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Regards,



Khrishna Murti, PhD

Head of Language Institute-HM Publisher

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Submitted to the journal “Bioscientia Medicina: Journal of Biomedicine and Translational Research (October 24th, 2022)

Efficacy of Exosome Adipose-Derived Stem Cells (ASCs-Exosome) Against Skin Flaps Transplantation In Plastic Surgery: A Systematic Literature Review

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Abstract

Background. Exosome is a small subset of extracellular vesicles with a size of about 50 nm – 200 nm, which are commonly found in various body fluids. Exosomes are rich in various proteins, and are cargoes that carry out the process of transportation and transportation between cells in the framework of cell communication. This is a new therapeutic modality that has the potential to trigger modulation and activity of the target cell, so ASCs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery.

Methods. The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries and Google Scholar), related to the use of ASCs-exosomes in skin flap transplantation repair in plastic surgery cases.

Results. A total of 5 studies were included in this systematic review. In general, the administration of ASCs-exosomes is more effective in the percentage of flap survival areas than placebo groups. There are 3 studies that state that the effectiveness of survival flap area is more than 70 percent compared to the placebo group which is only around 30-40 percent.

Conclusion. ASCs-exosomes have the potential to be developed in improving the survival rate of skin flap transplantation in plastic surgery cases.

Keywords: Adipose-derived stem cells; Exosome; Flap transplantation; Plastic surgery

1.Introduction

Fatty tissue is the main energy depot in the body. In recent years, adipose tissue has been studied to be developed as a control metabolism, homeostasis, immunity and regulation of satiety

in the body. Fatty tissue is generally divided into fat-storing adipose and adipose tissue stromal vascular fraction (SVF).¹⁻³ SVF is a collection of various immune cells, endothelial cells, and adipose-derived stem cells (ASCs), which are isolated through a series of enzymatic digestion processes. ASCs are very easy to develop and are precursors to be developed into various multipotent progenitor cells, such as osteoblasts, chondrocytes, myocytes, epithelial cells and neuronal cells.⁴⁻⁶ In addition, ASCs have various advantages over bone marrow stem cells, namely more accessible and minimally invasive, high proliferation, as well as the secretion of various growth factors, cytokines and extracellular vesicles.^{7,8}

Exosomes are a small subset of extracellular vesicles with a size of about 50-200 nm, which are commonly found in various body fluids. Exosomes are rich in various proteins, such as cytoskeletal proteins, transmembrane proteins and heat shock proteins. Exosomes are also rich in nucleic acids (DNA, mRNA, miRNA, long and short non-coding RNA), lipids and enzymes (GADPH, ATPase and PGK1).⁹ The advantage of ASCs-exosomes over ASCs, is in the ability of ASCs-exosomes in the protection of transportation activities so as to facilitate the application of ASCs-exosomes on the target network. Unlike ASCs, which do not have transportation activity protection facilities, ASCs will be difficult to apply to network targets.¹⁰⁻¹² Exosomes are cargoes that carry out the process of transporting and transporting between cells in the framework of cell communication. This is a new therapeutic modality that has the potential to trigger modulation and activity of the target cell, so ASCs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. Currently, there is still very little evidence-based data related to the use of ASCs-exosomes in optimizing skin flap transplantation repair in plastic surgery cases. The study aims to

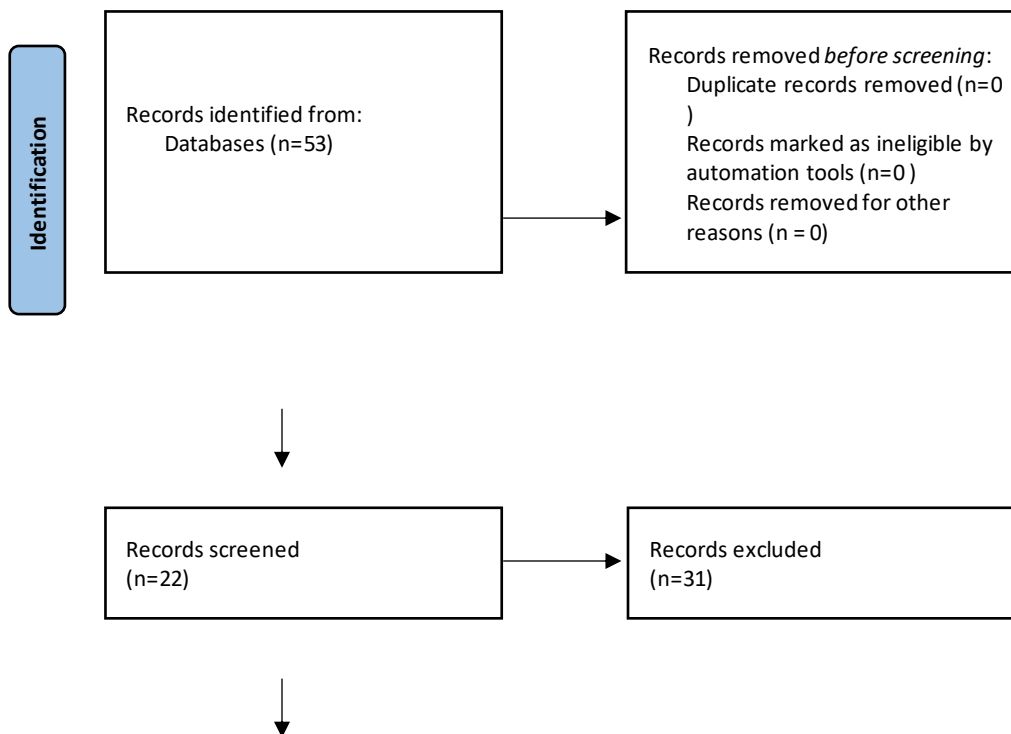
2.Methods

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries and Google Scholar), related to the use of ASCs-exosomes in skin flap transplantation repair in plastic surgery cases. The search was conducted using the terms: (1) "mesenchymal stem cells" OR "progenitor cells" OR "adipose-derived stem cells" OR "exosome adipose-derived stem cells" AND (2) "skin flaps" OR "skin flaps". The literature is limited to preclinical studies and published in English. The literature selection criteria are articles published in the form of original articles, skin flaps experimental models, control

groups only get liquid without therapeutic effect or no treatment, studies are carried out in the vulnerable period from 2012-2022 and the main outcome is the survival rate of skin flaps. Meanwhile, the exclusion criteria are animal models that are not related to skin flaps, ascs-exosome applications with other treatments, the absence of control groups and duplication of publications. This study follows the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

3.Results

A total of 5 studies were included in this systematic review. There were 53 potential studies at the beginning of the literature search process. A total of 22 studies passed for further screening and as many as 31 studies did not pass because the studies were conducted outside the vulnerable period 2012-2022. A total of 20 studies passed for the next stage and only 2 studies were issued because they were case reports. Of the 20 studies that passed the next stage, 15 were excluded because full-text was not biased to be accessed as many as 8 studies, publications not in English as many as 2 studies and as many as 5 studies did not have a control group (Figure 1).



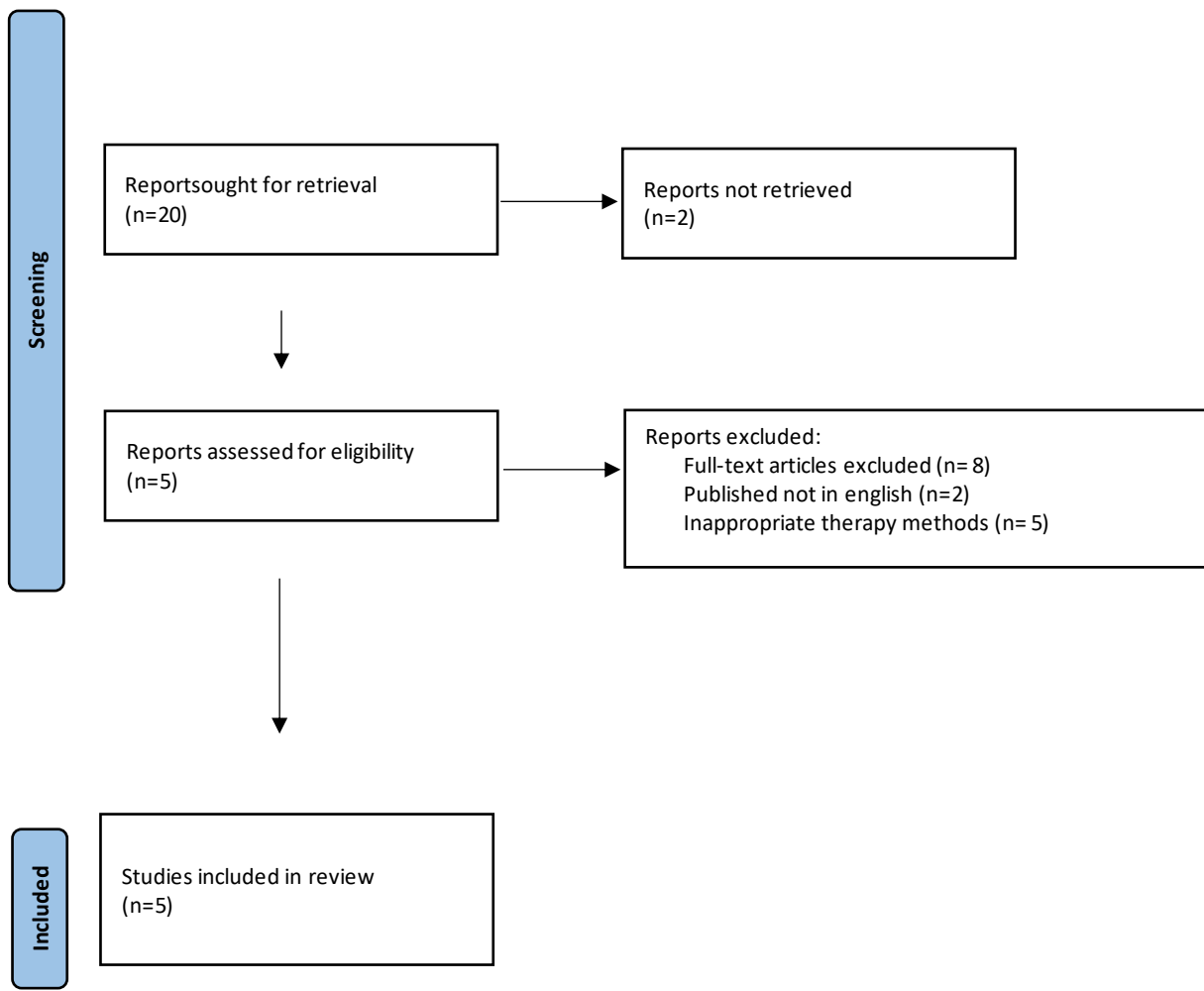


Figure 1. Flow diagram selection of studies

Table 1 shows the characteristics of the studies included in this systematic review. The majority of studies used a random type of skin flap and only one used an axial type. The area of skin flaps varied from 3-60 cm² in the study. Sebnayak 3 studies used xenogenic type transplants and 2 studies used allogenic transplant type. The control group almost all got PBS.

Table 1. Study Characteristics

Study	Type of skin flap	Skin flaps (cm ²)	Cell Type	Transplant type	Method of administration	Placebo	Outcome Flap Survival Area (%) VS Placebo
Feng et al. ¹³	Random	9	ASCs-exosomes	Xenogenic	Intra-arterial	Pbs	78.5±2.3 VS 46.9±3.3
Gao et al. ¹⁴	Random	3	ASCs-exosomes	Xenogenic	Subcutaneous Injection	Pbs	83.2±2.5 VS 45.7±3.1
Han et al. ¹⁵	Random	14	ASCs-exosomes	Allogenic	Subcutaneous Injection	Pbs	51.6±2.6 VS 31.2±2.9
Pak et al. ¹⁶	Random	12	ASCs-exosomes	Xenogenic	Subcutaneous Injection	Pbs	67.8±2.4 VS 39.6±2.8
Reichenberger et al. ¹⁷	Axial	60	ASCs-exosomes	Allogenic	Intravenous Injection	Pbs	73.9±3.3 VS 33.3±2.7

Table 1 shows that in general the administration of ASCs-exosomes is more effective in the percentage of flaps survival area than placebo groups. There are 3 studies that state that the effectiveness of survival flap area is more than 70 percent compared to the placebo group which is only around 30-40 percent.

4. Discussion

Flap transplantation is a fairly reliable repair modality in cases of trauma and organ reconstruction. The optimization of the flap transplantation process depends largely on the process of neovascularization and ischemia-reperfusion.¹⁸ The better the neovascularization and the better

the ischemia-reperfusion, the better the flap transplantation process will be. ASCs-exosomes have great potential to prevent ischemia-reperfusion injury for the optimization of flap transplantation. Exosome ASCs are able to optimize the process of angiogenesis to increase the viability of chondrocutaneous composite grafts for defect applications in the nose, auricles and skin. ^{7.20pm}

Various studies above show that ASCs-exosomes are able to optimally improve the survival status of skin flaps. ASCs-exosomes are able to increase the expression of miRNA-760 and decrease the expression of miRNA-423-3p, which will cause regulation of THE expression of ITGA5 and HDAC5, which leads to the initiation of vascularization in the skin flap. ²¹ Other studies have shown that ASCs-exosomes are rich in cytokine IL-6, where IL-6 is essential in the process of angiogenesis and flap repair. In addition, cytokine IL-6 has an anti-viral effect capable of providing infection protection for patients. ²² Other studies have shown that ASCs-exosomes induced with low dose hydrogen peroxide are able to repair neovascularization and are able to suppress inflammatory processes and tissue damage after ischemia-reperfusion injury. ^{23th}

5. Conclusion

ASCs-exosomes have the potential to be developed in improving the survival rate of skin flap transplantation in plastic surgery cases.

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Submission acknowledgement

Dear author(s),

Rachmat Hidayat*, Patricia Wulandari has submitted the manuscript "Efficacy of Exosome Adipose-Derived Stem Cells (ACSs-Exosome) on Skin Flaps Transplantation in Plastic Surgery: A Systematic Literature Review" to Bioscientia Medicina: Journal of Biomedicine and Translational Research. The paper will be screened by editor and reviewed by peer review.

Cordially,



Prof. Paula Magnano, PhD

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Peer Review Results

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HM Publisher

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Reviewer 1: Revision required

Efficacy of Exosome Adipose-Derived Stem Cells (ASCs-Exosome) Against Skin Flaps

Transplantation In Plastic Surgery: A Systematic Literature Review →1

Rachmat Hidayat^{1*}, Patricia Wulandari²

¹Department of Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

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#email: dr.rachmat.hidayat@gmail.com

Abstract →3

Background. Exosome is a small subset of extracellular vesicles with a size of about 50 nm – 200 nm, which are commonly found in various body fluids. Exosomes are rich in various proteins, and are cargoes that carry out the process of transportation and transportation between cells in the framework of cell communication. This is a new therapeutic modality that has the potential to trigger modulation and activity of the target cell, so ASCs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery.

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Keywords: Adipose-derived stem cells; Exosome; Flap transplantation; Plastic surgery →2

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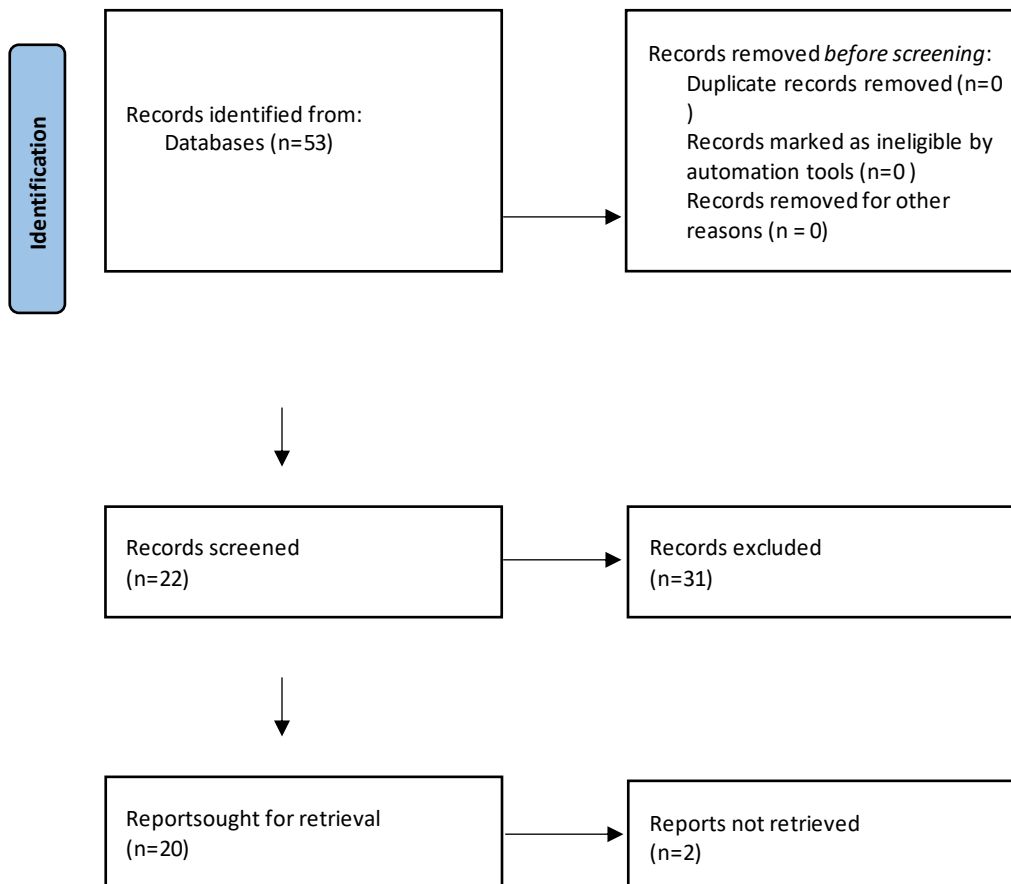
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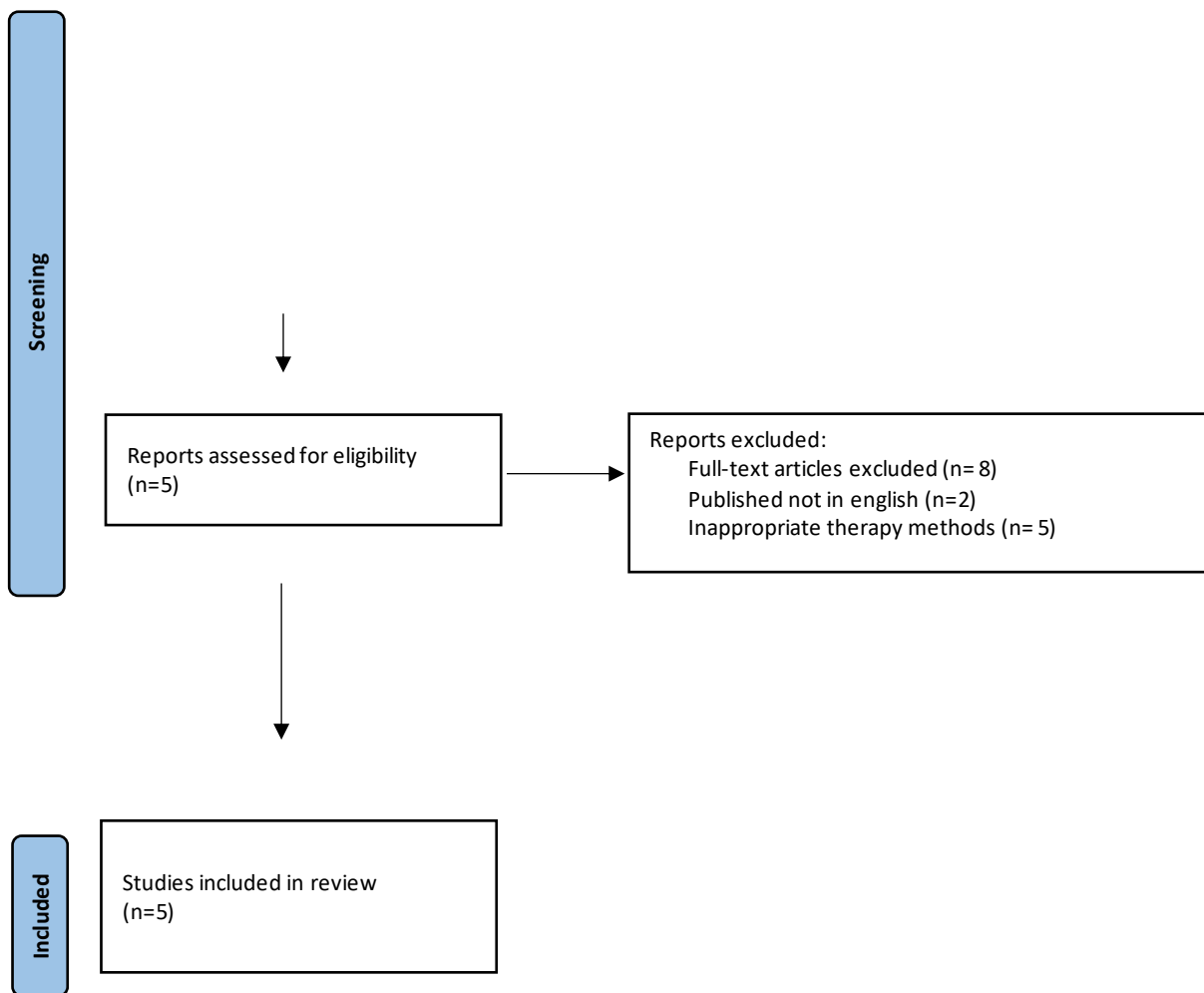


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6. References →9

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Reviewer Comment:

- 1→ Title of Manuscripts should be explained independent variable and dependent variable also subject of study.
- 2→ Keywords should be showed the main words of the study, the authors can use MeSH to develop keywords.
- 3→ Abstract should be showed the main of background, methods, results and conclusion of study.
 - Background abstract should be showed the urgency of study and why the study important,

in simple way.

- Conclusion should be wrote in simple way, specific to the main results. Conclusion in abstract should not showed statistic results.

4→ Introduction should be showed the urgency of study (epidemiology data), biological plausibility concept, and lack of knowledge in the study.

- Paragraph 1→ need improvement in urgency of study and explain more about epidemiology data. Authors do not only show the data, but try to elaborate and make comparison about the data from year to year.
- Paragraph 2 and 3 need improvement to focus in biological plausibility concept.

5→ Methods should be showed more about how the study develop. Methods should be showed the design of study; population, sample and sample size of study; inclusion criteria; place of study; ethical clearance steatment; independent and dependent variable; data analysis.

- Methods need to showed the design of study; population, sample and sample size of study; inclusion criteria; place of study; ethical clearance steatment; independent and dependent variable; data analysis, more specific but not to long.

6→ Results should be showed baseline characteristics subject of study, main results of study. Authors must be focused and try to make results no more table and figure.

7→ Discussion should be explored more biological plausibility, not only showed about statistical results.

8→ Conclusion should more specific and not more showed statistical results

9→ Authors must check the references for make update references. References should no more than 10 years.

Reviewer 2: Revision required

Efficacy of Exosome Adipose-Derived Stem Cells (ASCs-Exosome) Against Skin Flaps Transplantation In Plastic Surgery: A Systematic Literature Review

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Abstract→1

Background. Exosome is a small subset of extracellular vesicles with a size of about 50 nm – 200 nm, which are commonly found in various body fluids. Exosomes are rich in various proteins, and are cargoes that carry out the process of transportation and transportation between cells in the framework of cell communication. This is a new therapeutic modality that has the potential to trigger modulation and activity of the target cell, so ASCs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery.

Methods. The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries and Google Scholar), related to the use of ASCs-exosomes in skin flap transplantation repair in plastic surgery cases.

Results. A total of 5 studies were included in this systematic review. In general, the administration of ASCs-exosomes is more effective in the percentage of flap survival areas than placebo groups. There are 3 studies that state that the effectiveness of survival flap area is more than 70 percent compared to the placebo group which is only around 30-40 percent.

Conclusion. ASCs-exosomes have the potential to be developed in improving the survival rate of skin flap transplantation in plastic surgery cases.

Keywords: Adipose-derived stem cells; Exosome; Flap transplantation; Plastic surgery

1.Introduction→2

Fatty tissue is the main energy depot in the body. In recent years, adipose tissue has been studied to be developed as a control metabolism, homeostasis, immunity and regulation of satiety in the body. Fatty tissue is generally divided into fat-storing adipose and adipose tissue stromal

vascular fraction (SVF).¹⁻³ SVF is a collection of various immune cells, endothelial cells, and adipose-derived stem cells (ASCs), which are isolated through a series of enzymatic digestion processes. ASCs are very easy to develop and are precursors to be developed into various multipotent progenitor cells, such as osteoblasts, chondrocytes, myocytes, epithelial cells and neuronal cells.⁴⁻⁶ In addition, ASCs have various advantages over bone marrow stem cells, namely more accessible and minimally invasive, high proliferation, as well as the secretion of various growth factors, cytokines and extracellular vesicles.^{7,8}

Exosomes are a small subset of extracellular vesicles with a size of about 50-200 nm, which are commonly found in various body fluids. Exosomes are rich in various proteins, such as cytoskeletal proteins, transmembrane proteins and heat shock proteins. Exosomes are also rich in nucleic acids (DNA, mRNA, miRNA, long and short non-coding RNA), lipids and enzymes (GADPH, ATPase and PGK1).⁹ The advantage of ASCs-exosomes over ASCs, is in the ability of ASCs-exosomes in the protection of transportation activities so as to facilitate the application of ASCs-exosomes on the target network. Unlike ASCs, which do not have transportation activity protection facilities, ASCs will be difficult to apply to network targets.¹⁰⁻¹² Exosomes are cargoes that carry out the process of transporting and transporting between cells in the framework of cell communication. This is a new therapeutic modality that has the potential to trigger modulation and activity of the target cell, so ASCs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. Currently, there is still very little evidence-based data related to the use of ASCs-exosomes in optimizing skin flap transplantation repair in plastic surgery cases. The study aims to

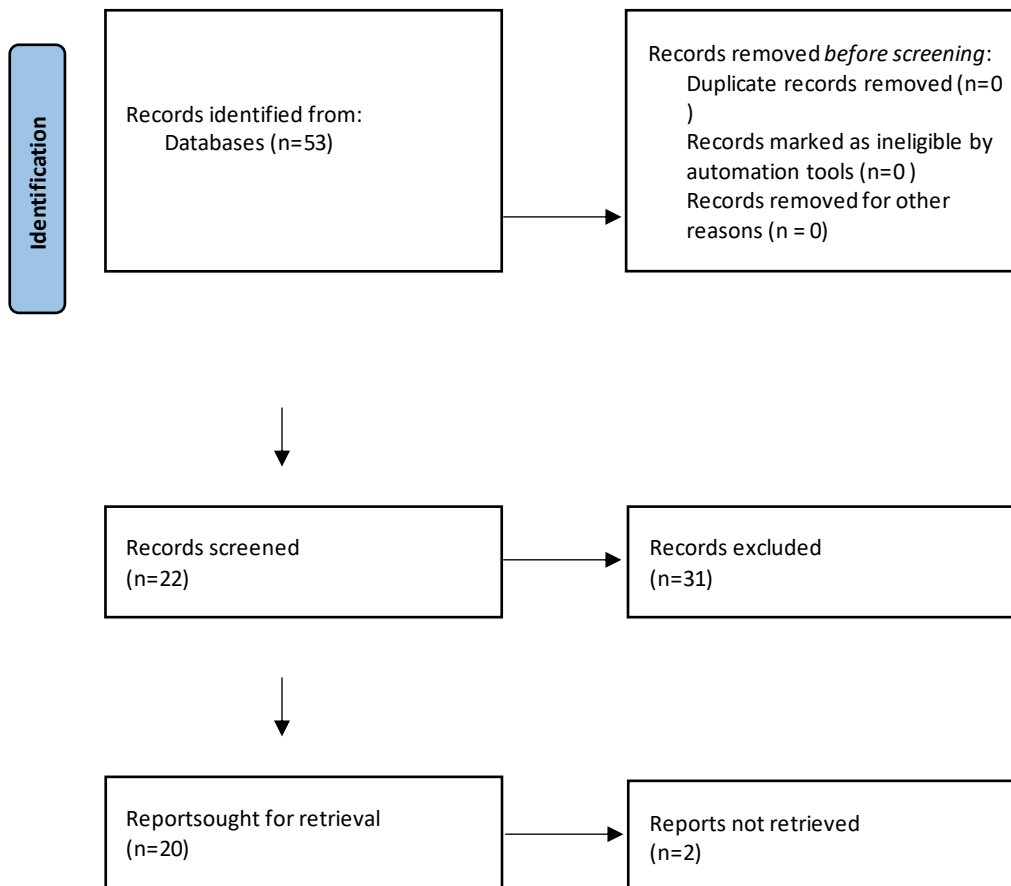
2.Methods →3

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries and Google Scholar), related to the use of ASCs-exosomes in skin flap transplantation repair in plastic surgery cases. The search was conducted using the terms: (1) "mesenchymal stem cells" OR "progenitor cells" OR "adipose-derived stem cells" OR "exosome adipose-derived stem cells" AND (2) "skin flaps" OR "skin flaps". The literature is limited to preclinical studies and published in English. The literature selection criteria are articles published in the form of original articles, skin flaps experimental models, control groups only get liquid without therapeutic effect or no treatment, studies are carried out in the

vulnerable period from 2012-2022 and the main outcome is the survival rate of skin flaps. Meanwhile, the exclusion criteria are animal models that are not related to skin flaps, ascs-exosome applications with other treatments, the absence of control groups and duplication of publications. This study follows the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

3.Results →4

A total of 5 studies were included in this systematic review. There were 53 potential studies at the beginning of the literature search process. A total of 22 studies passed for further screening and as many as 31 studies did not pass because the studies were conducted outside the vulnerable period 2012-2022. A total of 20 studies passed for the next stage and only 2 studies were issued because they were case reports. Of the 20 studies that passed the next stage, 15 were excluded because full-text was not biased to be accessed as many as 8 studies, publications not in English as many as 2 studies and as many as 5 studies did not have a control group (Figure 1).



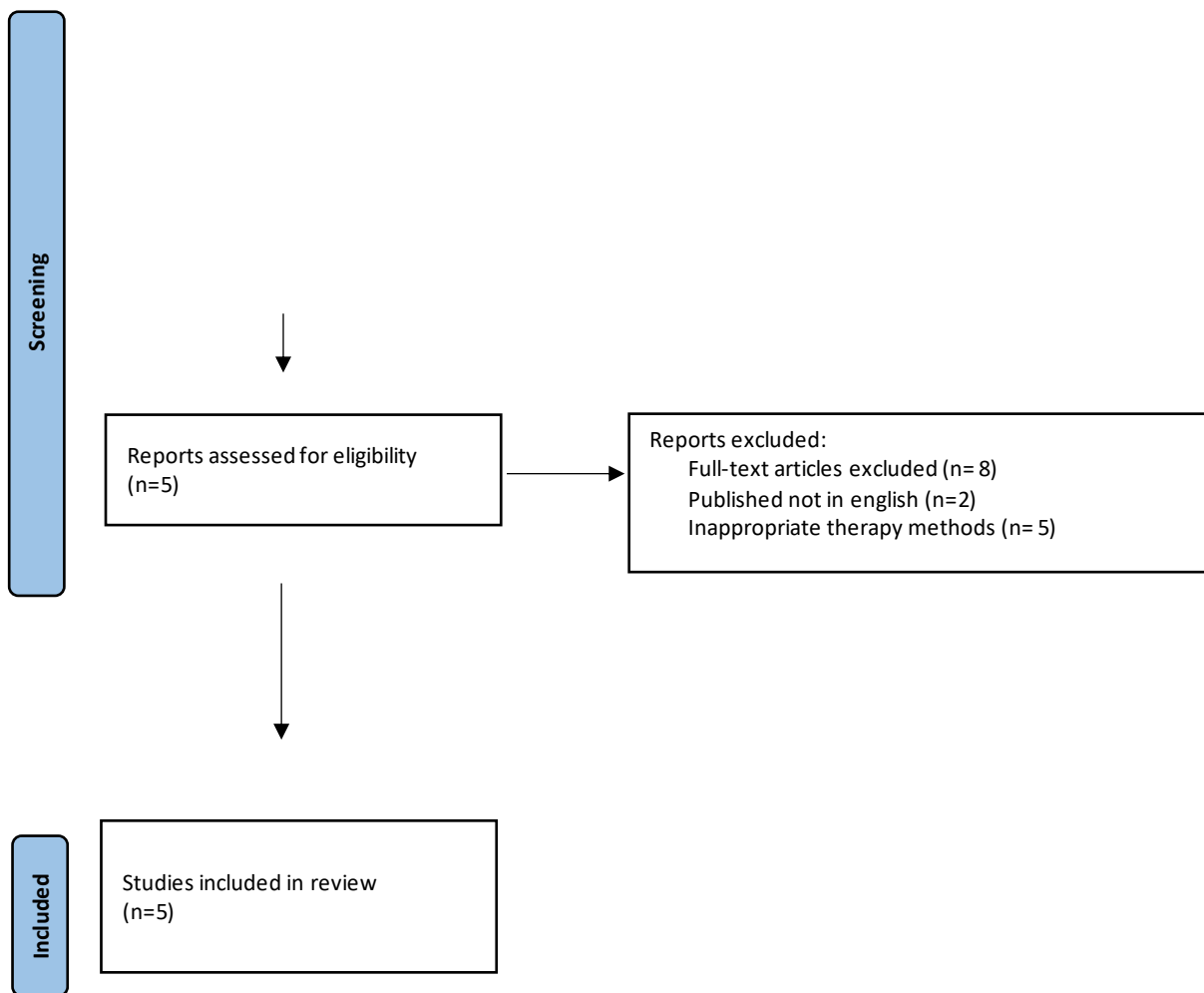


Figure 1. Flow diagram selection of studies

Table 1 shows the characteristics of the studies included in this systematic review. The majority of studies used a random type of skin flap and only one used an axial type. The area of skin flaps varied from 3-60 cm² in the study. Sebnayak 3 studies used xenogenic type transplants and 2 studies used allogenic transplant type. The control group almost all got PBS.

Table 1. Study Characteristics

Study	Type of skin flap	Skin flaps (cm ²)	Cell Type	Transplant type	Method of administration	Placebo	Outcome Flap Survival Area (%) VS Placebo
Feng et al. ¹³	Random	9	ASCs-exosomes	Xenogenic	Intra-arterial	Pbs	78.5±2.3 VS 46.9±3.3
Gao et al. ¹⁴	Random	3	ASCs-exosomes	Xenogenic	Subcutaneous Injection	Pbs	83.2±2.5 VS 45.7±3.1
Han et al. ¹⁵	Random	14	ASCs-exosomes	Allogenic	Subcutaneous Injection	Pbs	51.6±2.6 VS 31.2±2.9
Pak et al. ¹⁶	Random	12	ASCs-exosomes	Xenogenic	Subcutaneous Injection	Pbs	67.8±2.4 VS 39.6±2.8
Reichenberger et al. ¹⁷	Axial	60	ASCs-exosomes	Allogenic	Intravenous Injection	Pbs	73.9±3.3 VS 33.3±2.7

Table 1 shows that in general the administration of ASCs-exosomes is more effective in the percentage of flaps survival area than placebo groups. There are 3 studies that state that the effectiveness of survival flap area is more than 70 percent compared to the placebo group which is only around 30-40 percent.

4.Discussion →5

Flap transplantation is a fairly reliable repair modality in cases of trauma and organ reconstruction. The optimization of the flap transplantation process depends largely on the process of neovascularization and ischemia-reperfusion. ¹⁸ The better the neovascularization and the better

the ischemia-reperfusion, the better the flap transplantation process will be. ASCs-exosomes have great potential to prevent ischemia-reperfusion injury for the optimization of flap transplantation. Exosome ASCs are able to optimize the process of angiogenesis to increase the viability of chondrocutaneous composite grafts for defect applications in the nose, auricles and skin. ^{7.20pm}

Various studies above show that ASCs-exosomes are able to optimally improve the survival status of skin flaps. ASCs-exosomes are able to increase the expression of miRNA-760 and decrease the expression of miRNA-423-3p, which will cause regulation of THE expression of ITGA5 and HDAC5, which leads to the initiation of vascularization in the skin flap. ²¹ Other studies have shown that ASCs-exosomes are rich in cytokine IL-6, where IL-6 is essential in the process of angiogenesis and flap repair. In addition, cytokine IL-6 has an anti-viral effect capable of providing infection protection for patients. ²² Other studies have shown that ASCs-exosomes induced with low dose hydrogen peroxide are able to repair neovascularization and are able to suppress inflammatory processes and tissue damage after ischemia-reperfusion injury. ^{23th}

5. Conclusion →6

ASCs-exosomes have the potential to be developed in improving the survival rate of skin flap transplantation in plastic surgery cases.

6. References →7

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Reviewer Comment:

1 → Abstract should be showed the main of background, methods, results and conclusion of study.

- Background abstract should be showed the urgency of study and why the study important, in simple way.
- Conclusion should be wrote in simple way, specific to the main results. Conclusion in abstract should not showed statistic results.
- Keywords should be showed the main words of the study, the authors can use MeSH to develop keywords.

2→ Introduction should be showed the urgency of research which supported by epidemiology data, biological interaction concept, lack of knowledge in the research and also objective of research.

3→ Authors should be wrote methods about how the study develop. Methods should be showed the design of study; population, sample and sample size of study; inclusion criteria; place of study; ethical clearence steatment; independent and dependent variable; data analysis.

4→ Authors should be wrote results with baseline characteristics subject of study, main results of study. Authors must be focused and try to make results with no more table and figure.

5→ Discussion should be explored more biological plausibility, not only showed about statistical results.

6→ Conclusion should more specific and not more showed statistical results

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ARTICLE INFO

Keywords:

Adipose-derived stem cells
Exosomes
Flap transplantation
Plastic surgery

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ABSTRACT

Background: Exosomes are a small subset of extracellular vesicles with a size of about 50 nm – 200 nm, which are found in many body fluids. The exosome is rich in various proteins and is a cargo that carries out the process of transporting and transporting between cells in the context of cell communication. This becomes a potential new therapeutic modality in triggering the modulation and activity of target cells so that ACSs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. **Methods:** The literature search process was carried out in various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the use of ASCs-exosome in skin flap transplantation repair in plastic surgery cases. **Results:** A total of 5 studies were included in this systematic review. In general, ASCs-exosome administration was more effective in the percentage of flap survival area than in the placebo group. There are 3 studies that state that the effectiveness of flap area survival is more than 70 percent compared to the placebo group, which is only in the range of 30-40 percent. **Conclusion:** ASCs-exosome has the potential to be developed to improve the survival rate of skin flap transplantation in the case of plastic surgery.

1. Introduction

Fat tissue is the main energy depot in the body. In recent years, adipose tissue has been studied to be developed as a control of metabolism, homeostasis, immunity, and regulation of satiety in the body. Fat tissue is generally divided into fat-storing adipose and adipose tissue stromal vascular fraction (SVF).¹⁻³ SVF is a collection of various immune cells, endothelial cells, and adipose-derived stem cells (ASCs), which were isolated through a series of enzymatic digestion processes. ASCs are very easy to develop and are precursors to being developed into various multipotent progenitor cells, such as osteoblasts, chondrocytes, myocytes, epithelial cells, and neuronal cells.⁴⁻⁶ In addition, ACSs have various advantages over bone

marrow stem cells, namely more accessible and minimally invasive, high proliferation, and secretion of various growth factors, cytokines, and extracellular vesicles.^{7,8}

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the application of ASCs-exosome on target tissues. In contrast to ASCs, which do not have transportation activity protection facilities, ASCs will be difficult to apply to the target network.¹⁰⁻¹² Exosome is a cargo that carries out the process of transporting and transporting between cells in the context of cell communication. This becomes a potential new therapeutic modality in triggering the modulation and activity of target cells so that ACSs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. Currently, there is very little evidence-based data regarding the use of ACSs-exosome in optimizing skin flap transplantation repair in plastic surgery cases.

2. Methods

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the use of ASCs-exosome in skin flap transplantation repair in plastic surgery cases. The search was performed using the terms: (1) "mesenchymal stem cell" OR "progenitor cells" OR "adipose-derived stem cells" OR "exosome adipose-derived stem cells" AND (2) "skin flap" OR "skin flaps." The literature is limited to preclinical studies and published in English. The literature selection criteria

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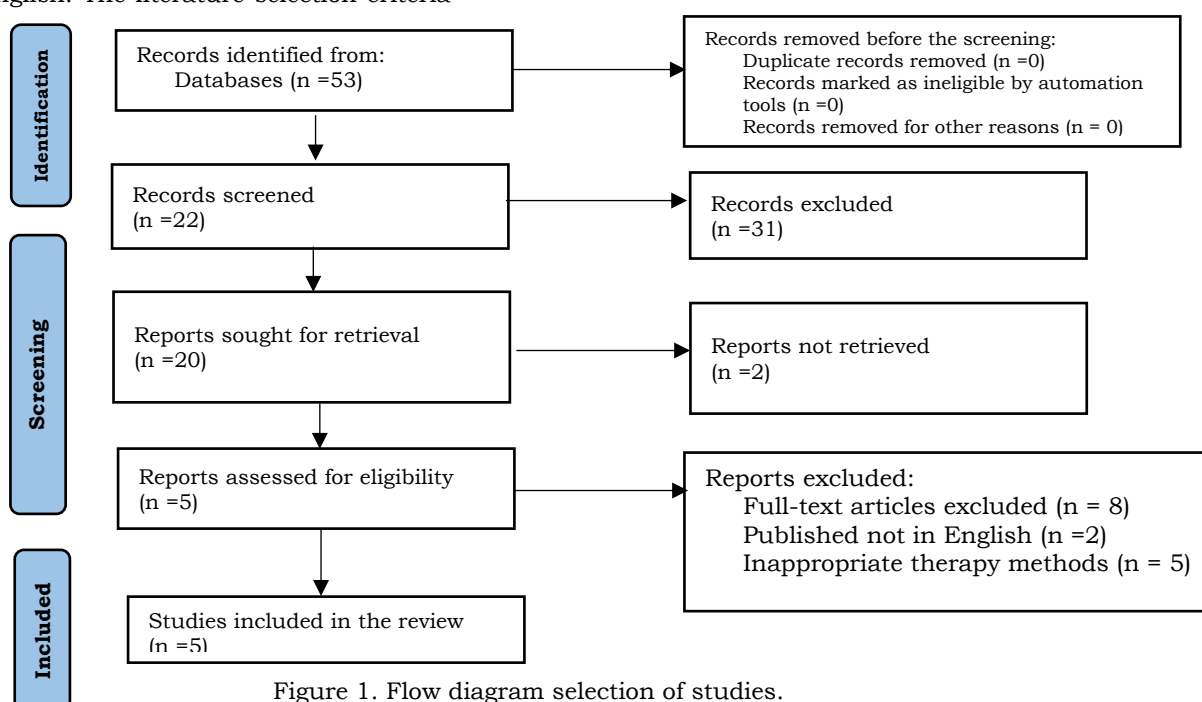


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4. Discussion

Flap transplantation is a reliable repair modality in cases of trauma and organ reconstruction. Optimization of the flap transplantation process is highly dependent on the process of neovascularization and ischemia-reperfusion.¹⁸ The better the neovascularization and the better ischemia-reperfusion, the better the flap transplantation process. ASCs-exosome has great potential to prevent ischemia-reperfusion injury in order to optimize flap transplantation. ASCs exosome is able to optimize the angiogenesis process to increase the viability of

chondrocutaneous composite grafts for the application of defects in the nose, earlobe, and skin.^{19,20}

Various studies above show that ASCs-exosome is able to optimally improve the survival status of skin flaps. ASCs-exosome was able to increase the expression of miRNA-760 and decrease the expression of miRNA-423-3p, which would lead to the regulation of the expression of ITGA5 and HDAC5, which led to the initiation of vascularization in skin flaps.²¹ Another study showed that the ASCs-exosome is rich in the cytokine IL-6, where IL-6 is very important in the process of angiogenesis and flap repair. In addition, the cytokine IL-6 has an anti-viral effect that can provide infection protection for patients.²² Another study showed that ASCs-exosome induced with low dose hydrogen peroxide was able to improve neovascularization and was able to suppress the inflammatory process and tissue damage after ischemia-reperfusion injury.²³

5. Conclusion

ASCs-exosome has the potential to be developed to improve the survival rate of skin flap transplantation in the case of plastic surgery.

6. References

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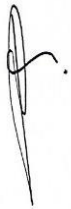
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Letter of Acceptance

Manuscript “Efficacy of Exosome Adipose-Derived Stem Cells (ACSs-Exosome) on Skin Flaps Transplantation in Plastic Surgery: A Systematic Literature Review“ by Rachmat Hidayat*, Patricia Wulandari, has been accepted to publish in Bioscientia Medicina: Journal of Biomedicine and Translational Research (Bioscmed) Vol 6 issue 11 in November 2022.

Cordially,



Prof. Paula Magnano, PhD

Editor



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ABSTRACT

Background: Exosomes are a small subset of extracellular vesicles with a size of about 50 nm – 200 nm, which are found in many body fluids. The exosome is rich in various proteins and is a cargo that carries out the process of transporting and transporting between cells in the context of cell communication. This becomes a potential new therapeutic modality in triggering the modulation and activity of target cells so that ACSs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. **Methods:** The literature search process was carried out in various databases (PubMed, Web of Sciences, EMBASE, Cochran Libraries, and Google Scholar) regarding the use of ASCs-exosome in skin flap transplantation repair in plastic surgery cases. **Results:** A total of 5 studies were included in this systematic review. In general, ASCs-exosome administration was more effective in the percentage of flap survival area than in the placebo group. There are 3 studies that state that the effectiveness of flap area survival is more than 70 percent compared to the placebo group, which is only in the range of 30-40 percent. **Conclusion:** ASCs-exosome has the potential to be developed to improve the survival rate of skin flap transplantation in the case of plastic surgery.

1. Introduction

Fat tissue is the main energy depot in the body. In recent years, adipose tissue has been studied to be developed as a control of metabolism, homeostasis, immunity, and regulation of satiety in the body. Fat tissue is generally divided into fat-storing adipose and adipose tissue stromal vascular fraction (SVF).¹⁻³ SVF is a collection of various immune cells, endothelial cells, and adipose-derived stem cells (ASCs), which were isolated through a series of enzymatic digestion processes. ASCs are very easy to develop and are precursors to being developed into various multipotent progenitor cells, such as osteoblasts, chondrocytes, myocytes, epithelial cells, and neuronal cells.⁴⁻⁶ In addition, ACSs have various advantages over bone

marrow stem cells, namely more accessible and minimally invasive, high proliferation, and secretion of various growth factors, cytokines, and extracellular vesicles.^{7,8}

Exosomes are a small subset of extracellular vesicles with a size of about 50-200 m, which are found in many body fluids. The exosome is rich in various proteins, such as cytoskeletal protein, a transmembrane protein, and heat shock protein. Exosomes are also rich in nucleic acids (DNA, mRNA, miRNA, long and short non-coding RNA), lipids, and enzymes (GADPH, ATPase, and PGK1).⁹ ACSs-exosome compared to ASCs is in the ability of ASCs-exosome to protect transport activity so as to facilitate

the application of ASCs-exosome on target tissues. In contrast to ASCs, which do not have transportation activity protection facilities, ASCs will be difficult to apply to the target network.¹⁰⁻¹² Exosome is a cargo that carries out the process of transporting and transporting between cells in the context of cell communication. This becomes a potential new therapeutic modality in triggering the modulation and activity of target cells so that ACSs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. Currently, there is very little evidence-based data regarding the use of ACSs-exosome in optimizing skin flap transplantation repair in plastic surgery cases.

2. Methods

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the use of ASCs-exosome in skin flap transplantation repair in plastic surgery cases. The search was performed using the terms: (1) "mesenchymal stem cell" OR "progenitor cells" OR "adipose-derived stem cells" OR "exosome adipose-derived stem cells" AND (2) "skin flap" OR "skin flaps." The literature is limited to preclinical studies and published in English. The literature selection criteria

are articles published in the form of original articles, an experimental model of skin flaps, the control group only received liquid without therapeutic effect or no treatment, studies were conducted in a timeframe from 2012-2022, and the main outcome was the survival rate of skin flaps. Meanwhile, the exclusion criteria were animal models that were not related to skin flaps, the application of ASCs-exosome with other treatments, the absence of a control group, and duplication of publications. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations.

3. Results

A total of 5 studies were included in this systematic review. There were 53 potential studies at the start of the literature search process. A total of 22 studies passed for further screening, and 31 studies did not pass because the studies were conducted outside the 2012-2022 timeframe. A total of 20 studies passed for the next stage, and only 2 studies were excluded because they were case reports. Of the 20 studies that passed the next stage, 15 were excluded because 8 studies could not access full text, 2 studies were not published in English and 5 studies did not have a control group.

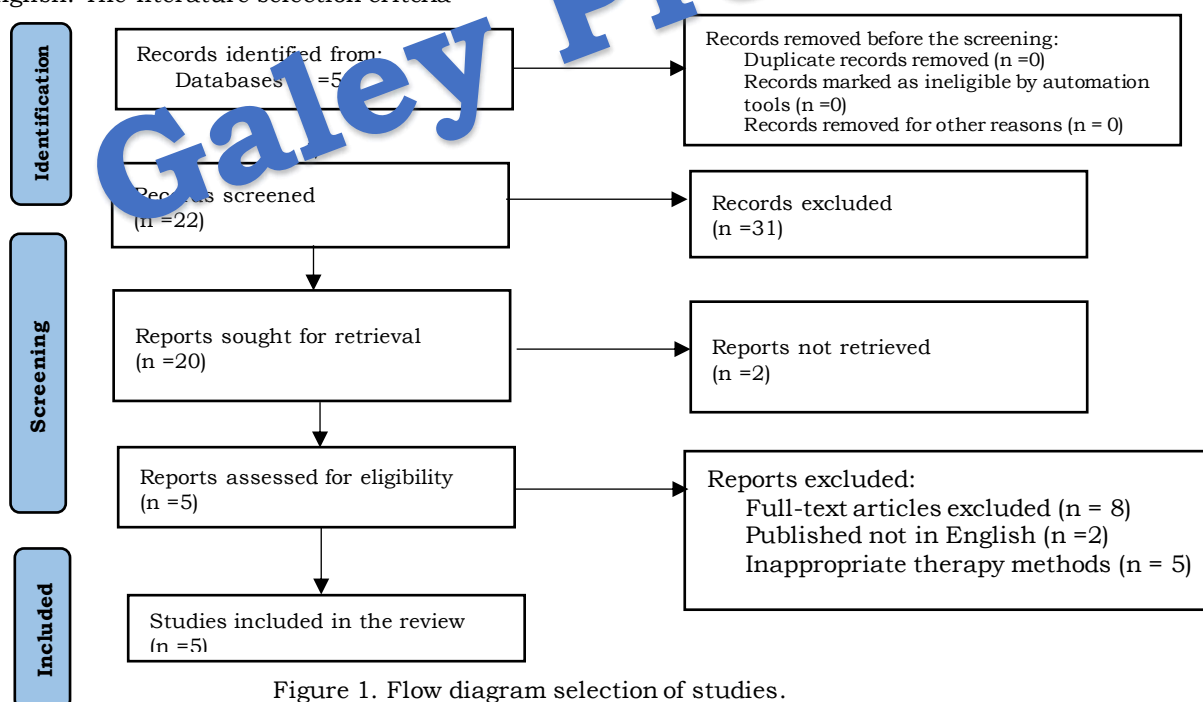


Figure 1. Flow diagram selection of studies.

Table 1 shows the characteristics of the studies included in this systematic review. The majority of studies used a random type of skin flap, and only one used the axial type. The area of the skin flaps varied

from 3-60 cm² in the study. A total of 3 studies used a xenogenic type transplant, and 2 studies used an allogenic type transplant. The control group almost all received PBS.

Table 1. Study characteristics

Study	Type of skin flap	Skin flap (cm ²)	Cell Type	Transplant type	Method of administration	Placebo	Outcome Flap Survival Area (%) VS Placebo
Feng et al. ¹³	Random	9	ASCs-exosome	Xenogenic	Intra-arterial	PBS	78.5±2.3 VS 46.9±3.3
Gao et al. ¹⁴	Random	3	ASCs-exosome	Xenogenic	Subcutaneous Injection	PBS	83.2±2.5 VS 45.7±3.1
Han et al. ¹⁵	Random	14	ASCs-exosome	Allogenic	Subcutaneous Injection	PBS	51.6±2.6 VS 31.2±2.9
Pak et al. ¹⁶	Random	12	ASCs-exosome	Xenogenic	Subcutaneous Injection	PBS	67.8±2.4 VS 39.6±2.8
Reichenberger et al. ¹⁷	Axial	60	ASCs-exosome	Allogenic	Intravenous Injection	PBS	73.9±3.3 VS 33.3±2.7

Table 1 shows that, in general, ASCs-exosome administration was more effective in the percentage of flap survival area than in the placebo group. There are 3 studies that state that the effectiveness of flap area survival is more than 70 percent compared to the placebo group, which is only in the range of 30-40 percent.

4. Discussion

Flap transplantation is a reliable repair modality in cases of trauma and organ reconstruction. Optimization of the flap transplantation process is highly dependent on the process of neovascularization and ischemia-reperfusion.¹⁸ The better the neovascularization and the better ischemia-reperfusion, the better the flap transplantation process. ASCs-exosome has great potential to prevent ischemia-reperfusion injury in order to optimize flap transplantation. ASCs exosome is able to optimize the angiogenesis process to increase the viability of

chondrocutaneous composite grafts for the application of defects in the nose, earlobe, and skin.^{19,20}

Various studies above show that ASCs-exosome is able to optimally improve the survival status of skin flaps. ASCs-exosome was able to increase the expression of miRNA-760 and decrease the expression of miRNA-423-3p, which would lead to the regulation of the expression of ITGA5 and HDAC5, which led to the initiation of vascularization in skin flaps.²¹ Another study showed that the ASCs-exosome is rich in the cytokine IL-6, where IL-6 is very important in the process of angiogenesis and flap repair. In addition, the cytokine IL-6 has an anti-viral effect that can provide infection protection for patients.²² Another study showed that ASCs-exosome induced with low dose hydrogen peroxide was able to improve neovascularization and was able to suppress the inflammatory process and tissue damage after ischemia-reperfusion injury.²³

5. Conclusion

ASCs-exosome has the potential to be developed to improve the survival rate of skin flap transplantation in the case of plastic surgery.

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Galexy Proof

CERTIFICATE

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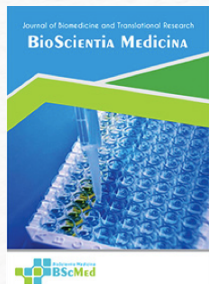
Efficacy of Exosome Adipose-Derived Stem Cells (ACSs-Exosome) on Skin Flaps Transplantation in Plastic Surgery: A Systematic Literature Review

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