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FAKULTAS KEDOKTERAN
DEPARTEMEN BEDAH PLASTIK REKONSTRUKSI DAN ESTETIK
Jalan Mayjen.Prof.Dr.Moestopo 47 Surabaya 60131 Telp. (031) 5020251, Fax (031) 5022472 Website : http://www.fk.unair.ac.id – E-mail : dekan@fk.unair.ac.id

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A	Identitas Karya Ilmiah	
1	**Judul :** Scoping Review: Effects of Probiotics against The Immune System in Burn patients	
2	**Nama Penulis** : Putri Ramadhani1,2 , Suharjono1*, Iswinarno Doso Saputro3 , Ria Fitrah Arfiani4 , Ulfa Syafli Nosa1,2	
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D	Kesesuaian antara lingkup / subjek area jurnal dengan karya ilmiah yang diusulkan	1. Alamat Web Jurnal : https://rjptonline.org/AbstractView.aspx?PID=2023-16-1-61 2. Kebenaran ISSN : 0974-3618 (Print) 0974-360X (Online) 3. Termasuk "Predatory" tidak (jurnal; penerbit) : **tidak masuk pada predatory** 4. Syarat komposisi Editor Board : l**ebih dari negara** 5. Syarat kontributor penulis artikel : **Penulis anggota** 6. Keberkalaan penerbitan : - terbitan pertahun 7. Subjek area dan katagori jurnal : Medicine : 8.
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REVIEW ARTICLE

Scoping Review: Effects of Probiotics against The Immune System in Burn patients

Putri Ramadhani[1,2], Suharjono[1]*, Iswinarno Doso Saputro[3], Ria Fitrah Arfiani[4], Ulfa Syafli Nosa[1,2]

[1]Department of Pharmacy Practice, Universitas Airlangga, Surabaya, East Java, Indonesia.
[2]Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences (STIFARM) Padang, West Sumatra, Indonesia.
[3]Department of Plastic and Reconstructive Surgery, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia.
[4]Department of Pharmacy, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia.
*Corresponding Author E-mail: **suharjono@ff.unair.ac.id**

ABSTRACT:

Background: One of the issues in burn patients is decreasing the body immune system and making it difficult to treat. Probiotics, which are commonly used to treat GI tract imbalances, are also known to be able to modulate the immune system. **Objectives:** This scoping review aims to explore literature about the effects of probiotics on the immune system in burn patients and to identify gaps in the existing literature. **Methods:** A systematic search was conducted in six electronic databases (*PubMed, ScienceDirect, Scopus, Cochrane, EBSCO/CINAHL, DOAJ* and other databases) to identify relevant peer-reviewed studies, with time limits from June 2005 until November 2020, using search terms with database-appropriate keywords. Articles were screened and assessed for eligibility. **Results:** We identified 901 articles. Of these, 10 articles met the inclusion criteria. In this *Scoping Review*, the proportion of probiotic combination types mostly used multi-strain probiotic combinations. The frequency and types of probiotic strains most widely used was *Lactobacillus spp* (58%). The highest concentration of oral probiotics route used was in the total probiotic cell content of 10^9 CFU (42%) and the duration of probiotic administration was 14 days (50%). Meanwhile, improvement of the immune system in burns has been shown by the laboratory outcome parameters (increased the secretion of IgA, decreased of CRP serum, IL-6, leukocytes, and neutrophils), and also the clinical outcome parameters (improvement of GI imbalance, decreased the mortality, decreased the risk of SIRS/sepsis, and shortened Length of Hospital Stay). **Conclusions:** To perform the modulation of the immune system in burns, the optimal dose, strain, and duration of probiotic administration has not been established or still varies widely. Therefore, more clinical studies are needed using placebos or controls to get better validity regarding the evidence of effectiveness and safety at various degrees of burns.

KEYWORDS: Probiotics, *Lactobacillus*, Multistrain, Immune System, Burns.

INTRODUCTION:

Burns are one of the most traumatic cases that occur in children and adults with high morbidity and mortality. The mortality rate for burns in the world is around 180,000 cases per year[1].

The prevalence of burn injuries in Indonesia in 2018 was 1.3%, which has increased by 0.7% compared to 2013 (0.6%). In the majority of burn cases, severe burns worsened by sepsis account for 80-85% of fatalities. The anomalies in the local skin barrier, alterations in normal flora, wound ischaemia, reduced defense factors, and suppression of cellular and humoral immunity all contribute to infection in burn patients. The suppression of the immune system is caused by a pro-inflammatory process that becomes more complicated in the treatment of burns[2].

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The development of Systemic Inflammatory Response Syndrome (SIRS) and sepsis associated with the translocation of pathogenic bacteria from the gastrointestinal tract to the systemic triggers an inflammatory response by releasing inflammatory mediators and apoptosis of immune cells, either cellular or humoral immunity[3].

One of the ways to stabilize the function of mucosal and systemic immunity, especially humoral immunity, in burn patients is by administering probiotics. Probiotics, according to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), are live microorganisms (bacteria or yeast) that, when given in sufficient amounts, can improve the balance of normal flora in humans and do not contain virulent or antibiotic-resistant properties. Probiotics that have been widely used for inflammatory diseases of the gastrointestinal tract also have the effect of modulating the immune system[4]. The way these probiotics work can be used to treat immunocompromised conditions in patients with severe burns through the apoptotic route, especially gastrointestinal epithelial cells[5]. Probiotics that have been widely researched and used are from the lactic acid bacteria, namely *Lactobacillus* and *Bifidobacterium*, which are able to stimulate the mucosal and systemic immune systems[6].

The use of probiotics as a therapeutic modality for burn patients has begun to be widely used. However, this use is still generally controversial, with clinical and pre-clinical trials showing varied results and there is no specific consensus or guideline regarding the use of probiotics in burns. Not many studies have also compared the effect of modulation of the immune system on single strain or multistrain probiotics in burns. In addition, there have been no scoping reviews examining the effectiveness of probiotics in the treatment of burn patients, especially in modulating the immune system. Therefore, it is necessary to conduct a study in the form of a scoping review to identify, assess, and interpret all the clinical scientific evidence regarding the effectiveness of using multi-strains and single strains probiotic that have the potential to increase the mucosal and systemic immune systems (humoral immunity).

MATERIALS AND METHODS:

Materials:

This scoping review was based on Arksey and O'Malley's protocol, which was further developed by Levac et al. and the Joanna Broggs Institute. This scoping review process follows the PRISMA checklist for scoping reviews. The five processes are: 1) defining an initial research topic, 2) identifying relevant studies, 3) study selection, 4) data charting, and 5) summarizing and reporting conclusions[7].

The subject of this study is a research article related to the effect of probiotics on modulating the immune system in burn patients. This research is a Scoping Review study which aims to identify, explore and assess the effect of probiotic administration on modulating the immune system in burn patients through a synthesis of literature studies. The types of research that were included in this study were 10 clinical trials in humans consisting of 8 randomized controlled trials (RCT) and 2 non-RCT (retrospective and prospective cohorts studies) which analyzed the effectiveness of mono-strain and multi-strain combination probiotics on the immune system in burn patients.

Research Question and Eligibility Criteria:

The Population-Concept-Context approach was used to create the research topic. The inclusion criteria for studies were as follows: 1) English-language articles of original research; 2) Quantitative human studies (RCT, observational cohort); 3) the research article that examined the use of probiotics in burn patients. Exclusion criteria included 1) research article using topical probiotics; 2) research that does not mention the type of probiotic strain/combination used in the intervention.

Search Strategy:

The literature was searched using PubMed, ScienceDirect, Scopus, Cochrane Databases of Controlled Trials and Systematic Reviews, EBSCO/CINAHL (Cumulative Index of Nursing and Allied Health Literature), DOAJ, and other databases for articles published in English from June 2005 until the search date of November, 2020. The reason for choosing the database is 5 databases provide the largest scientific evidence/literature in major healthcare databases. The literature search strategy is based on research questions and criteria that are filtered based on their relevance to the study. Search terms used included: "Burns", "Burn injury", "probiotics". These search terms are combined using Boolean Operators, which include the words AND and OR. Medical Subject Headings (MeSH), Boolean operators, truncation, and filters were used to develop a strategy to narrow or widen the search accordingly. For probiotics, there are several synonyms, namely "Lactobacillus" OR "Bifidobacteria" OR "Monostrain" OR "Multistrain", so that the search term "Burn injury" AND "Probiotics" OR "Lactobacillus" OR "Bifidobacteria" OR "Monostrain" OR "Multistrain".

Study Selection and Data Charting:

Article selection followed the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for Scoping Review (see Figure 1). One (1) author reviewed the screened articles by title and abstract for relevance. Full-text articles of

relevant studies then were reviewed and eliminated if they did not meet the inclusion criteria. Any uncertainty about the inclusion of any article was discussed with other authors and resolved by consensus. References were exported to Mendeley and duplicates were eliminated. Data extraction and charting were guided by key findings of included studies. Results were synthesized narratively and were mapped using a heat map, a pie chart, and a bar graph.

RESULT:

In the primary literature search process carried out by the database, it was found that there were 20 articles in the PubMed database, 358 articles in the Science Direct database, 34 articles in the Cochrane database, 46 articles in the Scopus database, 10 articles on CINAHL/EBSCO and several additional literature from other sources/databases. (DOAJ and J-STAGE). The results of the evaluation of article duplication showed 296 articles with the same title and were subsequently excluded from this study. The next evaluation is done by reviewing the title of each article that has been searched based on previously agreed keywords. Furthermore, an evaluation of the articles based on the abstract and quality assessment was carried out, so that the final results of 10 articles were obtained which would then be analyzed in this Scoping Review. The PRISMA flow diagram for selection of studies in scoping review are presented in Figure 1.

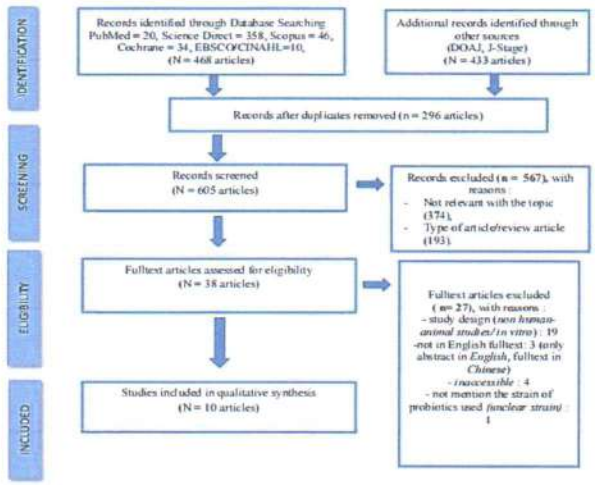

Figure 1: PRISMA Flow Diagram for Selection of Studies in Scoping Review (www.prisma-statement.org)

Characteristics of Research Subject In the Studies included in the Scoping Review (N=10)

Based on the proportion and the type of probiotic strains in the studies included in the Scoping review, mostly used the combination of multi-strain probiotic was 5 studies (50%). The combination of probiotic strain in the studies included are presented in a pie chart in Figure 2.

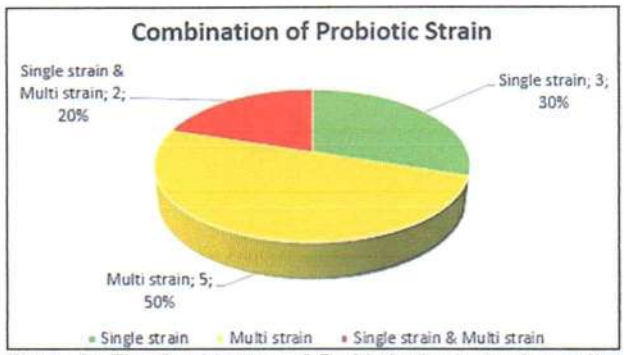

Figure 2: The Combination of Probiotic Strain in the studies included in the Scoping Review

Meanwhile, based on the frequency and types of probiotic strains in the studies included in the Scoping Review, the most frequently strain used were the *Lactobacillus spp.* with as many as 22 strains (58%) and the least frequency of strains used was *Streprococcus spp.* with as many as 6 strains (16%). The frequency and type of probiotic strain in the studies included are presented in a bar graph in Figure 3.

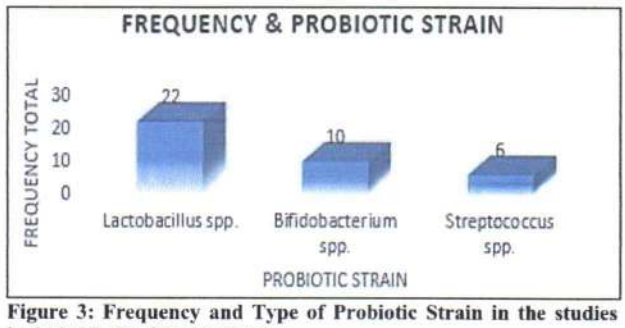

Figure 3: Frequency and Type of Probiotic Strain in the studies included in the Scoping Review

The concentration of oral probiotics in the studies included in this Scoping Review, mostly used the number of probiotic cell contents were 10^9 (CFU); 5 studies (42%), 10^8 (CFU); 4 studies (33%) in multi strains, 10^7 (CFU; 2 studies (17%) on a single strain and at least at a concentration of 10^6 (CFU) that is only 1 study (8%) on a single strain. The concentration of probiotic bacteria cell (CFU) in the studies included are presented in Table 1.

Table 1: The Concentration of Probiotic Bacteria Cell (CFU) in the studies included in the Scoping Review

Strain Combination	Amount of Probiotic Bacteria Cells (Cell Forming Unit/CFU)				
	Oral Route				
	10^5	10^6	10^7	10^8	10^9
Single strain	0	1	2	0	2
Multi strain	0	0	0	4	3
Total	0	1 (8%)	2(17%)	4(33%)	5 (42%)

The research conducted by Koren et al. (2007), who observed the effect of single strain probiotic on sepsis

and its complications in acute burn patients. The study used *L. acidophilus* bacteria (containing 3 x 10^8 CFU/g), with a daily dose of 2 capsules per day (age < 18 years), and 3 capsules per day for (> 18 years) and yogurt (containing 1.5 bacteria. x 10^9 CFU) as much as 2 cups per day[8]. In addition, a study by Tahir et al (2014), which observed the effect of probiotics on burn patients, used an oral probiotic preparation containing > 8 x 10^9 CFU/g of multistrain bacteria *Lactobacillus acidophilus, LA-5, Bifidobacterium BB-12, Streptococcus thermophilus, STY-31, Lactobacillus delbrueckii ssp. Bulgaricus, LBY-27* with a daily dose of 2 sachets per day[9].

Meanwhile, the initial dose of probiotics used in clinical trials in primary study interventions in the scoping review was mostly used on day 4 of 5 studies (50%). The initial dose of probiotic administration in the studies included are presented in a bar graph in Figure 4.

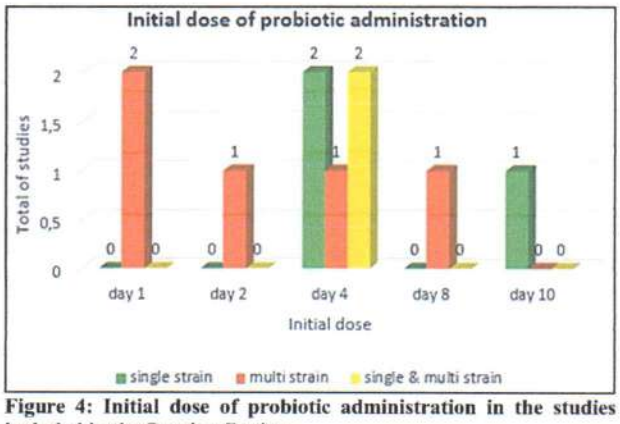

Figure 4: Initial dose of probiotic administration in the studies included in the Scoping Review

The duration of probiotic administration in clinical trials in the Scoping review was mostly used for 14 days of 5 studies (50%). The duration of probiotic administration in the studies included are presented in a bar graph in Figure 5.

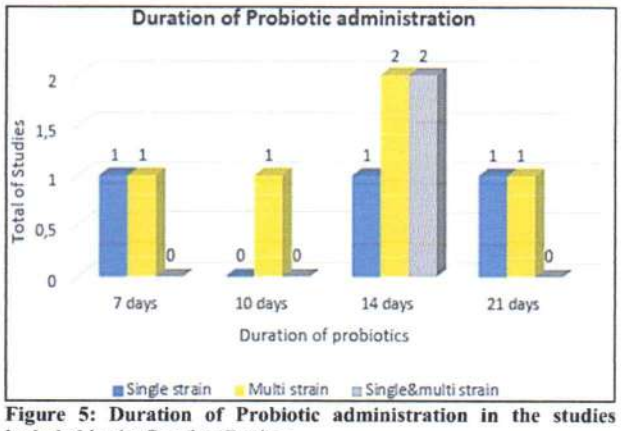

Figure 5: Duration of Probiotic administration in the studies included in the Scoping Review

In one of clinical study by El-Ghazely et al. (2016) was found that the mean IgA levels of the probiotic group increased significantly from day 7 (60.8±4.23mg/dl) to day 14 (98.3±4.89mg/dl) (p=0.033)[10]. The same thing was also shown by the research of Saputro et al. (2019). There was a significant increase in serum IgA levels in single-strain (p<0.001) and multi-strain (p=0.025) probiotics after 14 days of treatment. Meanwhile, on the 19th day (after treatment), the mean of IgA level in the single strain group increased to (1.89±0.98mg/ml) and the multi strain group also increased (2.10±1.09 mg/ml). However, there was no significant difference between the two groups on day 4 or day 19[11].

In a clinical study conducted by Perdanakusuma et al. (2019), there was a higher increase in SIgA levels in the probiotic group of *Bifidobacterium* strains than in the *Lactobacillus* group, although not statistically significant. After 14 days of treatment, fecal sIgA levels in the placebo group, *Lactobacillus* and *Bifidobacterium* showed a significant difference between groups (p=0.029). Significant differences were seen between placebo and *Bifidobacterium* (p=0.027) and between *Lactobacillus* and *Bifidobacterium* (p=0.024). The decrease in sIgA levels was 7.19±15.87mg/dl in placebo, 1.9920±14.76mg/dl in *Lactobacillus*, and an increase in sIgA levels in the *Bifidobacterium* group (58.26±77.41mg/dl), but the difference was not significant (p=0.083). *Bifidobacterium* single strain probiotic supplementation was found to be generally superior to *Lactobacillus* in enhancing intestinal immunity mediated by serum IgA secretion in burn patients in this study[12].

In addition, a similar clinical study, a prospective double-blind RCT trial by Hariani et al. (2019) using multistrain probiotics, it was found that there was a significant difference between the probiotic and control groups (p<0.0001). The mean sIgA level increased in the group given probiotics on day 4 (0.175mg/g) and on day 10(0.259mg/g). Meanwhile, in the group not given probiotics, the mean sIgA was 0.301mg/g on day 4, and on day 10 it decreased to 0.170mg/g (p = 0.004). The difference in mean sIgA levels in the group given probiotics increased by 61.25%, while in the group not given probiotics, sIgA levels decreased by 36.80%[13]. The summary of laboratory outcome measures of sIgA/*Immunoglobulin* A in inflammatory response modulation in the studies included are presented in Table 2.

Table 2. Summary of Laboratory Outcome Measures (sIgA/*Imunoglobulin* A) in Inflammatory Response Modulation in the studies included in the Scoping Review

Author/year	Serum level of IgA (Mean±SD)				
El-Ghazely, Mahmoud, Atia, and Eldip (2016)	**Results**	**Probiotic (mg/dl)**	**Control (mg/dl)**	**p-value**	
	Day-1	57.65 ± 4.65	58.30 ± 5.59		
	Day-4	43.15 ± 3.54	44.50 ± 4.04		
	Day-7	60.80 ± 4.23	57.90 ± 4.26		
	Day-14	98.30 ± 4.89	84.15 ± 4.11	0.003	
Hariani, Wahyudi, Dososaputro, and Sjaifuddin Noer (2019)	**Results**	**Probiotic (mg/g)** (p<0.0001)	**Placebo (mg/g)** (p=0.004)	**p-value**	
	Day-4	0.175	0.301	<0.0001	
	Day-10	0.259	0.170	0.004	
Perdanakusuma, Hariani, Nasser, and Datusanantyo (2019)	**Results**	**Placebo (mg/dl)**	**Lactobacillus group (mg/dl)**	**Bifidobacterium group (mg/dl)**	**p-value**
	Day-4	229.76 ± 61.08	225.91 ± 81.63	274.13 ± 83.95	0.524
	Day-19	222.56 ± 74.22	223.92 ± 68.89	332.38 ± 64.27	0.029
Saputro, Putra, Pebrianton, and Suharjono (2019)	**Results**	**Single strain (mg/ml)**	**Multi strain (mg/ml)**	**p-value**	
	Day-4	1.01 ± 0.67	0.96 ± 0.48	0.874	
	Day-19	1.89 ± 0.98	2.10 ± 1.09	0.683	

A prospective clinical trial RCT by El-Ghazely et al. (2016) found a significant decrease in serum C-reactive protein (CRP) in the probiotic group (p=0.032) from 38.3±3.58mg/dl (day 7) to 14.3±1.28mg/dl (day 14) compared to control[10]. However, contrasting results were obtained by the retrospective cohort study by Fleming et al. (2019). Serum CRP levels increased in the probiotic group (p=0.0046) from day 7(12.3±8.2 pg/ml) to day 14(12.4±5.1 pg/ml) compared to the control group, which decreased on day 7 (13.3±9.5pg/ml) to day 14(9.2±5 pg/ml)[14]. The summary of laboratory outcome measures of CRP/*C-Reactive Protein* Serum in inflammatory response modulation in the studies included are presented in Table 3.

Table 3. Summary of Laboratory Outcome Measures (CRP/*C-Reactive Protein* Serum) in Inflammatory Response Modulation in the studies included in the Scoping Review

Author/ year	Serum level of CRP/*C-Reactive Protein* (Mean±SD)			
El-Ghazely, Mahmoud, Atia, and Eldip (2016)	**Results**	**Probiotic (mg/dl)**	**Control (mg/dl)**	**p-value**
	Day-1	22.7 ± 1.52	23.1 ± 1.82	
	Day-4	42.8 ± 1.79	45.1 ± 1.79	
	Day-7	38.3 ± 3.58	43.5 ± 3.46	
	Day-14	14.3 ± 1.28	19.2 ± 1.79	0.032
Fleming *et al.* (2019)	**Results**	**Probiotic (pg/ml)**	**Placebo (pg/ml)**	**p-value**
	Day-7	12.3 ± 8.2	12.4 ± 5.1	
	Day-14	13.3 ± 9.5	9.2 ± 5.0	0.0068

IL-6 is released by T cells and is activated by macrophages during the acute phase response following injury or trauma and can cause inflammation or infection. IL-6 has pro and anti-inflammatory properties[15].

A prospective double-blind RCT clinical study conducted by Saputro et al. (2019) concluded that multi-strain probiotics decreased IL-6 levels, but there was no significant difference in the single-strain probiotic group from day 4(153.7±131.4pg/ml) to day 19(164.1±126.9 pg/ml). ml) (p=0.804) or multi-strain from day 4 (139.2±108.8pg/ml) to day 19(114.1±123.5pg/ml) (p=0.683)[11]. Meanwhile, it is also supported by previous pre-clinical studies by Argenta et al. (2016) also received probiotic therapy successfully suppressed the response of inflammatory cytokines (TNF-α, IL-6 and IL-10) in the liver[16]. The summary of laboratory outcome measures of IL-6/Interleukin-6 in inflammatory response modulation in the studies included are presented in Table 4.

Table 4: Summary of Laboratory Outcome Measures (IL-6/Interleukin-6) in Inflammatory Response Modulation in the studies included in the Scoping Review

Author/year	Serum level of *Interleukin*-6/IL-6 (Mean±SD)			
Saputro, Putra, Pebrianton, and Suharjono (2019)	**Results**	**Single strain (pg/ml) (n=8)**	**Multi strain (pg/ml) (n=9)**	**p-value**
	Day-4	153.7 ± 131.4	139.2 ± 108.8	0.804
	Day-19	164.1 ± 126.9	114.1 ± 123.5	0.683

Reducing the Incidence of SIRS/Sepsis:

Probiotics can be an additional therapeutic modality in reducing the incidence of infection, complications of sepsis, and reducing morbidity and mortality in patients with acute extensive burns. A prospective clinical trial RCT conducted by Putra et al. (2017) showed that in the multi-strain group, the average change in leukocyte levels decreased from day-4 (18.07 x 103/mm3) to day-19 (11.88 x 103/mm3) (p = 0.044) which means there

are significant changes in the decrease in leukocyte levels before and after multi-strain probiotic administration. As for neutrophils, in the multistrain group, the average change in neutrophil levels decreased significantly from day-4 (87.6%) to day-19 (79.58%) (p=0.011)[18].

In the study of El-Ghazely et al. (2016), they examined a tendency to decrease the incidence of infection in the probiotic group (7/35%) compared to the control (12/60%), but not significantly (p=0.113)[10]. The summary of laboratory outcome measures of leukocyte and neutrophil in SIRS/sepsis indicator in the studies included are presented in Table 5.

Table 5. Summary of Laboratory Outcome Measures (Leukocyte and Neutrophil) in SIRS/sepsis indicator in the studies included in the Scoping Review

Author/year	**Average Leukocyte and Neutrophil Level (Mean±SD)**			
Putra, Pebrianton, Suharjono, Iswinarno, and Rahayu (2017)	**Level of leukocytes (10^3/mm^3)**	**Mono strain (n=8)**	**Multi strain (n=9)**	**p-value**
	Day-4	16.90 ± 4.98	18.07 ± 7.14	0.705
	Day-19	15.68 ± 6.27	11.88 ± 4.90	0.189
	Level of Neutrophile (%)	**Mono strain (n=8)**	**Multi strain (n=9)**	**p-value**
	Day-4	86.3 ± 46.3	87.6 ± 6.9	0.709
	Day-19	87.01 ± 5.9	79.58 ± 3.9	0.026
El-Ghazely, Mahmoud, Atia, and Eldip (2016)	**Amount of TLC/*Total lymphocyte count* (cell/mm^3)**	**Probiotic**	**Control**	**p-value**
	Day-1	1926 ± 70	2005 ± 84	
	Day-4	1688 ± 76	1736 ± 90	
	Day-7	2075 ± 86	2053 ± 92	
	Day-14	2630 ± 89	2407 ± 83	0.076
Tahir *et al.* (2014)	**Amount of Leukocytes (10^3/mm^3)**	**Probiotic**	**Control**	**p-value**
		46/68 (67.64% CBC)	80/116 (68.96% CBC)	0.9685

Improving GI tract Imbalance:

Some evidence shows that multi-strain probiotics can reduce intestinal permeability by increasing the intercellular gap in the outer layer of the intestine, which is finally able to reduce the translocation of pathogenic bacteria from the intestine into the system[20].

In several studies, probiotics are believed to improve gastrointestinal balance disorders in burn conditions. One of the clinical study conducted by El-ghazely et al. (2016) in pediatric burn patients, showed a significant increase in the frequency of flatulence in the probiotic group (P = 0.006) and also a significant decrease in the frequency of diarrhea compared to the control group (p = 0.038)[10].

Similar results were also obtained in a clinical trial by Mayes et al. (2015) that patients in the probiotic group had a significantly higher incidence of flatulence (P < 0.02) and reduced diarrhea frequency and the need for laxative use[19]. While the clinical study by Saputro et al. (2019) stated that there was no incidence of diarrhea in the group of patients who were given probiotics[11]. The clinical study by Patsera et al. (2016) also found that probiotics were shown to reduce the incidence of antibiotic-associated diarrhea (Antibiotic Associated-Diarrhea) in pediatric burn patients and were able to reduce its severity 3-4 times[21].

However, contrasting results demonstrated by clinical studies by Fleming et al. (2019) that group A (giving probiotics for 3 days or more during the first week of treatment) experienced an increase in the frequency of diarrhea by 80% (p=0.001) compared to group C (control) which was only 35.7%[14].

Reducing the Mortality Rates:

In a clinical study by El-Ghazely et al. (2016), they did not find any mortality in either group (0%)[10]. Similar to the results of a clinical study by Tahir et al. (2014) that the mortality rate was lower in the probiotic group (5/22%) than the control group (11/26%) (p=0.9529)[9]. Another clinical study by Mayes et al. (2016) found a significantly higher mortality (P<0.005) in patients with TBSA > 40% in the control group than in burn patients receiving probiotics[19].

While the research results shown by Koren et al. (2007) in a retrospective cohort study evaluating the effect of Lactobacillus supplementation on sepsis in acute burn patients found that the mortality rate was lower in the probiotic group than in the control group (2 vs 7), but the difference was not significant (p=0.071). Meanwhile, in contrast to the 41-70% TBSA subgroup, the mortality rate was significantly lower in the probiotic group than in the control group (0 vs 5) (p<0.01). This contrasts with the literature that mentions burns of more than 20% of the total body surface area (TBSA), impaired immune system function proportional to the size of the burn[3]. These results were associated with the control group having a higher mortality rate, with fewer patients surviving and developing septic complications[8].

Reducing the Skin Graft and Shorten of LOS:
According to El Ghazely et al. (2016), there was a significant decrease (p=0.028) in the need for skin grafts 2(10%) in the probiotic group and 8(40%) in the control group, as well as a shortening of the length of stay of burn patients in the hospital (LOS/Length of Hospital Stay) (p=0.044) in the probiotic group (17.25±0.497) was significantly lower than the control group (21.9±2.178)[10]. Similar to the results of this study, Mayes et al. (2016) evaluated the safety and effectiveness of probiotics in pediatric burn patients. The results showed that the number of days required for operative procedures (skin graft/excision) was lower in the probiotic treatment group (2.3±0.5days) than the control (3.3±0.6) (p<0.23), and shorter wound healing time. (p<0.23)[19].

DISCUSSION:

This scoping review of 10 journal articles identified the clinical trial in humans, consisting of 8 prospective randomized controlled trials (RCT) and 2 retrospective and prospective cohort studies. In this study, all articles were analyzed using probiotic preparations, both mono-strain and multi-strain combinations as one component of the research experiment in each study.

Probiotic strains used for human consumption must be of human origin, non-pathogenic, and capable of surviving gastrointestinal transit in order to provide health benefits to humans[23]. Bacteria that meet the criteria as probiotics are generally lactic acid bacteria, especially *Lactobacillus* and *Bifidobacterium* species, but *Lactococcus, Streptococcus, Enterococcus* species, as well as some non-pathogenic *Eschericia coli* and yeast strains can also qualify as probiotics. Recent evidence suggests that probiotic strains can have the same activities as commensal bacteria, including immunomodulatory[24].

Preparations containing probiotics must meet the minimum criteria for probiotic bacteria of 10^6 CFU/ml at the expiration date, because the recommended minimum daily therapeutic dose is 10^8-10^9 cells. For mono strains, using a patented probiotic product consist of mixed bacteria with a composition containing one of *Lactobacillus strain* and/or one of *Bifidobacteria strain*, such as, *L. acidophilus*, *B. longum*, and *S. thermophilus*, with a total viable bacteria of 6 x 10^7 CFU/g. Meanwhile, multi-strain probiotic uses a patented probiotic product consisting of mix bacteria with the composition *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. breve, B. longum*, and *S.s thermophilus* with a total viable bacteria of more than 10^8 CFU/g to produce the composition optimal synergy bacteria[20].

Selection of appropriate probiotic strains to be able to give a positive effect must be appropriate as the basic ability to be able to induce an improvement in the intestinal immune response without modifying intestinal hemostasis. To be able to modulate the immune system, both the innate and adaptive immune systems, probiotic bacteria are dose dependent and strain dependent. Several strains of *Lactobacillus* and *Bifidobacteria* have been shown to induce the production of secretory IgA and IgG. High concentrations of IgA activity in the gastrointestinal tract are important to maintain a barrier against translocation of pathogenic bacteria, especially gram-negative bacteria[25]. This is considering that not all strains of *Lactobacillus* and *Bifidobacteria* have the same effect regarding the modulation of the immune system.

The concentration of probiotics required to exert a clinical effect is often stated as 10^6 cfu/ml in the small intestine and 10^8 cfu/g in the colon. Some literature states that to be able to provide benefits through modulation of the immune system, the recommended minimum daily dose of probiotics is in the range of 10^7-10^9. Several studies examining the benefits of probiotics on burns, types of probiotic strains and the daily dose used have not been widely established or still vary, so that, the results between these studies are also varied[23].

Based on several clinical studies that have been carried out, the recommended route of administration and dosage of probiotics to have an immunomodulatory effect in burn patients is the oral administration route with a daily dose of once-twice a day containing 10^7-10^9 CFU/g bacteria, and multi-probiotics. Strains are more recommended as a therapeutic modality in providing clinical effects in burn patients. This is also in accordance with some literature that to provide benefits through modulating the immune system, the recommended minimum daily dose of probiotics is in the range of 10^7-10^9 [26] The concentration of probiotics required to exert a clinical effect is often stated as 10^6 cfu/ml in the small intestine and 10^8 cfu/g in the colon [20].

In addition, the optimal duration of probiotic administration in burns is not yet fully known and how long probiotics are able to colonize, balance the intestinal microflora, and provide an immune response, especially in burns, is also not fully known[20]. Based on the literature, the initial dose of probiotics ranged from 1-7 days after the first dose of antibiotics. For strains of *Saccharomyces*, *Lactobacillus*, and *Lactobacillus spp.*, the combination with other species, ranged from 2-3 days, 1-3 days, and 1-7 days, respectively[23].

Changes in intestinal function as a cause of the development of sepsis in a critical direction, so that the

Scoping Review Effects of Probiotics against The Immune System in Burn patients

by Putri Ramadhani

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REVIEW ARTICLE

Scoping Review: Effects of Probiotics against The Immune System in Burn patients

Putri Ramadhani[1,2], Suharjono[1]*, Iswinarno Doso Saputro[3], Ria Fitrah Arfiani[4], Ulfa Syafli Nosa[1,2]

[1]Department of Pharmacy Practice, Universitas Airlangga, Surabaya, East Java, Indonesia.
[2]Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences (STIFARM) Padang, West Sumatra, Indonesia.
[3]Department of Plastic and Reconstructive Surgery, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia.
[4]Department of Pharmacy, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia.
*Corresponding Author E-mail: **suharjono@ff.unair.ac.id**

ABSTRACT:

Background: One of the issues in burn patients is decreasing the body immune system and making it difficult to treat. Probiotics, which are commonly used to treat GI tract imbalances, are also known to be able to modulate the immune system. **Objectives:** This scoping review aims to explore literature about the effects of probiotics on the immune system in burn patients and to identify gaps in the existing literature. **Methods:** A systematic search was conducted in six electronic databases (*PubMed, ScienceDirect, Scopus, Cochrane, EBSCO/CINAHL, DOAJ* and other databases) to identify relevant peer-reviewed studies, with time limits from June 2005 until November 2020, using search terms with database-appropriate keywords. Articles were screened and assessed for eligibility. **Results:** We identified 901 articles. Of these, 10 articles met the inclusion criteria. In this *Scoping Review*, the proportion of probiotic combination types mostly used multi-strain probiotic combinations. The frequency and types of probiotic strains most widely used was *Lactobacillus spp* (58%). The highest concentration of oral probiotics route used was in the total probiotic cell content of 10^9 CFU (42%) and the duration of probiotic administration was 14 days (50%). Meanwhile, improvement of the immune system in burns has been shown by the laboratory outcome parameters (increased the secretion of IgA, decreased of CRP serum, IL-6, leukocytes, and neutrophils), and also the clinical outcome parameters (improvement of GI imbalance, decreased the mortality, decreased the risk of SIRS/sepsis, and shortened Length of Hospital Stay). **Conclusions:** To perform the modulation of the immune system in burns, the optimal dose, strain, and duration of probiotic administration has not been established or still varies widely. Therefore, more clinical studies are needed using placebos or controls to get better validity regarding the evidence of effectiveness and safety at various degrees of burns.

KEYWORDS: Probiotics, *Lactobacillus*, Multistrain, Immune System, Burns.

INTRODUCTION:

Burns are one of the most traumatic cases that occur in children and adults with high morbidity and mortality. The mortality rate for burns in the world is around 180,000 cases per year[1].

The prevalence of burn injuries in Indonesia in 2018 was 1.3%, which has increased by 0.7% compared to 2013 (0.6%). In the majority of burn cases, severe burns worsened by sepsis account for 80-85% of fatalities. The anomalies in the local skin barrier, alterations in normal flora, wound ischaemia, reduced defense factors, and suppression of cellular and humoral immunity all contribute to infection in burn patients. The suppression of the immune system is caused by a pro-inflammatory process that becomes more complicated in the treatment of burns[2].

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The development of Systemic Inflammatory Response Syndrome (SIRS) and sepsis associated with the translocation of pathogenic bacteria from the gastrointestinal tract to the systemic triggers an inflammatory response by releasing inflammatory mediators and apoptosis of immune cells, either cellular or humoral immunity[3].

One of the ways to stabilize the function of mucosal and systemic immunity, especially humoral immunity, in burn patients is by administering probiotics. Probiotics, according to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), are live microorganisms (bacteria or yeast) that, when given in sufficient amounts, can improve the balance of normal flora in humans and do not contain virulent or antibiotic-resistant properties. Probiotics that have been widely used for inflammatory diseases of the gastrointestinal tract also have the effect of modulating the immune system[4]. The way these probiotics work can be used to treat immunocompromised conditions in patients with severe burns through the apoptotic route, especially gastrointestinal epithelial cells[5]. Probiotics that have been widely researched and used are from the lactic acid bacteria, namely *Lactobacillus* and *Bifidobacterium*, which are able to stimulate the mucosal and systemic immune systems[6].

The use of probiotics as a therapeutic modality for burn patients has begun to be widely used. However, this use is still generally controversial, with clinical and pre-clinical trials showing varied results and there is no specific consensus or guideline regarding the use of probiotics in burns. Not many studies have also compared the effect of modulation of the immune system on single strain or multistrain probiotics in burns. In addition, there have been no scoping reviews examining the effectiveness of probiotics in the treatment of burn patients, especially in modulating the immune system. Therefore, it is necessary to conduct a study in the form of a scoping review to identify, assess, and interpret all the clinical scientific evidence regarding the effectiveness of using multi-strains and single strains probiotic that have the potential to increase the mucosal and systemic immune systems (humoral immunity).

MATERIALS AND METHODS:

Materials:

This scoping review was based on Arksey and O'Malley's protocol, which was further developed by Levac et al. and the Joanna Broggs Institute. This scoping review process follows the PRISMA checklist for scoping reviews. The five processes are: 1) defining an initial research topic, 2) identifying relevant studies, 3) study selection, 4) data charting, and 5) summarizing and reporting conclusions[7].

The subject of this study is a research article related to the effect of probiotics on modulating the immune system in burn patients. This research is a Scoping Review study which aims to identify, explore and assess the effect of probiotic administration on modulating the immune system in burn patients through a synthesis of literature studies. The types of research that were included in this study were 10 clinical trials in humans consisting of 8 randomized controlled trials (RCT) and 2 non-RCT (retrospective and prospective cohorts studies) which analyzed the effectiveness of mono-strain and multi-strain combination probiotics on the immune system in burn patients.

Research Question and Eligibility Criteria:

The Population-Concept-Context approach was used to create the research topic. The inclusion criteria for studies were as follows: 1) English-language articles of original research; 2) Quantitative human studies (RCT, observational cohort); 3) the research article that examined the use of probiotics in burn patients. Exclusion criteria included 1) research article using topical probiotics; 2) research that does not mention the type of probiotic strain/combination used in the intervention.

Search Strategy:

The literature was searched using PubMed, ScienceDirect, Scopus, Cochrane Databases of Controlled Trials and Systematic Reviews, EBSCO/CINAHL (Cumulative Index of Nursing and Allied Health Literature), DOAJ, and other databases for articles published in English from June 2005 until the search date of November, 2020. The reason for choosing the database is 5 databases provide the largest scientific evidence/literature in major healthcare databases. The literature search strategy is based on research questions and criteria that are filtered based on their relevance to the study. Search terms used included: "Burns", "Burn injury", "probiotics". These search terms are combined using Boolean Operators, which include the words AND and OR. Medical Subject Headings (MeSH), Boolean operators, truncation, and filters were used to develop a strategy to narrow or widen the search accordingly. For probiotics, there are several synonyms, namely "Lactobacillus" OR "Bifidobacteria" OR "Monostrain" OR "Multistrain", so that the search term "Burn injury" AND "Probiotics" OR "Lactobacillus" OR "Bifidobacteria" OR "Monostrain" OR "Multistrain".

Study Selection and Data Charting:

Article selection followed the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for Scoping Review (see Figure 1). One (1) author reviewed the screened articles by title and abstract for relevance. Full-text articles of

relevant studies then were reviewed and eliminated if they did not meet the inclusion criteria. Any uncertainty about the inclusion of any article was discussed with other authors and resolved by consensus. References were exported to Mendeley and duplicates were eliminated. Data extraction and charting were guided by key findings of included studies. Results were synthesized narratively and were mapped using a heat map, a pie chart, and a bar graph.

RESULT:

In the primary literature search process carried out by the database, it was found that there were 20 articles in the PubMed database, 358 articles in the Science Direct database, 34 articles in the Cochrane database, 46 articles in the Scopus database, 10 articles on CINAHL/EBSCO and several additional literature from other sources/databases. (DOAJ and J-STAGE). The results of the evaluation of article duplication showed 296 articles with the same title and were subsequently excluded from this study. The next evaluation is done by reviewing the title of each article that has been searched based on previously agreed keywords. Furthermore, an evaluation of the articles based on the abstract and quality assessment was carried out, so that the final results of 10 articles were obtained which would then be analyzed in this Scoping Review. The PRISMA flow diagram for selection of studies in scoping review are presented in Figure 1.

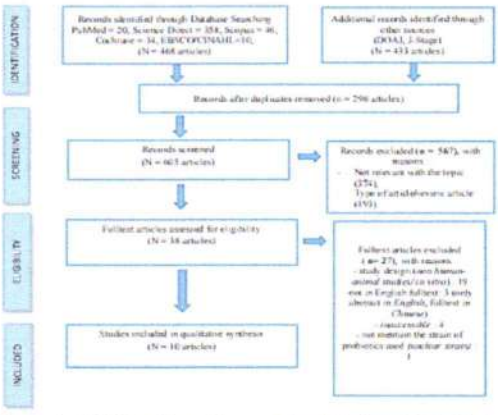

Figure 1: PRISMA Flow Diagram for Selection of Studies in Scoping Review (www.prisma-statement.org)

Characteristics of Research Subject In the Studies included in the Scoping Review (N=10)

Based on the proportion and the type of probiotic strains in the studies included in the Scoping review, mostly used the combination of multi-strain probiotic was 5 studies (50%). The combination of probiotic strain in the studies included are presented in a pie chart in Figure 2.

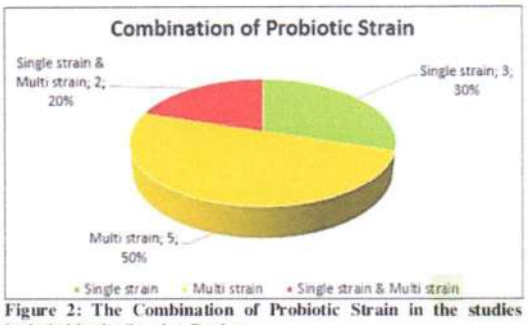

Figure 2: The Combination of Probiotic Strain in the studies included in the Scoping Review

Meanwhile, based on the frequency and types of probiotic strains in the studies included in the Scoping Review, the most frequently strain used were the *Lactobacillus spp.* with as many as 22 strains (58%) and the least frequency of strains used was *Streprococcus spp.* with as many as 6 strains (16%). The frequency and type of probiotic strain in the studies included are presented in a bar graph in Figure 3.

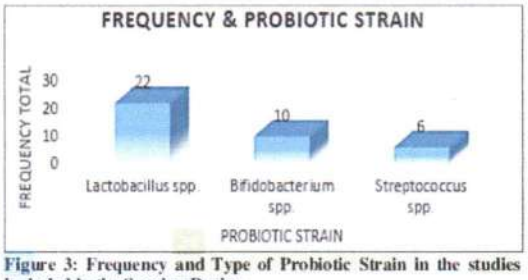

Figure 3: Frequency and Type of Probiotic Strain in the studies included in the Scoping Review

The concentration of oral probiotics in the studies included in this Scoping Review, mostly used the number of probiotic cell contents were 10^9 (CFU); 5 studies (42%), 10^8 (CFU); 4 studies (33%) in multi strains, 10^7 (CFU; 2 studies (17%) on a single strain and at least at a concentration of 10^6 (CFU) that is only 1 study (8%) on a single strain. The concentration of probiotic bacteria cell (CFU) in the studies included are presented in Table 1.

Table 1: The Concentration of Probiotic Bacteria Cell (CFU) in the studies included in the Scoping Review

Strain Combination	Amount of Probiotic Bacteria Cells (Cell Forming Unit/CFU)				
	Oral Route				
	10^5	10^6	10^7	10^8	10^9
Single strain	0	1	2	0	2
Multi strain	0	0	0	4	3
Total	0	1 (8%)	2(17%)	4(33%)	5 (42%)

The research conducted by Koren et al. (2007), who observed the effect of single strain probiotic on sepsis

and its complications in acute burn patients. The study used *L. acidophilus* bacteria (containing 3 x 10^8 CFU/g), with a daily dose of 2 capsules per day (age < 18 years), and 3 capsules per day for (> 18 years) and yogurt (containing 1.5 bacteria. x 10^9 CFU) as much as 2 cups per day[8]. In addition, a study by Tahir et al (2014), which observed the effect of probiotics on burn patients, used an oral probiotic preparation containing > 8 x 10^9 CFU/g of multistrain bacteria *Lactobacillus acidophilus, LA-5, Bifidobacterium BB-12, Streptococcus thermophilus, STY-31, Lactobacillus delbrueckii ssp. Bulgaricus, LBY-27* with a daily dose of 2 sachets per day[9].

Meanwhile, the initial dose of probiotics used in clinical trials in primary study interventions in the scoping review was mostly used on day 4 of 5 studies (50%). The initial dose of probiotic administration in the studies included are presented in a bar graph in Figure 4.

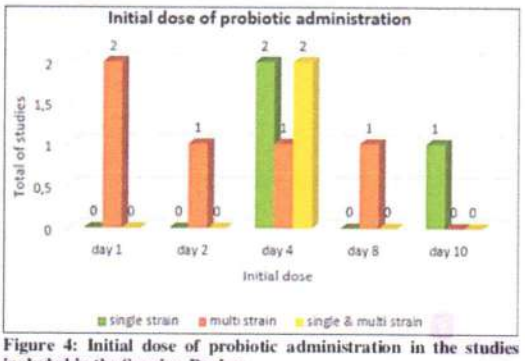

Figure 4: Initial dose of probiotic administration in the studies included in the Scoping Review

The duration of probiotic administration in clinical trials in the Scoping review was mostly used for 14 days of 5 studies (50%). The duration of probiotic administration in the studies included are presented in a bar graph in Figure 5.

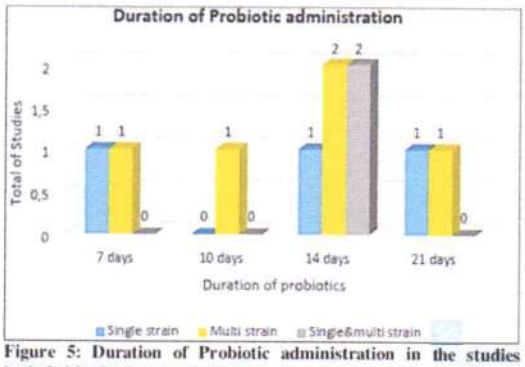

Figure 5: Duration of Probiotic administration in the studies included in the Scoping Review

In one of clinical study by El-Ghazely et al. (2016) was found that the mean IgA levels of the probiotic group increased significantly from day 7 (60.8±4.23mg/dl) to day 14 (98.3±4.89mg/dl) (p=0.033)[10]. The same thing was also shown by the research of Saputro et al. (2019). There was a significant increase in serum IgA levels in single-strain (p<0.001) and multi-strain (p=0.025) probiotics after 14 days of treatment. Meanwhile, on the 19th day (after treatment), the mean of IgA level in the single strain group increased to (1.89±0.98mg/ml) and the multi strain group also increased (2.10±1.09 mg/ml). However, there was no significant difference between the two groups on day 4 or day 19[11].

In a clinical study conducted by Perdanakusuma et al. (2019), there was a higher increase in SIgA levels in the probiotic group of *Bifidobacterium* strains than in the *Lactobacillus* group, although not statistically significant. After 14 days of treatment, fecal sIgA levels in the placebo group, *Lactobacillus* and *Bifidobacterium* showed a significant difference between groups (p=0.029). Significant differences were seen between placebo and *Bifidobacterium* (p=0.027) and between *Lactobacillus* and *Bifidobacterium* (p=0.024). The decrease in sIgA levels was 7.19±15.87mg/dl in placebo, 1.9920±14.76mg/dl in *Lactobacillus*, and an increase in sIgA levels in the *Bifidobacterium* group (58.26±77.41mg/dl), but the difference was not significant (p=0.083). *Bifidobacterium* single strain probiotic supplementation was found to be generally superior to *Lactobacillus* in enhancing intestinal immunity mediated by serum IgA secretion in burn patients in this study[12].

In addition, a similar clinical study, a prospective double-blind RCT trial by Hariani et al. (2019) using multistrain probiotics, it was found that there was a significant difference between the probiotic and control groups (p<0.0001). The mean sIgA level increased in the group given probiotics on day 4 (0.175mg/g) and on day 10(0.259mg/g). Meanwhile, in the group not given probiotics, the mean sIgA was 0.301mg/g on day 4, and on day 10 it decreased to 0.170mg/g (p = 0.004). The difference in mean sIgA levels in the group given probiotics increased by 61.25%, while in the group not given probiotics, sIgA levels decreased by 36.80%[13]. The summary of laboratory outcome measures of sIgA/*Immunoglobulin* A in inflammatory response modulation in the studies included are presented in Table 2.

Table 2. Summary of Laboratory Outcome Measures (sIgA/*Imunoglobulin* A) in Inflammatory Response Modulation in the studies included in the Scoping Review

Author/year	Serum level of IgA (Mean±SD)				
El-Ghazely, Mahmoud, Atia, and Eldip (2016)	**Results**	**Probiotic (mg/dl)**	**Control (mg/dl)**	**p-value**	
	Day-1	57.65 ± 4.65	58.30 ± 5.59		
	Day-4	43.15 ± 3.54	44.50 ± 4.04		
	Day-7	60.80 ± 4.23	57.90 ± 4.26		
	Day-14	98.30 ± 4.89	84.15 ± 4.11	0.003	
Hariani, Wahyudi, Dososaputro, and Sjaifuddin Noer (2019)	**Results**	**Probiotic (mg/g) (p<0.0001)**	**Placebo (mg/g) (p=0.004)**	**p-value**	
	Day-4	0.175	0.301	<0.0001	
	Day-10	0.259	0.170	0.004	
Perdanakusuma, Hariani, Nasser, and Datusanantyo (2019)	**Results**	**Placebo (mg/dl)**	**Lactobacillus group (mg/dl)**	**Bifidobacterium group (mg/dl)**	**p-value**
	Day-4	229.76 ± 61.08	225.91 ± 81.63	274.13 ± 83.95	0.524
	Day-19	222.56 ± 74.22	223.92 ± 68.89	332.38 ± 64.27	0.029
Saputro, Putra, Pebrianton, and Suharjono (2019)	**Results**	**Single strain (mg/ml)**	**Multi strain (mg/ml)**	**p-value**	
	Day-4	1.01 ± 0.67	0.96 ± 0.48	0.874	
	Day-19	1.89 ± 0.98	2.10 ± 1.09	0.683	

A prospective clinical trial RCT by El-Ghazely et al. (2016) found a significant decrease in serum C-reactive protein (CRP) in the probiotic group (p=0.032) from 38.3±3.58mg/dl (day 7) to 14.3±1.28mg/dl (day 14) compared to control[10]. However, contrasting results were obtained by the retrospective cohort study by Fleming et al. (2019). Serum CRP levels increased in the probiotic group (p=0.0046) from day 7(12.3±8.2 pg/ml) to day 14(12.4±5.1 pg/ml) compared to the control group, which decreased on day 7 (13.3±9.5pg/ml) to day 14(9.2±5 pg/ml)[14]. The summary of laboratory outcome measures of CRP/*C-Reactive Protein* Serum in inflammatory response modulation in the studies included are presented in Table 3.

Table 3. Summary of Laboratory Outcome Measures (CRP/*C-Reactive Protein* Serum) in Inflammatory Response Modulation in the studies included in the Scoping Review

Author/ year	Serum level of CRP/*C-Reactive Protein* (Mean±SD)			
El-Ghazely, Mahmoud, Atia, and Eldip (2016)	**Results**	**Probiotic (mg/dl)**	**Control (mg/dl)**	**p-value**
	Day-1	22.7 ± 1.52	23.1 ± 1.82	
	Day-4	42.8 ± 1.79	45.1 ± 1.79	
	Day-7	38.3 ± 3.58	43.5 ± 3.46	
	Day-14	14.3 ± 1.28	19.2 ± 1.79	0.032
Fleming *et al.* (2019)	**Results**	**Probiotic (pg/ml)**	**Placebo (pg/ml)**	**p-value**
	Day-7	12.3 ± 8.2	12.4 ± 5.1	
	Day-14	13.3 ± 9.5	9.2 ± 5.0	0.0068

IL-6 is released by T cells and is activated by macrophages during the acute phase response following injury or trauma and can cause inflammation or infection. IL-6 has pro and anti-inflammatory properties[15].

A prospective double-blind RCT clinical study conducted by Saputro et al. (2019) concluded that multi-strain probiotics decreased IL-6 levels, but there was no significant difference in the single-strain probiotic group from day 4(153.7±131.4pg/ml) to day 19(164.1±126.9 pg/ml). ml) (p=0.804) or multi-strain from day 4 (139.2±108.8pg/ml) to day 19(114.1±123.5pg/ml) (p=0.683)[11]. Meanwhile, it is also supported by previous pre-clinical studies by Argenta et al. (2016) also received probiotic therapy successfully suppressed the response of inflammatory cytokines (TNF-α, IL-6 and IL-10) in the liver[16]. The summary of laboratory outcome measures of IL-6/Interleukin-6 in inflammatory response modulation in the studies included are presented in Table 4.

Table 4: Summary of Laboratory Outcome Measures (IL-6/Interleukin-6) in Inflammatory Response Modulation in the studies included in the Scoping Review

Author/year	Serum level of *Interleukin*-6/IL-6 (Mean±SD)			
Saputro, Putra, Pebrianton, and Suharjono (2019)	**Results**	**Single strain (pg/ml) (n=8)**	**Multi strain (pg/ml) (n=9)**	**p-value**
	Day-4	153.7 ± 131.4	139.2 ± 108.8	0.804
	Day-19	164.1 ± 126.9	114.1 ± 123.5	0.683

Reducing the Incidence of SIRS/Sepsis:

Probiotics can be an additional therapeutic modality in reducing the incidence of infection, complications of sepsis, and reducing morbidity and mortality in patients with acute extensive burns. A prospective clinical trial RCT conducted by Putra et al. (2017) showed that in the multi-strain group, the average change in leukocyte levels decreased from day-4 (18.07 x 103/mm3) to day-19 (11.88 x 103/mm3) (p = 0.044) which means there

are significant changes in the decrease in leukocyte levels before and after multi-strain probiotic administration. As for neutrophils, in the multistrain group, the average change in neutrophil levels decreased significantly from day-4 (87.6%) to day-19 (79.58%) (p=0.011)[18].

In the study of El-Ghazely et al. (2016), they examined a tendency to decrease the incidence of infection in the probiotic group (7/35%) compared to the control (12/60%), but not significantly (p=0.113)[10]. The summary of laboratory outcome measures of leukocyte and neutrophil in SIRS/sepsis indicator in the studies included are presented in Table 5.

Table 5. Summary of Laboratory Outcome Measures (Leukocyte and Neutrophil) in SIRS/sepsis indicator in the studies included in the Scoping Review

Author/year	Average Leukocyte and Neutrophil Level (Mean±SD)			
Putra, Pebrianton, Suharjono, Iswinarno, and Rahayu (2017)	**Level of leukocytes (10^3/mm^3)**	**Mono strain (n=8)**	**Multi strain (n=9)**	**p-value**
	Day-4	16.90 ± 4.98	18.07 ± 7.14	0.705
	Day-19	15.68 ± 6.27	11.88 ± 4.90	0.189
	Level of Neutrophile (%)	**Mono strain (n=8)**	**Multi strain (n=9)**	**p-value**
	Day-4	86.3 ± 46.3	87.6 ± 6.9	0.709
	Day-19	87.01 ± 5.9	79.58 ± 3.9	0.026
El-Ghazely, Mahmoud, Atia, and Eldip (2016)	**Amount of TLC/*Total lymphocyte count* (cell/mm^3)**	**Probiotic**	**Control**	**p-value**
	Day-1	1926 ± 70	2005 ± 84	
	Day-4	1688 ± 76	1736 ± 90	
	Day-7	2075 ± 86	2053 ± 92	
	Day-14	2630 ± 89	2407 ± 83	0.076
Tahir *et al.* (2014)	**Amount of Leukocytes (10^3/mm^3)**	**Probiotic**	**Control**	**p-value**
		46/68 (67.64% CBC)	80/116 (68.96% CBC)	0.9685

Improving GI tract Imbalance:

Some evidence shows that multi-strain probiotics can reduce intestinal permeability by increasing the intercellular gap in the outer layer of the intestine, which is finally able to reduce the translocation of pathogenic bacteria from the intestine into the system[20].

In several studies, probiotics are believed to improve gastrointestinal balance disorders in burn conditions. One of the clinical study conducted by El-ghazely et al. (2016) in pediatric burn patients, showed a significant increase in the frequency of flatulence in the probiotic group (P = 0.006) and also a significant decrease in the frequency of diarrhea compared to the control group (p = 0.038)[10].

Similar results were also obtained in a clinical trial by Mayes et al. (2015) that patients in the probiotic group had a significantly higher incidence of flatulence (P < 0.02) and reduced diarrhea frequency and the need for laxative use[19]. While the clinical study by Saputro et al. (2019) stated that there was no incidence of diarrhea in the group of patients who were given probiotics[11]. The clinical study by Patsera et al. (2016) also found that probiotics were shown to reduce the incidence of antibiotic-associated diarrhea (Antibiotic Associated-Diarrhea) in pediatric burn patients and were able to reduce its severity 3-4 times[21].

However, contrasting results demonstrated by clinical studies by Fleming et al. (2019) that group A (giving probiotics for 3 days or more during the first week of treatment) experienced an increase in the frequency of diarrhea by 80% (p=0.001) compared to group C (control) which was only 35.7%[14].

Reducing the Mortality Rates:

In a clinical study by El-Ghazely et al. (2016), they did not find any mortality in either group (0%)[10]. Similar to the results of a clinical study by Tahir et al. (2014) that the mortality rate was lower in the probiotic group (5/22%) than the control group (11/26%) (p=0.9529)[9]. Another clinical study by Mayes et al. (2016) found a significantly higher mortality (P<0.005) in patients with TBSA > 40% in the control group than in burn patients receiving probiotics[19].

While the research results shown by Koren et al. (2007) in a retrospective cohort study evaluating the effect of Lactobacillus supplementation on sepsis in acute burn patients found that the mortality rate was lower in the probiotic group than in the control group (2 vs 7), but the difference was not significant (p=0.071). Meanwhile, in contrast to the 41-70% TBSA subgroup, the mortality rate was significantly lower in the probiotic group than in the control group (0 vs 5) (p<0.01). This contrasts with the literature that mentions burns of more than 20% of the total body surface area (TBSA), impaired immune system function proportional to the size of the burn[3]. These results were associated with the control group having a higher mortality rate, with fewer patients surviving and developing septic complications[8].

Reducing the Skin Graft and Shorten of LOS:
According to El Ghazely et al. (2016), there was a significant decrease (p=0.028) in the need for skin grafts 2(10%) in the probiotic group and 8(40%) in the control group, as well as a shortening of the length of stay of burn patients in the hospital (LOS/Length of Hospital Stay) (p=0.044) in the probiotic group (17.25±0.497) was significantly lower than the control group (21.9±2.178)[10]. Similar to the results of this study, Mayes et al. (2016) evaluated the safety and effectiveness of probiotics in pediatric burn patients. The results showed that the number of days required for operative procedures (skin graft/excision) was lower in the probiotic treatment group (2.3±0.5days) than the control (3.3±0.6) (p<0.23), and shorter wound healing time. (p<0.23)[19].

DISCUSSION:

This scoping review of 10 journal articles identified the clinical trial in humans, consisting of 8 prospective randomized controlled trials (RCT) and 2 retrospective and prospective cohort studies. In this study, all articles were analyzed using probiotic preparations, both mono-strain and multi-strain combinations as one component of the research experiment in each study.

Probiotic strains used for human consumption must be of human origin, non-pathogenic, and capable of surviving gastrointestinal transit in order to provide health benefits to humans[23]. Bacteria that meet the criteria as probiotics are generally lactic acid bacteria, especially *Lactobacillus* and *Bifidobacterium* species, but *Lactococcus*, *Streptococcus*, *Enterococcus* species, as well as some non-pathogenic *Eschericia coli* and yeast strains can also qualify as probiotics. Recent evidence suggests that probiotic strains can have the same activities as commensal bacteria, including immunomodulatory[24].

Preparations containing probiotics must meet the minimum criteria for probiotic bacteria of 10^6 CFU/ml at the expiration date, because the recommended minimum daily therapeutic dose is 10^8-10^9 cells. For mono strains, using a patented probiotic product consist of mixed bacteria with a composition containing one of *Lactobacillus strain* and/or one of *Bifidobacteria strain*, such as, *L. acidophilus*, *B. longum*, and *S. thermophilus*, with a total viable bacteria of 6 x 10^7 CFU/g. Meanwhile, multi-strain probiotic uses a patented probiotic product consisting of mix bacteria with the composition *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, and *S.s thermophilus* with a total viable bacteria of more than 10^8 CFU/g to produce the composition optimal synergy bacteria[20].

Selection of appropriate probiotic strains to be able to give a positive effect must be appropriate as the basic ability to be able to induce an improvement in the intestinal immune response without modifying intestinal hemostasis. To be able to modulate the immune system, both the innate and adaptive immune systems, probiotic bacteria are dose dependent and strain dependent. Several strains of *Lactobacillus* and *Bifidobacteria* have been shown to induce the production of secretory IgA and IgG. High concentrations of IgA activity in the gastrointestinal tract are important to maintain a barrier against translocation of pathogenic bacteria, especially gram-negative bacteria[25]. This is considering that not all strains of *Lactobacillus* and *Bifidobacteria* have the same effect regarding the modulation of the immune system.

The concentration of probiotics required to exert a clinical effect is often stated as 10^6 cfu/ml in the small intestine and 10^8 cfu/g in the colon. Some literature states that to be able to provide benefits through modulation of the immune system, the recommended minimum daily dose of probiotics is in the range of 10^7-10^9. Several studies examining the benefits of probiotics on burns, types of probiotic strains and the daily dose used have not been widely established or still vary, so that, the results between these studies are also varied[23].

Based on several clinical studies that have been carried out, the recommended route of administration and dosage of probiotics to have an immunomodulatory effect in burn patients is the oral administration route with a daily dose of once-twice a day containing 10^7-10^9 CFU/g bacteria, and multi-probiotics. Strains are more recommended as a therapeutic modality in providing clinical effects in burn patients. This is also in accordance with some literature that to provide benefits through modulating the immune system, the recommended minimum daily dose of probiotics is in the range of 10^7-10^9 [26] The concentration of probiotics required to exert a clinical effect is often stated as 10^6 cfu/ml in the small intestine and 10^8 cfu/g in the colon [20].

In addition, the optimal duration of probiotic administration in burns is not yet fully known and how long probiotics are able to colonize, balance the intestinal microflora, and provide an immune response, especially in burns, is also not fully known[20]. Based on the literature, the initial dose of probiotics ranged from 1-7 days after the first dose of antibiotics. For strains of *Saccharomyces*, *Lactobacillus*, and *Lactobacillus spp.*, the combination with other species, ranged from 2-3 days, 1-3 days, and 1-7 days, respectively[23].

Changes in intestinal function as a cause of the development of sepsis in a critical direction, so that the

intestine is known as the motor of the systemic inflammatory response. As a result, the function of the mucosal epithelial cells as a barrier is reduced (increased intestinal permeability) or lost and facilitates bacterial translocation. Bacteria that undergo translocation are generally normal intestinal flora that are commensal, turning into opportunistic ones, especially due to changes in the atmosphere in the intestinal lumen[22].

In critical illness conditions (burns), it is difficult to maintain the balance of the normal flora of the gastrointestinal tract. This is due not only to the condition of the disease, but also to pharmacological interventions such as the use of H2 receptor antagonists or proton pump inhibitors to prevent gastrointestinal bleeding or perforation, and the use of broad-spectrum antibiotics to treat infections[22].

In addition, several mechanisms of beneficial probiotic activity that can prevent sepsis in critical illness patients are competitive adherence to bacteria, release of bacteriocins to inhibit pathogen growth, stimulation of mucin and sIgA production, increased degradation of macromolecules that reduce the number of antigens, suppression of immune cell proliferation, inhibition of epithelial cell NF-Kb activation, modulation of apoptosis and maintenance of the epithelial barrier which in turn is able to modulate immune function[25].

The administration of probiotic *Bifidobacteria*, such as *B. longum* and *B. breve* in experimental rats, showed an increase in total immunoglobulin compared to controls. For *Lactobacillus* bacteria, strains that have been widely studied for the immune system and are able to stimulate IgA production are *L. acidophilus*, *L. casei*, *L. plantarum*, and L. rhamnosus[27]. There is no significant difference that multi-strain probiotics increase IgA levels more than mono-strains.

Burns are an inflammatory condition in which the body responds by releasing massive pro-inflammatory cytokines (IL-1, IL-6, TNF-α) which is followed by a decrease in anti-inflammatory mediators and apoptosis of immune cells, either by cellular or humoral immunity [15]. CRP is often used as a marker of systemic inflammation and its level in serum is an important indicator of the presence of an inflammatory process. CRP synthesis occurs in the liver and is triggered by the release of IL-6 in response to tissue damage or infectious stimuli [15]. In severe burns, there is a decrease in IgA, IgG, IgM, and IgE levels that occurs on day 2-3 post-burn[28]. SIgA is the main immunoglobulin present in mucosal secretions, which is the first line of defense of the mucosal surface[17]. With increasing levels of sIgA after administration of probiotics in burn patients, it is expected that the intestinal immune system will increase, thereby reducing bacterial translocation. Mortality and morbidity rates of burn patients will also be reduced [13]. Some evidence shows that multi-strain probiotics can reduce intestinal permeability by increasing the intercellular gap in the outer layer of the intestine, which is finally able to reduce the translocation of pathogenic bacteria from the intestine into the system[20].

In addition, probiotics can also reduce leukocyte and neutrophil levels. Thermal injury causes pathophysiological conditions that induce macrophage hyperactivity and has an impact on the downregulation or upregulation of several inflammatory cytokines that trigger leukocytosis conditions[8]. Meanwhile, neutrophils are a type of polymorphonuclear leukocyte (PMN) that plays an important role during the acute inflammatory phase. Neutrophils under inflammatory conditions in the circulation are predicted to increase 10-fold, from 5-10 hours to 5.4 days[16]. Specific probiotics have been shown to enhance local immunity by interacting with the surface of innate immune cells or directly activating lymphoid cells. In addition to modulating intestinal immunity, probiotics can also induce a systemic immune response[18].

Probiotics are not only easy to use and easy to use, but the development of their application is also expected to provide a new cost-effectiveness option when compared to other commercial products for treating burns. A number of clinical and pre-clinical research data also promise that an appropriate topical probiotic therapy regimen with the development of an appropriate dressing method for burns can be tolerated safely and as effectively as Silver Sulfadiazine cream. However, further research is needed to fully understand the cellular and molecular mechanisms that underpin this process. More importantly, probiotics have the ability to have independent effects on the host inflammatory response via immunomodulation, which is especially essential in burns where a severe inflammatory response is typical.

The strength of this scoping review is that the data extraction protocol and synthesis were predefined with the PRISMA checklist for scoping review, so that, the literature search could be systematic and comprehensive, to obtain relevant articles according to the research objectives. The limitation of this study is that it only focuses on articles published in English. The literature search is also limited by the time of publication (time-limited) which is 15 years. The reason for the time limitation was to identify studies relevant to current burn management. This review was carried out in a systematic manner against predefined protocols. However, a formal quality assessment of the studies was not carried out, because the scoping review studies here

analyzed the outcome reporting and did not attempt to analyze the effects of the intervention.

This scoping review study of the effects of probiotics on the immune system in burns will lead to the heterogeneity of outcomes between reported trials that are more likely to measure relevant outcomes, and increase the value of a systematic review of the effects of probiotics on burns. Many questions remain unanswered regarding the effectiveness of probiotics as a therapeutic modality to modulate the immune system in burn patients, including the appropriate type of probiotic strain, optimal dosage and duration of administration, side effects and contraindications. This study summarizes the scientific foundations, identifies literature gaps, and suggests some evidence for future research directions on the application of probiotics to burns that will provide information for researchers, practitioners, and healthcare professionals to adapt and/or produce research, rules, and the latest practice (clinical setting).

CONCLUSION:

The use of probiotics in burn patients has been shown to be able to increase the immune system in burns based on scientific evidence by laboratory outcome parameters (increased the secretion of Immunoglobulin A, decreased of CRP serum, IL-6, leukocytes, neutrophils and lymphocytes), and other clinical outcome parameters (improvement of gastrointestinal tract imbalance, reduced the mortality, reduced the risk of SIRS/sepsis, shortened Length of Hospital Stay).

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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