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Review Article

A REVIEW ON WOUND HEALING ACTIVITY OF DIETARY FLAVONOID NARINGENIN

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ABSTRACT

Wound is known as disruption in the integrity of a tissue. The mechanisms of regeneration and tissue repair consist of a series of molecular and cellular events that occur after the onset of a tissue lesion to rebuild the damaged tissue. The remodelling phases of the exudative, proliferative, and extracellular matrix are concurrent events that occur through the interaction of complex processes involving soluble mediators, blood cells and parenchymal cells. Exudative phenomena that occur after injury, lead to tissue edema growth. The proliferative stage aims to minimize the area of tissue damage by myofibroblasts and fibroplasia contracting. Angiogenesis and reepithelialisation processes can still be observed at this point. Endothelial cells are capable of differentiating into mesenchymal components and this distinction seems to be finely coordinated by a series of signalling proteins. Many of the medicines available today is derived from natural sources. Flavonoids are essential components of the human diet apart from their physiological functions in plants, even though they are not considered as nutrients. In this review, naturally occurring flavonoid is discussed which occur in citrus fruits, vegetables, nuts, and beverages like coffee, tea, and red wine, and also in medical herbs. They exhibit different pharmacological actions, like antioxidant, anti-allergic, anti-bacterial, anti-inflammatory, anti-mutagenic and anti-cancer activity. One of the flavanones is Naringenin which is the ordinary dietary poly-phenolic constituent of the citrus fruits (grapefruit and oranges) and vegetables. It is beneficial in various neurological, cardiovascular, gastrointestinal, rheumatological, metabolic, malignant disorders, and functionally, this ameliorative effect of naringenin is primarily attributed to its anti-inflammatory (via inhibiting staffing of cytokines and inflammatory transcription factors) and anti-oxidant (via scavenging of free radicals, bolstering of endogenous antioxidant defence system and metal ion chelation) effects.

Keywords: Cell proliferation, Inflammation, Flavonoids, Naringenin, Wound Healing

INTRODUCTION

Skin is the largest organ of the human body which covers a total area of about 20 square feet. It is the thin layer of soft outer tissue forming a covering of the body of living being. It helps in regulating the body temperature, protects from microbes and also permits the sensations and feeling of touch, heat and cold.

Skin performs various functions, some of the vital functions of skin are:

1. It Regulates and maintain body temperature.
2. It prevents the loss of essential body fluids,
3. It prevents the penetration of toxic substances.
4. It protects our body from harmful effects of the sun and other radiation.
5. It helps in excretion of toxic substances with sweat from the body.
6. It provides mechanical support and strength.
7. Its immunological function is mediated by cells of Islet of Langerhans.
8. It is the sensory organ for heat, touch, cold, socio-sexual and other emotional sensations.
9. Helps in Vitamin D synthesis from its precursors with the help of sunlight and introversion of steroids.

Wound healing

Wound is known as disruption in the integrity of a tissue. It is also defined as disruption of the cellular and anatomic continuity of a tissue, with or without microbial infection[1]. Wound is produced due to any accident or cut with sharp edged things. Wounds are those physical injuries that results in an opening of the skin that causes disturbance in the normal skin function and skin anatomy. Pain and swelling at the wound site is constantly produced by inflammatory mediators of unhealed wound. Wound care and wound maintenance involve a number of measures including dressing and administration of painkillers topical systemic

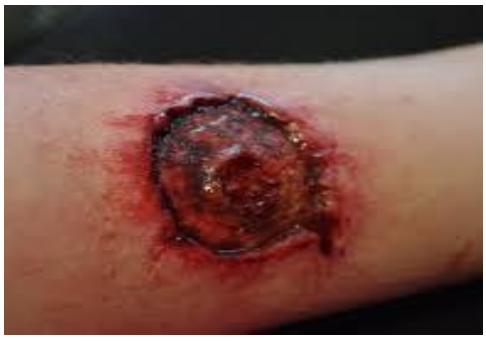


Fig 1: Wound on the skin

antimicrobial agents, use of anti-inflammatory agents and healing promoting drugs. The wounds result in the loss of the continuity of epithelium with or without the loss of underlying connective tissue. Wound may result of various physiological, mechanical and chemical factors.

Surgical, traumatic, toxic, or infectious or others are the causes of cutaneous wound[1] and to re-establish the integrity of a dented

tissue, from the moment an injury occurs an orderly complicated process which involve succession of events known as wound healing is initiated by the dented tissue itself[2-3]. Wound healing is the process which involves complex mechanisms involving hemostasis, inflammation, proliferation, and remodelling[4-5]. Diverse biochemical substances are recruited to enhance the healing process in each mechanism. The conversion by thromboxane synthase, of prostaglandin H2 into thromboxane A2 results in hemostasis initiated vasoconstriction[6].

Plasminogen activator inhibitor Type 1 inhibits an intrinsic fibrinolytic factor that tends to prevent hemostasis[7]. Accumulation of heme and heme proteins is resulted by inflammations which have pro-oxidative and pro-inflammatory activities which build up in the site of the wound to bring an expression of adhesion molecules, consequently ensuing in vascular permeability, and infiltration leukocytic[5]. The free radicals are released by infiltrating neutrophils that kills any contaminating organism which might want to colonize the wound[8-9]. Heme-oxygenase-1 (HO-1) having anti-inflammatory and antioxidant activities are over expressed which speed up wound healing process mainly amelioration of the inflammation, epithelialization (proliferation of epithelial cells) and angiogenesis/neo-vascularization of endothelial cells, and protection of endothelial cell apoptosis[10]. Matrix metalloproteinases are expressed which facilitate re-modelling of the extracellular matrix.

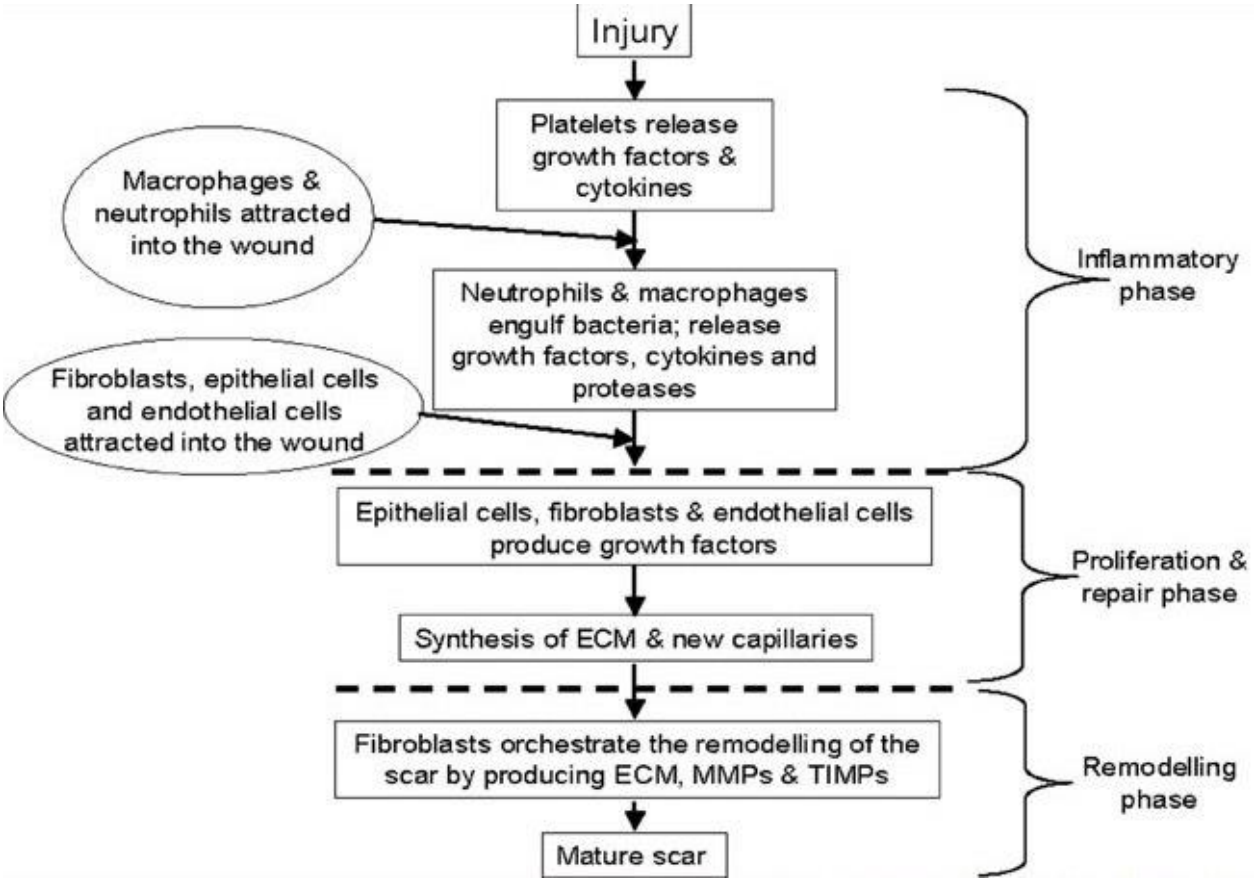


Fig 2: Physiology of wound healing[11]

The overall, assessable phenomena drawn in wound healing involves: Wound contraction, epithelialization, and granulation tissue formation[5]. The type of wound is the main concern for these phenomena to contribute to wound healing process. Wound contraction and epithelialization play an important role in healing of excision wounds whereas granulation tissue formation contributes to healing of dead space and re-sutured incision wounds [2,12]. Hence, there is a need for using different wound healing models for evaluating the substances for impending wound healing activity.

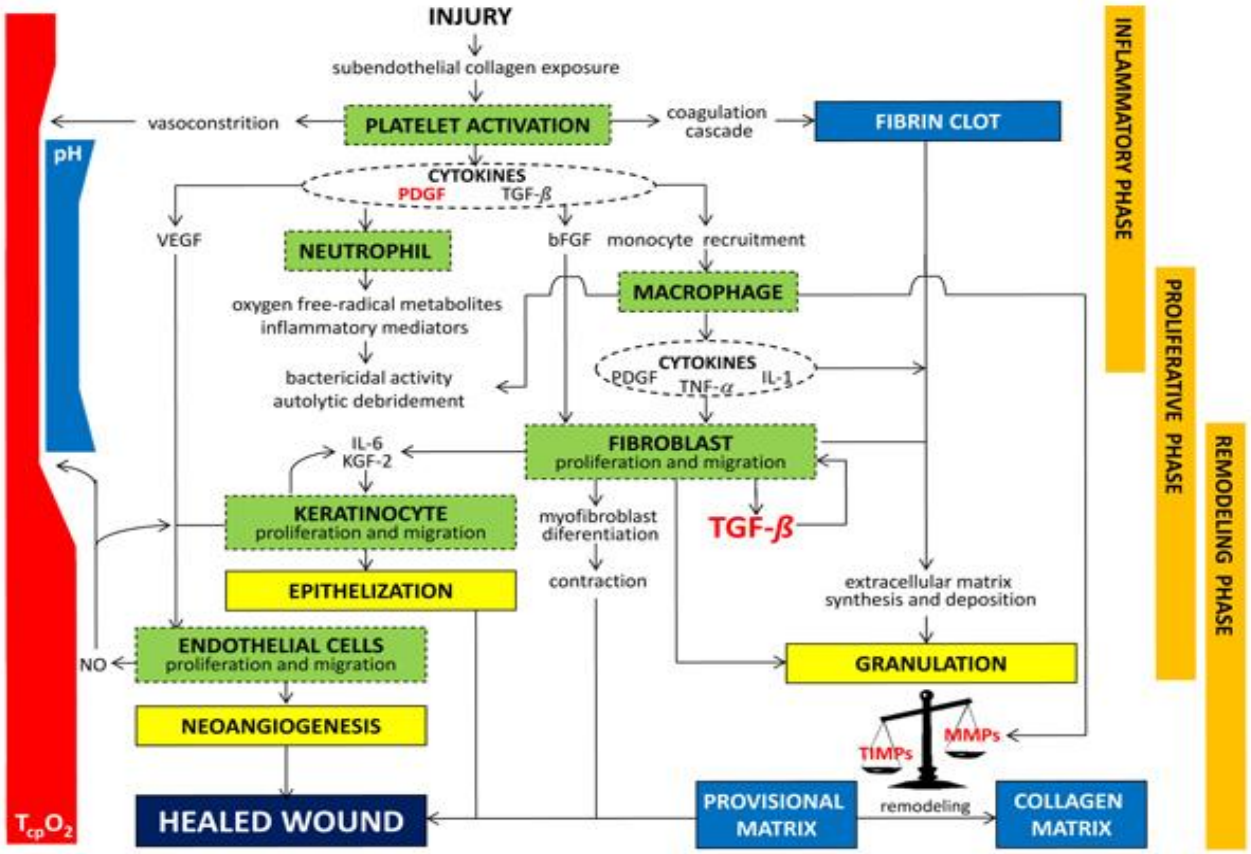


Fig 3: Wound Healing Process(12)

For occurrence of wound healing to there is a need of necessary biochemical substances. The time extent it takes for wound healing process need to be optimum and complete and it is directly dependent on the rate of availability of specific biochemical substances[13]. Wound contaminating organisms over and over again alter or extend the duration of wound healing process by the production of enzymes (biochemical substances) which can further destroy the wounded tissues and degrade or debase the biochemical substances that enhance wound healing process. For that reason, the medical professionals use drugs which may be applied topically, orally or systemic to cut down the duration, reduce complications likes overpowering microbial wound contamination of natural wound healing and attain most favourable healing [13]. Wound healing is case of orthodox medicine is achieved by using drugs that promotes wound healing process. On the other hand, these drugs are usually costly [14] and repeatedly they bring outside effects which are harmful to the recipient. Hence for this reason there is a need of cheaper and safe substitute or complementary substances that possibly will promote wound healing.

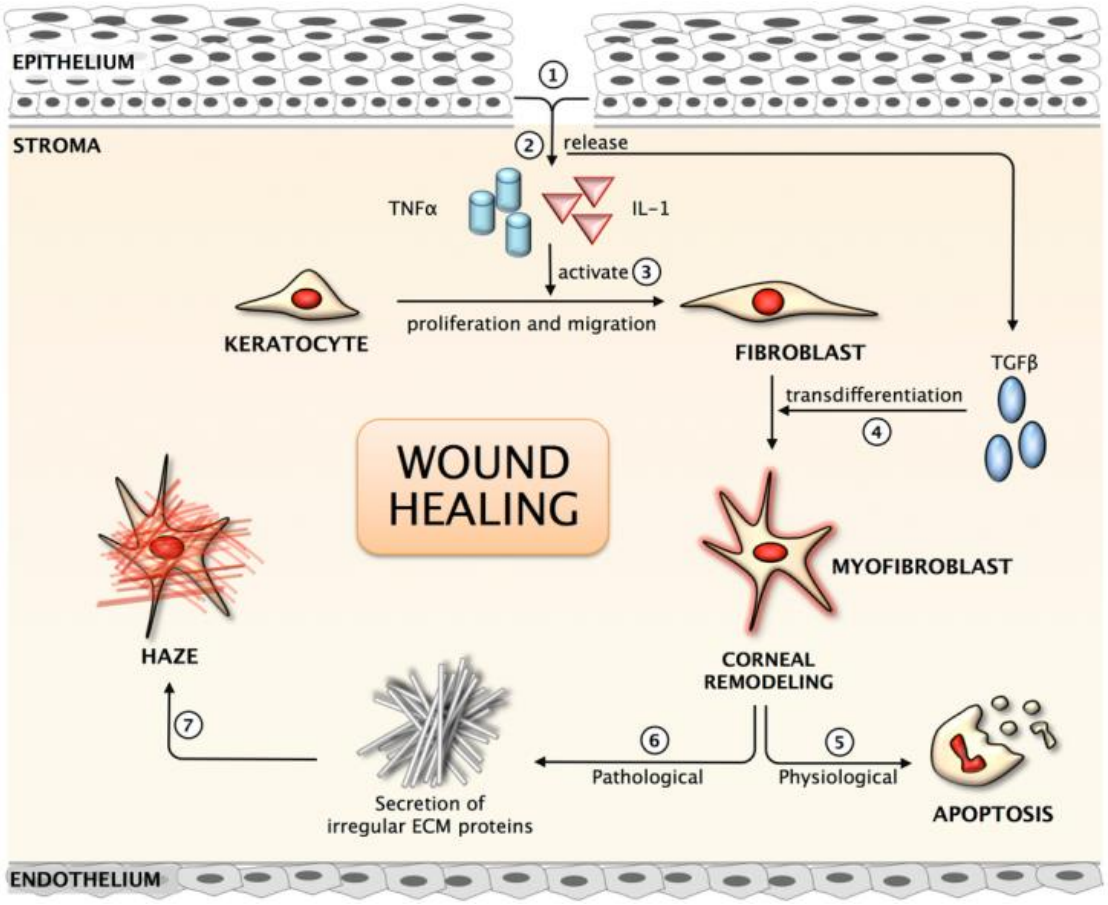


Fig 4: Basic of wound healing process[13]

Phases of wound healing:

There are three phases of wound healing namely:

Inflammatory phase[14-15]:

In this phase, clot formation starts, and it prepares the site for healing and also immobilizes the wound by causing and making it to swell and become painful, due to which movement becomes restricted. Then the fibroblastic phase starts rebuilding the structure, and then the remodeling phase provides the final form of the wounded skin.

The key features of inflammatory phase are:

- It occurs immediately after wound to 2-5 days.
- It involves haemostatic which includes vasoconstriction, platelet aggregation and clot formation, and it also involves inflammation which includes processes like vasodilation and phagocytosis.

Proliferative phase[14-15]:

- This phase starts from 2nd day of wound and lasts for 3 weeks.
- It involves various process of healing like granulation, constriction and epithelialization.

Remodeling phase[14-15]:

- It is also known as Maturation phase.
- It starts from 3rd week of wound and lasts for 2 years.
- In this phase, collagen formation begins which in turn increases the tensile strength of the wound.

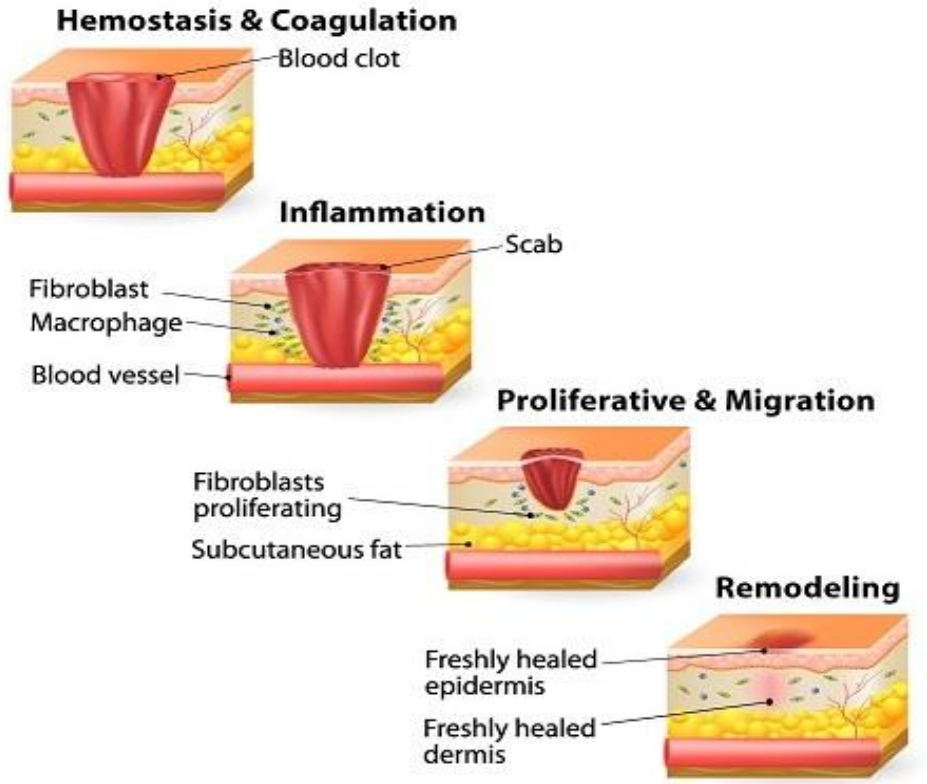


Fig 5: Phases of Wound Healing[16]

Classification of wounds [16-17]:

Wounds are categorized as open and closed wound on the underlying cause of wound creation of chronic and acute wounds on the basis of physiology of wound healing.

Open wounds

In this case blood escapes the body and bleeding is clearly visible. It is further classified as:

- Incised wounds,
- Laceration or tear wounds,
- Abrasions or superficial wounds,
- Puncture wounds,
- Penetration wounds and
- Gunshot wounds.

Closed wounds

In this case blood escapes the circulatory system but remains in the body. It includes Contusion or hematomas, bruises, blood tumor, crush injury etc.

Acute wounds

It is a tissue injury that normal proceeds through orderly and timely reparative process that result in sustained restoration of anatomic and functional integrity. Acute wounds are usually caused by cuts or surgical incisions and complete the wound healing process within expected time frame.

Chronic wounds

Chronic wounds are wounds which failed to improve or progress via the normal stages of healing and a state of pathologic inflammation. These types of wounds either require a long duration of time for their frequent healing. The most frequent causes of chronic wounds are local infection like hypoxia, trauma, foreign bodies and systemic problems such as diabetes mellitus, malnutrition, medications or immunodeficiency.

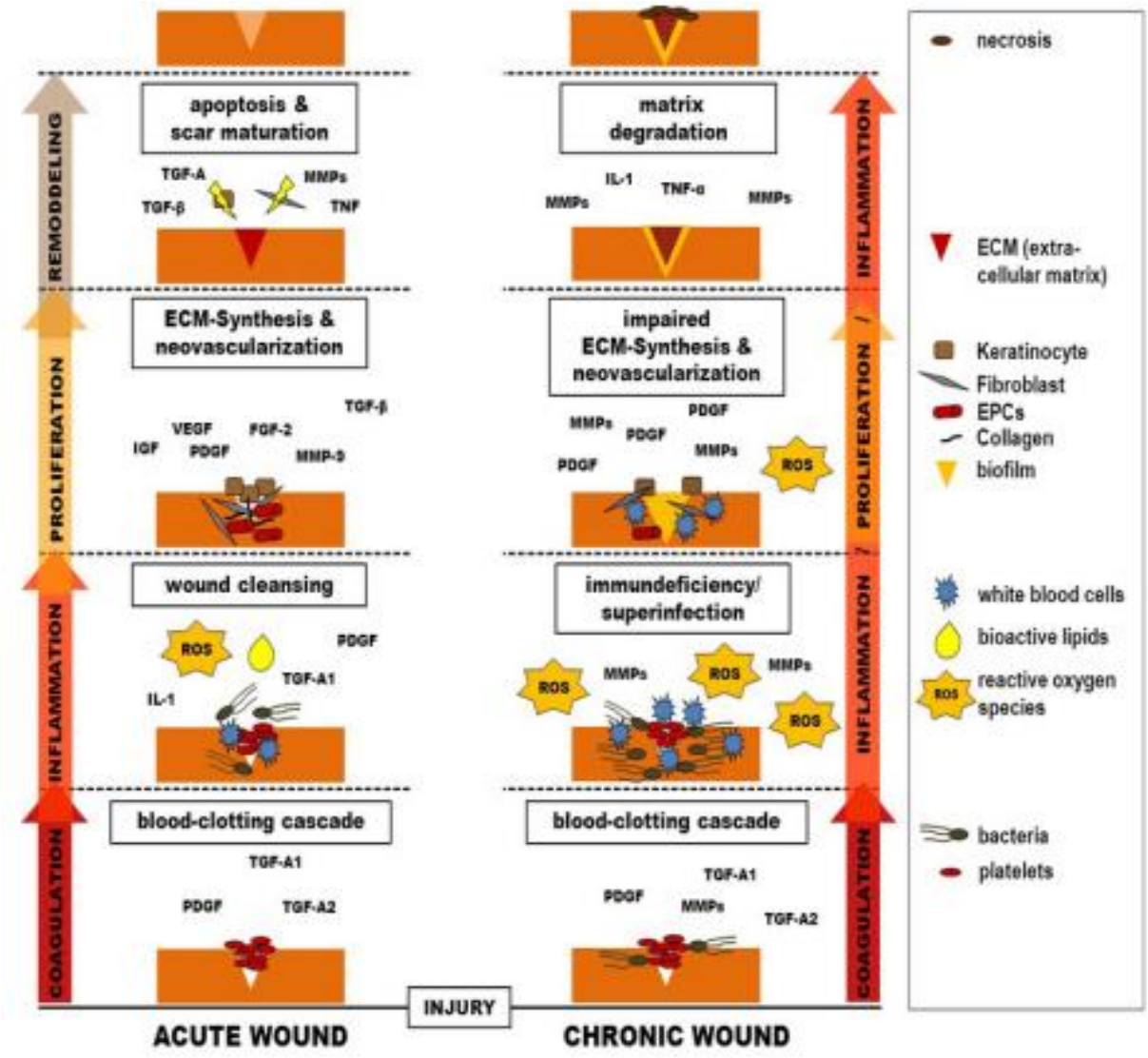


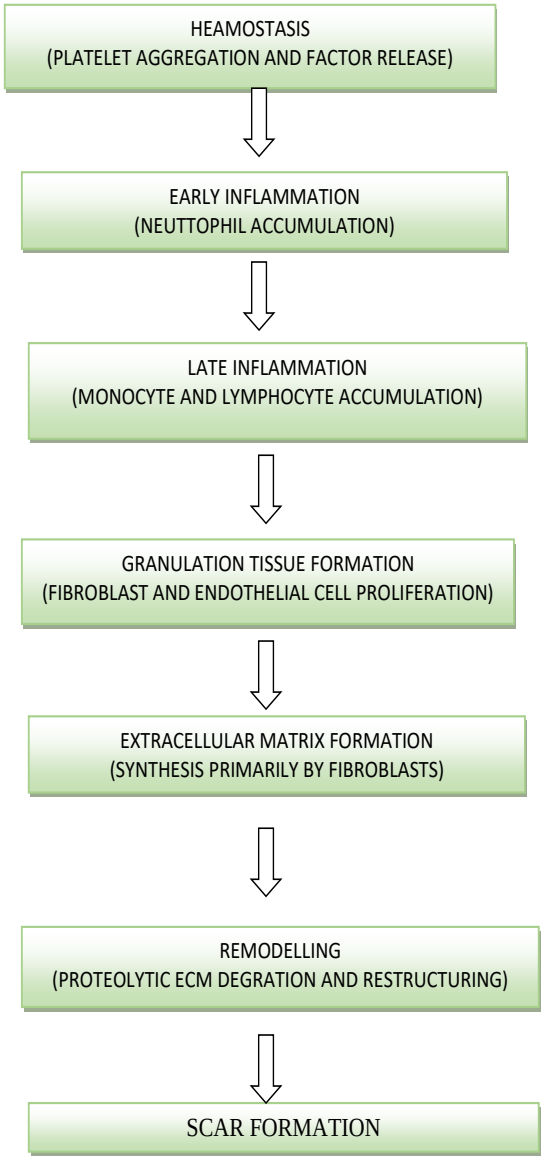
Fig 6: Wound healing of acute and chronic wound[17]

Mechanism of wound healing

There are two different mechanisms which contribute to wound healing. They are as under:

- Purse-string mechanism, where a ring of contractile protein forms at the edge of a wound and tighten like strings of a purse.
- Cell crawling, where cells reach out using arm-like projections known as filopodia and lamelliopodia, to drag themselves forward in order to close the gap. In some wounds, both mechanisms are thought to occur simultaneously, while in others only one of the two is initiated.
- As given by Ladoux, Trepat and colleagues they revealed a new mechanism where cells assemble supracellcular-contractile arcs that compress the tissue underneath the wound. They together given a technique to measure the nano-scale forces behind wound healing and, in doing so, they have discovered that the two currently accepted mechanisms are insufficient to fully explain the phenomenon of wound healing. Instead, they have revealed a new mechanism[17-27].

Healing sequence[17]:



Flavonoid

Flavonoid is the term which is derived from a Latin word "*flavus"* which means yellow. They come in the class of plant and fungus secondary metabolites. Flavonoids chemically have the general structure of a 15-carbon skeleton, which consists of 2 phenyl rings (A and B) and heterocyclic ring (C). This ring of carbon structure is abbreviated as C6-C3-C6. [28,29]

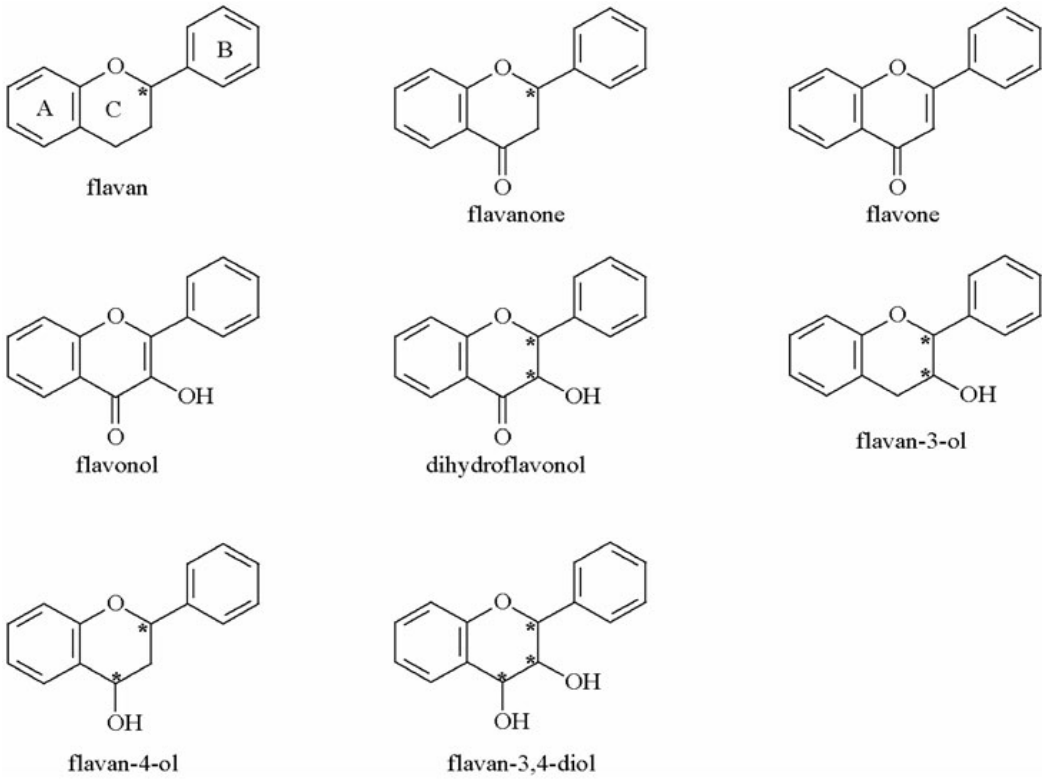


Fig 7: C6-C3-C6 backbone [28,29]

The term flavonoid is used to illustrate non-ketone polyhydroxy polyphenol compounds. Flavonoids are a broadly spreaded group of phytochemicals which have a benzo-pyrone nucleus, and more than 4,000 of diverse flavonoids have been described and classified into flavonols, flavones, flavanones, isoflavones, catechins and anthocyanidins[28-29]. In nature, flavonoids occur in citrus fruits, vegetables, nuts, and beverages like coffee, tea, and red wine, and also in medical herbs[30]. They are responsible for the different colors of plant parts and they are also one of the important constituents of the human diet. They exhibit different pharmacological actions, like antioxidant, anti-allergic, anti-bacterial, anti-inflammatory, anti-mutagenic and anti-cancer activity[28].

Table 1: Dietary Sources[28]

Flavonols	Flavan-3-ols	Flavones	Flavonones	Anthocyanidins
Onions	Apples	parsley	Oranges	Blueberries
Apples	Bananas	bell peppers	Grapefruit	Bananas
romaine lettuce	Blueberries	celery	Lemons	Strawberries
Tomatoes	Peaches	apples	Tomatoes	Cherries
garbanzo beans	Pears	oranges		Pears
almond	Strawberries	watermelon		Cabbage
turnip greens		chili peppers		Cranberries
sweet potatoes		cantaloupe		Plums
quinoa		lettuce		Raspberries
				garbanzo beans

Naringenin

Naringenin belongs to the flavanones and chemically known as 5,7-dihydroxy-2-(4-hydroxyphenyl)-chroman-4-one which is one of the ordinary dietary poly-phenolic constituents of the citrus fruits (grapefruit and oranges) and vegetables. Naringenin is a bitter, colourless flavanones[31]. It has been used for various neurological, cardiovascular, gastrointestinal, rheumatological, metabolic and malignant disorders. Functionally, this ameliorative effect of naringenin is primarily attributed to its anti-inflammatory (via inhibiting staffing of cytokines and inflammatory transcription factors) and anti-oxidant (via scavenging of free radicals, bolstering of endogenous antioxidant defence system and metal ion chelation) effects.

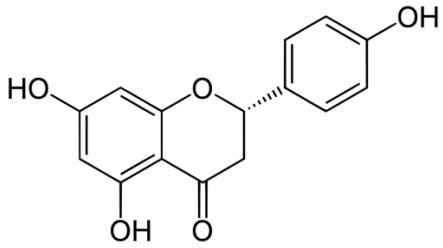


Fig 8: Structure of Naringenin[31]

Dietary sources of naringenin

Naringenin is been found in a variety of fruits and herb [32-33]; mainly

- Grapefruit
- Bergamot
- Sour orange
- Tart cherries
- Tomatoes
- Cocoa
- Greek oregano
- Water mint
- Beans

Bioavailability

- It is difficult to be absorbed on oral ingestion or administration. Is it been reported that only 15% of orally ingested naringenin will get well absorbed in the human Gastrointestinal tract (GIT).
- It is seems to be that the naringenin-7- glucoside form is less bioavailable than its aglycol form.
- Naringenin obtained from grapefruit juice provides much higher plasma concentrations than naringenin obtained from orange juice.

Metabolism

Naringenin is metabolised in such a manner: The naringenin 8-dimethylallytransferase enzyme which make use substance dimethylallyl diphosphate and (−) -(2*S*)-naringenin to produce and generate 8-prenylnaringenin and diphosphate.

Pharmacological properties of Naringenin

The various pharmacological properties of Naringenin are listed below:

- Naringenin inhibits the effect of cytochrome p450
- Antibacterial, antifungal, and antiviral activity.
- Anti-inflammatory activity.
- Anti-oxidant activity.
- Anti-cancer activity.
- Naringenin Enhances Immunity
- Antiadipogenic Activity.
- Cardioprotective Effects.

Anti-oxidant activity

The naringenin exhibited higher antioxidant ability and radical scavenger performance of hydroxyl and superoxide. Glycosylation attenuated the efficacy of inhibiting the enzyme xanthine oxidase, and the aglycone could serve as a more powerful metallic ion chelator than the glycoside. In addition, naringenin has shown greater dose-dependent efficacy in protecting against oxidative lipid damage. The flavanone has been effective at minimizing damage to DNA.[37]

Anti-inflammatory activity

Inflammatory bowel disease (IBD) pathogenesis such as ulcerative colitis (UC) is typically associated with a decreased antioxidant ability. The generation of free radicals such as reactive oxygen species (ROS) leads to lipid oxidation which inhibits the ability of cellular antioxidants and leads to prominent colonic inflammation. Naringenin is a flavonoid that occurs naturally and can be derived from citrus fruits, tomatoes, cherries, grapefruit and cocoa.Like other flavonoids, naringenin has been experimentally found to have many pharmacological potential, including anti-inflammatory due to the properties of naringenin to generate adequate hydroxyl (-OH) replacements that give it the ability to scavenge ROS.It has therefore considered that naringenin can decrease and/or strengthen pathological conditions in which oxidation or inflammation is considered to play a vital role[38].

Anticarcinogenic activity

Animal experiments involving rats and mice, as well as in vitro research using human cell lines, demonstrated the capacity of naringenin to inhibit carcinogenesis at three stages: tumor development, angiogenesis and growth of tumours. Naringenin is also known to cause dose-dependent cytotoxic and apoptotic effects in several cancer cell lines and to inhibit tumor growth in mice implanted with sarcoma S-180, indicating that naringenin can be used to inhibit tumor growth[34,35,36]. Cytotoxic effects were also induced in the lines of human cancer cells when high levels of naringenin (50 percent effective concentration: 150-560 μM) were administered. However, the use of flavonoids as cancer chemotherapeutic or preventive agents involves the production of novel flavonoids or naringenin derivatives that can induce cytotoxicity in a cell type-dependent manner at low concentrations[37-41].

Cardioprotective effects

Naringin has demonstrated a variety of properties that help protect the cardiovascular system including antihypertensive, lipid-lowering, insulin-sensitizing, anti-oxidant and anti-inflammatory properties. Naringin prevented age related increases in systolic blood pressure in spontaneously hypertensive stroke-prone rats, increased development of nitric oxide, enhanced endothelial function and decreased cerebral thrombotic tendencies. Naringin also prevented oxidative stress in the hearts of rats with myocardial infarction caused by isoprenaline[42-43].

Naringenin Enhances Immunity

Natural killer (NK) cells can recognise and destroy tumor cells, as well as cells infected with viruses, without pre-sensitization. NK cells express receptors that activate and inhibit and can differentiate between normal and tumor cells. The present study was designed to demonstrate the significance of NKG2D ligands' expression level on the Burkitt lymphoma cell line, Raji, in enhancing cytolytic activity of NK cells. Different flavonoids were used as stimulants to improve the NKG2D ligand expression. NK cell lysis activity against Raji was not altered by pretreatment with luteolin, kaempferol, taxifolin, and hesperetin to naringenin. However, naringenin therapy demonstrated an improved susceptibility to NK cell lysis compared with untreated control cells. The naringenin activity was attributed to increased expression of the NKG2D ligand. These findings provide evidence that the antitumor activity of naringenin could be triggered by targeting the expression of NKG2D ligand and indicate a potential immunotherapy function for cancer treatment[44].

CONCLUSION

Wound healing is a very complex, multifactor sequence of events involving several cellular and biochemical processes. The aim in these processes is to regenerate and reconstruct the disrupted anatomical continuity and functional status of the skin. Healing process, a natural body reaction to injury, initiates immediately after wounding and occurs in four stages. The first phase is coagulation which controls excessive blood loss from the damaged vessels. The next stage of the healing process is inflammation and debridement of wound followed by re-epithelisation which includes proliferation, migration and differentiation of squamous epithelial cells of the epidermis. In the final stage of the healing process collagen deposition and remodelling occurs within the dermis. It is well known for the prevention and cure of diseases using phytochemicals, especially flavonoids. Flavonoids are the main sources of fruits and vegetables. The relationship between structural functions of flavonoids is the epitome of major biological activities. It was

suggested that the biological properties of dietary flavonoids and their analogs like naringenin are due to multiple mechanisms of action including free radical scavenging, activation of survival genes and signaling pathways, chelation of transition metal ions, control of mitochondrial and bioenergetic functions, modulation of inflammatory response and even microbiota experiences.

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