Trend of Wound Healing Research Across in Indonesia Medical Plasma Activated Natural Substance as Wound Healing: A Systematic Review

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Abstract. Background: Medical plasma can generate biological molecules such as ROS and RNS. The medical aspect of plasma is conceptually related to its ability to produce biological molecules, specifically ROS and RNS (commonly abbreviated as RONS). Red dragon fruit extract is better at repairing granulation tissue and epithelialization tissue and increasing collagen synthesis so that it has the potential to heal wounds.

Aim: This review aims to highlight the trend of using the therapeutic technology of medical plasma and red dragon fruit plants, in an attempt to gather the necessary information for further investigation of its potential role in healing.

Methods: The protocol for the systematic review is created in accordance with the reporting items of interest for the systematic review. Furthermore, this review takes into account all wound healing studies that evaluate articles containing descriptors like wound healing.

Results: The results review show that red fruits are widely used for wound healing, and it have not result of combining plasma medicine and the red fruit compounds.

Conclusion: The review concludes by recommending red dragon fruit extract combined with medical plasma technology as a novel piece of research that is critical for the wound healing process.

Keywords: Hylocereus polyrhizus · Medical Plasma · Wound Healing

1 Introduction

Medical plasma is the fourth substance after solid, liquid and gaseous substances, which can produce biological molecules such as reactive oxygen and nitrogen species (ROS) (RNS). Properly controlled and the right dosage can accelerate wound healing and reduce

S. Pranata et al. (Eds.): LSISHS 2022, AHSR 60, pp. 362–374, 2023.
https://doi.org/10.2991/978-94-6463-132-6_41

bacteria in infected wounds [1]. Medical plasma treatment in the form of cold jet type causes a decrease in the production of IL-1, IL-8, IFN-γ, and TNF-α, as well as reducing biofilms produced by microbes [2].

Reactive Oxygen Species and Reactive Nitrogen Species are biomolecules that are abbreviated as RONS [3, 4]. RONS can be productive for health therapies both physiologically, pathophysiologicall [5]. The plasma-produced RONS, especially OH, O_2, O_3 and H_2O_2 are also antimicrobial [6]. New therapeutic technology in the form of medical plasma is one of the solutions in wound care. Medical plasma functions like a disinfectant that accelerates wound healing.

One of the main objectives of medical plasma research is to find ways to optimize the medical use of modern plasma as a health treatment with minimal side effects. The use of compounds in the liquid phase (solution or liquid), also known as the plasma-activated water (PAW) method, is one of the most recent advances in plasma medicine. The notion of plasma-liquid interaction in plasma developments in the medical field by combining plasma with extracted herbal substances is a major issue. Some studies focus for natural sources of phytochemicals that can promote with wound healing and contain antioxidants, one of which is the red dragon fruit (*Hylocereus polyrhizus*) [7]. The skin and flesh of the red dragon fruit have antioxidant properties due to their phenolic content, flavonoids, ascorbic acid, and betacyanin [8, 9].

The activity of flavonoids in wound healing is thought to be due to astringent properties and antibacterial role in increasing wound contraction and re-epithelization [10]. The dragon fruit extract is more effective at repairing granulation and epithelialization tissue and has been shown to increase collagen synthesis, giving it the potential to heal wounds [11]. Wound healing is a coordination process between cellular, humoral and connective tissue elements [12]. The wound healing mechanism occurs in four phases: hemostasis, inflammation, proliferation and maturation/re-modelling [13].

The hemostasis phase is a phase that occurs within a few minutes of injury. In hemostasis in the form of platelet aggregation and fibrin, the initial response involves local vasoconstriction that occurs for five-ten minutes, which stops the bleeding and the blood in the wound will clot [14].

The inflammatory phase begins within 24 h and lasts three-five days. Inflammatory cells release various enzymes and mediators that produce inflammatory signs: dolor (pain), rubor (redness), color (warmth), tumors (swelling) and loss of tissue function (*functio laesa*) [15].

The proliferation phase lasts five to seven days. This phase begins with the migration of fibroblasts into the wound following an injury. Various growth factors released by platelets and macrophages promote this process. Various growth factors stimulate the production of chemotactic, proliferation fibroblasts and collagenase. The process begins with matrix metalloproteinase (MMPs) production by fibroblasts [13]. Macrophages in the proliferation phase function to stimulate fibroblasts to produce collagen and elastin then an angiogenesis process occurs. Epithelialization occurs after growing a thin layer covering the wound [16]. The maturation phase is characterized by forming collagen tissue on the skin for wound healing [17]. Natural ingredient preparation techniques are critical for maximising the benefits of natural ingredients [18].

The red dragon fruit (*H. polyrhizus*) is one of the most popular tropical and subtropical fruits. This plant is grown in a variety of environments in Indonesia, including coastal regions and the highlands. This research aims to collect data from multiple studies discussing red dragon fruit's use in wound healing. In particular, this research aims to answer the following questions: [i] What is the current state of wound healing in Indonesia using medical plasma-activated materials? [ii] How does the healing trend of red dragon fruit change from year to year? [iii] What types of red dragon fruit parts were used by the researchers for wound treatment?

In some aspects, the study is focused on all the articles published in the last six years; everything is on google scholar. Secondly, this study investigates several wound healing articles using medical plasma technology and red dragon fruit materials as the main focus.

2 Methods

This research method uses a systematic review study. Various points of view, from scientific-based aspects to sample materials, were reviewed. Search the article primarily through the *Google scholar* database with the first keyword "*Medical plasma technology for wound healing*" then "*Combination of medical plasma and plants in wound healing*", "*Wound healing plants*", "*Red dragon fruit* or *H. polyrhizus"*.

2.1 Study Design

This review considers pre-clinical studies conducted on research activities using wound healing therapy tools Atmospheric pressure plasma jets generated with Argon medical grade gas are combined with red dragon fruit extracts as wound healing ingredients. The component populations (types of red dragon fruit parts), exposure (intervention), comparisons and outcomes of this review are as follows: Subject of study (the disease model). The red dragon fruit plant as a whole or its addition: extracts of bark, flesh, stems, and flowers used in the experimental group are considered an intervention. Red dragon fruit plants are utilised for medicinal purposes (extracts, creams, injections, gels or other preparations). There are no constraints on the medicinal plants' dose form, concentration, frequency of administration, dosage, intensity, or duration.

2.2 Eligibility Criteria

The following screening studies were chosen based on inclusion criteria: [i] Related subjects; studies of the use of medical plasma with a combination of various plant materials [ii] the use of the red dragon fruit plant as an acute as well as chronic wound healing [iii] reported in the Indonesian or english; [iv] As a search strategy, observational studies will be used, with publication dates ranging from 2017 to 2022. Study Selection following the guidelines from Snyder (2019), an independent investigation was completed in order to identify the study that matched the inclusion criteria for this evaluation. The title and abstract of the search notes are recognised and thoroughly reviewed to identify which inappropriate sources should be excluded by following the exclusion criteria. The other studies' articles (full text) are also obtained and analysed to see if they fit the inclusion criteria [19].

2.3 Extraction Data

Researchers extract data independently. Here are the data extracted: title, author, year of publication, type of study, type of wound, statistical method used, and plant parts. When multiple treatment groups were present in separate studies, those groups were combined to avoid presentation bias caused by different statistical comparisons with other groups.

2.4 Outcomes Measured

For the study of wound healing, using red dragon fruit is an acceleration in the healing phase process.

The data (variables) extracted for wound healing are (percentage and pg/ml, μg/ml). In wound healing tests involving laboratory animals, the main results are the percentage of shrinkage of the wound area, the formation of re-epithelialization and the percentage of collagen density at the end of the wound healing phase.

2.5 Bias Control Assasement

Each included study's risk of bias was independently assessed by a researcher. The following concerns are covered in the risk of inclination or quality evaluation in this review: completeness reports on using natural ingredients that can be combined with medical plasma and focus on the red dragon fruit plant's natural ingredients for wound healing. When all these criteria are met, the risk of possible bias is considered low, whereas the study of high-risk bias is omitted from the analysis.

3 Result and Discussion

Total of 1650 articles from relevant Google Scholar were identified independently for a preliminary review of both automated and manual searches Following the removal of duplicates by evaluating the relevant titles and abstracts, 42 publications were selected for full-text examination. Following a thorough assessment of each article, 19 were removed, leaving 23 articles, two of which were anti-inflammatory in vitro, and 21 wound healing in vivo.

The data from this reference is used to create Fig. 2, Tables 1 and 2. Trend analysis with medical plasma technology that can activate natural ingredients as a wound healing therapy can be found in Indonesia for the past six years. However, only a few journals have discussed this. The following are some of the medical plasma studies that can be seen in Table 1.

Table 1. Summarizing the types of materials used in wound healing were developed using medical plasma technology reported from various studies in Indonesia. In Table 1, the data shows that extract plants dominate the widely used ones. Trend data also reveals that not all studies report being able to heal wounds, while the material can inhibit the effectiveness of wound healing.

The reference data above is continued by looking at the use of natural ingredients, namely the trend of red dragon fruit being able as a wound healing ingredient for the last six years which is shown in Fig. 2.

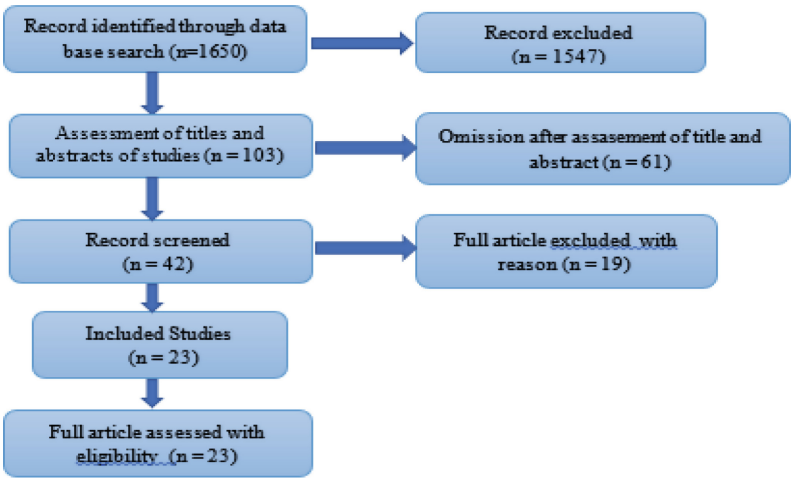

Fig. 1. These selection process of studies

The number of publications of articles shows how often the study was conducted in a given period. Following the graph shown in Fig. 1, the research journal uses red dragon fruit. No particular shift pattern occurs in the number of publications from year to year.

Nonetheless, referring to Fig. 1. The trend of dragon fruit, judging from the number of publications included in the criteria since 2019 has increased but decreased in the following year. Most studies result from researchers sensitivity to common problems around them. One of the most frequently found issues today is related to wound healing with the use of natural ingredients. For this reason, conducting research with plant materials is believed to be the most effective alternative way to deal with and overcome the problem.

With research, researchers could effectively identify red dragon fruit plants that might be able to heal wounds optimally. Various studies using plant parts of the red dragon fruit used for cell repair and healing of various types of wounds are shown in Table 2**.**

Summarizing the benefits of various parts of the red dragon fruit in Table 2, interestingly shows its effectiveness in treating wounds. The content of betacyanin *H. polyrhizus* red has potential as an antioxidant, due to its properties as a radical scavenger, thereby reducing oxidative damage [38].

Red dragon fruit has a high content of phenolic compounds. This compound is closely related to antioxidant activity, especially polyphenol groups such as flavonoids that are widely contained. This fruit contains natural antioxidant compounds, including flavonoids, phenolics, carotenoids and anthocyanins [39]. Dragon fruit contains a source of vitamins and minerals [33]. In addition, ascorbic acid (vitamin C) contained in red *H. polyrhizus* is also an antioxidant by reacting directly with superoxide anions, hydroxyl radicals, and singlet oxygen to inhibit the interaction between lipids and oxidants and prevent lipid peroxidation [40].

As seen in Table 1, the development of natural materials activated by medical plasma technology enables novelty in wound healing treatment therapies. The use of red dragon fruit has not been reported, so it is recommended that studies be carried out. The activation

Table 1. Studies in Indonesia have reported various materials activated by medical plasma in the last six years.

No	Type of plant	Plasma Source	Gas Type	Property	References
1.	Binahong	Atmospheric pressure plasma jet	Argon	Binahong may reduce the effectiveness of plasma jets in wound healing.	(Darmawati *et al.*, 2021) [20]
2.	Aloe Vera	Atmospheric pressure plasma jet	Argon	Aloe vera irradiated plasma jet with a distance of 20mm can accelerate healing in the proliferation phase.	(Nasruddin *et al.*, 2019) [21]
3.	Betel Leaf	Atmospheric pressure plasma jet	Argon	Mixing with Betel Leaf Extract can inhibit the effectiveness of wound healing.	(Setyowati e*t al.*, 2019) [22]
4.	Manuka Honey	Atmospheric pressure plasma jet	Argon	The use of manuka honey can prevent the formation of abnormal tissue in the wound than hydrocolloid dressings alone.	(Wahyuningtyas *et al.*, 2018) [23]
5.	Manuka Honey and Indonesian Honey	Atmospheric pressure plasma jet	Argon	The results of this study indicate that the combination of plasma with Manuka honey and Indonesian honey is effective in the granulation phase. Manuka honey accelerates the healing of acute wounds in the next phase.	(Wahyuningtyas *et al.*, 2017) [24].

test of the red dragon fruit with medical plasma has also not been reported worldwide in the past six years. The maceration method is recommended to be used in producing extract with some concentration, as obtained in previous studies. In addition, this study suggests the importance of chemical assays, which are often reported, to be fully

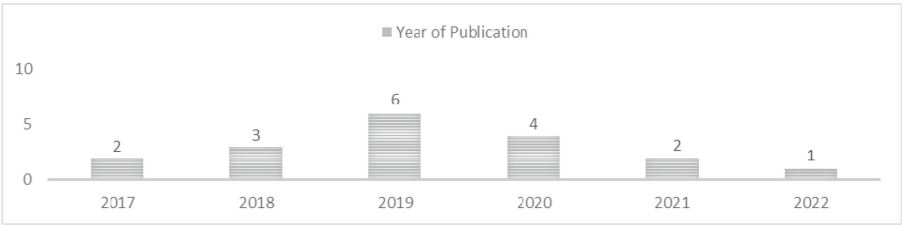

Fig. 2. The trend of the number of wound healing studies using red dragon fruit in the past six years

Table 2. Studies in the last six years reporting red dragon fruit plant used for wound healing

No	Uses	Part used	Main finding in red dragon treats wound	References
1.	Test of Macrophage Phagocytic Activity	Peel	Macrophage cell activity and nitric oxide production revealed that isolates at the highest concentrations of 100g/ml were able to activate macrophage cells and increase NO production.	(Wahdaningsih *et al.*, 2021) [25]
2.	Bleeding time in the tail of Balb-C	Peel	Red dragon fruit affects shortening the bleeding time.	(Kusumastuti *et al.*, 2021) [26]
3.	Well diffusion test method	Peel	Red dragon fruit peel has antibacterial activity against *S. Aureus* and shows higher antibacterial activity against MRSA than Methicillin-Susceptible *S. Aureus.*	(Aulia *et al.*, 2021) [27]
4.	Acute wound	Flesh	Accelerate wound healing during both the inflammation and proliferation phases.	(Takdir *et al.*, 2021) [28]
5.	Fibroblast cells (3T3BALB/C)	Peel	RDFP 70% ethanol extract has proven to be not toxic, particularly at a concentration below 250 μg/ml.	(Kylanel *et al.*, 2020) [29]

(*continued*)

Table 2. (*continued*)

No	Uses	Part used	Main finding in red dragon treats wound	References
6.	Socket wound healing	Peel	Increasing the expression of TGF- β, number of fibroblast and formation of new blood vessels	(Budi *et al*., 2020) [30]
7.	Acute wound	Peel	Could promote the healing process through the formation of collagen fibers density	(Wisnu *et al.,* 2020) [31]
8.	Second degree burns skin	Flesh	Cream can increase the amount of fibroblast cells	(Rahmadhana *et al*., 2020) [32]
9.	Acute wound	Flesh	An increase of EGF levels was not observed following RDFE treatment	(Tahir *et al.,* 2020) [33]
10.	Chronic periodontitis	Peel	Decrease the level of MDA in rats with chronic periodontitis	(Hendrik *et al.,* 2019) [34]
11.	Acute wound	Peel	Reduce for area expression of IL-2 and the number of mononuclear inflammatory cells	(Permata *et al*., 2019) [12]
12.	NIH-3T3 fibroblast cell line	Stem, flesh and flower	DNA damage protection was also demonstrated by stem, peel, and flower extracts in 95% aqueous ethanol. *H. polyrhizus* stem had high DPPH and ABTS radical scavenging activity.	(Yu *et al*., 2019) [9]

(*continued*)

Table 2. (*continued*)

No	Uses	Part used	Main finding in red dragon treats wound	References
13.	Normal human fibroblasts cell	Peel and flesh	Relatively safer to normal cells than the peel extracts	(Novi *et al.*, 2019) [8]
14.	Damage of the gastric mucosal tunica	Peel	Decrease MDA levels and improve the histopathology feature of the gastric in white rats induced by diazinon	(Mahdi *et al.*, 2019) [35]
15.	Lesi endometriosis	Peel	Inhibit endometriosis progressivity, signed by less granuloma formation	(Hapsari *et al.*, 2018) [36]
16.	Acute non-DM and DM	Flesh	Increase the growth of granulation tissue and epithelialization	(Tahir *et al.*, 2017) [37]

supportive if developed together with medical plasma technology. Antioxidant therapy is now widely used as a treatment for chronic diseases. Using natural antioxidants is more desirable due to their more compatible, cheaper, and less harmful effects on the body-natural antioxidant compounds found in plant parts such as bark, stems, and leaves [34].

Efforts to combine plant extracts with medical plasma can open up new possibilities in optimizing the effectiveness of wound care. To date, few scientific reports have examined the method [21]. The plasma that produces RONS, particularly hydrogen peroxide, oxygen, and ozone, is also [6]. Ozone stimulates oxygen metabolism and activates the immune system, widely used to treat infected wounds. These molecules can easily enter the cell membrane, damaging the double layer of phospholipids, proteins in the plasma membrane, and most intracellular components, such as nucleic acids, that cause cell death. Previous research has shown that atmospheric pressure jet-type medicinal plasma can promote inflammation and so speed the healing of acute wounds in balb/c mice experimental animals, re-epithelialization and wound contraction [41].

The development of plant extracts activated by plasma jets offers the possibility of novelty in wound healing treatment therapy. Jet-type medical plasma activity with argon gas is recommended. With medical plasma and new materials, wound management has become more effective. New therapeutic technologies are advantageous for healing wounds. The combination of herbal plants, red dragon fruit with medical plasma is a technological novelty that will open new research gates in wound care management. As obtained in previous studies, this method is recommended to be used in steps to continue the plant extract process.

4 Conclusion

This review suggests combining the skin of the red dragon fruit with the extract of the red dragon fruit with medical plasma technology as a novelty of research that is important to do for the wound healing process.

Acknowledgments. We would like to thank the Master of Clinical Laboratory Science, Postgraduate Program of Muhammadiyah Semarang University for promoting and supporting this research.

Author' Contributions. RA compiled the original idea, RA and KM sifted and summarized all the literature obtained. The Constitutional Court evaluates the creation of tables and schematics, as well as analyzes the bias of the study. The main text was written by RA.

SD and MDK are supervisors who guided and provided instructions on plasma medicine therapy, RA and MDK improved the English sentences in this article, and KM improved the writing by using health terms.

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