Original Research Report

THE EFFECT OF CABBAGE (*Brassica oleracea* var. *capitata* L.) EXTRACT ON MACROPHAGE AND BLOOD VESSEL COUNTS IN CLEAN WOUND TISSUE OF MALE RATS (*Rattus norvegicus*)

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ABSTRACT

Cabbage is a widely consumed vegetable known for its health benefits due to its rich nutrients and phytochemicals, especially phenolic compounds, which are known to have potent anti-inflammatory and antioxidant effects. This study aimed to investigate the effects of cabbage extract on wound healing by observing inflammatory responses in wound tissue. A total of 24 male rats were divided into four groups, with six rats in each group. The experiment was conducted for five days by administering cabbage extract to the treatment group and distilled water to the control group. Skin wound tissues were collected from all rats for histological observation by counting the number of macrophages and blood vessels. The results of the observation were analyzed statistically using an independent sample t-test with $p<0.05$. The results showed that the number of macrophages and blood vessels in the treatment group was significantly higher than the control group on the third day and significantly lower on the fifth day. In conclusion, the administration of cabbage extract can accelerate the inflammatory and proliferative phases of wound healing by promoting the migration of cells, including macrophages, resulting in accelerated angiogenesis. In addition, the decreased number of macrophages and blood vessels during the proliferative phase showed that the healing phase had reached a more advanced stage.

Keywords: Healthy lifestyle; anti-inflammation; cabbage extract; wound healing

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Highlights:
1. Cabbage extract application accelerates wound healing and has an anti-inflammatory effect.
2. Cabbage extract serves as an affordable source material for wound healing and anti-inflammation.

INTRODUCTION

A wound can be defined as any disturbance in the normal anatomical structure of the body's tissues, from subcutaneous tissue to deeper tissues such as tendons, muscles, nerves, and bones, which is usually accompanied by the tearing of blood vessels. Under certain conditions, the wound may fail the normal healing process which leads to the development of chronic wound (Abdurrahmat 2014, Chhabra et al. 2017). A wound in the chronic stage significantly reduces the patient's quality of life. It can cause permanent disability, immobility, and pain. It also requires continuous treatment, which results in an increase in economic burden (Šitum et al. 2014). Early wound care is necessary because it helps accelerate wound healing and prevent the development of chronic wounds. Anti-inflammatory agents are usually used by the general public for wound care. The use of anti-inflammatory agents from natural products can be a solution because they have minimal side effects, easily available ingredients, and an effective cost (Sumayyah & Salsabila 2017).

During the last three decades, there has been a rapid increase in the use of medicinal products and herbal supplements, with around 80% of people worldwide relying on herbal products as part of their primary health care. Apart from cultural beliefs, the use of plants as medicine is also supported by several studies, which have proved that various plants are known to contain a large number of bioactive compounds that provide various health benefits (Ekor 2014, Panche et al. 2016). Indonesia is a country with abundant natural resources due to the diversity in climate and geographical conditions that allow various types of plants to grow. It is possible for Indonesian people to take advantage of the various plants around them to meet various daily needs, one of which is medicine. Cabbage (*Brassica oleracea* var. *capitata* L.) is one of the plants that has the potential to be used as medicine. This plant is not only easily found and consumed in Indonesia but also all over the world. Cabbage contains various phytochemical compounds such as sulforaphane, flavonoids, glucosinolates, anthocyanins, phenolic acids, kaempferol, quercetin, and several other compounds that provide many benefits for improving a healthy lifestyle by acting as anti-inflammatory, antioxidant, antiviral, and antibacterial agents (Park et al. 2014, Lee et al. 2018).

The wound healing process until the integrity of the skin can return to its original state consists of three phases, i.e., inflammation, proliferation, and remodeling. The inflammatory phase consists of hemostasis and phagocytosis processes. Hemoestasis is the formation of a temporary wound matrix that functions to stop the bleeding, while phagocytosis is the process of cleaning the wound from the remnants of damaged tissue, pathogenic microorganisms, and apoptotic neutrophil cells (Krzyszczyk et al. 2018, Winarni et al. 2022). In the proliferative phase, granulation tissue is formed, replacing a temporary matrix with a new and stronger matrix. This matrix consists of fibroblasts, macrophages, and blood vessels. The last phase of the wound healing process is the remodeling phase, known as extracellular matrix maturation, which functions to maximize the structural integrity of the new tissue (Gonzalez et al. 2016, Landén et al. 2016).

In the healing of wounds, macrophages play a significant and constant role during the inflammatory, proliferative, and remodeling phases. When the inflammation subsides, the number of proinflammatory macrophages will be reduced, while the anti-inflammatory macrophages will be activated to regulate the process of tissue formation, including vascularization. Macrophages influence the formation of new vasculature because macrophages produce growth factors, including proangiogenic growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β) (Cañedo-Dorantes & Cañedo-Ayala 2019). This study was conducted to determine the effect of cabbage extract on the wound healing process by measuring the degree of inflammation through macrophages and blood vessel counts in the granulation tissue. The lower degree of inflammation indicates that wound healing occurs more rapidly (Rosique et al. 2015).

MATERIALS AND METHODS

This study was an experimental analytic study with a randomized posttest-only control group design. This study was conducted in the Biochemistry Laboratory, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. The research tools were cages, food, drinking water, a set of sterile surgical instruments to obtain the rats' wounded tissues, a 10% formalin buffer solution, and a light microscope. The materials included the experimental animals (*Rattus norvegicus*), ketamine and xylazine for anesthesia, distilled water, and 100% cabbage extract obtained from the Herbal Materia Medica Laboratory, Batu, Indonesia. The cabbage extract was produced by pharmacists at the Herbal Materia Medica Laboratory using a maceration method. A total of 3 kg of fresh cabbage was added to 96% ethanol as a solvent, then mashed with a blender and soaked in a glass container for 3x24 hours (Bhuana et al. 2021). The filtrate and the pulp were separated using a filter cloth, and the filtrate was evaporated until the solvent did not drip into the collecting flask. The result obtained was 100% cabbage extract in liquid form with a slightly thick consistency.

Experimental animals in this study were white male rats (*Rattus norvegicus*) obtained from the Biochemistry Laboratory, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. The criteria for the experimental animals in this study were male rats aged 2–4 months, with a weight of 130–150 grams and healthy conditions characterized by no anatomical abnormality and active movement. By using the Federer formula, 24 rats were used in this study. All rats were first adapted for one week and then anesthetized with ketamine and xylazine intramuscularly. The hair on the dorsal side near the spine was shaved, then the skin of the rat in that area was stretched between the fingers, and then an incision was made using a scalpel with a length of 1–1.5 cm and a depth of 2–3 mm (Gunawan et al. 2021).

Twenty-four rats were divided into four groups consisting of six rats each, i.e., two control groups

(K1 and K2) and two treatment groups (P1 and P2). The control groups were given distilled water topically twice a day, with a treatment duration of three days for K1 and five days for K2. The treatment groups were given cabbage extract topically twice a day, with a treatment duration of three days for P1 and five days for P2. After the treatment for the specified time was complete, the rats were euthanized, and the wounded tissues were obtained and put into a container containing 10% formalin for fixation and then processed into histological preparations with hematoxylin and eosin (HE) staining. Histological observations were made by counting the number of macrophages and blood vessels in the wound tissue using a light microscope with 400x magnification that was carried out in three fields of view (Sadikim et al. 2018). The collected data was then analyzed with the Shapiro-Wilk normality test, Levene homogeneity test, and independent sample t-test with $p<0.05$. The statistical analysis in this study used IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

The healing parameters observed in this study were the number of macrophage cells and newly formed blood vessels. The descriptive analysis results of the macrophage cells are presented in Table 1. The descriptive analysis results of the blood vessels are presented in Table 2.

Table 1. Distribution of the rats' macrophage cell count.

Group	Mean	Standard deviation	Minimum	Maximum
K1	30.00	2.828	26	33
K2	46.50	2.168	44	50
P1	35.33	2.733	33	40
P2	42.50	2.811	38	46

Table 2. Distribution of the rats' blood vessel count.

Group	Mean	Standard deviation	Minimum	Maximum
K1	13.67	2.503	10	17
K2	31.33	3.933	25	35
P1	20.67	3.204	17	25
P2	25.17	3.125	20	28

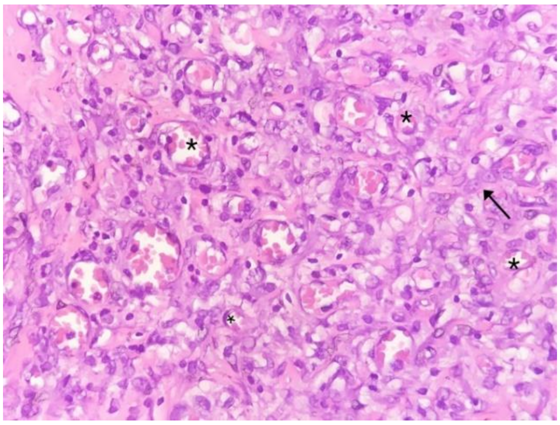
The Shapiro-Wilk normality test was performed and showed that the data on the macrophage and blood vessel counts in all groups (K1, K2, P1, and P2) were normally distributed ($p>0.05$). Afterwards, a homogeneity test was carried out using the Levene test, which showed that the data on the macrophage and blood vessel counts were homogeneous. There was no difference in data variation among all groups ($p>0.05$). The results of the normality and homogeneity tests revealed that the average numbers of macrophages and blood vessels were normally distributed and homogeneous. Therefore, an independent sample t-test was performed to determine the difference in the numbers of macrophages and blood vessels in skin wound tissue samples between the rats that received cabbage extract and those that received placebo (distilled water). The results of the test on macrophage count are presented in Table 3, while the results of the test on blood vessel count are shown in Table 4.

Table 3. Independent sample t-test of macrophage cells.

Groups	p
Day 3 (K1 and P1)	0.008
Day 5 (K2 and P2)	0.020
K (control group day 3 and day 5)	0.000
P (treatment group day 3 and day 5)	0.001

Table 4. Independent sample t-test of blood vessels.

Groups	p
Day 3 (K1 and P1)	0.002
Day 5 (K2 and P2)	0.013
K (control group day 3 and day 5)	0.000
P (treatment group day 3 and day 5)	0.034



Notes: (*) shows blood vessels; (→) shows macrophage cells.

Figure 1. Microscopic picture of rat skin wound with topical administration of cabbage extract on day 5.

DISCUSSION

In this study, the average number of macrophages was significantly higher on the third day and lower on the fifth day after the provision of cabbage extract. Immediately after injury, the danger signals, which are damage-associated molecular patterns (DAMP) released by damaged cells or pathogen-associated molecular patterns (PAMP) released by invading pathogens, will be detected by resident macrophages and will promote the activation of proinflammatory macrophages (M1) to cooperate with neutrophils in the phagocytosis of microbes, dead cells, cellular debris, and apoptotic neutrophils to produce proinflammatory mediators, as well as chemokines to recruit additional leukocytes to strengthen inflammation (Landén et al. 2016). The expression of various proinflammatory mediators and chemokines to recruit more leukocytes in the early phase of wound healing is in accordance with the results of the study on the third day, where the macrophage counts found in the control and treatment groups were significantly higher than the macrophage count of the same group on the fifth day. However, the number of macrophages in the treatment group on the third day was significantly higher than the number of macrophages in the control group on the same day. This showed that topical application of cabbage extract could accelerate the wound healing process by promoting faster migration of inflammatory cells to the wound site (Sarandy et al. 2015). The rapid macrophage migration in the treatment group was attributed to the effect of increasing the phagocytic capacity of macrophages by sulforaphane and the deactivation of macrophage migration inhibitory factor (MIF), which is an important inflammatory cytokine (Tilg 2015). In addition, flavonoids can induce or inhibit various enzyme systems in mammals, and some of these enzymes are involved in important pathways in the regulation of cell division and proliferation and inflammatory responses (Panche et al. 2016).

Macrophages are important inflammatory cells in the wound healing process that can change their phenotype from proinflammatory macrophages (M1) early in the process to anti-inflammatory macrophages (M2) in the middle stages of the healing process to continue coordinating wound repair (Shook et al. 2016). After the wound is clean, there will be an activation of anti-inflammatory macrophages (M2) that produce collagen precursors, completing the inflammatory phase due to prolonged M1 activation by downregulating proinflammatory tumor necrosis factor alpha (TNF-α) and interleukin 12 (IL-12), expressing anti-inflammatory mediators such as interleukin-1 receptor (IL-1R) and interleukin 10 (IL-10), promoting fibroblast migration and proliferation, producing vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), VEGF, insulin-like growth factor-1 (IGF-1), and high amounts of platelet-derived growth factor (PDGF) to promote angiogenesis (Landén et al. 2016, Krzyszczyk et al. 2018, Cañedo-Dorantes & Cañedo-Ayala 2019).

The decrease in the number of macrophages in the treatment group compared to the control group on the fifth day indicated a change in the phenotype of macrophages from pro-inflammatory to anti-inflammatory due to changes in the microenvironment (Torregrossa et al. 2021). In addition, the decrease in the number of macrophages also showed that on the fifth day, the wound healing process in the treatment group had entered a further proliferative phase compared to the control group on the same day. This was because the number of macrophages started to increase during the inflammatory phase, reached a maximum amount during the proliferative phase, and decreased progressively during the remodeling phase (Cañedo-Dorantes & Cañedo-Ayala 2019). Therefore, it was concluded that the effect of cabbage extract on wound healing met the characteristics of the ideal inflammatory response, which was fast and destructive but specific and not excessive.

The administration of cabbage extract showed a significant increase in the average number of blood vessels on the third day, but a decrease was observed on the fifth day. In the proliferative phase, there is massive migration and proliferation of keratinocytes mediated by macrophages to recover the epidermis and tissue regeneration with fibroblast migration and restoration of blood vessels (Shook et al. 2016). A significant increase in blood vessels in the treatment group on the third day (P1) proved that cabbage extract affects the wound healing process by accelerating angiogenesis for the reason that increased blood vessel formation can shorten wound healing time. In the wound healing process, VEGF expression normally increases in the first two to five days after injury to stimulate fibroblast proliferation and extracellular matrix production (Wang et al. 2016, Kurniawati et al. 2022). The higher number of blood vessels on the third day was in accordance with the number of macrophages on the same day because, apart from being phagocytes, the inflammatory phase macrophages also affect the formation of new blood vessels by expressing VEGF to stimulate angiogenesis as granulation tissue begins to form. This is considered a normal wound-healing mechanism (Torregrossa et al. 2021).

The number of blood vessels was in accordance with the number of macrophages in the treatment group on the same day. On the third day, the higher number of macrophages reaching the maximum number earlier than the control group also accelerated the proliferation process because the macrophages that regulate the proliferative phase are anti-inflammatory macrophages (M2), which produce proangiogenic factors such as insulin-like growth factor (IGF-1), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF) (Serra et al. 2017). This was supported by a significant decrease in blood vessel number, which was also in line with a decrease in macrophage number found in the treatment group on the fifth day, indicating that granulation tissue formation has occurred. While in the control group, on the same day, granulation tissue formation still occurred in an earlier or recently started phase because the blood vessel count of the group was still significantly higher.

The faster development of vascularization in the treatment group was also influenced by the strong antioxidant activity of flavonoids, such as phytochemicals with high amounts in cabbage, as they inhibit lipid peroxidation to increase vascularity. The effect of cabbage extract in inhibiting lipid peroxidation was proven in a study by Kim et al. (2020) in which three doses of cabbage extract (25, 50, and 100 mg/kg) were given for seven days and ranitidine hydrochloride was given for one day before the rat stomach was induced with hydrochloric acid (HCl) or ethanol to induce ulcerative lesions. At three doses of extract and ranitidine hydrochloride, there was a significant decrease in malondialdehyde levels. The decrease in malondialdehyde and catalase levels showed that cabbage extract at 100 mg/kg was significantly more potent than ranitidine hydrochloride. The phenolic compounds and glucosinolate present in cabbage also have the effect of reducing oxidative stress through the activation pathway of nuclear factor erythroid 2–related factor 2 (Nfr2), which is a transcription factor that can increase the transcription of various antioxidants and detoxification enzymes, thereby reducing the oxidative damage caused by reactive oxygen species (Sanlier & Guler Saban 2018, Ryou et al. 2021, Uuh-Narvaez & Segura-Campos 2021).

Strength and limitations

This study provides data regarding how cabbage extract can accelerate the wound healing process precisely by promoting the early migration of macrophages and accelerating the rate of angiogenesis. Studies on cabbage as an anti-inflammatory agent have been carried out before. However, microscopic parameter calculations in the form of macrophages and new blood vessels have not been performed. Time and cost limitations caused this study to only observe two microscopic parameters, while there were other parameters that could be observed as well.

CONCLUSION

Cabbage extract can accelerate the inflammatory and proliferative phases of wound healing by accelerating the migration of macrophages in the inflammatory phase so that the angiogenesis process also occurs faster. Cabbage extract also limits the degree of inflammation by significantly reducing the number of macrophages and blood vessels in the proliferative phase which indicated that granulation tissue had formed and the proliferative phase had reached a more advanced stage.

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Conflict of interest

None.

Ethical consideration

This research has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, with certification No. 139/EC/KEPK/FKUA/2021 on 4/6/2021.

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None.

Author contribution

NUT carried out the treatment of experimental animals and drafted the manuscript. WS contributed to the histological observations of macrophages and blood vessels. S contributed to the revisions of the manuscript.

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