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Effects of Mesenchymal Stem Cell Secretome on Cardiac Histopathological Changes in Doxorubicin-Induced Rats

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Abstract
Doxorubicin is an anthracycline chemotherapeutic agent widely used in clinical practice, but its application is limited by cardiotoxicity that damages myocardial structure and function. Mesenchymal stem cell secretome contains diverse bioactive molecules, including cytokines, growth factors, and extracellular vesicles, which contribute to tissue protection and cellular repair. This study aimed to evaluate the preventive and curative effects of secretome administration on histopathological changes in the hearts of doxorubicin-induced rats. Twenty-four rats were divided into four groups: without treatment (KS), cardiotoxicity group (KK), preventive secretome (P1), and curative secretome (P2). Histopathological assessment included degeneration, inflammatory infiltration, congestion, and necrosis using semi-quantitative scoring. Results showed no significant differences in degeneration, inflammatory infiltration, or congestion among groups. In contrast, necrosis scores differed significantly ($p = 0.002$), with the highest values observed in the KK group. Secretome administration in the P2 group demonstrated the most pronounced improvement, reflected by a greater reduction in necrosis scores compared to other groups. In conclusion, curative-phase secretome treatment provided the most effective histological improvement by reducing myocardial necrosis, indicating a stronger tissue repair response than preventive administration.

Keywords: Cardiotoxicity, COX-2, Caspase-3, Doxorubicin, Mesenchymal stem cell, Secretome.

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Efek Sekretom Sel Punca Mesenkimal terhadap Perubahan Histopatologi Jantung Tikus Terinduksi Doksorubisin

Abstrak
Doksorubisin merupakan obat kemoterapi golongan antrasiklin yang banyak digunakan, namun pemanfaatannya terbatas karena efek samping berupa kardiotoksisitas yang dapat merusak struktur dan fungsi miokard. Penelitian menunjukkan bahwa sekretom sel punca mesenkimal mengandung beragam molekul bioaktif seperti sitokin, faktor pertumbuhan, dan vesikel ekstraseluler yang berperan dalam perlindungan jaringan dan mendukung proses perbaikan seluler. Penelitian ini bertujuan untuk menilai pengaruh pemberian sekretom secara preventif dan kuratif terhadap perubahan histopatologi jantung tikus yang diinduksi doksorubisin. Dua puluh empat ekor tikus dibagi menjadi empat kelompok: kontrol sehat (KS), kontrol kardiotoksisitas (KK), sekretom preventif (P1), dan sekretom kuratif (P2). Penilaian histopatologi meliputi degenerasi, infiltrasi inflamasi, kongesti, dan nekrosis menggunakan skoring semi-kuantitatif. Hasil menunjukkan degenerasi, infiltrasi inflamasi, dan kongesti tidak menunjukkan perbedaan yang signifikan antar kelompok. Sebaliknya, parameter nekrosis memperlihatkan perbedaan bermakna ($p = 0,002$), dengan nilai tertinggi pada kelompok KK. Pemberian sekretom pada kelompok P2 menghasilkan perbaikan paling jelas, ditunjukkan oleh penurunan skor nekrosis yang lebih besar dibandingkan kelompok lainnya. Dapat disimpulkan, perbaikan histologis pada fase kuratif tampak paling jelas melalui penurunan derajat nekrosis miokard, yang menunjukkan respons perbaikan jaringan yang lebih efektif dibandingkan kelompok lainnya.

Kata Kunci: Doksorubisin, Histopatologi, Kardiotoksisitas, Sekretom, Sel Punca Mesenkimal.

1. Introduction

Cardiotoxicity of chemotherapeutic agents, particulaely anthracyclines such as doxurubicin (Dox), represents a major global clinical cahllenge that limits the efficacy of oncology therapy.[1] Over 20% of patients experience cardiac damage due to Dox, with systolic/diastolic dysfunction incidence reaching 57% among childhood cancer survivors.[2] In Indonesia, DOX remains the primary regimen for breast cancer (64.3%) and hematological malignancies, with significant usage increase (118-277 patients/year).[3,4]

Mesenchymal stem cells (MSCs) exhibit differentiation potential into replacement cardiomyocytes for those damaged by toxicity, while simultaneously secreting anti-inflammatory and paracrine factors that stimulate endogenous cardiac remodeling, myocardial angiogenesis, and inhibition of cardiomyocyte apoptosis.[5] The MSC secretome is a complex of proteins, cytokines, chemokines, and growth factors provides cardioprotection against doxorubicin toxicity by modulating oxidative stress, inflammation, and non-tumor cytotoxicity without compromising anticancer efficacy.[5] Proteomic analyses confirm regulation of cell proliferation/migration and inflammation, while preclinical studies demonstrate the effectiveness of 120 µg/kg IV dosing (twice weekly for 6 weeks) in reducing cardiotoxic biomarkers, myocardial hypoxia, and inflammation.[6]

The mesenchymal stem cell secretome demonstrates significant cardioprotective potential, with rat ischemia-reperfusion model studies confirming infarct size reduction, inflammation, and apoptosis via intravenous administration, alongside Phase I clinical trials verifying safety and improved left ventricular ejection fraction in acute myocardial infarction patients, primarily through microRNAs regulating inflammation, apoptosis, and angiogenesis.[5,7]

Biologically, MSC secretome has anti-inflammatory, anti-apoptotic, and antioxidant properties, and can stimulate tissue repair. Components such as interleukin-10, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and various microRNAs in extracellular vesicles play a role in maintaining cell membrane stability, suppressing inflammation, and supporting myocardial structure recovery. Although the benefits of secretome in organ damage have been reported, data on its role in doxorubicin-induced cardiotoxicity are still limited, particularly regarding the comparison between preventive and curative administration.[8,9]

Previous studies on myocardial protection against doxorubicin cardiotoxicity have focused on agents such as dexrazoxane (reducing necrosis by up to 65%), curcumin (reducing ROS by up to 40%), intact mesenchymal stem cells (increasing LVEF by up to 10%), and MSC exosomes (reducing TNF-α by up to 50%). A crucial research gap lies in the lack of direct comparisons regarding the timing of MSC secretome administration (preventive versus curative), despite peak myocardial necrosis occurring on days 3 to 7 post-doxorubicin induction—a critical period that remains unexplored in a head-to-head manner against histopathological parameters in animal models.[10–14]

This study was conducted to assess the effect of MSC secretome on histopathological changes in the heart of doxorubicin-induced rats. Four main parameters, namely degeneration, inflammatory infiltration, congestion, and necrosis, were used to evaluate the effects of secretome in both the preventive and curative phases. The findings from this study are expected to provide a more comprehensive understanding of the potential of secretome in reducing or repairing myocardial structural damage due to doxorubicin exposure.

2. Methods

2.1. Equipment

The equipment utilized in this study included a microtome (Leica 2235®, Germany), a light microscope (Olympus®, Japan), a slide warmer (Jisico®, Korea), a paraffin section mounting water bath (Electrothermal®, UK). Tissue embedding was performed using a paraffin embedding system (Slee Paraffin Embbeding Set, PT Rayty Brothers®). Additional laboratory instrumens comprised tissue cassettes, standard glassware, scalpel, forceps, tweezers, and other routine histopathological laboratory equipment.

2.2. Materials

The materials used in this study consisted of rat heart tissue samples, standard laboratory rat feed, and animal housing facilities. Reagents included 10% neutral buffered formalin for tissue fixation, graded ethanol solutions (70%, 80%, 96%) for dehydration, xylene for clearing, and paraffin wax for embedding. Albumin-coated glass slides were used for section mounting. Hematoxylin and eosin (H&E) stauns were applied for histological evaluation. Additional materials included distilled water, cover slips, entellan mounting medium, and standard laboratory consumables.

2.3. Procedures

This research is an experimental study employing a

posttest-only control group design using male Wistar rats (Rattus norvegicus) aged 10-12 weeks with body weights between 200-250 grams and in healthy condition. The study was approved by the Ethics Committee for Medical and Health Research, Faculty of Veterinary Medicine, Syiah Kuala University (Number: 311/KEPH/VII/2024). Rats were housed individually in rat cages, maintained under standard conditions (12 hrs light and 12 hrs dark cycle). They had been given standard pellet diet and water ad libitum throughout the study. The animals were adapted to the laboratory environment for seven days before being used in the study.

After acclimatization, the animals were randomly divided into four groups: without treatment (KS), cardiotoxicity group (KK), preventive secretome (P1), and curative secretome (P2). Rats in the KK, P1 and P2 groups were fasted for 8 hrs prior to doxorubicin administration. Cardiotoxicity was induced by a single intraperitoneal injection of doxorubicin at a dose 10 mg/kg BW (concentration 10 mg/5mL). In the P1 group, MSC secretom (0.15 mL) was administered intravenously immediately after doxorubicin injection, whereas in the P2 group, the same dose was administered on day 5 after induction.

Doxorubicin preparation was obtained from the Executive Polypharmacy of dr. Zainoel Abidin General Hospital in Banda Aceh, with the complete research ethics certificate presented. In group P1 (T1), 0.15 mL of mesenchymal stem cell secretome was administered intravenously immediately after doxorubicin induction as a preventive measure against tissue damage. The secretome used was derived from human umbilical cord mesenchymal stem cells, produced in a CPOB-certified laboratory facility and approved by the Indonesian Ministry of Health. Meanwhile, group P2 (T2) received the same dose of 0.15 mL mesenchymal stem cell secretome intravenously on day 5 post-doxorubicin induction as a curative therapy.[15]

On day 12, all experimental animals from the four groups were euthanized via cervical dislocation. Cardiotoxicity status was confirmed by proteinuria examination results showing +3 to +4 values, indicating cardiotoxicity in the rats. In this study, 100 mg of heart tissue was homogenized using a homogenizer in 1 mL of Phosphate Buffered Saline (PBS) on an ice surface to maintain enzyme and protein stability. The resulting homogenate was centrifuged at 14,000 g for 15 minutes at 4°C. The supernatant obtained was stored at -20°C until analysis. Subsequently, heart organs were collected from each rat for further preparation and analysis histopathological examination.[15,16] This study did not include a standard comparator (such as dexrazoxane) because the primary focus was to compare the timing of MSC secretome administration (preventive vs. curative) as a locally innovative therapy.

2.3.1. Histopathological examination.

Heart tissues were collected and fixed in 10% neutral buffered formalin for 24-48 hrs. Tissue processing was performed using a standard paraffin-embedding technique. Dehydration was carried out through a graded ethanol series consisting of 70% ethanol for 6 hrs, followed by 80%, 96% and absolute ethanol, each for 2 hrs. Immersion in absolute ethanol was performed twice to ensure complete dehydration.16 The tissues were subsequently cleared in xylene for 2 hrs to remove residual alcohol and infiltrated with molten paraffin wax. Paraffin infiltration was conducted twice, each for 1.5 hrs, until complete impregnation was achieved. The tissues were then embedded in paraffin blocks and sectioned using a microtome at a thickness of 5 µm. The sctions were floated on warm water to remove folds, mounted onto albumin-coated glass slides, and dried on a slide warmer at 37°C for 12 hrs.[16]

Hematoxylin and eosin (H&E) dating was performed for histopathological evaluation. The slides were deparaffinized in xylene twice and rehydrated through descending ethanol concentrations (absolute to 90%), each for 3 min, followed by rinsing in distilled water for 3 min. The sections were stained with hematoxylin for 2 min, washed under running tap water, and counterstained with eosin for 2 min.[16] After staining, the sections were dehydrated through 96% ethanol (twice), absolute ethanol (twice), and xylene (twice). Finally, the slides were mounted using Entellan®, covered with coverslips, and allowed to dry prior to microscopic evaluation. The prepared slides were examined under a light microscope in three randomly selected fields of view to assess histopathological changes in cardiac tissue.[16]

Histopathological scoring for cardiac damage is evaluated based on four main parameters using a semi-quantitative scale from 0 to 3. Myocardial fiber degeneration is scored as 0 for no degeneration, 1 for mild degeneration (focal), 2 for moderate degeneration (multifocal), and 3 for severe degeneration (diffuse). Inflammatory cell infiltration is scored as 0 for no infiltration, 1 for mild infiltration (limited), 2 for moderate infiltration (spread across several areas), and 3 for severe infiltration (diffuse or forming large foci). Vascular congestion or hemorrhage receives a score of 0 if not observed, 1 for mild congestion (limited), 2 for moderate congestion, and 3 for severe congestion. Finally, cardiac muscle cell necrosis is scored as 0 for none, 1 for focal necrosis, 2 for multifocal necrosis, and 3 for extensive necrosis.[3]

2.3.2. Data Analysis

Data obtained from the cardiotoxicity rat model study, including degenerative cells, inflammatory cells, congestive cells and necrotic cells were analyzed using statistical software. Initial data analysis involved the Shapiro-Wilk test for normality assessment and Levene's test for homogeneity of variances across groups. If data were normally distributed, one-way Analysis of Variance (ANOVA) was performed with a significance level of $p < 0.05$; significant results were followed by post-hoc Least Significant Difference (LSD) analysis. For non-normally distributed data, the non-parametric Kruskal-Wallis test was applied at $p < 0.05$, with significant results followed by Mann-Whitney U post-hoc tests.[17,18]

3. Result

Statistical data analysis revealed a non-normal distribution. Data are presented as median (minimum – maximum). Histopathological analysis using the Kruskal–Wallis test showed no significant differences in degenerative cells, inflammatory cells, or congestive cells parameters across groups. In contrast, the necrosis parameter exhibited a significant difference between groups (p=0.002), as shown in Table 1. The cardiotoxicity group (KK) had the highest necrosis score, confirming that cell death was the primary manifestation of doxorubicin-induced myocardial damage.

Distribution of necrosis scores in Figure 1 shows the highest increase in the KK group, while P1 and especially P2 show a clear decrease in scores. This confirms that MSC secretome is able to suppress the degree of myocardial damage through both preventive and curative mechanisms.

The cardiotoxic control group (KK) exhibited a markedly higher level of myocardial necrosis compared to the other experimental groups. Statistical analysis revealed that the P1 and P2 groups had significantly lower necrosis levels than the KK group. Overall, these findings indicate that secretome administration significantly attenuated myocardial necrosis in the cardiotoxicity model.

Figure 1 presents photomicrographs of heart tissue from various experimental groups (NC, PC, P1, P2) stained with hematoxylin-eosin (HE) at 400x magnification. Arrows on the images indicate four main histopathological parameters: (a) cardiomyocyte degeneration, (b) myocardial necrosis, (c) vascular congestion, and (d) inflammatory cell infiltration. This figure illustrates the comparison of doxorubicin-induced histological damage and the protective effects of MSC secretome administration in a rat cardiotoxicity model.

4. Discussion

This study indicates that MSC secretome administration does not affect histopathological parameters of cellular degeneration, inflammation, or congestion in a low-dose cumulative doxorubicin (DOX; 10 mg/kg) cardiotoxicity model. This is consistent with findings that acute myocardial inflammation and degeneration can spontaneously reverse within 12 days of observation. Podyacheva et al. reported DOX-induced myofibril degeneration and cardiomyocyte cytoplasmic vacuolization in a rat model. however, these changes vary by dosing protocol and duration, while MSC-derived exosomes reduce inflammation without consistently affecting all histological parameters significantly.[19]

The Kruskal–Wallis test revealed a significant difference in myocardial cell necrosis (p=0.002). Post-hoc Mann–Whitney tests indicated that the KK group differed significantly from the KS, P1, and P2 groups. These findings suggest that MSC secretome effectively suppresses doxorubicin-induced histological damage, restoring conditions close to physiological normalcy. This aligns with prior reports indicating that necrosis is the primary manifestation of doxorubicin

Table 1. Hystopathology of Wistar rat heart tissue

Group	Histopatology Median (Min-Max)				P Value
	Degenerative cells	Inflammatory cells	Congestive cells	Necrotic cells	
KS	1,00 (1,00-2,33)	1,16 (1,00-2,33)	1,33 (1,00-2,67)	1,83 (1,33-2,00)	0,564[a]
KK	1,66 (1,00-2,00)	1,50 (1,00-2,00)	1,67 (1,33-3,00)	2,66 (2,33-3,00)	0,774[b]
P1	1,50 (1,00-2,00)	1,33 (1,00-1,33)	1,50 (1,00-1,67)	1,66 (1,33-2,00)	0,569 [a]
P2	1,67 (1,00-2,67)	1,50 (1,00-2,00)	1,67 (1,00-2,33)	1,83 (1,67-2,00)	0,002 [a]

[1] KS: without treatment; KK: single dose of doxorubicin 10 mg/kgBW intraperitoneally; P1: Doxorubicin + MSC secretome 0.15 mL intravenously immediately after induction; P2: Doxorubicin+ MSC secretome 0.15 mL intravenously on day 5 post-induction. Kruskal-Wallis test with significant p-value < 0.05. Superscripts with symbols a, b indicate results from post-hoc Mann-Whitney U tests. Different symbols denote significant differences between groups.

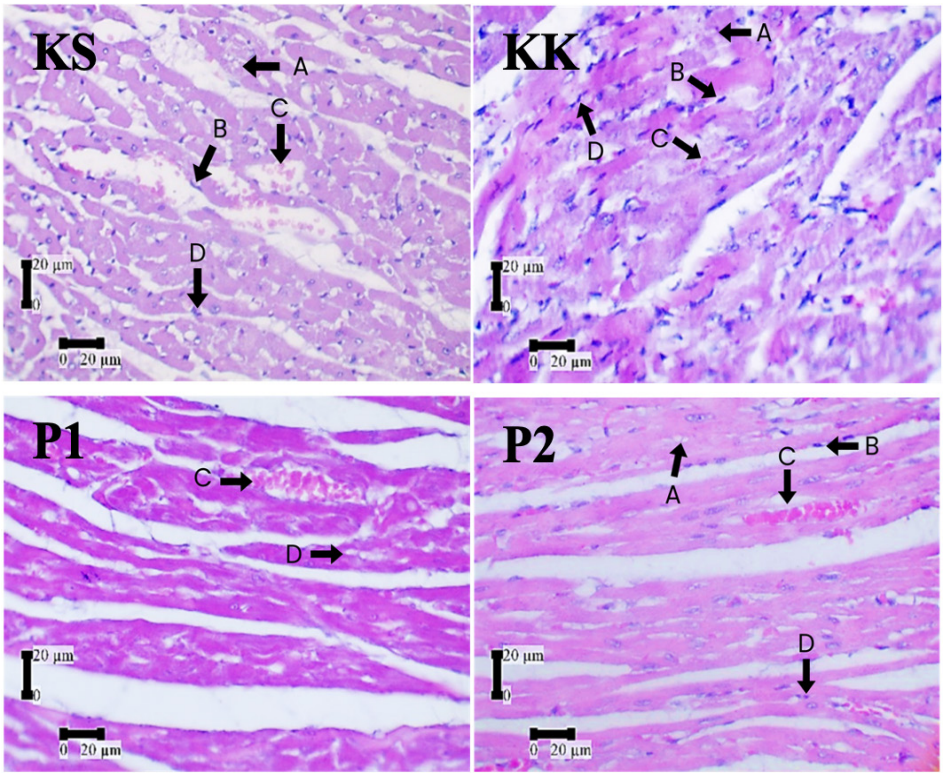

Figure 1. Photomicrograph of Wistar rat heart tissue using Hematoxylin & Eosin (H&E) staining. (a) Degenerative cells; (b) Necrosis; (c) Congsetion; (d) Inflamatory cells.

cardiotoxicity, resulting from reactive oxygen species (ROS) accumulation and mitochondrial dysfunction that trigger cell membrane damage and cytoplasmic lysis.[20]

Preventive MSC secretome administration (P1) demonstrated protective effects, evidenced by significantly reduced necrosis scores compared to the cardiotoxicity control (CC) group. This mechanism is likely mediated by paracrine factors such as VEGF, IGF-1, and HGF, which exhibit anti-apoptotic, antioxidant, and pro-regenerative activities, while suppressing reactive oxygen species (ROS) production and preserving cardiomyocyte mitochondrial integrity.[21,22] Additionally, MSC secretome contains extracellular vesicles (EVs) carrying protective microRNAs (miR-21, miR-210) that inhibit pro-apoptotic and inflammatory pathways, thereby preventing oxidative stress-induced necrosis.[23]

In addition to growth factors, MSC secretome also contains extracellular vesicles (EVs) that carry protective microRNAs, such as miR-21, miR-210, and miR-146a. These microRNAs can suppress NF-κB activation, reduce the expression of pro-inflammatory cytokines (TNF-α, IL-1β), and inhibit cardiomyocyte apoptosis.[23] These effects are mediated by bioactive components of the secretome, such as IL-10, TGF-β, and exosomal microRNAs (miR-21-5p, miR-146a, miR-96), which inhibit NF-κB activation and reduce the expression of COX-2, TNF-α, and IL-1β, thereby accelerating histological integrity recovery.[23,24]

The histological improvements observed in the P2 group are closely associated with the activation of cytoprotective pathways and adaptive myocardial remodeling. MSC secretome is known to enhance the expression of heme oxygenase-1 (HO-1) and Nrf2, two key transcription factors involved in endogenous antioxidant defense. Activation of this pathway stimulates the synthesis of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which neutralize reactive oxygen species (ROS), thereby preventing membrane lipid peroxidation and further necrosis.[7,25]

Additionally, tissue improvement is also presumed to be influenced by the immunomodulatory effects of MSC secretome, which reduce the infiltration of pro-inflammatory immune cells into cardiac tissue. Previous studies have shown that MSC exosome administration can inhibit neutrophil migration and M1 macrophage activation while promoting reparative M2 macrophage polarization.[26,27] This supports the histological observations showing reduced leukocyte infiltration and improved myocardial fiber organization in the P2 group.

Several translational studies report that MSC secretome components also contain matrix metalloproteinases

(MMP-2, MMP-9) and tissue inhibitors (TIMP-1), which facilitate post-injury tissue remodeling, restore extracellular matrix balance, and reduce long-term myocardial fibrosis.[27] Thus, the reparative effects observed histologically in the P2 group not only indicate cellular morphological recovery but also tissue stabilization at the matrix level, contributing to improved myocardial function.

This research holds high scientific significance as one of the first experimental studies in Indonesia to directly compare the effectiveness of preventive (P1) versus curative (P2) mesenchymal stem cell (MSC) secretome administration in a doxorubicin-induced cardiotoxicity Wistar rat model, focusing on histopathological necrosis as the primary parameter (p=0.002). The finding that curative administration on day 5 resulted in necrosis reduction approaching healthy control group (KS) levels addresses a critical knowledge gap regarding optimal secretome therapy timing, which remains underexplored in both national and international literature. This is particularly relevant to Indonesia, where doxorubicin remains first-line chemotherapy for breast cancer (64.3% of cases) and hematological malignancies, with significant annual patient increases (118-277 cases), offering potential to reduce cardiovascular morbidity in the local oncology population.

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5. Conclusion

The most prominent histological improvement in the curative phase is indicated by a decrease in the degree of myocardial necrosis. This finding indicates that the administration of secretome after injury is able to optimize the tissue repair mechanisms that are already active in response to damage. During this phase, cells and tissues stressed by exposure to doxorubicin begin to activate endogenous reparative pathways, including antioxidant, anti-inflammatory, and cellular regeneration processes. The presence of secretome in this condition provides additional support through its bioactive factors that strengthen these healing processes, thereby accelerating the recovery of cell membrane integrity and preventing the expansion of the necrotic area. Therefore, the curative group showed more consistent and effective improvement results compared to other groups, confirming the potential of secretome as a therapeutic intervention in injured myocardial tissue.

Conflict of Interest

The authors declare that there are no conflicts of interest, financial or otherwise, that could have influenced the conduct or interpretation of this study.

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