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Original Article

Mesenchymal stem cell secretome therapy on inflammation: A systematic review

[Terapia con secretoma de células madre mesenquimales sobre la inflamación: Una revisión sistemática]

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Abstract

Context: With recent biochemical studies, inflammation has been considered a therapeutic target. Mesenchymal stem cells are considered a therapeutic option because of the immunomodulatory effects of their bioactive factors, the secretome.

Aims: To systematically review the potential of mesenchymal stem cell secretome therapy on inflammation through its effects on biomarker characteristics, organ damage, and survival rate.

Methods: This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A literature search was performed in PubMed, ScienceDirect, and ProQuest, and through citation searching for records published in the last ten years. The eligibility criteria of the identified study as follows: Population (P): Human, animal, or *in vitro* models with inflammatory disease; Intervention (I): Stem cell secretome administration; (C): Healthy human, animal, or *in vitro* models; and Outcome (O): Inflammatory biomarker statistics, organ injury, or survival rate. AXIS tool was used to assess the quality of the records.

Results: 3,258 records were found. The duplicates and undesired articles were excluded with automation tools. 38 relevant records were further identified through citation searching. The screening and exclusion of records based on the inclusion and exclusion criteria left 24 eligible studies. The studies show that secretome improves the biomarker characteristics by reducing proinflammatory cytokines levels while increasing anti-inflammatory cytokines levels. Many studies show that secretome also improved organ injury and survival rate.

Conclusions: Secretome alleviates inflammation with its immunomodulatory effects, which may be associated with improvements in organ injury and overall outcome.

Keywords: disease; inflammation; mesenchymal stem cells; secretome; therapeutics.

Resumen

Contexto: Con los recientes estudios bioquímicos, la inflamación se ha considerado una diana terapéutica. Las células madre mesenquimales se consideran una opción terapéutica debido a los efectos inmunomoduladores de sus factores bioactivos, el secretoma.

Objetivos: Revisar sistemáticamente el potencial de la terapia con secretoma de células madre mesenquimales sobre la inflamación a través de sus efectos sobre las características de los biomarcadores, el daño orgánico y la tasa de supervivencia.

Métodos: Este estudio se realizó de acuerdo con la declaración Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Se realizó una búsqueda bibliográfica en PubMed, ScienceDirect y ProQuest, y mediante la búsqueda de citas de registros publicados en los últimos diez años. Los criterios de elegibilidad del estudio identificado fueron los siguientes: Población (P): Modelos humanos, animales o *in vitro* con enfermedad inflamatoria; Intervención (I): Administración de secretoma de células madre; (C): Modelos humanos sanos, animales o *in vitro*; y Resultado (O): Estadísticas de biomarcadores inflamatorios, lesión de órganos o tasa de supervivencia. Se utilizó la herramienta AXIS para evaluar la calidad de los registros.

Resultados: Se encontraron 3.258 registros. Los duplicados y los artículos no deseados se excluyeron con herramientas de automatización. Además, se identificaron 38 registros relevantes mediante la búsqueda de citas. El cribado y la exclusión de registros en función de los criterios de inclusión y exclusión dejaron 24 estudios elegibles. Los estudios muestran que el secretoma mejora las características de los biomarcadores al reducir los niveles de citocinas proinflamatorias y aumentar los niveles de citocinas anti-inflamatorias. Muchos estudios muestran que el secretoma también mejoró la lesión de órganos y la tasa de supervivencia.

Conclusiones: El secretome alivia la inflamación con sus efectos inmunomoduladores, lo que puede estar asociado con mejoras en la lesión de órganos y el resultado global.

Palabras Clave: células madre mesenquimales; enfermedad; inflamación; secretoma; terapéutica.

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INTRODUCTION

Inflammation is one of the protective adaptive responses against cell injury, microbial infection, trauma, or toxin in vascularized tissue that involves an influx of immune cells and the release of various mediators to the affected site (Ansar and Ghosh, 2016). In acute response, cellular and molecular interaction minimizes injury and contributes towards the resolution of inflammation. However, uncontrolled and untreated acute inflammation will develop into chronic inflammation and cytokine storm, leading to organ failure and even death. Chronic inflammatory disease has been known as a significant cause of death worldwide, contributing to more than 50% of deaths (Chen et al., 2017; Furman et al., 2019; Hirano, 2021; Zhou et al., 2021). With the development of biochemical studies on the potential inflammatory mediators and biomarkers, inflammation has been considered a therapeutic target (Ansar and Ghosh, 2016).

Mesenchymal stem cell (MSC) therapy has been considered an option for treating inflammatory diseases. These cells are capable of producing bioactive factors to exert immunomodulatory effects. This series of bioactive factors, secretome, has been shown to modulate the immune response in inflammatory disease by modulating the innate and adaptive immune cells. The immunomodulatory processes include the upregulation of anti-inflammatory cytokines such as IL-4 and IL-10, the downregulation of proinflammatory cytokines such as IL-1 and TNF-α, and inducing macrophages polarization to the anti-inflammatory M2 macrophages (Munoz-Perez et al., 2021; Regmi et al., 2019; Zhao et al., 2021).

Secretome consists of cytokines, growth factors, and extracellular vesicles (EVs), including microvesicles (MVs) and exosomes (Fathi-Kazerooni et al., 2022). The main advantage of secretome is its ability to yield similar effects to MSC without the risk of tumorigenicity and immunogenicity. Aside from being easier to mass-produce, the safety, effectiveness, and dose of secretome can be monitored like conventional drugs. Another benefit of secretome is the lack of concern regarding cell survival after transplantation (Daneshmandi et al., 2020; González-González et al., 2020; Vizoso et al., 2017). Secretome offers therapeutic effects such as tissue regeneration and anti-inflammatory response (Jahandideh et al., 2018).

Possessing immunomodulatory and regenerative effects, secretome is potentially more effective than anti-inflammatory agents. These biological activities help maintain immune homeostasis and increase the regeneration of damaged tissue. However, there has yet to be a systematic review detailing the effects of secretome on various inflammatory conditions, while secretome application on inflammation has been widely studied (Jayaramayya et al., 2020; Műzes and Sipos, 2022). Therefore, this systematic review aims to assess the potential of secretome therapy on inflammation through its effects on biomarker characteristics, organ damage, and survival rate.

MATERIAL AND METHODS

Literature search

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The relevance of the study is determined with the inclusion criteria formulated using Population, Intervention, Comparison and Outcomes (PICO). The PICO for this review is as follows: Population (P): Human, animal, or *in vitro* models with inflammatory disease; Intervention (I): Stem cell secretome administration; (C): Healthy human, animal, or *in vitro* models; and Outcome (O): Inflammatory biomarker statistics, organ injury, or survival rate. Case-control, cohort, clinical trials, randomized controlled trials, cross-sectional, retrospective, prospective, pilot, and observational studies were included as well. Case reports, review articles, books, comments, abstracts, correspondence, encyclopedias, editorials, and non-English articles were excluded.

A literature search was conducted in PubMed, ScienceDirect, and ProQuest with the keywords "(Stem Cell OR Mesenchymal Stem Cell OR Mesenchymal Stromal Cell) AND (Secretome OR Exosome OR Extracellular Vesicles OR Soluble Factors) AND (Inflammation OR Inflammatory Disease)" to find studies published in the last ten years (2013-2023). Record identification was also performed through citation searching. After the initial selection through screening, potentially relevant articles were retrieved for full-text analysis. Eligible articles were chosen in accordance with the inclusion and exclusion criteria of this study.

The articles were screened and reviewed by four independent reviewers (T.B., F.F., S.I., A.M.M.). The quality of the study and the risk of bias were assessed with AXIS tool (Downes et al. 2016). Any disagreements will be resolved by reevaluating the articles using the checklist and discussion with other investigators (M.I.S., N.K.J., D.M., A.P., I.B.P.). The final decision was taken based on the agreement of all reviewers.

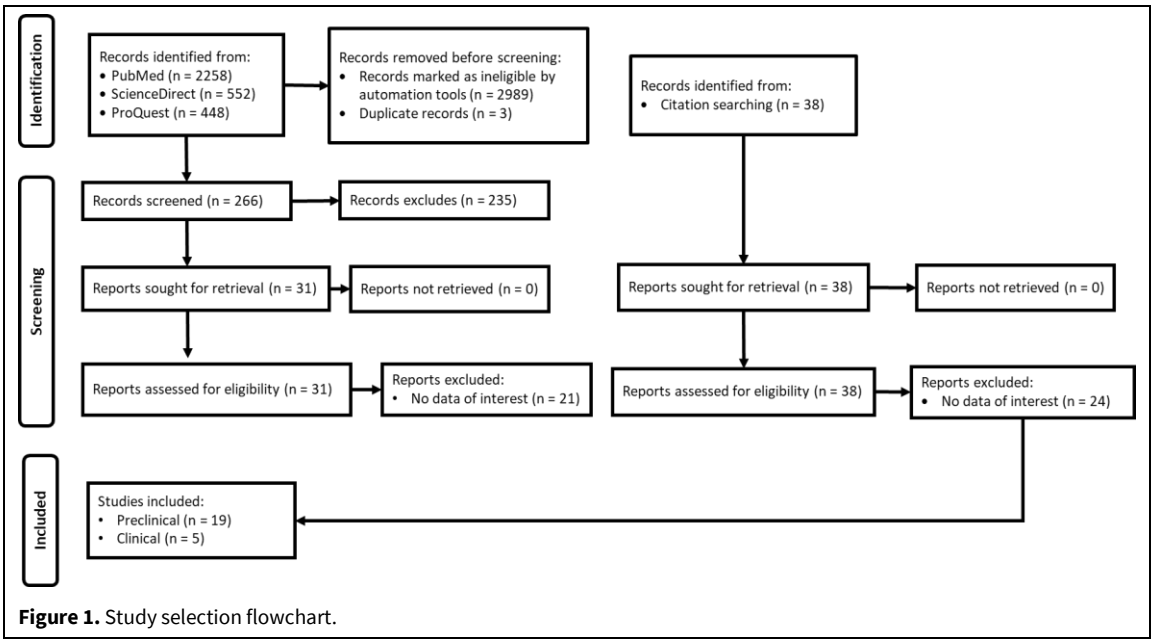

Figure 1. Study selection flowchart.

Data analysis

Articles were retrieved from the PubMed, ScienceDirect, and ProQuest databases for studies on secretome administration in inflammatory conditions. For preclinical studies, all articles were reviewed for the animal model and the inflammation induction process, the type of secretome, biomarker characteristics, organ injury, and survival. For clinical studies, the articles were reviewed for the condition, the study phase, the type of secretome, biomarker characteristics, organ injury, and survival. Articles that did not clearly indicate the exposure and outcome variables were excluded. The selected studies were compiled using Mendeley Citation Manager. The findings were presented in a table and described with a narrative synthesis approach.

RESULTS

A total of 3,258 mesenchymal stem cell secretome and inflammation records was found in PubMed, ScienceDirect, and ProQuest, with 2,989 records excluded by automation tools and 3 duplicates excluded. Next, we screened the titles and abstracts and excluded 235 records, all of which were available for full-text retrieval. Then, a full-text screening was performed on the remaining studies, and 21 records were further excluded as they had no data of interest. Record identification was also performed through citation searching, and there were 38 relevant records, all of which were available for retrieval. Then, a full-text screening was performed on the remaining studies, and 24 records were excluded as they had no data of interest. Lastly, the 24 eligible studies were analyzed, which consisted of 19 animal and *in vitro* studies and 5 human studies (Fig. 1). The quality assessment of the records is presented in Fig. 2.

Tables 1 and 2 summarize the analysis of the studies. Clinical studies on the use of secretomes in inflammation have been conducted on COVID-19, but many clinical trials are still ongoing.

DISCUSSION

Main finding

Mice are mainly used in preclinical studies of secretome effects on inflammation. Genomic studies have highlighted the genetic homology between mice and humans. These studies, together with the development of methods for creating transgenic, knockout, and knock-in mice, have resulted in powerful research tools and led to a dramatic increase in the use of mice as research models. Studies in mice have made many contributions to human biology, particularly the immune system. This research has led to the discovery of major histocompatibility complex (MHC) genes and T cell receptors, as well as the regulation of antibody synthesis and many other features of the immune system. In addition, the small size makes mice cost-effective models and facilitates large-scale studies. However, the use of mice in research is not to perfectly replicate diseases or disease mechanisms, but rather to obtain specific functional information (Perlman, 2016; Vandamme, 2014).

Many preclinical studies focused on the effect of secretome on colitis. Colitis is a form of inflammatory bowel disease (IBD), a chronic and recurrent inflammatory disease of the bowel. In colitis, NF-κB pathway is activated, causing the production of various

Reference	Q1[a]	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Average[b,c]	Remark
(An et al., 2020)	4	4	3	4	4	4	4	4	4	3	4	3	3	2	0	0	4	13.5	Moderate
(Cao et al., 2019)	3	3	3	4	4	4	4	4	4	4	4	4	4	3	0	1	4	14.25	Moderate
(Duan et al., 2020)	3	3	3	4	4	3	4	4	4	4	4	4	4	3	0	1	4	14	Moderate
(Fathi-Kazerooni et al., 2022)	4	4	4	4	4	3	4	3	4	3	3	4	4	3	0	1	4	14	Moderate
(Harrell et al., 2020)	2	4	3	4	4	4	3	4	4	4	3	4	4	3	0	0	4	13.5	Moderate
(Jahandideh et al., 2018)	4	4	2	2	3	3	4	4	4	4	4	3	4	3	0	0	4	13	Moderate
(Jaimes et al., 2017)	3	4	1	4	4	4	4	4	4	2	4	4	4	4	0	0	0	12.5	Moderate
(Kearney et al., 2022)	3	4	3	4	4	4	3	4	4	4	4	4	3	4	4	1	4	15.25	High
(Kim et al., 2020)	4	4	3	3	4	3	4	4	4	4	3	3	4	4	3	1	4	14.75	Moderate
(Lai et al., 2018)	4	3	0	4	4	4	3	4	4	4	4	4	4	3	2	1	4	14	Moderate
(Legaki et al., 2016)	3	4	3	4	4	1	4	4	4	4	4	4	4	4	2	0	4	14.25	Moderate
(Liao et al., 2016)	2	4	3	4	4	1	4	4	4	4	4	4	4	4	0	1	4	13.75	Moderate
(Liu et al., 2019)	3	4	1	3	4	2	4	4	4	4	4	4	4	4	0	1	4	13.5	Moderate
(Liu et al., 2020)	4	4	0	4	4	1	4	4	4	4	3	4	4	3	4	0	4	13.75	Moderate
(Sengupta et al., 2020)	4	4	4	4	4	4	3	4	4	3	4	3	4	4	0	0	4	14.25	Moderate
(Shi et al., 2021)	4	3	2	3	4	3	4	4	4	4	4	4	4	2	4	1	4	14.5	Moderate
(Shologu et al., 2018)	4	4	1	4	3	3	4	4	4	4	4	4	4	3	0	1	4	13.75	Moderate
(Sun et al., 2021)	4	4	1	4	4	3	4	4	4	4	4	4	4	4	0	1	4	14.25	Moderate
(Wang et al., 2016)	4	4	1	4	4	4	4	4	4	4	3	4	4	3	4	0	4	14.75	Moderate
(Yang et al., 2022)	3	4	3	3	4	4	4	4	4	3	3	4	4	4	0	1	4	14	Moderate
(Zhou et al., 2022)	4	4	1	3	4	3	4	4	4	4	4	4	4	4	2	1	4	14.5	Moderate
(Zhu et al., 2022)	4	4	2	4	4	4	4	4	4	3	3	4	4	3	2	1	4	14.5	Moderate

Q1. Were the aims/objectives of the study clear?

Q2. Was the study design appropriate for the stated aim(s)?

Q3. Was the sample size justified?

Q4. Was the target/reference population clearly defined? (Is it clear who the research was about?)

Q5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?

Q6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?

Q7. Were the risk factor and outcome variables measured appropriate to the aims of the study?

Q8. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?

Q9. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., p-values, confidence intervals)

Q10. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?

Q11. Were the basic data adequately described?

Q12. Were the results internally consistent?

Q13. Were the results presented for all the analyses described in the methods?

Q14. Were the authors' discussions and conclusions justified by the results?

Q15. Were the limitations of the study discussed?

Q16. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?

Q17. Was ethical approval or consent of participants attained?

[a] Questions 7, 13, and 14 in AXIS tool are not included in the appraisal because they do not fit the criteria for study

[b] Articles with an average score below 12.5 are marked "low", 12.5 to 15 are marked "moderate", and above 15 are marked "high"; articles categorized as "low" are excluded

[c] The average scores are calculated from means of four authors in quality appraisal

Figure 2. Quality assessment of studies

proinflammatory cytokines (Cai et al., 2021; Chen et al., 2017; Maghfiroh et al., 2021). In our systematic review, we found that secretome administration does not only reduce the levels and expression of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, but also increases the levels and expression of anti-inflammatory cytokines such as IL-10 in the serum and colonic tissue. Histopathological examination of the colon in colitis mice given secretome therapy showed improved tissue integrity and increased colon length (An et al., 2020; Cao et al., 2019; Duan et al., 2020; Legaki et al., 2016; Liao et al., 2016; Liu et al., 2019; Sun et al., 2021).

Two preclinical studies observed the effects of secretome on neuroinflammation. In neuroinflammation, the binding of toll-like receptor (TLR)-4 to lipopolysaccharide (LPS) will activate microglia, which will lead to the release of various proinflammatory cytokines, free radicals, and neurotoxic compounds (Chen et al., 2017; Kaur et al., 2020). Similar to the previously discussed studies on colitis, secretome administration also reduced levels of proinflammatory cytokines and increased levels of anti-inflammatory cytokines (Jaimes et al., 2017; Zhou et al., 2022). Histopathological examination of the brains of mice given secretome showed improvements in the

Table 1. Summary of the preclinical studies on the usage of secretome in various inflammatory diseases.

Reference	Animal model or condition	Disease	Type of secretome	Biomarker characteristics	Organ injury	Survival
(An et al., 2020)	Mouse, dextran sodium sulfate (DSS)	Colitis	Canine adipose (AD)-MSC EV preconditioned with TNF-α and IFN-γ	Decreased mRNA relative expression of TNF-α, IL-1β, IFN-γ Increased mRNA relative expression of IL-10	Improved integrity of colonic tissues	Not determined (ND)
(Cao et al., 2019)	Mouse, DSS	Colitis	Mouse bone marrow (BM)-MSC EV	Decreased serum IFN-γ and TNF-α levels Increased serum IL-10 levels Increased M2 polarization	Milder structural damage in colonic lesions	ND
(Duan et al., 2020)	Mouse, 2,4,6-trinitrobenzene sulfonic acid (TNBS)	Colitis	Human placenta MSC EV	Decreased expression level of IL-1β, TNF-α, IFN-γ, IL-6 in colon tissues Increased expression level of IL-10 and TGF-β in colon tissues Reduced oxidative stress	Increased colon length	Improved
(Harrell et al., 2020)	Mouse, cigarette smoke	Chronic airway inflammation	Human placenta MSC exosome	Decreased serum TNF-α, IL-1β, and IFN-γ levels	Significantly lower number of lung-infiltrated leucocytes Preserved alveolar and blood vessel structures in the lungs Improved pulmonary function	ND
(Jahandideh et al., 2018)	Mouse, LPS	Acute systemic inflammation	Human embryonic-derived stem cell (ESC)-MSC unconditioned, trimetazidine (TMZ)-, diazoxide (DZ)-, and MG132-preconditioned secretome	Increased serum IL-10 levels No significant changes in serum TNF-α, IFN-γ, IL-6 and IL-1β levels	Reduced inflammatory infiltrate in lungs Decreased necroinflammatory score of kidneys Decreased necroinflammatory score of liver in TMZ- and DZ-preconditioned secretome treatment	Improved
(Jaimes et al., 2017)	Mouse BV2 cells, LPS	Microglia inflammation	Mouse BM-MSC MV	Decreased TNF-α, IL-6, and IL-1β levels in the cell culture	ND	ND
(Kearney et al., 2022)	Horse, LPS	Radiocarpal joint synovial inflammation	Equine BM-MSC secretome preconditioned with equine IFN-γ and TNF-α	Decreased synovial fluid TNF-α	Decreased radiocarpal joint circumference	ND

Table 1. Summary of the preclinical studies on the usage of secretome in various inflammatory diseases (continued...)

Reference	Animal model or condition	Disease	Type of secretome	Biomarker characteristics	Organ injury	Survival
(Kim et al., 2020)	Human epidermal keratinocytes (HaCaT) cells, TNF-α/IFN-γ stimulated	Atopic dermatitis	Human umbilical cord (UC)-MSC secretome	Decreased IL-6 and TNF-α production in HaCaT cells	ND	ND
(Lai et al., 2018)	Mouse, bone marrow and spleen cells injection	Chronic graft *versus* host disease (GvHD)	Human BM-MSC exosome	Increased IL-10-expressing Treg cells	Less epidermal fibrosis with a decreased thickness of the dermis and less loss of hair follicles Less lung fibrosis Alleviated liver fibrosis	Improved
(Legaki et al., 2016)	Mouse, DSS	Colitis	Human spindle shaped amniotic fluid (SS-AF)-MSC secretome	Decreased mRNA relative expression of TNF-α and IL-1β in colon tissues Increased mRNA relative expression of IL-10 in colon tissues	Significantly decreased extension and severity of the colon inflammation	ND
(Liao et al., 2016)	Mouse, TNBS	Colitis	Mouse BM-MSC soluble factor IGFBP7	Decreased mRNA expression of TNF-α, IL-6, and IL-1β Increased mRNA expression of IL-10	Increased colon length	Improved
(Liu et al., 2019)	Mouse, oral DSS and intrarectal TNBS infusion	Colitis	Human BM-MSC exosome	Decreased expression of IFN-γ, IL-1β, IL-6, and TNF-α Increased expression of IL-10	Increased colon length Maintained intestinal structural integrity Significantly reduced disruptions of the architecture, crypt loss, and infiltration of inflammatory cells	Improved
(Liu et al., 2020)	Mouse, CLP	Sepsis	Mouse BM-MSC TGF-β1	Decreased plasma IL-1β and IL-6 levels Increased plasma IL-10 levels	Decreased injury scores in lung, liver, and spleen	ND
(Shi et al., 2021)	Mouse, *P. aeruginosa* intratracheal instillation	Pneumonia	Human AD-MSC EV	Decreased BALF levels of IL-6 and TNF-α Increased BALF levels of IL-10	Less inflammatory cells infiltrating interalveolar septa and respecting alveolar space and lung architecture Reduced histological severity of lung injury	Improved
(Shologu et al., 2018)	Rat alveolar epithelial cells, hypoxia	Lung ischemia-reperfusion injury	Human BM-MSC and AD-MSC secretome	Decreased IL-6 levels Increased TNF-α and IL-10 levels	ND	ND

Table 1. Summary of the preclinical studies on the usage of secretome in various inflammatory diseases (continued...)

Reference	Animal model or condition	Disease	Type of secretome	Biomarker characteristics	Organ injury	Survival
(Sun et al., 2021)	Mouse, CLP	Sepsis	Mouse BM-MSC exosome	Decreased serum TNF-α, IL-1β, IL-6 Increased serum IL-10	Improved kidney, liver, and lung damage	Improved
(Wang et al., 2016)	Mouse, allogeneic hematopoietic stem cell transplantation (allo-HSCT)	Acute GvHD	Human UC-MSC EV	Decreased serum TNF-α and IFN-γ levels Increased serum IL-10 levels	Attenuated histological changes in large intestine, liver and skin	Improved
(Yang et al., 2022)	Mouse, imiquimod (IMQ)	Psoriasis	Human amniotic epithelial cells (AEC)-SC secretome	Decreased relative mRNA levels of TNF-α, IL-1β, IL-6 in the lesion	Decreased neutrophil infiltration in the lesion	ND
(Zhou et al., 2022)	Mouse and mouse BV2 cells, LPS	Neuroinflammation	Human NSC secretome	Decreased mRNA expressions of TNF-α, IL-1β, and IL-6 in the cortex and hippocampus Increased mRNA expressions of IL-10 in the cortex and hippocampus Decreased TNF-α, IL-1β, and IL-6 levels in BV2 cells Increased IL-10 levels in BV2 cells	Significantly abolished gliosis in the brain Reduced shrunken neurons in the cortex and hippocampus	ND

Table 2. Summary of the clinical studies that use secretome in inflammatory diseases.

Reference	Condition	Phase	Type of secretome	Biomarker characteristics	Organ injury	Survival
(Fathi-Kazerooni et al., 2022)	COVID-19	I/II	Human menstrual stem cell (MenSC) secretome	Reduced C-reactive protein (CRP) levels	Significant improvement in lung lesions	Improved
(Harrell et al., 2020)	Chronic obstructive pulmonary disease (COPD)	ND	Human placenta MSC exosome	ND	Improved pulmonary status Significantly alleviated emphysematous changes in the lungs	ND
(Kim et al., 2020)	Atopic dermatitis	ND	Human UC-MSC secretome	ND	Improved skin stratum corneum and strengthened skin barrier in lesion and non-lesion	ND
(Sengupta et al., 2020)	COVID-19	ND	Human BM-MSC exosome	Reduced CRP levels	ND	83% survival rate
(Zhu et al., 2022)	COVID-19	IIa	Human AD-MSC exosome	Reduced CRP and IL-6 levels	Different degrees of resolution of pulmonary lesions	ND

form of decreased gliosis and areas of shrinking neurons in the cortex and hippocampus (Zhou et al., 2022).

There are also preclinical studies on the effect of secretome on systemic inflammation, such as sepsis and GvHD. In systemic inflammation, the most common cause of mortality is organ dysfunction due to cytokine storm. This systemic inflammatory syndrome involves immune response dysregulation in the form of increased levels of circulating cytokines (Fajgenbaum and June, 2020). Secretome administration can improve this condition by reducing proinflammatory cytokines and increasing anti-inflammatory cytokines in serum. In addition, the administration of secretome was also found to repair damage to various organs such as the lungs, liver, spleen, kidneys, and colon (Jahandideh et al., 2018; Lai et al., 2018; Liu et al., 2020; Sun et al., 2021; Wang et al., 2016). The survival of mice with secretome treatment was also found to increase compared to mice without secretome treatment (Jahandideh et al., 2018; Lai et al., 2018; Sun et al., 2021; Wang et al., 2016).

Preclinical studies of secretome treatment on GvHD found that secretome improved skin injury and fibrosis (Lai et al., 2018; Wang et al., 2016). Two studies observed the effect of secretome on inflammatory skin diseases such as atopic dermatitis and psoriasis (Kim et al., 2020; Yang et al., 2022). Among the many types of skin inflammation, psoriasis and atopic dermatitis are the more common chronic inflammatory skin diseases. Psoriasis and atopic dermatitis share several features, such as infiltration of immune cells in the skin, changes in the expression of several proinflammatory cytokines, and changes in the barrier (Bozek et al., 2020; Song et al., 2022). As shown in the studies, secretome can reduce the expression of proinflammatory cytokines in skin cells and neutrophil infiltration in the lesions (Kim et al., 2020; Yang et al., 2022).

The term cytokine storm was first used by Ferrara to describe cytokine dysregulation in GvHD. Since the COVID-19 pandemic, cytokine storm has returned to the spotlight because of its association with the severity and mortality of COVID-19 (Hu et al., 2021; Tang et al., 2021). It is triggered by immune and inflammatory responses induced by the infection and associated with elevated CRP levels, which play a role in endothelial cell dysfunction, thrombus formation, and coagulation cascade activation, eventually leading to organ failure (Luan et al., 2021; Valle et al., 2023; Wahyuni et al., 2022). Therefore, clinical studies often study the effect of secretome administration on the inflammation that occurs in COVID-19. As shown by the studies above, secretome administration not only lowered CRP and IL-6 levels but also improved lung lesions in COVID-19 patients (Fathi-Kazerooni et al., 2022; Sengupta et al., 2020; Zhu et al., 2022). Secretome administration also improved lung injury in preclinical studies of mice with pneumonia and chronic airway inflammation (Harrell et al., 2020; Shi et al., 2021).

Lastly, a preclinical study observed the effect of secretome on radiocarpal joint synovial inflammation. In the study, administering secretome was found to reduce the synovial fluid TNF-α (Kearney et al., 2022). The main pathogenesis of joint inflammation involves an increase in cytokines that cause articular cartilage degradation and a decrease in chondrogenesis-inducing factors. For instance, in the pathogenesis of rheumatoid arthritis (RA), IL-1 is a major inflammatory factor. Activation of IL-1 causes migration of inflammatory cells into the joint and synovium and also induces other proinflammatory cytokines, such as TNF-α and IL-6, that aggravate the damage (Chow and Chin, 2020; Kim et al., 2017; Zhang, 2021).

Secretome is a cell-secreted substance consisting of soluble and vesicular fractions of MSCs with various therapeutic properties. The soluble fraction of MSCs contains many immunomodulatory molecules, cytokines, chemokines, and growth factors. Meanwhile, the vesicular fraction consists of extracellular vesicles (EV) that can decrease IL-6 and IL-12p70 production with the expression of IL-10 and transforming growth factor (TGF)-β (González-González et al., 2020; Jeppesen et al., 2019; Műzes and Sipos, 2022).

IL-10 is a potent immunoregulatory molecule targeting almost all types of leukocytes. IL-10 binds to IL-10R, triggering the JAK-STAT signaling pathway that culminates in the activation of STAT1, STAT3, and STAT5 (Rojas et al., 2017; Senousy et al., 2022). STAT3 plays a vital role in the effect of IL-10 on immune cells. While IL-6 also activates STAT3, the activation by IL-10 leads to different effects. This is due to the induction of the suppressor of cytokine signaling 3 (SOCS3), which regulates the kinetics of STAT3 activation. Because SOCS3 does not block STAT3 activation by IL-10, STAT3 activation is maintained and will provide an anti-inflammatory effect (Cevey et al., 2019; Hillmer et al., 2016).

Several growth factors within secretome offer immunoregulatory effects. For instance, together with hepatocyte growth factor (HGF), TGF-β will suppress T-cell proliferation. HGF also polarizes macrophages to M2 phenotype, increasing the production of IL-10 and TGF-β. These factors will alleviate ongoing inflammation and promote repair and regeneration (Han et al., 2022; Yuan et al., 2019).

Limitations of the study and future perspectives

The limitation of this study is the wide variety of organs involved in inflammation, which may lead to a difference in the improvement due to the difference in the pharmacodynamics of secretome against each inflammatory condition. A narrower focus on the involved organs is recommended for future systematic reviews on the potential of secretome in improving the outcome of an inflammatory condition.

The immunomodulatory and regenerative potential of secretome has made it an attractive alternative therapeutic choice for inflammatory conditions, either as a main or adjuvant therapy. However, the usage of secretome has yet to be extensively studied in clinical trials, perhaps due to the novelty of this therapy. More trials will be needed before secretome can be used in clinical applications.

CONCLUSION

The use of secretome in experimental animal models and *in vitro* studies has shown the therapeutic potential of secretome. Secretome alleviates inflammation by reducing proinflammatory cytokines levels and expressions while increasing anti-inflammatory cytokines levels and expressions. This study also discovers improvements in the healing of damaged organs and survival, which may be associated with the regulated inflammatory responses upon secretome administration.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Sari MI	Jusuf NK	Munir D	Putra A	Putra IB	Bisri T	Farhat F	Ilyas S	Muhar AM
Concepts or ideas	x		x	x					
Design		x			x	x			
Definition of intellectual content	x								
Literature search					x	x	x	x	x
Data acquisition	x	x	x	x					
Data analysis	x	x	x	x					
Manuscript preparation	x	x	x	x					
Manuscript editing					x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x	x

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