Chapter 5

Wound Healing: Contributions from Plant Secondary Metabolite Antioxidants

Victor Y.A. Barku

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.81208

Abstract

Plants by their genetic makeup possess an innate ability to synthesize a wide variety of phytochemicals that help them to perform their normal physiological functions and/or to protect themselves from microbial pathogens and animal herbivores. The synthesis of these phytochemicals presents the plants their natural tendency to respond to environmental stress conditions. These phytochemicals are classified either as primary or secondary metabolites. The secondary metabolites have been identified in plants as alkaloids, terpenoids, phenolics, anthraquinones, and triterpenes. These plant-based compounds are believed to have diverse medicinal properties including antioxidant properties. Plants have therefore been a potential source of antioxidants which have received a great deal of attention since increased oxidative stress has been identified as a major causative factor in the development and progression of several life-threatening diseases, including neurodegenerative and cardiovascular diseases and wound infection. Consequently, many medicinal plants have been cited and known to effect wound healing and antioxidant properties. This chapter briefly reviews antioxidant properties of medicinal plants to highlight the important roles medicinal plants play in wound healing.

Keywords: wound healing, antioxidants, phytochemicals, reactive oxygen species, plants

1. Introduction

Plant-derived drugs have been part of the human race in the healthcare for thousands of years [1]. Throughout the world, a huge percentage of population depends upon the use of plant-based medicine because of their easy availability and also due to the lack of better healthcare alternatives. Plant-based medicines or herbal medicines have been effective and safe traditional methods practiced in many countries including China, India, and most African countries for the treatment of various diseases [2]. A large number of plant extracts, concoctions, poultices, decoctions, or pastes are equally used in many countries for treatment of diseases, cuts, wounds, and burns. Thus, since antiquity, several medicinal plants and plant-based strategies are widely known for their significant role in wound healing and skin regeneration as well as their therapeutic applications [2].

Wound is an injury that damages the dermal layer of the skin. Several factors contribute to wound generation, e.g., accidental traumas or surgery, and in certain cases, this dermal injury may have a devastating outcome [2, 3]. Wound healing is the natural process which leads to restore the structural and functional integrities of injured tissues. It involves several biochemical and cellular pathways, in order to repair the lesions and to restore the physiological conditions. Fortunately, the human body has the inbuilt capacity to promote this repairing process. However, there can be impairment of this sophisticated repairing process leading to chronic or non-healing wounds, which may result in severe clinical complications or even patient death. Deficiencies in nutritional factors which are essential in cellular differentiation, immune functioning, and collagen formation may result to the failure of wound healing process [4]. Additionally, oxygen- and nitrogen-centered reactive species are known to play crucial roles in regulating healing [2, 5]. Hence, high concentrations of these reactive species are present in wound sites. Unfortunately, these substances can induce harmful effects on cells and tissues and even promote oxidative stress that generates lipid peroxidation, damage of deoxyribonucleic acid (DNA), and enzyme inactivation, including free radical scavenger enzymes [6]. This necessitates the involvement or use of antioxidants which may represent potential therapeutic tools to enhance and accelerate wound healing process.

Several phytoconstituents such as triterpenes, alkaloids, and polyphenols show antioxidant and antimicrobial effects and are able to promote one or more mechanisms of the reparative process [7]. Accordingly, numerous plant extracts have been employed to promote wound healing with a high degree of success [8]. Many wound healing medicinal plants have been investigated to possess antioxidant properties. In other dimensions, numerous studies conducted over the years showed the great potential of plants in promoting wound healing, by virtue of their high contents in antioxidant properties. This document therefore intends to throw more light on the existing literature on wound healing potentials of medicinal plants and their antioxidant properties.

2. Wound

A physical, chemical, thermal, microbial, or immunological action on the living tissue may result in disruption of a cellular, anatomical, and functional continuity of the living tissue [9]. This phenomenon results in an injury to the skin or the underlying tissue or organ termed a wound. A wound is therefore damage or disruption to the normal anatomical structure and function [10, 11]. This can range from a simple break in the epithelial integrity of the skin or it can be deeper, extending into subcutaneous tissue with damage to other structures such as tendons, muscles, vessels, nerves, parenchymal organs, and bones [12, 13].

Wound can result through accident or intentional etiology or as a result of a disease process. Wounding, irrespective of the cause and whatever the form, damages the tissue and disrupts the local environment within it [14].

2.1. Types of wounds

Based on the underlying cause of wound creation, wounds may be classified into two main groups: open and closed wounds. In open wounds, the skin is broken, and the underlying tissue is exposed to the outside environment allowing blood to leave the body. These are wounds in which there is loss of superficial surface covering the tissue such as loss of skin. Such wounds are opened to invasion by microorganisms [15]. Open wounds consist of abrasion or glazes, laceration, incision, puncture, avulsion, cuts, blisters, penetration, and gunshot wounds. In closed wounds, the skin is intact, and the underlying tissue is not directly exposed to the outside world. The superficial surface covering the wound is not lost. The wound occurs under the surface of the skin without affecting the skin and hence does not involve any external bleeding. Infection of these wounds is rare, and it may resolve without any treatment if it is not extensive. Examples of closed wounds are contusion (bruises), hematomas, and crush injuries.

Wound can also be classified as either internal or external based on the wound origin. Internal wounds result from impaired immune and nervous system functions and/or decreased supply of blood, oxygen, or nutrients to that area, such as in cases of chronic medical illness (diabetes, atherosclerosis, and deep vein thrombosis). External wounds are usually caused by penetrating objects or non-penetrating trauma. Penetrating wounds result from trauma that breaks through the full thickness of the skin, reaching down to the underlying tissue and organs, and include stab wounds (trauma from sharp objects, such as knives), skin cuts, surgical wounds (intentional cuts in the skin to perform surgical procedures), and gunshot wounds (wounds resulting from firearms).

Non-penetrating wounds are usually the result of blunt trauma or friction with other surfaces; the wound does not break through the skin and may include abrasions (scraping of the outer skin layer), lacerations (a tear-like wound), contusions (swollen bruises due to accumulation of blood and dead cells under the skin), and concussions (damage to the underlying organs and tissue on the head with no significant external wound).

Depending on the healing time, wound can further be classified as either acute or chronic wounds [14]. Acute wounds heal uneventfully (with no complications) in the predicted amount of time, while chronic wounds take a longer time to heal and might have some complications.

The presence of foreign material and bacteria leads to another way to classify wounds. A wound that has dirt, fragments of the causative agent, bacteria, or other foreign materials is determined to be contaminated or infected. A wound with no foreign materials or debris inside is determined to be clean [15].

3. Wound healing

Wound healing is a complex and dynamic process of replacing devitalized and missing cellular structures and tissue layers. The wound healing process can be divided into three or four distinct basic phases. Inflammatory, fibroblastic or proliferation, and maturation or remodeling constitutes the three-phase division [16, 17]. In the four-phase concept, there are the hemostasis phase, the inflammatory phase, the proliferation phase, and the remodeling phase. In the three-phase approach, the hemostasis phase is contained within the inflammatory phase [18]. The normal physiology of wound healing depends on low levels of reactive oxygen species (ROS) and oxidative stress [19, 20]. An overexposure to oxidative stress leads to impaired wound healing. Free radicals are highly unstable molecules, and ROS are a form of free radicals that include the oxygen atom as well as reactive molecules such as superoxides and peroxides. Although normally formed as a by-product of metabolism and are reactive to invading organisms, overproduction leads to an increased load of free radicals and ROS known as oxidative stress. Free radicals attack and remove electrons from all types of molecules in the cell, including nucleic acids in DNA, proteins, and polyunsaturated fatty acids in cell membranes or organelle membranes. When free radicals attack proteins, they break peptide bonds in the protein backbone, changing the protein structure and altering its functionality [21]. All of these processes are detrimental to the proliferation of new cells in the healing process of epithelial wounds. ROS are likely needed at some basal level for wound healing. The importance of ROS to wound healing is illustrated by studies demonstrating that total suppression of oxidant production results in impaired healing, just as excessive amounts of oxidants do. ROS have also been implicated as important mediators of cell signaling and inflammation in wound repair. Although ROS production is physiologic, excessive production can be harmful.

3.1. Reactive oxygen species (ROS)

Oxidation is a basic part of the aerobic life and our metabolism. The body uses oxygen (O_2) to produce energy by oxidizing glucose. In the biochemical process involving oxygen, i.e., during oxidation, many highly unstable reactive molecules called free radicals are produced. The free radicals are atoms or molecules having odd number of electrons. Atoms of oxygen or nitrogen having central unpaired electron are called reactive oxygen or nitrogen species [22, 23]. These species are natural by-products produced by the normal metabolism of oxygen in living organisms. These reactive oxygen species (ROS) are various forms of activated oxygen which causes oxidative damage. They include free radicals such as superoxide anion radicals $(O_2)^-$, hydroxyl radicals ($OH^{\cdot}$), and non-free radical species such as peroxyl radicals $(O_2)^{-2}$ and singlet oxygen ($^1O_2$) which are various forms of activated oxygen generated in the body [24].

In small amounts, these ROS can be beneficial as signal transducers and growth regulators. However, during oxidative stress, large or excessive amounts of these ROS can be produced and may be dangerous and harmful to the body. The free radicals have the potential to damage biological tissues by disrupting cell membranes. This then affects the ability of the cell to transport substances across the membranes. The immune system is vulnerable to oxidative stress. Oxidative stress refers to an imbalance between the production of free radicals and the antioxidant defense system. It is the accumulated damage due to free radical activity in the human body. Excessive amounts of ROS may be a primary cause of biomolecular oxidation. The ROS have the ability to attack numerous molecules in the membrane that contain carbon–carbon double bonds (C═C). For instance, polyunsaturated fatty acids are particularly sensitive to free radicals. The free radicals are destructive to these molecules including proteins and lipids through oxidation [25]. As a result, ROS have the potential of causing peroxidation of membrane lipids, aggression of tissue membranes and proteins, or damage to DNA and enzyme and generally by oxidizing low-density lipoproteins (LDL). This may result in significant damage to cell structure, contributing to various diseases, such as cancer, stroke, diabetes, arthritis, hemorrhagic shock, coronary artery diseases, cataract, cancer, and acquired immune deficiency syndrome (AIDS) as well as age-related degenerative brain diseases [26]. Under normal circumstances, the cell can reduce the impact of these free radicals and ROS by an endogenous system, i.e., by the body's natural antioxidant defense mechanisms. Physiologic antioxidant defenses include the ROS-detoxifying enzymes superoxide dismutase (SOD), catalase, glutathione peroxidases, and peroxiredoxins [27]. However, the following factors or conditions may contribute to the overproduction of ROS and antioxidant depletion: the mitochondrial electron transport chain; excessive stimulation of nicotinamide adenine dinucleotide phosphate (NADPH); exposure to environmental pollutants such as cigarette smoke, ultraviolet (UV) rays, radiation and toxic chemicals which weaken the body's defense system; and exposure to explosion-generated shock waves [28, 29]. It becomes evidently clear that the devastating impact of ROS can only be reduced successfully through exogenous systems. There is therefore the need to provide the body with a constant supply of antioxidants through dietary supplementation. Antioxidants are postulated to help control wound oxidative stress and thereby accelerate wound healing. They are important mediators in regulating the damage that is potentially incurred by biological molecules such as DNA, protein, lipids, and body tissue in the presence of reactive species.

3.2. Antioxidants

Antioxidants are substances that prevent oxidation to occur. They are compounds that detoxify ROS to prevent their damaging effects through multi-mechanisms. Antioxidants may offer resistance against the oxidative stress by scavenging free radicals, inhibiting lipid peroxidation and thus preventing disease. Antioxidants have the ability to prevent, delay, or ameliorate many of the effects of free radicals. During certain diseased state, as well as during aging, there is a need to boost the antioxidant abilities, thereby potentiating the immune mechanism [30]. The antioxidants preserve and stimulate the function of immune cells against homeostatic disturbances [31].

Synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tertiary butylhydroquinone (TBHQ) are commonly employed as preservatives or additives by pharmaceutical, cosmetic, and food companies [32]. The free radicals are known to be scavenged by these synthetic antioxidants. However, reports on the involvement of synthetic antioxidants in chronic diseases and their adverse side effects leading to carcinogenicity have restricted their use in foods. Therefore, attention has been focused on natural antioxidants mainly from plant sources [33, 34].

3.3. Plants as important sources of natural antioxidants in wound healing

There is great interest in the use of natural products, which include compounds derived from fruits, plants, and herbs. Plants have an innate ability to synthesize a wide variety of phytochemicals. Plants do not only provide the carbohydrates, proteins, and fats necessary in the diet of man and other animals but also produce a vast range of organic materials to perform their normal physiological functions and to protect themselves from microbial pathogens and animal herbivores and to respond to environmental stress conditions. Hence plants accumulate a range of low- and high-molecular weight secondary metabolites that play important roles in ROS metabolism and avoidance of uncontrolled oxidation of essential biomolecules.

Consequently, plants have efficient complex enzymatic and non-enzymatic antioxidant defense systems to avoid the toxic effects of free radicals. Enzymatic systems include SOD, catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), while non-enzymatic systems consist of low-molecular weight antioxidants (ascorbic acid, glutathione, proline, carotenoids, phenolic acids, flavonoids, etc.) and high-molecular weight secondary metabolites such as tannins [35, 36]. **Figure 1** gives a summary of the different classifications of antioxidants.

Among all secondary metabolites, phenolic compounds have been mentioned to be largely the contributory compound to antioxidant activity of plants since they have shown promising antioxidant activity in many in vivo and in vitro studies. Phenolic compounds exhibit a considerable free radical scavenging (antioxidant) activity, which is determined by their reactivity as hydrogen or electron-donating agents, the stability of the resulting antioxidant-derived radical, their reactivity with other antioxidants, and finally their metal-chelating properties [37, 38]. Similarly, polyphenols derived from plants are of great importance because of their potential antioxidant and antimicrobial properties [39]. Plant phenolics are mainly classified into five major groups as phenolic acids, flavonoids, lignans, stilbenes, and tannins. These classes of phytochemicals are found to have excellent antioxidant activity and are widely available for the treatment of a multitude of cutaneous ailments. Many studies have presented plants to possess great potential for wound healing because they are versatile as antioxidant and antimicrobial sources. Medicinal plants and their active compounds have been used in medicine since ancient times and are well known for their abilities to promote wound healing and prevent infection without grave side effects [40].

Flavonoids are a group of polyphenolic compounds with known properties which include free radical scavenging, inhibition of hydrolytic and oxidative enzymes, and anti-inflammatory action [41]. The best-described property of almost every group of flavonoids is their capacity to act as antioxidants. The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species. Flavonoids may have an additive effect to the endogenous scavenging compounds. Many in vitro studies have demonstrated the potent peroxyl radical scavenging abilities of flavonoids, which contribute to inhibiting lipid peroxidation and oxidation of LDL [42].

Flavonoids are known to possess protective effects in biological systems due to their capacity to transfer free radical electrons, chelate metal catalysts, activate antioxidant enzymes, reduce alpha-tocopherol radicals, and inhibit oxidases [43]. Flavonoids have lower redox potentials hence are able to reduce highly oxidizing free radicals by forming less reactive flavonoid radicals. As a result, they are able to prevent lipid peroxidation which is one of the most important actions of free radicals that leads to cellular membrane damage and, ultimately, to cell death [44]. Flavonoids are also able to scavenge nitric oxide which forms in combination with superoxide free radicals the highly damaging peroxynitrite and also to inhibit xanthine oxidase, an important biological source of superoxide radicals that can react with hydrogen peroxide to produce a more toxic hydroxyl radical [44].

Other flavonoids such as quercetin, kaempferol, myristin, apigenin, and luteolin also have anti-oxidative activity in many in vitro studies [45]. It has been observed that anthocyanins, which were one of the main antioxidant components in red wine, were the most effective, both in scavenging ROS and in inhibiting lipoprotein oxidation [46]. Quercetin is also known to have inhibited iron-catalyzed Fenton reaction (reaction between superoxide radicals with hydrogen peroxide).

The exogenous (dietary) antioxidants are mainly derived from food and medicinal plants, such as fruits, vegetables, cereals, mushrooms, beverages, flowers, spices, and traditional medicinal herbs [47]. A large number of plant species and their phytochemicals have diverse medicinal properties, and almost majority of these plants have been found to possess excellent antioxidant activity within in vitro assays.

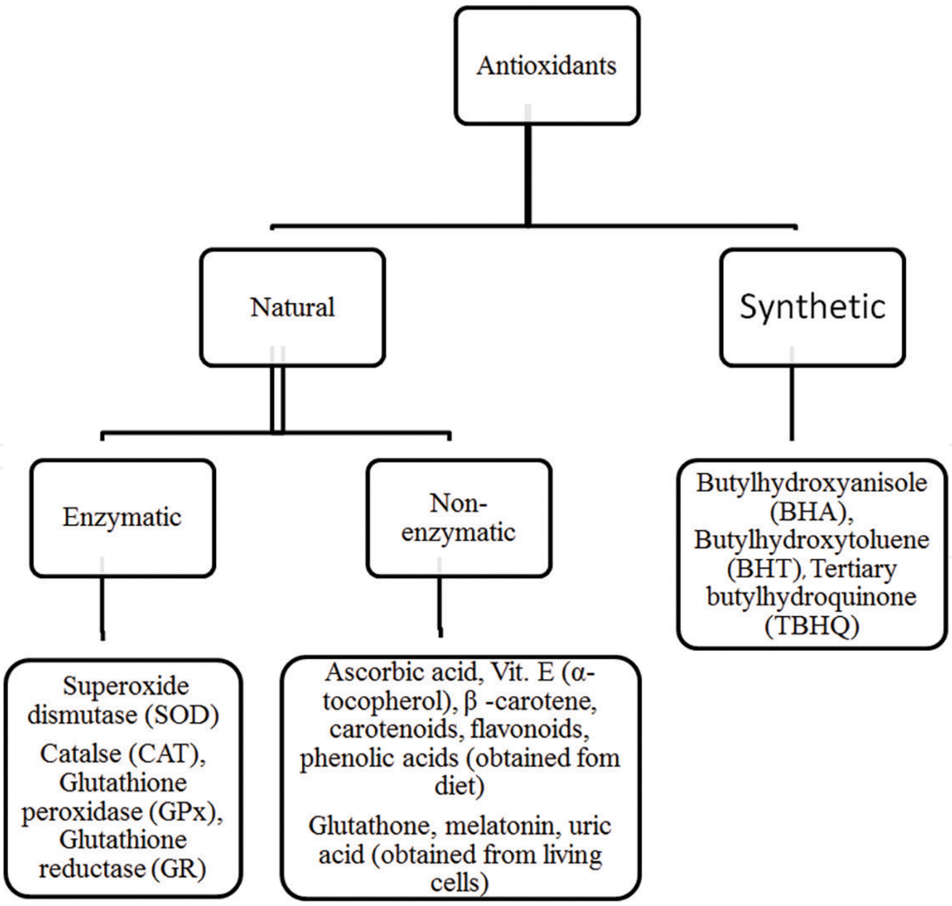

Figure 1. Flow chart showing the different classifications of antioxidants.

The natural function of vitamin E which is present in vegetable oils, nuts, and other fatty plant-based foods is to prevent oxidation. Vitamin E therefore acts as antioxidant when consumed. It helps to prevent degradation of cell membranes in regions containing C═C bonds. Some other antioxidants operate by different mechanisms, reacting with oxygen molecules (O_2) to prevent the production of free radicals. Additionally, there are numerous dietary antioxidants that can be consumed which contribute to an enhanced cellular protection. Ascorbic acid, for example, effectively scavenges ROS and resynthesizes α-tocopherol [48].

Similarly, a number of plants and plant isolates have been reported to protect free radical-induced damage in various experimental models. In recent times, focus on plant research has increased all over the world, and a large body of evidences has been collected to show the immense potential of medicinal plants used in various traditional systems. Green tea, for example, contains catechin components that are known to stimulate antioxidant activity by scavenging free radicals, inhibiting pro-oxidant enzymes and stimulating antioxidant enzymes [49]. Majority of these plants are endowed with free radical scavenging molecules, such as vitamins, terpenoids, phenolic acids, lignins, stilbenes, tannins, flavonoids, quinones, coumarins, alkaloids, amines, betalains, and other metabolites, which are rich in antioxidant activities [50].

Various plant products have been used in the treatment of wounds over the years. Wound healing phytochemical compounds fight infection, promote blood clotting, and accelerate the healing process. Numerous phytochemical compounds have been identified and synthesized from medicinal plants that have unique properties associated with the mechanism of wound healing. Interestingly, many of these wound healing plants investigated displayed antioxidant potential as their major unique properties. A plethora of examples of medicinal plants appears in literature to have shown both wound healing and antioxidant properties.

Clausena anisata (Willd) Hook. (Rutaceae) is a shrub widely used in many parts of West Africa including Ghana as therapeutic alternatives for the management of wounds and treatment of other bacterial and fungal infections. In a study conducted on the ethanol leaf, extract of *C. anisata* was found to exhibit antioxidant property with the half maximal inhibitory concentration (IC50) of 32.9 μg/mL. The extract enhanced the rate of wound closure and also exhibited high influence on proliferation of fibroblasts and levels of fibrous connective tissues in the wound bed [51].

Croton bonplandianum has been credited with potential to cure liver diseases, swelling of the body, cure against ring worms, and skin diseases. An investigation on the ethanolic and aqueous extracts of the dried leaves of *C. bonplandianum* on experimental excision wounds inflicted on Wistar Albino rats of either sex showed a definite, positive effect on wound healing, with significant increase in wound contraction. Antioxidant property of the extracts was also confirmed by 2,2-diphenyl-1-picryl-hydrazyl (DPPH) and nitric oxide scavenging activity [52].

Leucas lanata Wall. ex Benth. (Lamiaceae) is a medicinal plant whose juice has been traditionally used by local peoples to treat stomachache, headache, whooping cough, and as an antidote for reptile poison. Fresh leaves are applied externally for wound healing and for absorbing pus when placed on the affected area. A study designed to evaluate wound healing potential of *L. lanata* through the excision wound model and functional changes in biochemical indicators of antioxidant parameters using 10% (w/w) ointment of 50% ethanol extract showed a remarkable wound healing activity. In the study of uninfected wounds, epithelization period was reduced from 24.66 ± 0.97 for the control group treated with blank ointment to 12.16 ± 0.36 for the group treatment. Similarly, in the case of infected wounds with *Staphylococcus epidermidis*, the percentage of wound contraction was significantly enhanced. Also, the extract significantly increased superoxide dismutase and catalase and reduced glutathione when compared with the control group of infected and uninfected wounds [11].

Limonia acidissima Linn. is used traditionally in India for the treatment of tumors, asthma, wounds, cardiac debility, and hepatitis. Wound healing investigations using the excision, incision, and dead space wound models were carried out on the 200 and 400 mg/kg methanol extract doses. The wound contracted progressively when treated with the extracts. In the wounding healing, results for the incision and dead space models, breaking strength, hydroxyproline, and granulation tissue weight, as well as SOD and catalase all increased significantly ($p < 0.05$), following treatment with the extract and standard drug, when compared with the control group. Thus, the extract not only promoted wound healing but also exerted antioxidant activity [53].

Marrubium vulgare L. (Lamiaceae) is a gray-leaved herbaceous perennial medicinal plant well known for several pharmaceutical activities. It is traditionally employed against respiratory infections such as bronchitis, coughs, and asthma. An experiment carried out on the hydroalcoholic leaf extract showed a good activity, with the half maximal effective concentration (EC50) of 38.56 ± 0.10 μg/mL (DPPH assay). A preliminary MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide-tetrazolium dye] test with 5 μg/mL concentration was noncytotoxic and able to improve fibroblast growth. This capability was subsequently confirmed by the results of in vitro wound healing test that led to the conclusion that *M. vulgare* might be effective against skin injuries [2].

Morinda citrifolia (Noni) has been traditionally used to treat broken bones, deep cuts, bruises, sores, and wounds. It is also reported to have a broad range of nutritional and therapeutic values for cancer, infection, arthritis, diabetes, asthma, hypertension, and pain. Investigating the effect of *M. citrifolia* leaves on experimental wounds and lipid peroxide levels in rats resulted in ample evidences confirming that *M. citrifolia* enhances wound healing by acting on various phases of the wound healing process. There was a significant increase in wound contraction rate, skin breaking strength that reflected increased collagen levels. The findings from the investigation also showed a decrease in lipid peroxide level in the *M. citrifolia*-treated group [54].

Musa paradisiaca (plantain) is a crop in the genus *Musa* that is indigenous to tropical and subtropical countries. To validate the ethnotherapeutic claims of the plant in skin diseases, wound healing activity was studied, besides antioxidant activity to understand the mechanism of wound healing activity. Methanol and hexane extracts of *M. paradisiaca* peel were used to evaluate the biological activity (antioxidant and wound healing) on the regenerative process of the epithelial tissue. The two extracts showed a good inhibition of DPPH radical; the hexane has an activity of 94.25% and methanol 87.33% at a concentration of 125 μg/mL compared with BHT 43.22% as a control. Wound closure was significantly more advanced in the treated groups (methanol 94.62%, hexane 88.39%) compared with control groups 81.75% at

15 days. The results suggested that extracts obtained with methanol has potential to stimulate the healing process in a close relation to antioxidant properties more that hexane extracts [55].

Phaleria macrocarpa is a traditional medicinal plant from New Guinea, Papua Island, and Indonesia. It is used to treat cancer, diabetes, ulcers, and hypercholesterolemia. Topical application of *P. macrocarpa* fruit extracts on skin excision wounds in rats resulted in an improved wound contraction rate and considerable reduction in healing time. The extract showed significant healing effect on excision wounds and demonstrated an important role in the inflammation process by increasing antioxidant enzyme activities, thereby accelerating the wound healing process and reducing tissue injury [56].

Polygonatum odoratum is an important herbal medicine used in folk medicine for the treatment of various elements. Its leaf extract is known to have possessed strong antioxidant, antibacterial, and anti-breast cancer activity. Topical application of ethanol leaf extract of this plant on the rate of wound healing closure using male Sprague Dawley rats in an excision wound healing model significantly accelerated the rate of wound healing with less inflammatory cells and more collagen with angiogenesis [57].

Sphaeranthus amaranthoides is a medicinal plant used in folklore medicine in India for the treatment of skin diseases. The evaluation of antioxidant activity of the methanol extract and its flavonoid fraction by using DPPH free radical scavenging activity, total antioxidant capacity, and total phenolic content showed variable degrees of antioxidant activity. When wound healing activity was studied in excision wound model in rats, both the methanol extract and the flavonoid fraction exhibited better wound healing activity than the standard drug (silver sulfadiazine). The methanolic extract and flavonoid fraction significantly enhanced the rate of wound contraction and the period of epithelialization comparable to silver sulfadiazine [58].

In my study of wound healing medicinal plants, 26 wound healing plants used among the people of Kpando Traditional Area for effective wound healing have been identified. In vitro investigations on four of these plants, namely, *Anogeissus leiocarpus*, *Amaranthus spinosus*, *Corchorus olitorius*, and *Combretum dolichopetalum*, exhibited wound healing efficacies and antioxidant properties.

The enhanced wound healing potency of various herbal extracts, therefore, may be partly attributed to free radical scavenging action of the phytoconstituents present in plant extracts.

4. Conclusions

Many plants used traditionally in treatment of wound possess antioxidant activity. It is evidently clear that wound healing and repair are accelerated by applying plant extracts that are rich in antioxidant phytochemicals. The assertion made that wound healing and antioxidant activity coexist, to some extent, can be confirmed. Researchers are encouraged to intensify their search for plants for the treatment of wounds with novel antioxidant activity that could be beneficial in therapeutic practice.

Acknowledgements

I am grateful to the University of Cape Coast for their support.

Conflict of interest

Author declared no conflict of interest.

Author details

Victor Y.A. Barku

Address all correspondence to: vbarku@ucc.edu.gh

Department of Chemistry, School of Physical Sciences, University of Cape Coast, Ghana

References

[1] Balachandar R, Saran Prakash L, Ashok Kumar K, Ragavi A, Gurumoorthy P. Antioxidant activity and wound healing potential of selected medicinal plants. Journal of Chemical and Pharmaceutical Sciences. 2014;**2**:100-103

[2] Amri B, Martino EID, Vitulo EID, Corana F, Ben-Kaâb LB, Rui M, et al. *Marrubium vulgare* L. leave extract: Phytochemical composition, antioxidant and wound healing properties. Molecules. 2017;**22**:1851. DOI: 10.3390/molecules22111851T

[3] Frykber RG, Banks J. Challenges in the treatment of chronic wounds. Advances in Wound Care. 2015;**4**:560-582

[4] Mackay D, Miller AL. Nutritional support for wound healing. Alternative Medicine Review. 2003;**8**:359-377

[5] Schwentker A, Vodovotz Y, Weller R, Billiar TR. Nitric oxide and wound repair: Role of cytokines? Nitric Oxide. 2002;**7**:1-10

[6] Edwards J, Howley P, Cohen IK. In vitro inhibition of human neutrophil elastase by oleic acid albumin formulations from derivatized cotton wound dressings. International Journal of Pharmaceutics. 2004;**284**:1-12

[7] Somashekar Shetty B. Wound healing and indigenous drugs: Role as antioxidants: A review. Research and Reviews: Journal of Medical and Health Sciences. 2013;**2**(2):5-15

[8] Fikru A, Makonnen E, Eguale T, Debella A, Mekonnen GA. Evaluation of in vivo wound healing activity of methanol extract of *Achyranthes aspera* L. Journal of Ethnopharmacology. 2012;**143**:469-474

[9] Ammar I, Bardaa S, Mzid M, Sahnoun Z, Rebaii T, Attia H, et al. Antioxidant, antibacterial land in vivo dermal wound healing effects of Opuntia flower extracts. International Journal of Biological Macromolecules. 2015;**81**:483-490

[10] Paarakh PM, Chansouria JPN, Khosa RL. Wound healing activity of *Annona muricata* extract. Journal of Pharmacy Research. 2009;**2**:404-406

[11] Dixit V, Verma P, Agnihotri P, Paliwal AK, Rao CV, Husain T. Antimicrobial, antioxidant and wound healing properties of *Leucas lanata* Wall. ex Benth. The Journal of Phytopharmacology. 2015;**4**(1):9-16

[12] Kayode OA. Epidemiological study on wound distribution pattern in horses presented at two veterinary clinics in south west, Nigeria between 2007-2010. Journal of Dairy, Veterinary & Animal Research. 2017;**5**(4):00148. DOI: 10.15406/jdvar.2017.05.00148

[13] Alonso JE, Lee J, Burgess AR, Browner BD. The management of complex orthopaedic injuries. The Surgical Clinics of North America. 1996;**76**(4):879-903

[14] Velnar T, Bailey T, Smrkolj V. The wound healing process: An overview of the cellular and molecular mechanisms. The Journal of International Medical Research. 2009; **37**:1528-1542

[15] Open Wound Basics. https://www.woundcarecenters.org/article/wound-basics/open-wound-basics

[16] Gilmore MA. Phases of wound healing. Dimensions in Oncology Nursing. 1991;**5**(3):32-34

[17] Mercandetti M. Wound Healing and Repair, 2017. Available from: https://emedicine.medscape.com/article/1298129-overview

[18] Maxson S, Lopez EA, Yoo D, Danilkovitch-Miagkova A, Leroux MA. Concise review: Role of mesenchymal stem cells in wound repair. Stem Cells Translational Medicine. 2012;**1**(2):142-149

[19] Dunnill C, Patton T, Brennan J, Barrett J, Dryden M, Cooke J, et al. Reactive oxygen species (ROS) and wound healing: The functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. International Wound Journal. 2017;**14**:89-96. DOI: 10.1111/iwj.12557

[20] Nita M, Grzybowski A. The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxidative Medicine and Cellular Longevity. 2016;**2016**:3164734. DOI: 10.1155/2016/3164734

[21] Underdown MJ. Antioxidants and wound healing [thesis]. East Tennessee: East Tennessee University; 2013

[22] Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;**408**(6809):239-247

[23] Sathya M, Kkilavani R. Phytochemical screening and in vitro antioxidant activity of *Saccharum spontaneum Linn*. International Journal of Pharmaceutical Sciences Review and Research. 2013;**18**(11):75-79

[24] Visioli F, Keaney JF, Halliwell B. Antioxidants and cardiovascular disease; pancrease or tonics for tired sheep. Cardiovascular Research. 2000;**47**(3):409

[25] Tosun M, Ercisli S, Sengul M, Oezr H, Polat T, Ozturk E. Antioxidant properties and phenolic content of eight salvia species from Turkey. Biological Research. 2009;**42**:175-181

[26] Parr A, Bolwell GP. PhEnols in the plant and in man: The potential for possible nutritional enhancement of the diet by modifying the phenols content or profile. Journal of the Science of Food and Agriculture. 2000;**80**:985-1015

[27] Arouma OI. Nutrition and health aspect of free radical and antioxidants. Food and Chemical Toxicology. 1994;**32**:671-683

[28] Elsayed NM, Gorbunov NV. Interplay between high energy impulse noise (blast) and antioxidants in the lung. Toxicology. 2003;**189**:63-67

[29] Valkov M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry & Cell Biology. 2006;**7**(1):45-78

[30] Devasagayam TPA, Sainis KB. Immune system and antioxidants, especially those derived from Indian medicinal plants. Indian Journal of Experimental Biology. 2002;**40**:639-655

[31] De la Fuente M, Victor M. Antioxidants as modulators of immune function. Immunology and Cell Biology. 2000;**78**(1):n49-n54

[32] Nguyen Q, Eun J. Antioxidant activity of solvent extracts from Vietnamese medicinal plants. Journal of Medicinal Plant Research. 2011;**5**(13):2798-2811

[33] Dehghan G, Shafiee A, Ghahremani M, Ardestani S, Abdollahi M. Antioxidant potential of various extracts from Ferulaszovitsiana in relation to their phenolic contents. Pharmaceutical Biology. 2007;**45**(9):1-9

[34] Kai-Wei L, Chiung-Hui L, Huang-Yao T, Horng-Huey K, Bai-Luh W. Antioxidant prenylflavonoids from *Artocarpus communis* and *Artocarpus elasticus*. Food Chemistry. 2009; **115**:558-562

[35] Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Reviews. 2010;**4**(8):118-126. DOI: 10.4103/0973-7847.70902

[36] Kasote DM, Katyare SS, Hegde MV, Bae H. Significance of antioxidant potential of plants and its relevance to therapeutic applications. International Journal of Biological Sciences. 2015;**11**(8):982-991. DOI: 10.7150/ijbs.12096

[37] Tuadhar ET, Rao A. Plasma protein oxidation and total antioxidant power in premenstrual syndrome. Asian Pacific Journal of Tropical Medicine. 2010;**3**(3):237-240

[38] Wojdylo A, Oszmianski J, Czmerys R. Antioxidant phenolic compounds in 32 selected herbs. Food Chemistry. 2007;**105**:940-949

[39] Kumbhare MR, Guleha V, Sivakumar T. Estimation of total phenolic content, cytotoxicity and in vitro antioxidant activity of stem bark of Moringa oleifera. Asian Pacific Journal of Tropical Disease. 2012; **2**(2):144-150

[40] Budovsky A, Yarmolinsky L, Ben-Shabat S. Effect of medicinal plants on wound healing. Wound Repair and Regeneration. 2015;**23**:171-183

[41] Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. Lancet. 1995;**341**:454-457

[42] Castelluccio C, Paganga G, Melikian N, Bolwell GP, Pridham J, Sampson J, et al. Antioxidant potential of intermediates in phenylpropanoid metabolism in higher plants. FEBS Letters. 1995;**368**:188-192

[43] Hirano R, Sasamoto W, Matsumoto A, Itakura H, Igarashi O, Kondo K. Antioxidant ability of various flavonoids against DPPH radicals and LDL oxidation. Journal of Nutritional Science and Vitaminology (Tokyo). 2001;**47**:357-362

[44] Cuyckens F, Claeys M. Mass spectrometry in structural analysis of flavonoids. Journal of Mass Spectrometry. 2004;**39**:1-15

[45] Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet. 1993;**341**:454-457

[46] Ghiselli A, Nardini M, Baldi A, Scaccini C. Antioxidant activity of different phenolic fractions separated from an Italian red wine. Journal of Agricultural and Food Chemistry. 1998;**46**:361-367

[47] Dong-Pi X, Li Y, Meng X, Zhou T, Zhou Y, Zheng J, et al. Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. International Journal of Molecular Sciences. 2017;**18**:96. DOI: 10.3390/ijms18010096

[48] Williamson J, Hughes CM, Davison GW. Exogenous plant-based nutraceutical supplementation and peripheral cell mononuclear DNA damage following high intensity exercise. Antioxidants. 2018;**7**:70. DOI: 10.3390/antiox7050070

[49] Modi AJ, Khadabadi SS, Deokate UA, Farooqui IA, Deore SL, Gangwani MR. *Argyreia speciosa* Linn. F: Phytochemistry, pharmacognosy and pharmacological studies. Journal of Pharmacognosy and Phytotherapy. 2010;**293**:34-42

[50] Amutha Iswarya Devi J, Kottai Muthu A. Phytochemical screening, antioxidant activities and total phenolic content of ethanolic extract from whole plant of *Saccharum spontaneum* (Linn.). International Journal of Chemical and Pharmaceutical Sciences. 2014;**5**(2):112-118

[51] Agyepong N, Agyare C, Ossei PPS, Duah Boakye Y. Antioxidant and in vivo wound healing activities of *Clausena anisata*. European Journal of Medicinal Plants. 2015;**10**(2):1-8

[52] Divya S, Naveen Krishna K, Ramachandran S, Dhanaraju MD. Wound healing and in vitro antioxidant activities of *Croton bonplandianum* leaf extract in rats. Global Journal of Pharmacology. 2011;**5**(3):159-163

[53] Ilango K, Chitra V. Wound healing and anti-oxidant activities of the fruit pulp of *Limonia Acidissima* Linn (Rutaceae) in rats. Tropical Journal of Pharmaceutical Research. 2010;**9**(3):223-230

[54] Pandurang Rasal VP, Sinnathambi A, Ashok P, Yeshmaina S. Wound healing and antioxidant activities of *Morinda citrifolia* leaf extract in rats. Iranian Journal of Pharmacology and Therapeutics. 2008;**7**:49-52

[55] Canales-Aguirre A, Carvallo-Aceves A, Manzano-Chávez L, Padilla-Camberos E, Lugo-Cervantes E. Wound healing and antioxidant activities of extracts from *Musa paradisiaca* L. peel. Planta Medica. 2008;**74**:PD9. DOI: 10.1055/s-0028-1084684

[56] Abood WN, Al-Henhena NA, Abood AN, Al-Obaidi MMJ, Ismail S, Abdulla MA, et al. Wound-healing potential of the fruit extract of Phaleria macrocarpa. Bosnian Journal of Basic Medical Sciences. 2015;**15**(2):25-30

[57] Mughrabi FF, Hashim H, Mahmood AA, Suzy SM, Salmah I, Zahra AA, et al. Acceleration of wound healing activity by *Polygonatum odoratum* leaf extract in rats. Journal of Medicinal Plant Research. 2014;**8**(13):523-528. DOI: 10.5897/JMPR10.451

[58] Geethalakshmi R, Sakravarthi C, Kritika T, Arul Kirubakaran M, Sarada DVL. Evaluation of antioxidant and wound healing potentials of *Sphaeranthus amaranthoides* Burm.f. Bio Med Research International. 2013;**2013**:7. DOI: 10.1155/2013/607109

IntechOpen