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A Systematic Review of Procyanidins: Updates on Current Bioactivities and Potential Benefits in Wound Healing

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ABSTRACT

Introduction: Procyanidins are a class of flavonoids found in many fruits and plants and have been used as traditional medicine or other homemade remedies, particularly for wound healing. This study systematically reviews the available literature on the potential benefits of procyanidins for wound healing in human cells.

Materials/Methods: Relevant keywords consisting of "Procyanidin" AND "Wound healing" was explored in databases including PubMed, Google Scholar, Nature, and Science Direct. This is a systematic review following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results: Seven (7) articles met the established inclusion and exclusion criteria. Procyanidins presented a potential benefit in cellular proliferation and migration, antibacterial, anti-inflammatory, and antioxidant activity in wound healing.

Conclusion: Procyanidins are beneficial for developing therapies in wound healing, and our review provides a scientific basis for future research.

KEYWORDS: Human cell; Procyanidins; Systematic review; Wound healing

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INTRODUCTION

Procyanidins are a subclass of flavonoids comprised of monomers, oligomers, and polymers (1). They consisted of flavan-3-ol units, epicatechins, and catechins. It is a type of polyphenolic polymer that can be found in legumes, fruits, grains, and leaves. It also can be found in chocolates, apples, cocoa powder, grapes, red wine, kiwi, pears, banana, lettuce, cinnamon, and pumpkin. Procyanidin has many benefits such as antioxidant, anticancer, antitumor, anti-inflammatory, immunosuppressive, anti-allergy, protective properties against chronic disease and metabolic disorders, antibacterial, and antivirus (2).

The skin has many vital functions, such as a barrier between the body and the external environments, sensing extrinsic stimuli even regulating thermostability. It is composed of the epidermis and dermis. Cutaneous wound healing is a complicated physiologic process formed by the collaboration of many cells and their products. The four main phases of wound repair are hemostasis, inflammation, proliferation, and remodelling (3–5).

METHODS

Relevant keywords, including "Procyanidin" AND "Wound healing", were inputted into search engines, including PubMed, Google Scholar, Nature, and Science Direct. Data pooling was performed from 1 to 20 December 2021. Acquired studies were screened to exclude non-human studies, human experimental studies, unrelated study topics, a publication of more than ten years, and studies published in languages besides English and Indonesian. Collected studies were then reviewed to ensure synchronous outcomes and enable comparison. This study is in line with the PRISMA flow diagram, and the data summary was extracted in a table. This study aims to review the effect of procyanidin in wound healing.

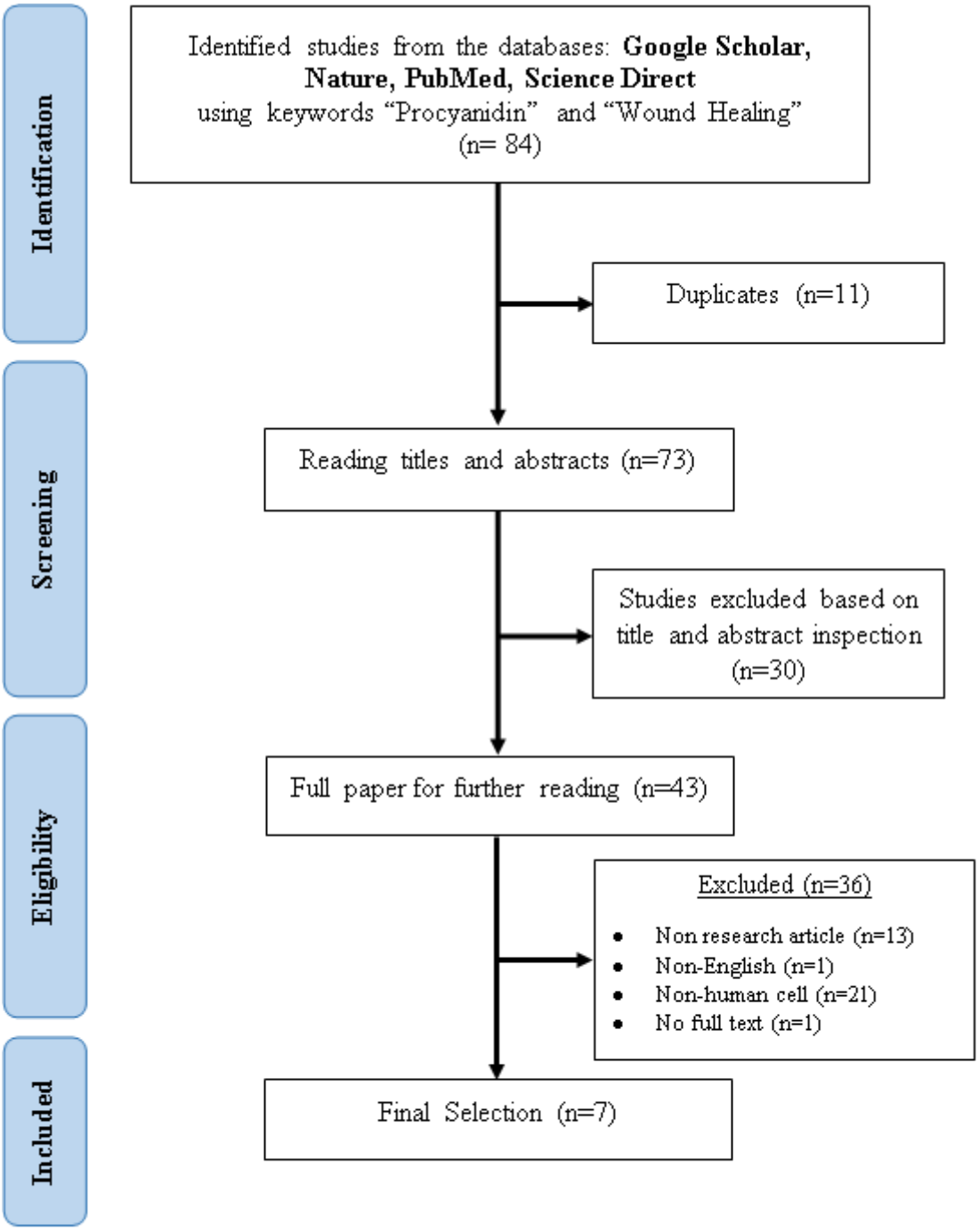

Fig. 1. PRISMA Flowchart of the searching process and study selection

RESULTS

The database search identified 84 records for preliminary review. After we removed duplicates, 73 references were screened based on their title and abstract, and we submitted 43 articles for a full-text review. Of all studies that have been reviewed, there were 36 studies excluded and seven studies included in this systematic review (Fig.1).

The characteristics of the included studies are summarized in Table.1. In this review, only one of the selected articles was published in more than the last five years, which points to the current invention and relevance of the subject. The main mechanisms of action were cell migration, antioxidant, and anti-inflammatory activity. The primary outcome studies were to accelerate the wound healing process.

Table 1. Overview of the characteristics of the included studies

Country/ Year	Samples	Material	Method	Outcome	References
Germany, 2015	*C. mucronatum* leaves	Primary natural human epidermal keratinocytes (pNHEK) and dermal fibroblasts (pNHDF)	Samples extraction, CLSM, Western Blot analysis, immunoblot assay	*C. mucronatum* inhibited cellular proliferation and triggered skin cells into terminal cellular differentiation.	E. Kisseih et al. (2015)
The United States, 2019	Wild Alaskan berry (*Vaccinium uliginosum L., Empetrum nigrum L., Vaccinium vitis-idaea L.*)	Primary human dermal fibroblasts (HDFa, Invitrogen, C-013-5C)	Samples extraction, ANC determination via HPLC and LC-MS, PAC composition by normal-phase HPLC-FLD analysis, Cell culture, cell viability, dose range determination, cell migration assay, fluorescence imaging analysis, scratch wound healing assay, qPCR array transcription profiling	Procyanidin B2 and its structural metabolites demonstrated anti-inflammatory activities. Still, they appeared to promote wound repair via increasing mitochondrial basal respiration, ATP production, and maximum respiratory capacity, potentially contributing to upregulated expression of integrins and other molecules regulating the ECM.	Esposito et al. (2019)
South Korea, 2017	Oligomeric procyanidin	Normal human fibroblast cell line, Hs27	Cell culture, cell cytotoxicity assay, OPC treatment, real-time PCR, Western Blot analysis of procollagen type I, Immunocytochemistry for localization of procollagen type I	OPC did not affect cell proliferation and necrosis. OPC inhibited procollagen secretion, resulting in cytoplasmic accumulation.	Kim et al. (2017)

China, 2020	Procyanidin B2 (PCB2)	Human umbilical vein endothelial cells (HUVECs)	Cell culture, qRT-PCR, Western blotting	PCB2 attenuates the ER stress induced by high glucose or tunicamycin. PCB2 ameliorated high glucose-triggered ER stress and endothelial dysfunction.	Nie et al (2020)
Poland, 2021	Leaves of: *R. nigum L., V. myrtillus L., R. fruticosus L., F. vesca L.*	BJ Cells, HaCaT cells (normal human keratinocytes)	Samples extraction, DPPH radical scavenging assay, Cell viability assay, Scratch wound assay	All samples show antioxidant activity and stimulate keratinocyte migration.	Ziemlewska (2021)
Argentina, 2018	"San Andreas" strawberry and "Black Satin" blackberry crude extracts	Primary human dermal fibroblasts isolated from adult skin (HDFa)	Samples extraction, HPLC-PDA and LC-ESI-MS analysis, Cell culture, ROS assay, NO assay, Anti-inflammatory assay, Skin fibroblast migration, and proliferation assay	CEs of both samples enhanced cell production and migration and have antioxidant and anti-inflammatory activity	Van de Valde (2018)
Turkey, 2016	Aerial parts (flowers and leaves) of wild-grown *Bellis perennis*	Human lung carcinoma cell, Colon adenocarcinoma cell, Normal skin fibroblast cell lines	Samples extraction, Cell culture, Antibacterial activity assay, Anti-inflammatory activity assay, Antioxidant activity assay	*Bellis perennis* has antibacterial, anti-inflammatory, and antioxidant activity.	Karakas et al. (2016)

DISCUSSION

Wound healing is a complex, continuous process supported by many cellular events coordinated to repair tissue damage (5). Many cells have been participating in the wound healing process, such as cytokines, chemokines, growth factors, mononuclear cells, skin cells, regulatory molecules, and extracellular matrix. The process has been organized in four continuous steps: the hemostasis phase, the inflammatory phase, the proliferative phase, and the remodelling phase (3–5)

Many fruits and herbs have been used as traditional medicine or other homemade treatment, particularly for wound healing. Numerous studies indicate those materials are rich in bioactive compounds, especially polyphenols and flavonoids. Procyanidins are members of the proanthocyanidin class of flavonoids, which is recently very interesting to discuss due to their benefits for health. Unfortunately, there are still few studies examining their use in wound healing.

Proliferation and Cell Migration Activity

Cell migration plays a vital role in tissue formation and reparation. It is also associated with maintaining tissue homeostasis and immune response (6).

Conversely, in 2018 Van de Velde reported the potential cell migration found in polyphenolic compounds of blackberry and strawberry extract. Fibroblast migration was found in the positive control after 48h using anthocyanin-enriched fractions (AEFs). Moreover, anthocyanin also induced keratinocytes and increased the production of VEGF (7).

In line with the previous study, Esposito et al. reported a fibroblast migration, supporting active tissue repair and promoting skin cell proliferation and migration (8). Furthermore, in 2021 Ziemlewska et al. performed a scratch wound assay, and the results showed that the migration process of the tested cells is affected, to varying degrees, by the analyzed extracts of procyanidin from four different plants. The extract of *R. fruticosus L.* leaves at a concentration of 1.0% could sturdily stimulate keratinocyte migration, resulting in almost a complete wound closure.

Many works of literature found that the proliferation of cells depends on the compound of plant origin. The concentration of compounds in each extracted plant largely determines their effect and performance on cells. In line with the statement, many studies have shown that these compounds are dose-dependent. (6).

While in other studies it has contradictory results. In 2015, Kisseih et al. reported that *C. mucronatum* extract inhibited cellular proliferation but found cellular differentiation. Two typical markers of keratinocyte differentiation were found in cells: involucrin and cytokeratin K10 X. Lower concentration of *C. mucronatum* extract (0.01–1μg/mL) expressed a more robust expression of cytokeratin but not involucrin (9).

Collagen synthesis plays a vital role in the remodelling phase. Kim et al. reported that OPC inhibited secretion of procollagen type I in Hs27 cells. It resulted in almost complete suppression in more than 10μg/mL concentration. The overabundance of collagen deposition causes keloid, hypertrophic scar, and fibrosis. OPC induces the accumulation of procollagen in the cytoplasm but does not affect procollagen gene expression, mRNA expression, and enzymes of collagen biosynthesis (10).

Antibacterial Activity

Karakas et al. tested the antibacterial activity of *Bellis prennis L*. (common daisy) with the disc diffusion assay. *Bellis prennis L*. (common daisy), for a long time known as a wound-healing plant in Europe, is a medicinal plant. In this study, the extract of the flowers exhibited a broad spectrum of activity against Gram-positive (*S. aureus, S. epidermidis, and S. pyogenes*) and Gram-negative bacteria (*E. cloacea*). The antibacterial activity of the flower extracts occurred due to the high phenolic content (11).

Anti-inflammatory Activity

Procyanidin B2 and its structure show anti-inflammatory activities. However, it appeared to support wound healing by increasing ATP production, basal mitochondrial respiration, and upregulated expression of integrins and other molecules regulating the ECM (8). Van de Velde also reported that all polyphenol extracts significantly suppressed COX-2 gene expression and the chronic pro-inflammatory gene IL-6 (7). In their study, Karakas et al. determined the anti-inflammatory activities of procyanidin by measuring the ability to prevent cellular nitric oxide (NO) production. They reported that the plants' phenolic, flavonoid, and terpenoid constituents strongly inhibit LPS-induced NO secretion. NO is an endogenous free radical species. It is synthesized in many living tissues and is a valuable promoter of physical homeostasis, from L-arginine by nitric oxide synthase (NOS). High levels of NO are highly associated with the pathophysiology of numerous inflammation diseases (11).

Antioxidant Activity

The DPPH assay showed a significant correlation between the total phenolic content and the radical scavenging activity. Increasing procyanidin concentrations may enhance free radical scavenging activity (6,11). Moreover, Van de Velde suggested that anthocyanin components may be less active against oxidative stress than proanthocyanidin (7).

In a high glucose setting, X. Nie et al. reported that PCB2 significantly attenuated the endoplasmic reticulum stress. It inhibited the activation of IRE1α, PERK, and ATF6 pathways. PCB2 also decreased the mRNA levels of the ER stress response genes, including GRP78, ATF3, ATF4, and CHOP (12).

Cell Toxicity

The amount and type of phenolic content of extracts depend on three things. Firstly, it depends on the part of the plant material. Secondly, it is subject to the type of extraction solvent, and thirdly, it depends on the extraction method used. Procyanidin B2 from *C. Mucronatum* extract did not influence the cell viability at 0.17 – 172 μm but strongly decreased cellular proliferation at higher concentrations (9). Extract of blackberry and strawberry in the range of 50-250 μm/mL would not reduce the cell viability (7).

Furthermore, in 2021, analyses demonstrated that the higher concentrations of procyanidin extracts inhibit the viability and metabolism of the cell lines tested. Cytotoxicity tests executed on keratinocytes (HaCaT) revealed the most advantageous effect at a concentration up to 1.0%. Conversely, concentrations of all tested extracts equal to or greater than 5.0% lessen the keratinocyte's viability and proliferation. It shows the reduction of cellular metabolism associated with concentration's cytotoxic effect. A higher concentration may cause cell death. The results showed that 0.5-1.0% concentration of analyzed plants promotes fibroblasts and keratinocyte proliferation (6). However, Kim et al. reported that Oligomeric Procyanidins (OPCs) have no cytotoxic effect on cells (10).

CONCLUSION

This study shows some plants (flowers and fruits) contain high amounts of polyphenols and flavonoids, which are very beneficial for wound healing due to their antibacterial, antioxidant, and anti-inflammatory activities. This could be considered as an alternative for wound healing treatment. Some studies report *in vivo* application in animals; however, future research should be intensified on the practical use.

Acknowledgments

None.

Conflict of Interest

None.

Availability of Data and Materials

The published articles include all data that are used in this study.

Ethics Approval and Consent to Participate

None.

REFERENCES

I. Bitzer ZT, Glisan SL, Dorenkott MR, Goodrich KM, Ye L, O'Keefe SF, et al. Cocoa procyanidins with different degrees of polymerization possess distinct activities in models of colonic inflammation. J Nutr Biochem. 2015 Aug;26(8):827–31.

II. Dasiman R, Nor NM, Eshak Z, Mutalip SSM, Suwandi NR, Bidin H. A review of procyanidin: Updates on current bioactivities and potential health benefits. Vol. 12, Biointerface Research in Applied Chemistry. AMG Transcend Association; 2022. p. 5918–40.

III. Cañedo-Dorantes L, Cañedo-Ayala M. Skin acute wound healing: A comprehensive review. Int J Inflam. 2019;2019.

IV. Gonzalez ACDO, Andrade ZDA, Costa TF, Medrado ARAP. Wound healing - A literature review. Vol. 91, Anais Brasileiros de Dermatologia. Sociedade Brasileira de Dermatologia; 2016. p. 614–20.

V. Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes: Cellular Mechanisms of Wound Repair. Open Biol. 2020;10(9).

VI. Ziemlewska A, Zagórska-Dziok M, Nizioł-Łukaszewska Z. Assessment of cytotoxicity and antioxidant properties of berry leaves as by-products with potential application in cosmetic and pharmaceutical products. Sci Rep [Internet]. 2021;11(1):1–14. Available from: https://doi.org/10.1038/s41598-021-82207-2

VII. Van de Velde F, Esposito D, Grace MH, Pirovani ME, Lila MA. Anti-inflammatory and wound healing properties of polyphenolic extracts from strawberry and blackberry fruits. Food Res Int [Internet]. 2019;121:453–62. Available from: https://doi.org/10.1016/j.foodres.2018.11.059

VIII. Esposito D, Overall J, Grace MH, Komarnytsky S, Lila MA. Alaskan Berry extracts promote dermal wound repair through modulation of bioenergetics and integrin signaling. Front Pharmacol. 2019;10(SEP):1–15.

IX. Kisseih E, Lechtenberg M, Petereit F, Sendker J, Zacharski D, Brandt S, et al. Phytochemical characterization and in vitro wound healing activity of leaf extracts from Combretum mucronatum Schum. & Thonn.: Oligomeric procyanidins as strong inductors of cellular differentiation. J Ethnopharmacol. 2015;174:628–36.

X. Kim BJ, Park JK, Kim BK, Park SJ, Kim MK, Lee C won, et al. Oligomeric Procyanidins (OPCs) Inhibit Procollagen Type I Secretion of Fibroblasts. Tissue Eng Regen Med. 2017;14(3):297–306.

XI. Karakas FP, Turker AU, Karakas A, Mshvildadze V, Pichette A, Legault J. In vitro cytotoxic, antibacterial, anti-inflammatory, and antioxidant activities and phenolic content in wild-grown flowers of common daisy—A medicinal plant. J Herb Med [Internet]. 2017;8:31–9. Available from: http://dx.doi.org/10.1016/j.hermed.2016.11.003

XII. Nie X, Tang W, Zhang Z, Yang C, Qian L, Xie X, et al. Procyanidin B2 mitigates endothelial endoplasmic reticulum stress through a PPARδ-Dependent mechanism. Redox Biol. 2020;37:101728.