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Clinical outcomes in acute ischemic stroke with probiotic intervention: the role of elevated serum level of short chain fatty acid (scfa)

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Abstract

Stroke is an acute cerebrovascular disease, noted as the second leading cause of global mortality after ischemic heart disease. An understanding of the brain-gut axis has shed light on the role of the immune system in the pathogenesis of stroke. Currently, the use of probiotics in overcoming intestinal microbiota imbalances is very broad, including in vascular disorders. This study aimed to assess the effect of probiotic (Lactobacillus acidophilus) intervention on changes in Short Chain Fatty Acid (SCFA) serum levels in acute ischemic stroke clinical outcome. This study were pre and posttest control group design. A total of 35 samples were collected consecutively and divided into two groups which is the intervention group given probiotic for 14 days as add-on with the standard therapy and the control group only given standard therapy. Intervention group showed alteration of serum SCFA level higher than control group (Δ 10.19 vs Δ 4.23). NIHSS Score after 14 days showed a significant result on both groups but the alteration on intervention group were highly changed (Δ -3.77 vs Δ -1.23) . Based on the Spearman Correlation test, there is a negative correlation between Serum SCFA Level with NIHSS score on intervention group($p < 0.05$; $r = -0.494$). Probiotic intervention plays an important role on increasing SCFA levels and thus improve the outcome of acute ischemic stroke seen by lower NIHSS score after 14 days.

Keywords: Acute ischemic stroke, Probiotic, Short Chain Fatty Acid

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1. Introduction

Stroke is an acute cerebrovascular disease, ranking as the second leading cause of death globally after ischemic heart disease, and the third most common cause of disability worldwide, following heart disease and cancer [1]. In Indonesia, stroke-related deaths have reached 252,473, accounting for 14.83% of total mortality and ranking seventh in the world. Ischemic stroke represents the most prevalent type [1,2]. The pathophysiology of stroke is quite intricate, involving various processes such as energy failure, excitotoxicity, oxidative stress, blood-brain barrier disruption, inflammation, necrosis, apoptosis, and more, summarized within an ischemic cascade [1,2]. Of all stroke patients, around one-third can make a full recovery, one-third

experience mild to moderate functional impairments, and the remaining third suffer severe functional deficits, confining them to bed. Current research predominantly focuses on identifying risk factors, elucidating the pathogenesis, and enhancing stroke outcomes. The involvement of the immune system in stroke pathogenesis elucidates the activation of adaptive immunity, which is initiated and directed towards the brain within hours to several days after a stroke. These immune cells can be modulated by the gut microbiota [3,4]. The role of the immune system in the pathomechanism of stroke has been extensively studied. Cerebral blood vessel occlusion initiates acute ischemic damage, followed by the activation of local immune cells and peripheral immune cell trafficking. Initially, innate immune cells mitigate brain damage by clearing cellular debris and neutralizing neurotoxins. However, the impact of amplified adaptive immune responses contributes to the progression of ischemic brain injury. Consequently, immunomodulation (immunotherapy) has become a promising stroke management concept. Systemic immune responses occurring during the attack contribute to increased mortality and long-term disability. Recent studies have demonstrated that stroke outcomes can be influenced by gut microbiota composition, although the beneficial mechanisms of gut microbiota manipulation remain unclear.

Li et al (5) conducted a study evaluating gut microbiota characteristics through fecal samples of stroke patients, revealing significant gut microbiota dysbiosis associated with the production of short-chain fatty acids (SCFAs). Research into commensal microbiota and their contributions to health and disease is a dynamic and burgeoning field, particularly in stroke pathogenesis and progression. Microbiota impact ischemic stroke outcomes by modulating antigen-specific immune responses in the central nervous system through the involvement of SCFAs [6,7]. Several current studies focus on the relationship between gut microbiota, specifically in the gut, and the incidence of acute ischemic stroke, further elucidating the bidirectional communication of the gut-brain axis. The gut and brain are interconnected through various mechanisms, including neuronal, immunological, metabolic, and endocrine pathways [8]. Gut microbiota dysbiosis is a risk factor for hypertension, vascular dysfunction, diabetes mellitus, and obesity [9]. According to Chen et al and Benakis et al [10] and [11], this dysbiosis is also a risk factor for ischemic stroke, and conversely, central nervous system dysfunction affects gastrointestinal function through the vagus nerve, neurotransmitters, endocrine pathways, and immune responses. Cerebral ischemia leads to gut microbiota dysbiosis, increasing intestinal permeability, disrupting the gut barrier, and promoting microbiota translocation. Studies in animal models show that gut microbiota can regulate neuroinflammation processes and influence brain recovery. Stroke can alter the gut bacterial composition, causally related to proinflammatory T cell polarization and worsened ischemic stroke outcomes [12,13]. To date, clinical outcomes of acute ischemic stroke remain unsatisfactory, with high mortality rates and long-term disabilities posing significant challenges. Difficulties in controlling risk factors, long-term treatment, along with economic and social factors, often hinder the improvement of clinical outcomes.

The use of probiotics for stroke is currently limited and mainly in the in vivo experimental stage. Singh et al [12] concluded that probiotics have cerebroprotective effects mediated by high levels of short-chain fatty acids (SCFAs), enhancing the immune system and improving clinical outcomes. This study aim to evaluate the clinical outcome using National Institute of Health Stroke Scale (NIHSS) of acute ischemic stroke with supplementation of probiotic compare to standard therapy.

2. Methods

2.1 Study Design and Subjects Recruitment

This was an experimental research with pre and posttest group design involving the first acute ischemic stroke patients which was conducted at Wahidin Sudirohusodo hospital and some satellite teaching hospitals. Patients with first attack acute ischemic stroke with an onset of 0 - 7 days diagnosed based on history, physical examination and CT-Scan of the head, aged 40 - 60 years, and willing to be included in the study by signing a letter of consent. All the protocols in this study were approved by the Ethic committee of the Faculty of Medicine, Hasanuddin University (No. 333/UN4.6.4.5.31/PP36/2022). All the participants were divided into two groups after met the inclusion criteria, those are intervention group and control group. All groups were given standard therapy include anti aggregation (aspilet 80 mg), neuroprotector (citicholin 250 mg/12 hour intravenously) and mecobalamin 500 mcg/24 hour. For intervention group will be given supplementation of probiotic (Lactobacillus acidophilus) 2x 10^7 CFU for 14 days.

2.2 Serum SCFA level

SCFA level were measured by collecting blood sample from respondents twice, at admission and at day 15 on both groups. Serum level of SCFA were measured using Human Short-Chain Fatty Acid (ScFA) ELISA kit.

2.3 NIHSS Score

Outcome of Stroke were measured using National Institute of Health Stroke Scale (NIHSS). This Scale were measured twice on both groups, at admission and at day 15. This Scale composed of 13 item, each of which scores a specific ability between 0 – 4. For each item, a score 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. Total score is 0 – 42 which categorized by mild stroke when NIHSS < 5, Moderate stroke (NIHSS 5 – 15) and moderate to severe stroke (NIHSS 16 – 25), and severe stroke (NIHSS> 25).

2.4 Statistical Analysis

The collected data was processed through statistical analysis using the SPSS ver. 25. By using Wilcoxon test, the serum SCFA level analyze in both groups since the datas were not normally distributed. The correlation between the change of serum SCFA level and NIHSS score were analyze using Spearman Correlation test.

3. Results

As many as 35 acute ischemic stroke patients were included in this study. There are 18 subjects in intervention

group and 17 subjects as control group. The baseline characteristic of all subjects were summarized in Table 1. The mean age of subjects in the two groups was not much different (51 and 52 years). However, this age does not provide a meaningful relationship to the clinical outcome of acute ischemic stroke ($p > 0.001$). Nineteen males were recorded, 12 were in the intervention group and 7 subjects in the control group. Of the 16 female subjects, 6 were in the intervention group and 10 were in the control group. Based on statistical tests, it was found that there was no relationship between gender and clinical outcomes (*p value* = 0.171). The mean serum SCFA level in the intervention group was 15.58 at the beginning of the measurement and increased to 25.77 after probiotic supplementation ($p = 0.000$) while in the control group, SCFA levels also increased from 17.98 to 22.21 ($p = 0.001$). Both groups showed significancy of serum SCFA level, however greater changes were seen in the intervention group. The alteration of serum SCFA level on both groups clearly showed in figure 1. Delta of both groups counts from the substraction of the mean of post and pre test. NIHSS score in both group showed decrease after supplementation where in intervention group, alteration more drastically compared to control group ($p= 0.000$; $p = 0.001$) . Figure 2 above shows the alteration of NIHSS score compared on two groups. The median of NIHSS score in intervention group highly different after 14 days of probiotic supplementation. Compared the two group, the NIHSS score in intervention group were decrease 3.77 points, while in control group decrease of NIHSS score were 1.23 points. This change was significant in both groups ($p = 0.001$). By using Spearman's Rho Correlation, the relationship between alteration of serum SCFA level and NIHSS score were analyze. Table 2 showed a significant relationship was obtained in the intervention group with a negative correlation ($r= -0.494$; $p<0.05$)), compared to the control group ($r= -0.343$; $p = 0.177$)). Thus it can be concluded that changes in SCFA in the intervention group have a stronger correlation than in the control group.

4. Discussion

4.1 Respondent Characteristics

In this study, the incidence of acute ischemic stroke was found to be more common in men (54%) than women (46%). Globally, the incidence of stroke tends to be higher in men [14,15]. The incidence of ischemic stroke according to [16] was also recorded more in men, namely around 57.38% with a male to female ratio of 1.9:1, in line with the study by [17] which states that acute ischemic stroke attacks are more common in men. The risk factors for stroke that are more dominant in men are hypertension and diabetes mellitus type 2 accompanied by bad lifestyles such as smoking and alcohol which cause many vascular disorders such as small-vessel occlusion and atherosclerosis. In the group of women aged 45-74 years, the risk of stroke is lower than men in the same age range [18, 19] also reported that more than 60% of men experienced ischemic stroke but what is interesting is that women tend to have a higher severity level of acute stroke than men.

In this study, it was found that the highest prevalence of stroke was in the age range 45-54 years. Several studies show almost the same results, including [20] stating that the age group that most often experiences strokes are those aged ≥50 years, however, it is not impossible that strokes can occur in the age group ≤40 year. Other studies show the incidence of stroke at a younger age, [21] shows that the incidence of stroke, both ischemic and hemorrhagic, is around 28 per 100,000 people aged between 20 and 44 years. According to [22] although the incidence of ischemic stroke is rare in the young age group, individuals aged between 18 and 40 years are still at risk of experiencing acute ischemic stroke due to risk factors such as diabetes mellitus and dyslipidemia. Aging is an irreversible risk factor associated with ischemic stroke, and older patients experience higher rates of mortality and health impacts, as well as the recovery process. poorer functioning compared to younger individuals [23]. Stroke severity levels in the mild, moderate and severe categories tend to be higher in the male population compared to women. However, in the very severe category, there is an increased incidence in women compared to men [24]. The severity of stroke in women ranges from an NIHSS score of 2-10, while in men it ranges from an NIHSS score of 2-7 [25].

4.2 Changes in SCFA levels on clinical outcomes of acute ischemic stroke after probiotic intervention

In this study, significant changes in SCFA levels were found to reduce NIHSS scores as an indication of improved clinical outcomes after 14 days of probiotic intervention. This is in line with research using experimental animals which shows that increasing SCFA increases clinical improvement through immunological mechanisms [26]. This is caused by the activation of microglia and inhibition of axonal damage. In addition, SCFAs produced by probiotics play a role in polarizing T cells in the intestinal compartment and stimulating anti-inflammatory T cells. A study by [27] found that high SCFA levels were associated with increased pro-inflammatory markers such as IL-6, TNF-α, VCAM1, IL-17, and MCP-1 but were not associated with baseline NIHSS scores. the incidence of ischemic stroke, infarct volume, and brain edema. This study was different because it did not carry out probiotic intervention but only looked at SCFA levels and NIHSS scores at the start of the stroke event. High SCFA levels indicate high levels of fatty acids produced from metabolites of the microbiota in the intestine. According to Zhang X. et al [28] SCFA levels in stroke patients are lower than those in the control group, especially acetate and propionate. Acetic acid and propionate play an important role in regulating the Gut-Brain Axis in post-stroke patients by improving the immune system and energy metabolism. Acetic acid, as the most dominant SCFA metabolite, is metabolized by the liver and then transported to peripheral tissues and will later play a role in cholesterol metabolism and lipogenesis, easily penetrating the blood-brain barrier and may have a role in the appetite regulation center. Research on experimental animals shows that SCFA metabolites, namely acetate, butyrate and propionate, can increase tight junction proteins thereby improving the integrity of the blood-brain barrier [29].

Table 1: Subject Characteristics

Variables	Intervention Group (n=18)		*p-value*	Control Group (n=17)		*p-value*
	Pre	**Post**		**Pre**	**Post**	
Age (years) mean±SD	51,59±6,51			52,65±8,10		0,73
Sex (male/female)	12/6			7/10		0,171
SCFA mean±SD	15,58 (±8,94)	25,77 (±10,37)	0,000	17,98 (±11,71)	22,21 (±14,18)	0,000
NIHSS mean±SD	5,44 (±2,81)	1,67 (±1,57)	0,000	4,82 (±3,14)	3,59 (±2,93)	0,001

Wilcoxon test

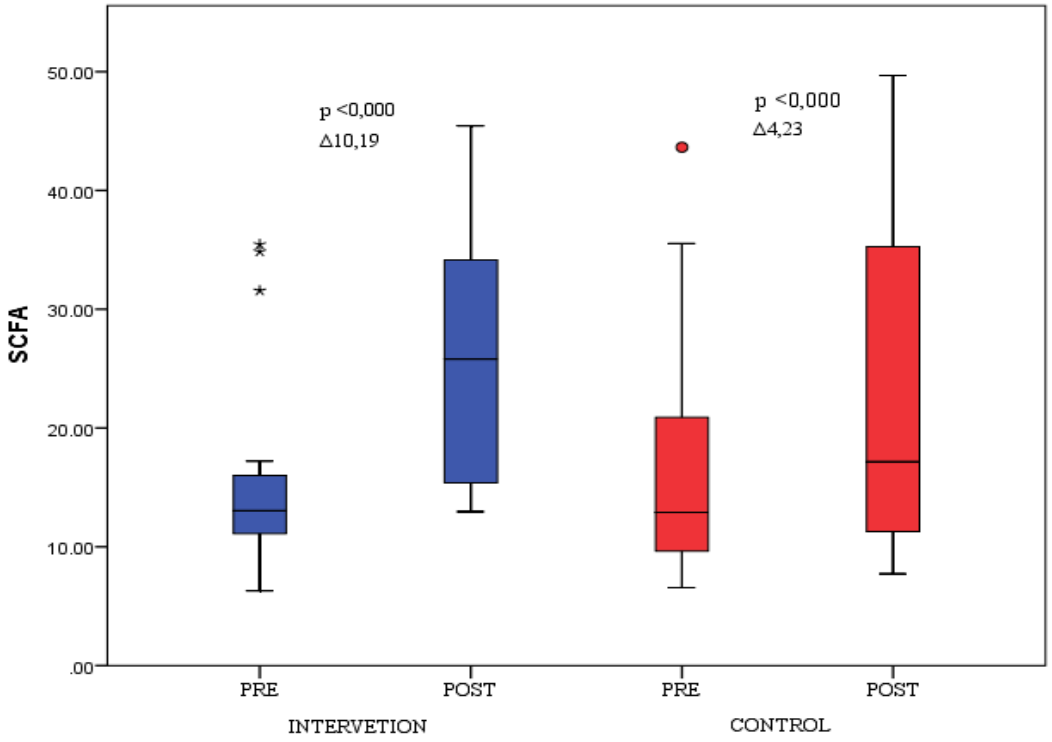

Figure 1: Boxplot comparison of changes in SCFA levels in the intervention and control groups

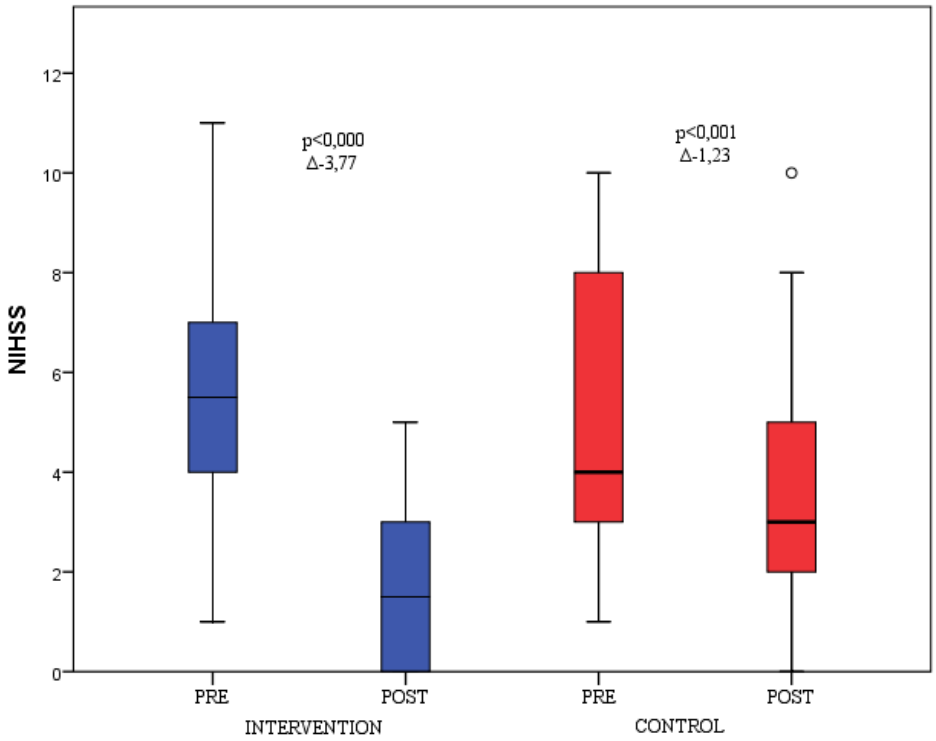

Figure 2: Boxplot comparison of changes in NIHSS scores in the intervention and control groups

Table 2: Correlation between changes in SCFA levels and changes in NIHSS scores

Variable	NIHSS	
	R	*p-Values**
SCFA		
Intervention group	-0,494	0,037
Control group	-0,343	0,177

**Spearman Rho correlation*

The immunomodulatory role of SCFAs is possible through inhibition of histone deacetylase (HDAC) and activation of G protein-coupled receptors (GPR) such as free fatty acid receptor-3 FFAR3 (GPR41), FFAR2 (GPR43) and hydroxycarboxylic acid receptor (GPR109A). In addition, SCFAs play a role in T cell polarization in the intestinal space by increasing the number of regulatory T cells (Treg) and suppressing T helper cells 17 (Th17) and Th 1 cells and directs the immune response towards anti-inflammatory [13,26,30]. SCFA produced from probiotics, apart from being a source of energy for cells, also influences the maturity of microglia and influences neuron function. SCFA can modulate levels of neurotransmitters and neurotrophic factors such as Nerve Growth Factor (NGF), Glial Cell line-derived Neurotrophic Factor (GDNF) and BDNF which regulate the growth, survival and differentiation of nerve cells and synapses in the central nervous system [31]. SCFA can regulate Brain Derived Neurotrophic Factor (BDNF) expression and also modulate the effects of increasing the pro-inflammatory neurotransmitters IL-17 and IL-10 which have neuroprotective properties [32]. In the study, enrichment in certain bacteria was associated with functional improvement after 3 months from stroke onset. SCFA as a fermentation product from intestinal microbiota is a very potential pro-regeneration modulator of post-stroke neuronal plasticity at several structural levels through circulating lymphocytes and microglial activation [26]. In the correlation test, the two groups appear to have a negative correlation but the intervention group has a stronger correlation. Many things can confuse SCFA levels, including nutritional status and dietary patterns. The large difference in changes in SCFA levels after 14 days of probiotic intervention proves the previous hypothesis that there is an increase in SCFA levels which contributes well to the outcome of acute ischemic stroke. In research by [26] it is stated that SCFA supplementation can increase the concentration of SCFA in circulation and can trigger therapeutic effects in the recovery period after experiencing

chronic stroke. In addition, SCFA produced by probiotics can trigger neuroinflammation and play a role in helping repair cognitive dysfunction and brain damage. Probiotics can also improve negative emotions in ischemic stroke patients including anxiety and depression that appear 3 months after stroke onset [33,34].

5. Conclusion

There is an improvement in the clinical outcome of acute ischemic stroke with probiotic intervention by increasing the serum level of SCFA especially in acute ischemic strokes of mild and moderate degree. Supplementation of probiotic will become promising therapy for stroke and need further research especially as primary prevention.

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References

[1] M. Sotomayor-Sobrino, A. Ochoa-Aguilar, L. Méndez-Cuesta, C. Gómez-Acevedo. (2019). Neuroimmunological interactions in stroke. Neurología (English Edition). 34(5): 326-335.

[2] Y. Guo, P. Li, Q. Guo, K. Shang, D. Yan, S. Du, et al. (2013). Pathophysiology and biomarkers in acute ischemic stroke - A review. Tropical Journal of Pharmaceutical Research. 12(6):1097–105.

[3] N. Arpaia, C. Campbell, X. Fan, S. Dikiy, H. Liu, J.R. Cross, et al. (2014). HHS Public Access. 504(7480):451–5.

[4] D. Battaglini, P.M. Pimentel-Coelho, C. Robba, C.C. dos Santos, F.F. Cruz, P. Pelosi P, et al. (2020).Gut Microbiota in Acute Ischemic Stroke: From Pathophysiology to Therapeutic Implications. Vol. 11, Frontiers in Neurology. Frontiers Media S.A.

[5] N. Li, X. Weng, C. Sun, X. Wu, M. Lu, Y. Si, et al. (2019). Change of intestinal microbiota in cerebral ischemic stroke patients. BMC Microbiology. 19;19(1).

[6] J. Lee, J. d'Aigle, L. Atadja, V. Quaicoe, P. Honarpisheh, B.P. Ganesh, et al. (2020). Gut Microbiota-Derived Short-Chain Fatty Acids Promote Poststroke Recovery in Aged Mice. Circ Res. 127(4):453–65.

[7] K. Winek, O. Engel, P. Koduah, M.M. Heimesaat, A. Fischer, S. Bereswill, et al. (2016). Depletion of Cultivatable Gut Microbiota by Broad-Spectrum Antibiotic Pretreatment Worsens Outcome After Murine Stroke. Stroke. 47(5):1354–63.

[8] A. Thornell, M. Salami. (2021). Interplay of Good Bacteria and Central Nervous System: Cognitive Aspects and Mechanistic Considerations. Available from: www.frontiersin.org.

[9] D.J. Durgan, J. Lee, L.D. McCullough, R.M.J. Bryan. (2019). Examining the Role of the Microbiota-Gut-Brain Axis in Stroke. Stroke. 50(8):2270–7.

[10] R. Chen, P. Wu, Z. Cai, Y. Fang, H. Zhou, Y. Lasanajak, et al. (2019). Puerariae Lobatae Radix with chuanxiong Rhizoma for treatment of cerebral ischemic stroke by remodeling gut microbiota to regulate the brain-gut barriers. The Journal of Nutritional Biochemistry. 65:101–14.

[11] C. Benakis, C. Poon, D. Lane, D. Brea, G. Sita, J. Moore, et al. (2020). Distinct Commensal Bacterial Signature in the Gut Is Associated With Acute and Long-Term Protection From Ischemic Stroke. Stroke. 51(6):1844–54.

[12] V. Singh, R. Sadler, S. Heindl, G. Llovera, S. Roth, C. Benakis, et al. (2018). The gut microbiome primes a cerebroprotective immune response after stroke. J Cereb Blood Flow Metab. 38(8):1293–8.

[13] C. Tan, Q. Wu, H. Wang, X. Gao, R. Xu, Z. Cui, et al. (2020). Dysbiosis of Gut Microbiota and Short-Chain Fatty Acids in Acute Ischemic Stroke and the Subsequent Risk for Poor Functional Outcomes. Journal of Parenteral and Enteral Nutrition.

[14] C.D. Bushnell, S. Chaturvedi, K.R. Gage, P.S. Herson, P.D. Hurn, M.C. Jiménez, et al. Sex differences in stroke: Challenges and opportunities. Vol. 38, Journal of Cerebral Blood Flow and Metabolism. SAGE Publications Ltd; 2018. p. 2179–91.

[15] K. Norman, M. Eriksson, M.V. Euler. (2022). Sex Differences in Ischemic Stroke Within the Younger Age Group: A Register-Based Study. Frontiers in neurology. 14;13.

[16] K.Z. Alawneh, M.Al-. Qawasmeh, L.A. Raffee, B. Abuzayed, D.A.B. Hani, K.M. Abdalla, et al. (2020). A snapshot of Ischemic stroke risk factors, sub-types, and its epidemiology: Cohort study. Annals of Medicine and Surgery. 1;59:101–5.

[17] B. Sarecka-Hujar, I. Kopyta. (2021). The impact of sex on arterial ischemic stroke in young patients: From stroke occurrence to poststroke consequences. Vol. 8, Children. MDPI AG.

[18] M. Jiang, C. Ma, H. Li, H. Shen, X. Li, Q. Sun, et al. (2020). Sex Dimorphisms in Ischemic Stroke: From Experimental Studies to Clinic. Vol. 11, Frontiers in Neurology. Frontiers Media S.A.

[19] A.K. Bonkhoff, M.D. Schirmer, M. Bretzner, S. Hong, R.W. Regenhardt, M. Brudfors, et al. (2021). Outcome after acute ischemic stroke is linked to sex-specific lesion patterns. Nat Commun. 1;12(1).

[20] M. Tang, M. Yao, Y. Zhu, B. Peng, L. Zhou, J. Ni. (2020). Sex differences of ischemic stroke in young adults—A single-center Chinese cohort study. Journal of Stroke and Cerebrovascular Diseases. 1;29(9).

[21] T. Yahya, M.H. Jilani, S.U. Khan, R. Mszar, S.Z. Hassan, M.J. Blaha, et al. (2020). Stroke in young adults: Current trends, opportunities for prevention and pathways forward. American journal of preventive cardiology. 3:100085.

[22] Y. Ohya, R. Matsuo, N. Sato, F. Irie, K. Nakamura, Y. Wakisaka, et al. (2022). Causes of ischemic stroke in young adults versus non-young adults: A multicenter hospital-based observational study. PLoS One. 1;17(7 July).

[23] M. Roy-O'Reilly, L.D. McCullough. (2018). Age and sex are critical factors in ischemic stroke pathology. Vol. 159, Endocrinology. Oxford University Press. p. 3120–31.

[24] C.T. Ong, Y.S. Wong, S.F. Sung, C.S. Wu, Y.C. Hsu, Y.H. Su, et al. (2017). Sex-related differences in the risk factors for in-hospital mortality and outcomes of ischemic stroke patients in rural areas of Taiwan. PLoS One. 1;12(9).

[25] F. Irie, M. Kamouchi, J. Hata, R. Matsuo, Y. Wakisaka, J. Kuroda, et al. (2015). Sex differences in short-term outcomes after acute ischemic stroke: The fukuoka stroke registry. Stroke. 6;46(2):471–6.

[26] R. Sadler, J.V. Cramer, S. Heindl, S. Kostidis, D. Betz, K.R. Zuurbier, et al. (2020). Short-chain fatty acids improve poststroke recovery via immunological mechanisms. Journal of Neuroscience. 29;40(5):1162–73.

[27] N. Henry, J. Frank, C. McLouth, A.L. Trout, A. Morris, J. Chen, et al. (2022). Short Chain Fatty Acids Taken at Time of Thrombectomy in Acute Ischemic Stroke Patients Are Independent of Stroke Severity But Associated With Inflammatory Markers and Worse Symptoms at Discharge. Frontiers in immunology. 12(January):1–17.

[28] X. Zhang, X. Wang, H. Zhao, R. Cao, Y. Dang, B. Yu. (2023). Imbalance of Microbacterial Diversity Is Associated with Functional Prognosis of Stroke. Neural Plasticity. 6297653.

[29] A. Olsson, S. Gustavsen, T.D. Nguyen, M. Nyman, A.R. Langkilde, T.H. Hansen, et al. (2021). Serum Short-Chain Fatty Acids and Associations With Inflammation in Newly Diagnosed Patients With Multiple Sclerosis and Healthy Controls. Frontiers in immunology. 12(May):1–13.

[30] S.B. Chidambaram, A.G. Rathipriya, A.M. Mahalakshmi, S. Sharma, T.A. Hediyal, B. Ray, et al. (2022). The Influence of Gut Dysbiosis in the Pathogenesis and Management of Ischemic Stroke. Vol. 11, Cells. MDPI.

[31] S.N. Renamastika, D.R. Wahyuningrum, V.A. Putri, R. Aisy. (2021). PREBIOTICS FOR ACUTE ISCHEMIC STROKE. International Journal of Pharmacy and Pharmaceutical Sciences. 1;1–10.

[32] H. Sun, M. Gu, Z. Li, X. Chen, J. Zhou. (2022). Gut Microbiota Dysbiosis in Acute Ischemic Stroke Associated With 3-Month Unfavorable Outcome. Frontiers in neurology. 28;12.

[33] L. Liu, X. Ni, T. Tian, X. Li, F. Li, M. Sun, et al. (2020). Effect of regulating gut microbiota using probiotics on functional changes in the brain: Protocol for a systematic review. Vol. 10, BMJ Open. BMJ Publishing Group.

[34] J. Zhang, Q. Tang, L. Zhu. (2021). Could the Gut Microbiota Serve as a Therapeutic Target in Ischemic Stroke? Evidence-based Complementary and Alternative Medicine.