antibacterial activity, it is stated that Gram-positive bacteria whose outer membrane consists of more peptidoglycan layers than Gram-negative whose outer membrane consists of lipopolysaccharides namely lipids, polysaccharides, and proteins <sup>[8]</sup>. The cell wall of Gram-negative bacteria contains much less peptidoglycan than Gram-positive so the permeability of Gram-positive bacteria is lower than the permeability of Gram-negative bacteria. With low permeability, the active substance from the methanol extract of plant leaves will have difficulty penetrating the cell membrane of Gram-positive bacteria so the antibacterial effect is less optimal. Flavonoid compounds have the ability to form complexes with bacterial cell proteins through hydrogen bonds. As a result, the permeability function of bacterial cells is disrupted and bacterial cells undergo lysis and cell death <sup>[7]</sup>.

Flavonoid compounds are thought to have a mechanism of action that denatures bacterial cell proteins and irreparably damages cell membranes. Flavonoids are also lipophilic, which will damage microbial membranes because flavonoids contain phenol compounds <sup>[9]</sup>. The growth of bacteria *Staphylococcus aureus* and *Staphylococcus epidermidis* can be disrupted due to acidic phenol compounds. Besides, phenol also has the ability to denature proteins and damage cell membranes. Acidic conditions in the presence of phenols can affect the growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* <sup>[10,11]</sup>.

## 4. Conclusion

Based on the results, it can be concluded that the ethanol extract of andaliman fruit shows significant antibacterial



activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* at various concentrations, with the largest zone of inhibition at a concentration of 300 mg/mL. These results demonstrate the potential of andaliman as a source of natural antibacterial agents that can be used in the development of health products. However, more research is needed to understand its mechanism of action and potential side effects. Ethanol extract of andaliman fruit has potential as an interesting alternative in the development of natural antibacterial agents.

## Disclosure statement

The authors declare no conflict of interest.

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# Role of MAPK and JNK Signaling Pathways in Skin Cancer Progression and Therapeutic Approach

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**Abstract:** Mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathways exhibit complex signal transduction pathways that modulate multiple processes and the deregulated form of MAPK is involved in many types of cancers including skin cancer. These signaling pathways regulate cellular processes such as differentiation, inflammation, cell proliferation, and survival. Moreover, MAPKs are crucial signaling pathways in regulating various cellular processes, including cell proliferation, differentiation, survival, and apoptosis. Their dysregulation is commonly observed in cancer, making them attractive targets for therapeutic intervention. The critical mechanisms and pathways of MAPKs and JNKs in skin cancer including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma are summarized in this review. In addition to providing new insights into MAPK and JNK pathways in cancer progression and proliferation, we also offered the significance of the mechanism of JNK in drug resistance and the association of KLF4 in influencing JNKs for future endeavors to be targeted as therapeutic approaches as understanding the molecular aspects of these signaling pathways are crucial for novel therapeutic breakthroughs.

**Keywords:** Cancer; MAPK and JNK pathways; Deregulation; Treatment

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## 1. Introduction

Mitogen-activated protein kinase (MAPK) pathways comprise three kinases that regulate various cellular signaling processes, the main upstream kinase (MAPKKK) controls multiple inside and outside signals and stimulates the middle kinase (MAPKK) through phosphorylation. Only MAPKs can phosphorylate and activate MAPKs, which usually have a large number of substrates that carry out distinct cell fate selections appropriate for the received information<sup>[1]</sup>. The suppression of upstream stimulants is a common aspect of MAPK substrate phosphorylation. This arrangement is equivalent to a negative feedback booster since it ensures resilience against noise and graded reactions by combining negative feedback from the finished product back to the source message with signal enhancement via the 3-tiered kinase pathway<sup>[2]</sup>. MAPKs respond to a broad range of input indications, such as



signals from surroundings and internal stress, along with physiological stimuli comprising hormones, cytokines, and growth regulators. As a result, they are generally divided into two categories: stress- and mitogen-responsive MAPKs. The classic examples of both categories include P38 and JNK as stress-responsive MAPKs and ERK as mitogen-responsive MAPKs <sup>[3]</sup>. From a biological perspective, the differentiation is imprecise since all three groups react to an extensive range of stimuli that intersect. Since many disorders disrupt MAPK signaling, medicinal developers have focused on developing drugs that target its kinase elements over the past 20 years <sup>[4]</sup>.

c-Jun N-terminal kinases (JNKs) belong to the family of MAPKs and are responsible for influencing cellular activities such as inflammation, migration, cell proliferation, apoptosis, and differentiation. JNK was initially identified as cycloheximide, a stress-activated protein kinase (SAPK), in the liver of mice <sup>[5]</sup>. It was later dubbed “JNK” to highlight its function in phosphorylating and activating the c-Jun transcription element. JNK1 (MAPK8), JNK2 (MAPK9), and JNK3 (MAPK10) are the three members of the JNK kinase family that are controlled by three different genetic loci in the human genome <sup>[6]</sup>. While JNK1 and JNK2 are prevalent in most tissues, JNK3 expression primarily occurs in the brain, with smaller amounts also identified in the heart and testes. JNKs are similar to other MAPKs highly stimulated in reaction to ultraviolet radiation, cytokines, stress, and chemicals that damage DNA; they are also less commonly induced by activation of G-protein-coupled receptors (GPCRs), serum, and growth factors <sup>[7]</sup>. Two upstream mitogen-activated protein kinase kinases (MAP2Ks) (MKK4 and MKK7) phosphorylate JNKs specifically on the threonine (Thr183) and tyrosine (Tyr185) residues, hence initiating the JNK cascade. Apoptosis signal-regulating kinase (ASK)1/2, MEKK1-4, MLK2 and 3, TPL-2, DLK, TAO1 and 2, TAK1, and other mitogen-activated protein kinase kinase kinases (MAP3Ks) are among the upstream mechanisms that promote MKK4 and MKK7. Every MAP3K might have a distinct stimulus response <sup>[8]</sup>.

Mitogen-activated protein kinase 8 (*MAPK8*) gene also known as C-Jun N-terminal kinases 1 (*JNK1*) is located on chromosome 10q11.22 and is associated with the phosphorylation of c-Jun at position serine 63 and serine 73 in those cells that are under the influence of ultraviolet radiations. C-Jun N-terminal kinases are associated with SAPKs, encoded by three types of genes, which are *MAPK8* (*JNK1*), *MAPK9* (*JNK2*), and *MAPK10* (*JNK3*), producing many products through splicing <sup>[9]</sup>. The significant component of the MAPK family is C-Jun N-terminal kinases. The increase in activity of *MAPK8* can control the proliferation of cells positively and the MAPK family is involved in many pathways such as cell survival, stress response, migration, apoptosis, proliferation, and differentiation associated with activated protein 1 (AP1) transcription factors. All these functions connect with other central signaling transduction pathways <sup>[10]</sup>. Several factors are responsible for the AP1 transcriptional activity like ultraviolet radiations, viral infection, cellular stress, growth factors, and cytokines. These factors are important in many pathways like differentiation, inflammation, proliferation, and apoptosis. Moreover, MAPK pathways are highly influenced by various external stimuli such as ultraviolet radiations and inflammatory cytokines <sup>[11]</sup>. Every MAPK cascade has at least three kinds of kinases such as a mitogen-activated protein kinase (MAPK), a mitogen-activated protein kinase kinase (MEK), and an MEK kinase (MEKK). MEK is phosphorylated by initiated MEKK, which leads to phosphorylation of MAPK. Many different types of targets are phosphorylated by these activated MAPKs like transcriptional factors. The mostly used MAPKs are MAPK8, MAPK9 (JNK1, JNK2), P38 kinases, and ERK kinases (ERK1, ERK2) <sup>[12]</sup>. MAPK pathway consists of many regulator proteins (kinase c and ras), AP1 (transcription factors), and MAPK module. Phosphorylation and activation of these sequential kinases cause the increased activity of AP1 transcriptional factor as well as DNA response element binding to the target gene <sup>[13]</sup>. All these processes lead to the enhanced transcription of the target gene. This pathway commands keratinocyte proliferation, differentiation, and apoptosis and is also associated

with tumor development and progression. The MAPK pathways are involved in the activation of many genes in keratinocyte differentiation <sup>[14]</sup>.

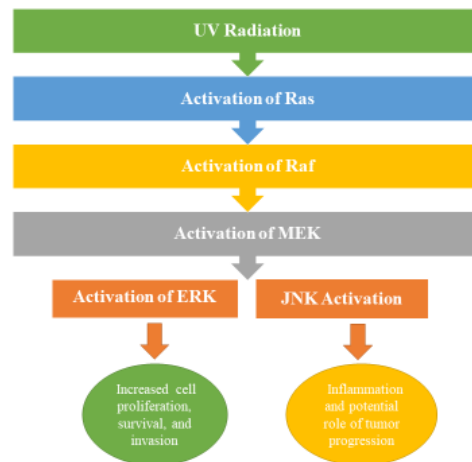
The activation of MAPK kinases is associated with the signal coming from membrane receptors by TRAF2/6 protein. AP1 transcription factors like Fos and Jun family members act as the downstream target for MAPK pathways that function for gene transcription regulation <sup>[15]</sup>. These c-Jun and c-Fos are proto-oncogenes in many types of cancer. In many cases, targeting of MAPK is associated with the responsive behavior of target genes that are involved in regulating many cellular pathways like cell cycle progress, migration, and survival <sup>[16]</sup>. In addition, MAPK is involved in the phosphorylation and expression of the *P53* tumor suppressor gene. For that reason, lower expression of *P53* causes cell senescence. The target for the MAPK signaling is the *P53* tumor suppressor gene involved in *P53* phosphorylation on ser34. The binding of JNK with phosphorylated *P53* stabilizes the *P53* protein by inhibiting the degradation of ubiquitin. From these studies, it was concluded that the MAPK family (JNK) is necessary in controlling the expression of *P53*. MAPK pathway activation is involved in many diseases and disorder conditions including prostate carcinoma, glioma, atherosclerosis, diabetes, arthritis, colon cancer, squamous cell carcinoma (SCC), and skin cancer <sup>[17-19]</sup>.

The upregulation of the MAPK pathway (Ras/RAF/MEK/ERK (MAPK) pathway) induces approximately more than 40% of cancer cases. One gene family that frequently has mutations in cancer is *RAS*. *KRAS* mutations are a particularly common type of cancer, and they include colorectal and pancreatic ductal adenocarcinomas <sup>[20]</sup>. On the membrane, *RAS* is often triggered after growth factor receptors. *H-RAS*, *K-RAS*, and *N-RAS* are the three gene isoforms of *RAS*. Despite having very similar sequences, they serve multiple purposes that result in various physiological processes. RafA, RafB, and RafC are the three isoforms of the RAF protein family kinases, together with two closely related pseudokinases (KSR1/2) <sup>[21]</sup>. Furthermore, 8% of tumors have *BRAF* alterations, which are highly prevalent in melanomas. The most common mutation frequency in this conventional route is 22% for *RAS*, 8% for *BRAF*, and <1% for *MEK*, although *ERK* alterations are sporadic. By activating *RTK* and *RAS*, the three-layered MAPK-signaling pathway is started. Several physiological processes are regulated by the three RAF subtypes, as well as downstream MEK1/2 and ERK1/2 from a constitute-signaling mechanism <sup>[22]</sup>. Crucial functions for the P38 MAPK cascade are seen in signaling cascade actions. The four members of P38 kinase in mammals are P38 $\alpha$ , P38 $\beta$ , P38 $\gamma$ , and P38 $\delta$ . The downstream effector and upstream activator exhibit different levels of expression. The regulation of cell development, proliferation, and death is mediated by P38 MAPK. MKK4 kinase, a component of JNK, can also phosphorylate it. Normally, MKK3 and MKK6 kinases stimulate it <sup>[23]</sup>. Typically, upon activation, the P38 protein moves from the cytoplasm to the nucleus in order to control downstream signaling molecules. Three subtypes of JNK exist: JNK1, JNK2, and JNK3. While JNK1 and JNK2 are found in many different tissues, JNK3 is mostly found in the testis, cardiac myocytes, and neural tissues. They react to a range of stresses, including oxidative stress and chemicals that damage DNA. Comparable to the P38 MAPK pathway, JNK MAPK is primarily activated by the upstream kinases MKK4 and MKK7. This necessitates the dual phosphorylation of Tyr and Thr residues in their activation loops within a conserved Tyr-Pro-Thr motif. This facilitates the control of several biological procedures, such as growth, differentiation, and autophagy <sup>[24,25]</sup>.

An additional protein kinase involved in the triple MAPK-signaling pathway is called ERK5. Three varieties exist: ERKa, ERKb, and ERKc, a transcriptional transactivation domain and a nuclear localization signature are components of the C-terminal extension of ERK5. MEK5 phosphorylation is the method by which it is activated <sup>[26]</sup>. ERK5 has the ability to bind to many residues between its C-terminus when its kinase region is active. Following their characterization, phosphorylation-specific antibodies against S753 and T732

were developed. The transcription levels of *ERK5* vary across different tissues, with the brain, thymus, and spleen exhibiting the highest levels of expression. This signaling system is linked to malignancies and takes a role in the growth, differentiation, and destruction of cells <sup>[27]</sup>.

The possible mechanism of initiation of the JNK pathway in tumor progression is given in **Figure 1**.



**Figure 1.** The activation of JNK signaling and ERK pathways by activating Ras, Raf, and MEK on UV radiation exposure. MEK activation plays a significant role in MAPK signaling pathways.

## 2. JNK regulation

### 2.1. JNK regulation of cell cycle progression

Several cellular activities, such as cell migration, survival, growth, senescence, apoptosis, and stress reactions, are mediated by the JNK signaling pathway. Premature senescence and growth arrest of mouse embryonic fibroblast cells in G2/M are caused by genetic knockdown of *MKK7*. JNK controls the G2/M transition and the advancement of the G1 cell cycle <sup>[28]</sup>. In Jurkat cells, JNK is activated during the G2/M transition. In human HeLa cervical cancer cells, activated JNK was similarly discovered to be concentrated in the centromeres during early S-phase to late anaphase, with the greatest expression during metaphase <sup>[29]</sup>. Phosphorylation of c-Jun occurs regularly during mitosis and the initial stages of the G1 phase. It has also been discovered that JNK stimulates mitosis via Aurora B Kinase. NIH-3T3 fibroblasts and CIGC ovarian granulosa cells undergo G2/M transition suppression when JNK is inhibited pharmacologically or genetically by small interfering (siRNA)-mediated methods. This is because JNK suppression inhibits Aurora B kinase, ultimately leading to a reduction of histone-H3 (Serine 10) phosphorylation <sup>[30]</sup>.

### 2.2. JNK regulation of cell survival and apoptosis

JNK has contradictory functions in both apoptosis and cell maintenance. Tumor necrosis factor (TNF $\alpha$ )-induced cell suicide can affect JNK1 and JNK2 fibroblasts, suggesting that JNK facilitates cell survival. According to the research, JNK is necessary for the development of the JunD transcription element, which works with NF- $\kappa$ B in promoting the development of genes that are favorable for survival in fibroblasts, like cIAP-2 <sup>[31]</sup>. By downregulating FoxO1, JNK has also been shown to increase the lifespan of fibroblast-like synoviocytes in rheumatoid arthritis. Research from other sources indicates that JNK enhances cell survival by working in concert with NF- $\kappa$ B and

JAK/STAT. However, it is widely recognized that JNK is crucial for apoptosis. By phosphorylating Bad and Bim, JNK specifically affects mitochondria <sup>[32]</sup>. These pro-apoptotic proteins counteract the effects of anti-apoptotic proteins like Bcl-2 and Bcl-xL. Furthermore, JNK triggers the breakdown of cytochrome c (Cyt C) via a Bid-Bax-dependent process. This results in the assembly of apoptosomes made up of Apaf-1, caspase-9, and Cyt C, and in turn, activates caspase 9-dependent apoptosis <sup>[33]</sup>. Additionally, JNK blocks TRAF2/IAP1 signaling by causing Smac/Diablo to be released from mitochondria and activating caspase 8 as a consequence. Endoribonuclease 1 $\alpha$  (IRE1 $\alpha$ )/transmembrane kinase needing inositol requires TRAF2 recruitment in order to stimulate ASK1 and JNK, which in turn inhibits anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Mcl-1. JNK triggers apoptosis in response to DNA damage through P53 phosphorylation, P73 stabilization, and P53/P73-dependent production of pro-apoptotic molecules Bax and Puma <sup>[30,34]</sup>.

### 3. MAPK family and squamous cell carcinoma

The tumorigenic effect of the *MAPK8 (JNK1)* gene has been observed in the human squamous cell carcinoma model, where human keratinocytes were subjected to the analysis of gene regulation in immunodeficient mice. In this model, it was proved the importance of JNK1 and c-Jun in human epidermal tumors activated by tumorigenic Ras. Therefore, the coupling of c-Jun with oncogenic Ras is responsible for the conversion of normal human epidermal cells to malignancy. Contrary to this, JNK1 is also involved in the blockage of Ras-induced NF- $\kappa$ B stimulation, which was previously involved in the activation of human epidermal cell senescence and growth arrest <sup>[20]</sup>. Therefore, the understanding of initiation of JNK1 and Ras is necessary because this creates a molecular environment for tumorigenesis.

In SCC, JNK expression is commonly seen and SCC cell lines and tissues have higher levels of JNK2 phosphorylation than healthy keratinocytes as well as healthy skin specimens. JNK1 demonstrated a tumor suppressor role, in opposition to JNK2. Mice lacking JNK1 had a greater prevalence of papilloma than mice of the wild type. These results are consistent with the fact that constitutively active MKK7 and MKK7-JNK2 fusion proteins—but not MKK7-JNK1—can link with the oncogenic Ras (V12) to convert normal keratinocytes into lesions resembling SCC, provided that c-Jun activity is maintained <sup>[35]</sup>. Furthermore, c-Jun can combine with Ras to cause epidermal cancer, but not JunB. Finally, by inhibiting JNK, squamous cell carcinoma antigen 1 (SCCA1) keeps keratinocytes from going through apoptotic cellular death. These findings suggest that epidermal cancer is promoted by MKK7, JNK2, and c-Jun, but not by JNK1 or JunB <sup>[3]</sup>.

In K14-CYLDm transgenic mice, epidermis-targeted expression of a catalytically deficient CYLD mutant (CYLDm) resulted in enhanced JNK stimulation, lysine-63 (K63)-ubiquitination, and phosphorylation of the transcription elements c-Jun and c-Fos. K14-CYLDm mice treated with DMBA/TPA had more papillomas; by week 32, 66% of these had progressed to SCC and metastasized. Applying the JNK inhibitor SP600125 topically to K14-CYLDm mice eliminated skin cancer spread to lymph nodes and dramatically decreased the frequency of tumors generated by DMBA/TPA. Histone H3's lysine 9 and 36 residues are particularly demethylated by the demethylase KDM4A. When comparing metastatic human SCC tissues to primary SCC tissues, there was a rise in protein concentrations corresponding with higher transcription of KDM4A, c-Jun, and FOSL1 (Fra1). Moreover, FRA1 was discovered to promote the growth and multiplication of head and neck SCC cells in a way that was related to c-Jun <sup>[30]</sup>.

JNK function has been studied in both human and animal tissue models of SCC. Ultraviolet light or a two-



stage chemical carcinogenesis procedure with a single topical dosage of 7,12-dimethylbenzanthracene (DMBA) and monthly 12-O-tetradecanoylphorbol-13-acetate (TPA) are commonly used to produce skin cancers in animal research. Compared to their WT counterparts, *Jnk1*<sup>-/-</sup> mice showed a greater degree of tumor formation kinetics and carcinoma development, indicating a high susceptibility to DMBA/TPA-induced skin tumorigenesis. The higher amount of TPA-induced AP1 DNA interaction ability and activation of extracellular signal-regulated kinases and Akt were implicated in the improved tumor growth phenotype observed in *Jnk1*<sup>-/-</sup> animals [36]. These results support the idea that Serpin SCC antigen (SCCA1)-induced JNK1 inhibition inhibits ultraviolet-induced epithelial cell division and, as a result, enhances carcinogenesis. On the contrary, fewer papillomas grew in JNK2-deficient (*Jnk2*<sup>-/-</sup>) mice than in WT mice after a DMBA/TPA chemical assault, suggesting that these mice remained immune to tumor formation. Moreover, the *Jnk2*<sup>-/-</sup> papillomas showed noticeably lower levels of AP1 and Erk activity and were not likely to develop into cancer. These data suggest that JNK1 and JNK2 have opposing roles in the development of skin cancer, with JNK2 acting as a tumor promoter [37]. The regenerated human SCC model, in which primary human keratinocytes were employed for skin regrowth on immunodeficient mice after undergoing multiplex gene transduction to produce genes under examination, also revealed the carcinogenic consequences of JNK2. Applying this approach, it was proved that JNK2 and c-Jun are necessary for the aggressive human epidermal neoplasia that is caused by oncogenic Ras and NF-κB blockage. Furthermore, it only takes the production of constitutively active mutations of c-Jun, JNK2 (MKK7-JNK2 fusion), or MKK7 to partner with oncogenic Ras and cause malignant transformation in normal human epidermal cells [38]. On the other hand, Ras-driven human epidermis cancer cannot be sufficiently promoted by the expression of active MKK7-JNK1 fusion protein. JNK2 and c-Jun, but not JNK1, are substantially activated in human SCC, which is consistent with the results from experimental animals and indicates that these compounds are therapeutically important [39]. Interestingly, JNK2 but not JNK1 enhances Ras-induction of glycolysis, a procedure that produces energy and is frequently employed by cancer cells. This is sometimes referred to as the Warburg effect. Conversely, JNK2 inhibits NF-κB activation triggered by Ras, which has been shown to cause growth inhibition and senescence in human epidermal cells. Hence, JNK2 and Ras coactivation create the ideal metabolic and molecular milieu needed for carcinogenesis [40]. JNK targets AP1 proteins downstream in murine SCC cell lines and is less likely to develop tumors *in vitro* and *in vivo* when the dominant-negative mutant of c-Jun (DNc-Jun, also called TAM67) is expressed. Epidermal elimination of c-Jun frequently decreases cancer development of murine skin caused by chemicals, ultraviolet light, or the oncogene of the papillomavirus. Furthermore, skin cancers produced by Ras do not grow malignantly in animals lacking c-fos. These results highlight the critical function that AP1 plays in the development of skin tumors [41]. However, because AP1 activity is so diverse, distinct AP1 subunits have varying roles across various biological activities. For instance, the malignant phenotype of converted rat keratinocytes is enhanced by JunB overexpression *in vitro*, indicating that JunB may be involved in tumor formation [42]. Conversely, JunB reduces carcinogenesis as evidenced by the JB6(P-) SCC cells' immunity to tumor advancement, as well as the inhibition of cell growth and the epithelial-to-mesenchymal transition (EMT) of various SCC cell lines. The latest research has demonstrated that exogenous expression of JunB prevents epidermal neoplasia caused by co-expression of MKK7 and Ras oncogene and that the nuclear level of JunB is decreased in spontaneous human SCC, which is consistent with these latter results [43]. These findings demonstrate the opposing roles of c-Jun and JunB in neoplasia and epidermal development.

The roles of MAPK and JNK signaling in skin cancer types such as BCC, SCC, and melanoma are given in **Table 1**.

**Table 1.** Roles of MAPK and JNK signaling in skin cancer

Skin cancer type	MAPK/JNK signaling	Role	Mechanism of action	Upregulation/downregulation	Therapeutic target
Basal Cell Carcinoma (BCC)	MAPK, JNK	Promotes cell proliferation, survival, and invasion	Activation of downstream transcription factors (e.g., AP-1, Elk-1) leading to increased expression of genes involved in cell cycle progression, anti-apoptosis, and matrix metalloproteinases	Upregulated expression	MAPK/JNK inhibitors
Squamous Cell Carcinoma (SCC)	MAPK, JNK	Promotes cell proliferation, survival, invasion, and angiogenesis	Similar to BCC, with additional roles in inflammation and immune response	Upregulated expression	MAPK/JNK inhibitors, combination therapies
Melanoma	MAPK (ERK, MEK)	Drives cell proliferation, survival, migration, and invasion	Activation of downstream effectors (e.g., ERK, p90RSK) leading to increased expression of genes involved in cell cycle progression, anti-apoptosis, and cell motility	Higher expression	MAPK inhibitors (e.g., MEK inhibitors), combination therapies

#### 4. MAPK family, JNK pathways, and basal cell carcinoma

The association of MAPK with BCC has been studied. The target c-Jun for MAPK was found to be reactive and expressive in many basal cell carcinoma samples. In basal cell carcinoma, MAPK and c-Jun are significant for the tumorigenic activity of Hedgehog/Gli proteins. In addition, the signaling pathways of Hedgehog/GLI proteins are linked with signaling pathways of epidermal growth factor receptors to move the tumorigenic condition in the mouse basal cell carcinoma cell line <sup>[44]</sup>.

In BCC, the sonic hedgehog (SHH)/GLI signaling pathway is primarily involved, and GLI-induced cell cycle progression was decreased by JNK reduction with SP600125 and c-Jun siRNA knockdown, suggesting that JNK and c-Jun are critical for Hedgehog (HH)/GLI-driven BCC. Elevated JNK expression in HaCaT keratinocytes was associated with the BCC-like phenotype brought on by SHH activation. Furthermore, in a BCC tumor model created by injecting TetON inducible CRISPR-Yap ASZ mouse cells subcutaneously into immunocompromised (nu/nu) mice, it was discovered that the Yap null cancers showed lower degrees of pJNK1/2 and pJun(S63/S73) than the WT BCC cancers following a one-week doxycycline therapy <sup>[45]</sup>. Furthermore, SP600125-treated BCC cells and YAP-negative BCC clones showed a considerable reduction in c-Jun mRNA. Lastly, it was shown that the WNT gene family member WNT16B was elevated in BCC tissues. In a JNK-dependent way, this boosted the growth of primary and immortalized human keratinocytes. When combined, these findings suggest that the SHH, YAP, and WNT signaling pathways work with the JNK signaling pathway as a crucial mediator to support BCC <sup>[46]</sup>. Additionally, the JNK function has lately been associated with BCC. In human BCC specimens, the JNK target c-Jun is substantially active. Furthermore, GLI-mediated target gene activation and cell cycle advancement are eliminated by siRNA-mediated c-Jun gene suppression or the pharmaceutical JNK inhibitor SP600125. These results suggest a role for JNK and c-Jun in the carcinogenic activity of Hedgehog/GLI proteins in BCC. Furthermore, the oncogenesis of a mouse BCC cell line is discovered to be driven by the Hedgehog/GLI signaling system working in concert with the epidermal growth factor receptor signaling pathway. Here, c-Jun activation by MEK/ERK is necessary for GLI-driven carcinogenesis, but not JNK. When combined, JNK plays a cell-context-dependent role in BCC <sup>[47]</sup>.

## 5. Melanoma

The growth and migration of melanoma cells are encouraged by the JNK/AP1 axis, which is frequently active in both benign and malignant melanoma. According to one study, JNK is active in more than 75% of benign nevi, and its function is thought to be to limit unchecked cell survival or multiplication. For patients with superficial spreading melanomas, stimulation of JNK is linked to growing cells and decreased relapse-free survival time during tumor growth. It is well recognized that there is a functional contradiction in the JNK signaling pathway between cell survival and proliferation. This contradiction can be seen in the contentious functions that JNK/AP1 proteins play in melanoma<sup>[30]</sup>. Aspirin-induced inhibition of B16 melanoma cell growth is mediated by JNK stimulation. The growth and soft agar colony formation of human and mouse melanoma cell lines are increased upon expression of dominant negative mutants of c-Jun or c-Fos, respectively. This suggests that AP1 inhibits the proliferation of melanoma cells. In opposition to these conclusions, more recent research has identified the JNK signaling axis as having a significant involvement in melanoma<sup>[48]</sup>. One important step in the development of melanoma tumors is the constitutively active MEK-ERK signaling axis activation of JNK and c-Jun. Target genes like cyclin D1 and *RACK1* have increased transcription as a result of ERK's raised c-Jun transcription and stability. The JNK-AP1 pathway is forced to function as a feed-forward process by *RACK1*, which in turn permits PKC to phosphorylate and increase JNK function. Our recent research has demonstrated that CYLD loss-of-function and JNK activity correlate in human melanoma, which is consistent with these findings<sup>[49]</sup>. Intravenous tumor growth analysis in mice is used to determine whether exogenous production of MKK7 or c-Jun inhibits the inhibition of melanoma growth and metastasis caused by CYLD. On the other hand, as demonstrated in melanoma cells 1205Lu and WM983B, respectively, JNK reduction with the small molecule inhibitor SP600125 causes melanoma cell proliferation arrest or apoptosis through P53-dependent production of P21 cell cycle inhibitor and induction of P53, Bad, and Bax apoptotic molecules<sup>[50]</sup>. Furthermore, JNK1 but not JNK2-directed gene silencing reduces the development and growth of melanoma cells. When combined, these data highlight the critical function that the JNK1-AP1 signaling pathway plays in the development of melanoma tumors<sup>[51]</sup>.

The proliferation, invasion, and metastasis of WM164 melanoma cells were eliminated by siRNA-mediated suppression of JNK1 and JNK2. Similarly, the development of melanoma cell lines expressing substantial amounts of pJNK1 was suppressed by JNK1-specific gene silencing. These results show that most malignant melanoma cell lines and tissues studied had enhanced JNK activity, which is linked with lower levels of CYLD. After subcutaneous and tail vein injections, respectively, the development of melanoma xenografts in the skin and lung was suppressed by the restoration of CYLD expression in metastatic human melanoma cell lines<sup>[52]</sup>. Co-expression of a c-Jun mutant or permanently active MKK7 inhibited CYLD-inhibited metastasis and development of melanoma. Additionally, JNK/c-Jun facilitates MALT1-driven melanoma cell migration and development. The CREB/MITF/c-Jun melanogenesis axis was suppressed by upregulation of Urothelial Cancer Associated 1 (UCA1), but it was enhanced by *UCA1* gene silencing<sup>[53]</sup>. It was shown that PRDM5 (PRDI-BF1 and RIZ domain-containing) enhanced melanoma migration and multiplication by upregulating JNK in a mouse melanoma model. A tumor-associated gene called *SHARPIN* is elevated in a lot of malignancies. These findings suggest that JNK2 is necessary for the aggressiveness of melanoma and its tolerance to *BRAF* suppression<sup>[54]</sup>.

## 6. Roles of JNK in melanoma progression and treatment

Melanoma resistance to treatment is significantly influenced by JNK/c-Jun. In particular, by its relationship

with MITF and induction of immune-suppressive myeloid cells into the tumor microenvironment, c-Jun stimulates the dedifferentiation of melanoma and the generation of inflammatory mediators. Decreased JNK phosphorylation is thought to be the reason behind the inhibition of A875 malignant melanoma cell growth caused by shRNA-mediated gene silencing of c-FLIP, Fas-associated mortality domain-like interleukin-1 $\beta$ -converting enzyme (FLICE)-like regulating protein <sup>[55]</sup>. Decreased pJNK transcription was seen in conjunction with cell proliferation inhibition produced by inhibition of IL-1 $\beta$  in IL-1 $\beta$ -positive melanoma cells. In stage III melanomas, immunohistochemistry revealed that 20% of the 51 instances had positive pJNK expression, 75% of cases had high JNK expression, and all pJNK-positive tumors were IL-1 $\beta$ -positive. JNK is triggered by IL-1 $\beta$  in melanoma, as demonstrated by the reduction of pJNK in A375 and WM793 melanoma cells by siRNA-mediated gene suppression of IL-1 $\beta$  without altering total JNK concentrations <sup>[30,56]</sup>.

The JNK/AP1 pathway plays a significant role in the adaptive reactions to vemurafenib, a MEK inhibitor. BRAF inhibitor-naïve and resistant melanoma cells experienced death and decreased cell proliferation when JNK reduction was applied with the small molecule drug BI-78D3. After being treated with PF-3758309, a PAK inhibitor, melanoma cells showed enhanced stimulation of JNK,  $\beta$ -catenin, and the mTOR signaling pathway <sup>[57]</sup>. Additionally, melanoma cell survival was significantly reduced by shRNA-mediated gene suppression of JNK and  $\beta$ -catenin. Furthermore, suppression of the JNK cascade made *BRAF* mutant melanoma cells more susceptible to genetically altered vaccinia virus-mediated cell death <sup>[13]</sup>. Interestingly, JNK has also been shown to trigger apoptosis in melanoma cells. Plant-derived quercetin is a polyphenol chemical that increased pJNK expression *in vitro* and *in vivo*, causing A375SM and A375P melanoma cells to undergo apoptosis. Similarly, adding protein-bound polysaccharides produced from the *Coriolus versicolor* fungus to the human SKMel-188 melanoma cell line caused apoptosis and raised ROS levels, both of which were reduced by SP600125 <sup>[58]</sup>.

In short, JNK proteins have unique and significant functions in a variety of skin malignancies. JNK1/2 stimulates Jun/Fos in BCC and improves its relationship with phosphorylated ATF2, which in turn amplifies the carcinogenesis triggered by SHH/GLI <sup>[30]</sup>. MKK4/7 stimulates JNK1 and JNK2 in SCC. While JNK2 stimulates tumorigenesis in an AP1-dependent manner, JNK1 produces apoptosis. By suppressing the JNK2/AP1 process, CYLD suppresses SCC, whereas SCCA1 enhances SCC by inhibiting JNK1. The melanoma cell growth and migration are stimulated by the MALT1, MKK4/7, and JNK/AP1 signaling cascade, whereas it is inhibited by CYLD <sup>[59]</sup>.

## 7. JNK pathway and drug resistance

JNK was identified as a kinase activity that phosphorylates and activates JUN transcription elements to transmit oncogenic RAS activation to nuclear transcription. Upon cloning, it was shown that stress cues including ultraviolet irradiation potentially stimulate the kinase. The idea that oncogenic and stress signals could be connected emerged from this discovery. Subsequent investigation into this relationship led to the conclusion that JNK mostly increases cell stress reactions and apoptosis brought on by inflammatory cytokines and environmental stressors, while ERK primarily boosts proliferation in reaction to mitogenic growth regulators <sup>[60]</sup>. This differentiation was supported by early findings that these routes frequently function as antagonists and mutually impede one another. Over the previous 25 years, a plethora of studies have refined this straightforward idea. This brings us back to our initial finding, which was that JNK serves two roles and may regulate apoptosis as well as cell transformation via a range of pathways that intersect with ERK in part <sup>[61]</sup>. Further supporting this dual function is genetic evidence.



The skin, gut, breast, prostate, and hematological systems can all experience a decrease in carcinogenesis when JNK1/2 is present. For example, JNK1 and JNK2 elimination in the mouse mammary epithelium enhances genetic instability and starts significant tumor formation, while the upstream JNK activator MKK4 is frequently altered in breast cancer<sup>[30]</sup>. However, a number of solid tumors, including malignancies of the liver, colon, skin, lung, and brain also frequently exhibit hyperactivation of the JNK process, suggesting that JNKs are tumor promoters<sup>[37]</sup>. For example, animals immune to the production of skin cancer by a traditional two-stage paradigm combining chemical mutagenesis of *HRAS* with proinflammatory phorbol ester therapy were produced by deleting *JNK2* or *MKK4* in keratinocytes. Similarly, *JNK1* deletion significantly reduced the mice's vulnerability to chemically caused stomach cancer<sup>[62]</sup>.

A prime example of JNK's dual impact on tumorigenesis is hepatocellular cancer. On the one hand, JNK1 promotes hepatocyte proliferation by decreasing the production of CDKN1A, a cell cycle inhibitor, and is hyperactivated in hepatocellular cancer. On the other side, increased tumor development results from knocking down both *JNK1/2* in hepatocytes, which is caused by increased cell division and adaptive hyperproliferation of remaining hepatocytes<sup>[63]</sup>. Furthermore, by fostering a favorable tumor microenvironment, liver immune cells' proinflammatory cytokines triggered by JNK signaling add to this phenotype. As a result, the precise function of JNK depends on the tissue and environment, and knowledge of these factors is necessary to comprehend and take advantage of the role that this network plays in drug sensitivity and resistance<sup>[64]</sup>. Despite the large and even contradictory body of work on this subject, several recurring motifs appear. Therefore, instead of attempting to thoroughly go into contradictory specifics, we concentrate on developing common ideas via instructive instances. To put it succinctly, JNK can promote cancer stem cell renewal, cell migration, and cancer cell survival to promote tumor malignancy and medication resistance, or it can activate apoptotic processes to counteract tumor growth<sup>[65]</sup>.

## 8. *KLF4* and *JNK1* (*MAPK8*)

Early embryonic development depends on the multistage process known as epithelial-mesenchymal transition (EMT), which can be disrupted by several clinical circumstances, including tissue fibrosis and the spread and metastasis of malignant tumors. Significant changes in gene expression during the development and development of an EMT result in significant changes in cell shape, adhesions between cells and in the matrix, as well as the ability of cells to move and invade<sup>[66]</sup>. Here, we have identified *KLF4* as one important regulator of EMT utilizing genome-wide gene expression profiling. Interestingly, *KLF4* is a significant EMT regulator; its deletion causes a loss of epithelial structure as well as a partial initiation and amplification of EMT, whereas its production suppresses EMT and preserves the epithelial topology of breast cancer cells and mammary epithelial cells<sup>[67]</sup>. Furthermore, we discover that *KLF4* inhibits cell movement while promoting cell growth and development<sup>[68]</sup>. This idea is at odds with other research that shows *KLF4* promotes migration in the human breast cancer cell lines MCF7 and MDA-MB-231 and suppresses cell growth in a colon cancer cell line. *KLF4* was shown to be downregulated in MCF7 cells following E-cadherin deletion, and recent research also showed that *KLF4* inhibits cell migration and invasion in MDA-MB-231 cells<sup>[69,70]</sup>.

*KLF4* is well-known for playing two roles in transcription: a repressor and an activator. *KLF4* could serve a crucial role in preserving the cell shape of mammary epithelial cells, according to earlier research. In addition to binding directly to the E-cadherin gene activator and up-regulating E-cadherin expression, it also effectively suppresses the regulation of Snail1, one of the main transcriptional repressors of E-cadherin gene expression<sup>[71]</sup>.

KLF4 attachment to the regulators of the Snail1 (*SNAIL*) and E-cadherin (*CDH1*) genes has also been discovered by the combination of genome-wide gene expression monitoring and ChIP-Seq data analysis. As Snail1 expression is markedly up-regulated with KLF4 reduction in lack of TGF $\beta$ , it indicates that KLF4 regulates Snail1 expression. Snail1 production is, nevertheless less in KLF4 reduction cells when TGF $\beta$  is present, indicating that KLF4-mediated control of the *Snail1* gene is a complicated mechanism requiring additional transcription elements in addition to KLF4 that either promote or inhibit Snail1 transcription<sup>[72]</sup>. Conversely, in the presence of TGF $\beta$ , deletion of KLF4 results in a stimulation of Twist1 expression, which could serve as the primary facilitator of EMT in the mesenchymal state. *KLF4* transcription reduction did not affect Snail2, Zeb1, Zeb2, or other key EMT regulators' expression. Furthermore, we discovered other genes whose expression is either directly promoted or suppressed by KLF4<sup>[73]</sup>. Additionally, *KLF4* transcriptional inhibition directly targets several mesenchymal genes, including  $\beta$ -catenin (*CTNNB1*), vimentin (*VIM*), and N-cadherin (*CDH2*). All of the information points to a paradigm where KLF4 suppresses mesenchymal genes and induces the production of genes specific to the epithelium in order to preserve epithelial shape<sup>[74]</sup>. Mesenchymal genes become active and epithelial gene expression is lost when KLF4 function is lost during EMT. KLF4 has been shown to play an identical impact in the switching of fibroblasts into induced pluripotent stem (iPS) cells. In this process, KLF4 is one of the essential reprogramming variables that triggers CDH1 expression, which in turn causes the MET and reprogramming of fibroblasts<sup>[73,75]</sup>. These findings provide more evidence that KLF4-mediated transcription regulation plays a crucial role in both the creation and maintenance of epithelial cell integrity. Additionally, KLF4 suppresses many angiogenesis-related genes, such as Endothelin-1 (*EDN1*) and VEGF-A (*VEGFA*). These findings indicate a crucial step in fostering tumor angiogenesis, aggressive tumor growth, and metastasis is the decrease of *KLF4* transcription during EMT<sup>[76]</sup>.

*JNK1* (*MAPK8*) constitutes one of the transcriptionally suppressed target genes of KLF4. When KLF4 is lost during TGF $\beta$ -driven EMT, JNK1's expression is increased, and it plays a crucial role in both the initiation of apoptosis and the completion of EMT and cell motility. JNK1 is a serine-threonine protein kinase that belongs to the mitogen-activated protein kinases (MAPK) family<sup>[77]</sup>. It is essential for cellular reactions to external inputs and takes a role in some signaling processes. JNK1 is mostly phosphorylated at serine-63 and serine-73 residues as a result of cytokines and cellular stressors such as ultraviolet radiation. Such stimulation of JNK is necessary to sustain the mitochondrial apoptosis signaling cascade and to cause ultraviolet-induced apoptosis in primary murine embryonic fibroblasts<sup>[78]</sup>. Additionally, JNK1 and their target transcription element AP1 (Jun/Fos) have been linked to EMT in previous studies. These findings are consistent with the ability of JNK1 to phosphorylate paxillin, a focal adhesion adaptor necessary for effective cell movement and the creation of focal adhesion plaques<sup>[79]</sup>. Here, the essential function that JNK1 plays in EMT, cell migration, and the initiation of apoptosis when its primary transcriptional inhibitor, KLF4, is lost. It has been shown in current research that in different animal models of breast cancer, defects in JNK1, JNK2, or composite JNK1 and 2 enhance the growth of primary tumors. Therefore, KLF4 inhibits the creation of metastases while promoting the progression of primary tumors and preventing apoptosis by reducing the expression of the *JNK1* gene<sup>[80]</sup>.

Furthermore, a higher disease-free survival rate in patients is correlated with elevated KLF4 expression. Nevertheless, the outcomes of the experiments also show that KLF4 increases the growth of initial tumors by giving cells a survival benefit and preventing liver and lung metastases. All of the information presented here collectively reveals basic ideas about how transcription elements such as *KLF4* control changes in cell destiny by directly impacting the transcription of underlying genes<sup>[81]</sup>. Finally, *KLF4* and its transcriptional effectors are

desirable targets for the establishment of innovative treatment strategies due to their crucial roles in maintaining epithelial distinction and preventing EMT and metastasis. Interestingly, JNK1 functions that are increased when KLF4 activity is lost may provide a treatment pathway for metastatic illness <sup>[82,83]</sup>.

## 9. Future directions and conclusion

One of the main causes of many malignancies is the uncontrolled stimulation of particular proteins in the MAPK signaling cascade. As a result, blocking this signaling system effectively could be a useful approach to treating tumors. In light of the negative consequences of the current MAPK inhibitors, investigating natural molecules offers a fresh approach to the management of cancer. Furthermore, the available data unequivocally demonstrates that MAPK cascades are feasible strategies for cancer treatment. The ERK pathway is among the most widely used targets in clinical practice. However, metabolic and epigenetic modulators, as well as stress-activated MAPK cascades like JNK, have significant modulatory effects that can alter whether cancer cells respond to both targeted treatments and chemotherapies. Nevertheless, these responsibilities are context-specific and hard to predict with conventional techniques of empirical investigation. Numerous biological procedures, such as the cell cycle, cell differentiation, growth, apoptosis, and inflammatory reactions are regulated by JNK proteins. JNK signaling dysfunction is intrinsically associated with both melanoma and non-melanoma skin malignancies. However, the isoform-specific and cell-type-specific responses continue to restrict and challenge our knowledge of JNK actions in these illnesses.

Finally, the future of targeting MAPK and JNK pathways in cancer treatment is bright, with several promising avenues including precision medicine, novel drug development, combination with immunotherapy, and overcoming drug resistance. Advances in genomics and molecular profiling will enable the identification of specific genetic alterations within these pathways in individual patients, aim to selectively kill cancer cells, and may involve the development of combination therapies, targeted drug delivery systems, or novel inhibitors for future prospective.

## Disclosure statement

The author declares no conflict of interest.

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