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Research Article

# Non inferiority trial of *Channa striata* extract on endothelial glycocalyx layer protection in septic patient: a prospective cohort study

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## Abstract

**Introduction:** Sepsis causes significant damage to the endothelial glycocalyx layer, which albumin can protect against. Unfortunately, human albumin is quite expensive, so cheaper substitutes must be found without sacrificing effectiveness. Albumin extract *Channa striata* is one that is commonly used in Indonesia.

**Objectives:** Conducted a non-inferiority study between human albumin and *Channa striata* extract in protecting the glycocalyx layer through syndecan-1 levels.

**Materials and methods:** Prospective cohort study of adult patients with early sepsis with hypoalbuminemia (<4 g/dL) treated at ICU Dr Moewardi Hospital between May and October 2021 and got human albumin or *Channa striata* extract as therapy. The *Channa striata* group was oberved in two separated groups. The control groups with human albumin 20% 100 ml single dose and the *Channa striata* group with 15 gram extract of *Channa striata* in two days, then syndecan-1 levels were compared before treatment and on the third day of the study.

**Results:** We discovered a statistically significant decrease in syndecan-1 levels in both the study ($p = 0.013$) and control groups ($p = 0.027$) from the 44 samples we obtained.

**Conclusion:** In both groups, we found a significant decrease in syndecan-1 levels. This demonstrates that *Channa striata* extract is not inferior to human albumin in terms of glycocalyx layer protection. And it has a higher economic value because the price is lower.

## Keywords

sepsis, *Channa striata*, albumin, syndecan-1, glycocalyx

## Introduction

According to the Global Burden of Disease, sepsis kills more than 10 million people each year and contributes to 3–10 deaths per 1,000 people in high-income countries (Rudd et al. 2020). One of the first signs of sepsis is that it can cause changes in the composition of the glycocalyx as a result of inflammatory factors and oxidative stress (Iba and Levy 2019; Sullivan et al. 2021). Syndecan-1 levels are a commonly used biomarker in assessing glycocalyx layer damage (Ushiyama et al. 2016; Bertrand and Bollmann 2019) Some study demonstrated to animal models to see the damage to the glycocalyx that giving albumin was suf-

ficient to maintain the glycocalyx (Uchimido et al. 2019; Aldecoa et al. 2020).

Glycocalyx is a semipermeable layer for albumin molecules, and the presence of albumin in Glycocalyx is a determining factor of its filter function. In addition, albumin carries sphingosine-1-phosphate, which inhibits the activity of Matrix metallo proteinase which damages the endothelial glycocalyx layer. In vitro study of albumin from *Channa striata* extract, showed that it can reduce levels of macrophages, Tumor Nuclear Factor (TNFα), Interferon (IFN-ɤ), interleukin 6 (Il-6), Nuclear Factor (NFκβ) which are pro-inflammatory cytokines that promote damage to the glycocalyx layer (Delaney et al. 2011; Ferroni et al. 2014; de Melo Bezerra Cavalcante et al. 2016; Dwijayanti et al. 2016; Ekren et al. 2017; Song and Goligorsky 2018; Aldecoa et al. 2020).

This albumin is quite expensive, particularly for developing countries, so there is a need for substitutes, one of which is albumin extracted from *Channa striata* which is already common in Indonesia. For addition, the average cost of human albumin 20% 100 cc in Indonesia was ± USD 115, and for *Channa striata* extract 30 gram cost ± USD 34, and there were several studies showing the effectiveness of *Channa striata* extract in increasing albumin levels compared to human albumin, although there is no research on costs effectiveness (Dwijayanti et al. 2016; Kania et al. 2020; Suhendi et al. 2020; Isamahendra et al. 2021; Ramadhanti et al. 2021). As a result, studies comparing the non-inferiority of *Channa striata* extract to human albumin in preventing damage to the glycocalyx layer as measured by syndecan-1 levels in sepsis patients are required.

# Materials and methods

## Study setting

The study used an analytic observational study design with a prospective cohort study method. The aim of study is non inferiority trial between *Channa striata* extract and human albumin. We grouped sepsis patients who met the qSOFA 2 criteria, were 18 years old, and were hospitalized in the intensive care unit at RSUD DR Moewardi with a sampling period of 2021 into two groups. Control and *Channa striata* group were followed by a three-day evaluation of the patient.

The research sample was obtained using a consecutive sampling technique, whereas every patient who met inclusion criteria during the study period would be included in study without randomization until sample was fulfilled, we just observed it which sample were included in control or *Channa striata* groups. The sample of this study consisted of adult patients who entered the Intensive Care Installation of RSUD Dr Moewardi Surakarta in May-October 2021 with a diagnosis of sepsis and met the qSOFA 2 criteria, the following inclusion criteria were met:

### *Inclusion criteria:*

- Adult patients (> 18 years) admitted to the intensive care unit of RSUD Dr Moewardi Surakarta with a diagnosis of sepsis who meet the criteria of qSOFA ≥ 2 in 2021 and had hypoalbuminemia (< 4 g/dl) and get human albumin or *Channa striata* extract as their treatment.

### *Exclusion criteria:*

Exclusion criteria are the conditions of subjects who meet the inclusion criteria but are unable to participate in the study.

- Patients with severe trauma and a bleeding class of more than 2.
- Those who have a history of nephrotic syndrome.

## Ethical aspect

Permission to conduct research was obtained from the Faculty of Medicine, Sebelas Maret University, RSUD Dr. Moewardi Surakarta's Ethical Eligibility Committee, as outlined in the Ethical Eligibility letter. The study was carried out with the goal of not violating medical practice ethics or conflicting with human research ethics.

## Study setting

The patient were separated in two groups, the human albumin group as control and the *Channa striata* group. We observed patient sepsis who had hypoalbuminemia (albumin < 4 g/dl) and received human albumin 20 gram or *Channa striata* extract 15 gram for two days. And then we collected 5 cc of venous blood and 3 cc of arterial blood before being given albumin, and the venous blood sample was placed in a tube containing EDTA and arterial blood. After measuring syndecan-1, creatinine, albumin, urea, sodium, potassium, chloride, blood sugar, and the PaO2/FiO2 ratio in a tube containing citrate. On the third day, 5 cc of blood was drawn and placed in an EDTA-containing tube. Syndecan-1 levels were measured in blood samples. In this study, *Channa striata* group, Onoiwa from nucleus pharma, a nano particle *Channa striata* extract with freeze dryer methods that was approved by our national agency of drug and food control was used in our hospital, and in control group *albapure* human albumin 20% from *dexa medica* was also used in our hospital.

## Data analysis

The Shappiro-Wilk test was used to determine the normality of the results. A paired t-test was performed for the same group and an independent t-test was performed between the two groups for normal and homogeneous results. If the distribution was abnormal and nonhomogeneous, the non-parametric Wilcoxon test for the paired group and the Mann-Whitney test for the two groups were used. STATA version 16.1 was used for the statistical analyses.

## Results

According to Table 1, the average patient's age was 52 years old, with 60% male and 40% female. According to the data in Table 1, the patient had an increase in blood sugar and a decrease in the PaO2/FiO2 ratio with moderate grade of Acute Respiratory Distress Syndrome.

**Table 1.** Demographic characteristics.

| | Median | Mean | Std.Deviation | n |
|---|---|---|---|---|
| Gender | | | | |
| Male | | | | 26 |
| Female | | | | 18 |
| Age (years) | 53.5 | 52.34 | 11.497 | |
| Initial Syndecan-1 (ng/ml) | 8.398 | 7.83241 | 1.630153 | |
| Creatinine (mg/dL) | 0.9 | 1.303 | 1.7989 | |
| Ureum (mg/dL) | 40 | 50.45 | 37.605 | |
| Sodium (mmol/L) | 131.5 | 131.02 | 5.394 | |
| Blood sugar (mg/dL) | 194.5 | 211.27 | 47.965 | |
| PaO2/FiO2 (mmHg) | 93.5 | 113.69 | 54.5845 | |
| Albumin (g/dL) | 3.45 | 3.395 | 0.5811 | |
| Chlorida (mmol/L) | 99 | 100.00 | 3.870 | |
| Potassium (mmol/L) | 3.9 | 3.98 | 0.65 | |
| Lactat (mmol/L) | 4.05 | 4.361 | 1.567 | |

**Table 2.** Characteristic between groups.

| Variabel | Mean ± SD | | n | | *p* |
|---|---|---|---|---|---|
| | Human albumin intravena | Albumin *Channa striata* | Human albumin intravena | Albumin *Channa striata* | |
| Gender | | | | | 0.329* |
| Male | | | 14 | 12 | |
| Female | | | 7 | 11 | |
| Age (years) | 54.52 ± 10.04 | 50.35 ± 12.56 | | | 0.162* |
| Initial Syndecan-1 (ng/mL) | 7.99 ± 1.46 | 7.68 ± 1.78 | | | 0.503** |
| Creatinine (mg/dL) | 1.71 ± 2.54 | 0.92 ± 0.38 | | | 0.517** |
| Ureum (mg/dL) | 57.43 ± 45.19 | 44.09 ± 28.61 | | | 0.192** |
| Sodium (mmol/L) | 131.57 ± 5.51 | 130.52 ± 5.35 | | | 0.810* |
| Blood sugar (mg/dL) | 221.52 ± 54.33 | 201.91 ± 40.26 | | | 0.054** |
| PaO2/FiO2 (mmHg) | 122.98 ± 65.07 | 105.21 ± 42.61 | | | 0.672** |
| Albumin (g/dL) | 3.25 ± 0.61 | 3.52 ± 0.52 | | | 0.072** |
| Chlorida (mmol/L) | 100.10 ± 4.53 | 99.91 ± 3.24 | | | 0.531* |
| Potassium (mmol/L) | 3.95 ± 0.59 | 4 ± 0.71 | | | 0.804** |
| Lactat (mmol/L) | 4.36 ± 1.78 | 4.35 ± 1.38 | | | 0.438** |

* t tes independent; ** mann whitney independent test; *** pearson chi square test.

After dividing the data on patient demographic characteristics by group, from Table 2 we obtained homogeneous values for all the initial variables between groups, as indicated by p values greater than 0.05. This demonstrates that the two groups had similar characteristics at the start of the study and were not statistically significantly different.

**Table 3.** Syndecan-1 distribution.

| Syndecan-1 Distribution | 1st day (ng/ml) | 3rd day (ng/ml) |
|---|---|---|
| Range | 7.573 | 7.108 |
| Mean [SD] | 7.83 (1.63) | 6.805 (1.71) |

In our study the dependent variable that we examined was syndecan-1 variable. Where is the distribution of the levels of syndecan-1 results obtained as shown in Table 3. From the table above we find that the initial syndecan-1 level was 7.83 ng/ml and on the third day the level decreased to 6.805 ng/ml.

**Table 4.** Changes in syndecan -1 levels on the first and third days.

| Syndecan -1 changes | Sample (n) |
|---|---|
| Increase | 8 |
| Decrease | 36 |
| P | 0.001* |

* Wilcoxon signed rank test.

From further data (Table 4) on changes in syndecan-1 levels, we found that on the third day the majority of samples experienced a decrease in syndecan -1 levels in a total of 36 samples, and there were 8 samples that increase in syndecan-1 levels on the third day.

**Table 5.** Administration of *Channa striata* extract albumin compared to human albumin on the difference in syndecan -1 levels.

| | Syndecan-1 on 1st day | Syndecan-1 on 3rd day | p |
|---|---|---|---|
| Albumin extract *Channa striata* | 7.99 ± 1.46 | 6.99 ± 1.76 | **0.027*** |
| Human Albumin 20% | 7.68 ± 1.78 | 6.63 ± 1.68 | **0.013*** |
| P | 0.503** | 0.459** | |

* Wilcoxon signed rank test; ** mann whitney independent test.

After dividing the syndecan -1 levels by study and control groups (Table 5), we discovered that the *Channa striata* group had a 1.05 ng/ml decrease in syndecan -1 levels. Syndecan-1 levels in the control group fell as well, the difference was 1 ng/ml between 1st and 3rd day. On the 1st day, the level of syndecan-1 wasn't different between two groups ($p = 0.503$), as well as on the 3rd day ($p = 0.459$). On the 1st and 3rd days, both groups showed a significant decrease in syndecan-1 levels ($p = 0.013$ and $p = 0.027$, respectively), indicating that albumin can protect the glycocalyx layer and the protective effect on the glycocalyx layer was balanced between two groups.

## Discussion

There is damage to the endothelial glycocalyx layer in sepsis patients, and one of the biomarkers assessed is syndecan-1, whereas sepsis patients with elevated syndecan-1 have a worse prognosis than those who do not have elevated syndecan-1. Because the endothelial glycocalyx layer is composed of albumin, albumin is given to septic patients who have already damaged the endothelial glycocalyx layer. The endothelial glycocalyx layer is a semi-permeable layer for albumin molecules, and the presence of albumin in the layer determines its filter function. The endothelial surface layer is the functional unit of the endothelial glycocalyx layer and the albumin it contains (Ince et al. 2016; Schött et al. 2016; Joffre and Hellman 2021; Piotti et al. 2021).

Although albumin is an important component of the endothelial surface layer and administration of albumin

appears to be a reasonable suggestion for maintaining and improving the vascular barrier, experiments in isolated organs have shown that the endothelial surface layer can still function well at albumin concentrations as low as 10 g/L. As a result, failure of vascular barrier function in severe acute illness is caused by damage to the endothelial structures of the glycocalyx caused by hypervolemia, ischemia, or other forms of systemic inflammation, rather than hypoalbuminemia (Taverna et al. 2013; Caironi et al. 2014; Vincent et al. 2014; Vincent et al. 2016; Aldecoa et al. 2020).

The endothelial glycocalyx layer, on the other hand, can be stabilized by supplementing albumin in the endothelial surface layer. Furthermore, albumin contains sphingosine-1-phosphate, which inhibits Matrix Metallo Protein (MMP) activity on the endothelium. According to several studies, giving albumin for fluid resuscitation in septic patients can reduce mortality. According to some research on experimental animals, giving albumin in sepsis succeeded in reducing edema and maintaining fluid balance, as well as preventing more severe damage to the glycocalyx (Vincent et al. 2016; Aldecoa et al. 2020; Wiedermann 2020).

Aside from albumin, which has long been known to have anti-inflammatory benefits, *Channa striata* extract albumin contains other complex proteins, omega-3 fatty acids, amino acids such as glycine, histidine, cysteine, glutamine, and tryptophan, vitamins A, D3, and E, and the mineral magnesium, which also functions as an anti-inflammatory. According to some study, *Channa striata* extract albumin in vitro was able to inhibit pro-inflammatory cytokines such as TNF-, IL-6, which directly affect the formation of ROS, which is a source of damage to the endothelial glycocalyx layer and a source of organ failure in sepsis patients (Dwijayanti et al. 2016; Kania et al. 2020; Suhendi et al. 2020; Ramadhanti et al. 2021).

The protective effect of albumin on endothelial glycocalyx layer has been shown in our research to reduce lining damage, which is characterized by a decrease in syndecan-1 levels from 7.83 ng/ml to 6.805 ng/ml for 3 days. This research backs up previous findings that albumin administration can protect the endothelial glycocalyx layer. Syndecan-1 levels stabilized in both the treatment and control groups, with both groups significantly lowering syndecan-1 levels ($p = 0.013$ and $p = 0.027$) from the first day levels. It also shows that administration of *Channa striata* extract albumin is able to stabilize the endothelial glycocalyx layer when compared to 20% human albumin intravenously because previous studies have shown that administration of *Channa striata* extract albumin is able to increase albumin levels equivalent to human albumin, so with comparable albumin levels, it turns out from our research that the protective effect on the glycocalyx layer is similar.

## Conclusion

In our study, albumin from *Channa striata* extract was found to be non-inferior than human albumin in protecting the endothelial glycocalyx layer by significantly lowering syndecan-1 levels in septic patients. Even in terms of economic value, albumin derived from *Channa striata* extract outperforms human albumin because, in addition to being less expensive (1/3 the price of human albumin), the raw material is easy to obtain in developing countries with tropical climates. But, because the sample size was relatively small, so it's need further study with complex and more participant and with better design such as randomized control trial.

## Conflict of interest

The authors declare that they have no conflict of interest.

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All procedures in studies involving human participants were carried out in accordance with the institutional and/or national research committee's ethical standards (Dr Moewardi Hospital ethical committee number 1.130 on September 29th, 2020), as well as the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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