International Journal of Ecophysiology Vol. 05, No. 01, 2023 | 36-41

talenta PUBLISHER

Internasional Journal of Ecophysiology

Immunomodulatory Effect of Ethanol Extract of Pirdot Leaf (*Saurauia vulcani* Korth) on CD4+ and IL-2 Hepatic Profile in Tyfoid Fever

Haslinda[1],Rina amelia [1], M.Ichwan[1],Dwirita Anggraini[1], Yunita Sari Pane[2]*

1[Magister student, Biomedical science, Faculty of Medicine, Universitas Sumatera Utara, Medan,Indonesia] , Haslinda0852@gmail.com

1[Department of Community Medicine and Public Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia],rina2@usu.ac.id

1[Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Sumatera Utara,Medan, Indonesia],m.ichwan@usu.ac.id

1[Department of Anatomy, Faculty of Medicine,Universitas Sumatera Utara,Medan, Indonesia], dwirita@usu.ac.id

2[Farmacology department, Biomedical science, Faculty of Medicine, Universitas Sumatera Utara , Indonesia] yunita@usu.ac.id;*

Abstract. [Typhoid fever is an acute febrile disease caused by *Salmonella typhi* bacteria that is obtained orally either through food or from drinks.Many immunological activities that occur due to salmonella infection so that immunomodulators are needed to speed up the healing of one of them by using pirdot leaves. Pirdot leaves are widely distributed in Indonesia, especially in the Lake Toba area of North Sumatra.This plant has many bioactive components, one of which is flavonoids.The flavonoid component of pirdot Leaf has been widely studied and is believed to improve the immune system because it is able to increase the production of IL-2 which is involved in the activation and proliferation of lymphocyte cells and can increase T CD4 cells. T CD4+ it self is a signal transduction marker in the mechanism of typhoid fever that can activate *Antigen Precenting Cell* (APC) to provide resistance to foreign substances.]

Keyword: [Typhoid fever, pirdot leaf ethanol extract,*Salmonella typhimurium*, IL2, CD4+]

Received [14 December 2022] | Revised [15 January 2023] | Accepted [25 February 2023]

*Corresponding author at: [Farmacology department, Biomedical science, Faculty of Medicine, Universitas Sumatera Utara]

E-mail address: [Haslinda0852@gmail.com]

DOI: 10.32734/ijoep.v5i1.12315
Journal Homepage: http://ijoep.usu.ac.id

1 Introduction

Typhoid fever one acute febrile illness, which is life-threatening and is the cause of health problems. Each year worldwide there are 26 million cases of typhoid fever and 5 million cases of paratyphoid infection resulting in 215,000 deaths[1].According to WHO it is estimated that around 11-21 million cases of typhoid fever worldwide and every year an estimated 128,000-161000 deaths occur, the most cases are in South Asia and Southeast Asia [2]. In Indonesia, typhoid fever is an endemic disease that reaches 500 cases per 100,000 population per year [3].

In typhoid fever *Salmonella typhi* acts as a foreign substance so that the immune system will protect the body from infectious agents, if the immune system is sufficient to fight infectious agents then no infection occurs, and vice versa the body will be easily exposed to infectious agents if the immune system in the body is insufficient [4]. The immune system itself is divided into two, namely non-specific immune response or natural immune system (innate immunity) and specific immune response or adaptive immune system (acquired immunity) also occurs in *Salmonella typhimurium* infection.

The nonspecific immune response is a defense system that is directed not only at one type of antigen but can be several antigens. *Salmonella typhi* infection causes bacteremia, so that all body tools can be affected, including the liver, especially the liver is a reticuloendothelial organ that functions in eliminating bacteria. In typhoid fever, *Salmonella typhi* acts as a foreign substance that cannot be recognized by the body's defense system, so it is necessary to activate the T CD4+signal transduction. T CD4+ is a signal transduction marker in the mechanism of typhoid fever, *Salmonella thypi* enters the cell directly activates *Antigen Precenting Cell* (APC) to provide resistance to foreign substances to activate T cells with the help of T CD4+ to secrete inflammatory cytokines such as IL1, IL2, IL4 and IL-12 [4]. Previous research proved that the decrease in typhoid fever was evaluated by assessing T CD4+levels. So it was concluded that T CD4+ one of the immune system that plays a role against salmonella infection that provides protection both in lymphoid and non-lymphoid tissues, one of which is the liver [5].

The high activity of CD4 + leads to activation of T and Thelper cells in the inflammatory mechanism. Activation of T cells causes the release of inflammatory cytokines INF and IL-2 is high, as a response of the entry of foreign substances in the body as a marker in the phagocytosis of foreign substances in neutralizing the abnormal state of high levels of T CD4+ cells. So that both are interrelated in the mechanism of typhoid fever so that high levels of T CD4+ cells cause high levels of IL-2. Several previous studies have proven that there is a relationship between T CD4+ cells and IL-2 levels[6].

Plants that have many potential bioactive chemicals one of them is the pirdot plant. Bioactive chemical components detected in 3 leaves pirdot alkaloids, flavonoids, saponins, triterpenoids, and tannins [7]. Flavonoids can increase the body's defense system because they are able to

increase the production of IL-2 which is involved in the activation and proliferation of lymphocyte cells [8], and can affect T CD4+ cells, then cause Th1 cells to be activated. Previous research data prove that, the administration of extracts and red blood cells of sheep in mice caused an increase in IL-2 due to anti-inflammatory effects caused by the content of flavonoids pirdot leaves[7] .

Pirdot Plant

Pirdot *(Saurauia vulcani* Korth.) is a plant of the genus Saurauia spread in Indonesia. Pirdot is found only in Lake Toba watershed of North Sumatra, Indonesia [7]. Pirdot leaves are also found found from Lumban Julu, Sipangan Bolon, brand, to Sipiso-piso [9]. Plants that have many potential bioactive chemicals one of them is the pirdot plant. Bioactive chemical components detected in 3 leaves pirdot alkaloids, flavonoids, saponins, triterpenoids, and tannins [10]. The function of flavonoids is very much as antifungals, antioxidants, antibacterial and antiinflammatory digestive and Wound Skin parts [11]. From several studies have shown that the immunomodulatory activity on flavonoids can also regulate innate and adaptive immunity which has previously been proven that in the laboratory flavonoid compounds can increase the production of IL-2 can increase the proliferation and differentiation of T cell lymphocytes, B cells and NK cells. Lymphocyte proliferation that occurs will affect T CD4+ cells, which will activate Th1 cells [12]

Salmonella typhimurium

Salmonella typhimurium can cause an extensive disease that is part of the salmonella bacteria group. Salmonella typhi has the characteristics of Gram-negative rod bacteria, does not spore, moves with flagella, and is facultative anaerobic [13]. The main symptoms of typhoid fever are fever and malaise, but serious complications can occur, such as intestinal bleeding or perforation, encephalitis, respiratory infections, and abscess metastasis [14].

The structure of the antigen for salmonella it self is that the bacterium has three antigen structures, namely antigen Vi (capsule), H (flagellum), and O (somatic). For O (somatic) antigens are resistant to heating to a temperature of 100°C, acids and alcohols. H Antigen (flagellum) will be damaged on heating with temperature more than 60°C, acid, and alcohol. antigen Vi (capsule) is a polysaccharide polymer with acidic properties that breaks down at 60°C heating with the addition of acid and phenol for 1 hour, and is present on the outside of bacteria [13].

Pathogenesis of *Salmonella typhimurium*

In the early stages of typhoid fever is transmitted through food or drink contaminated with human feces containing Salmonella typhimurium bacteria, then s bacteria *S.typhimurium* enters

the body and the bacteria enter the payers patches of the mucous surface of the intestinal tract by activating M cells, the body has specific epithelial cells that will capture and carry antigens to the luminal to be captured by phagocytic cells. The inflammatory process is followed by bacterial phagocytosis by neutrophils, macrophages and the formation of T and B cells.The infecting bacteria can persist in the *Mesenteric lymph nodes* (MLNs), bone marrow and gall bladder for life, and there is periodic division on the mucosal surface through the bile ducts or *mesenteric lymph nodes* (MLNs) of the small intestine, and shedding can occur from the mucosal surface. T cells can secrete *Interferon* (IFN-γ), which plays a role in controlling intracellular salmonella replication. Production (IFN-γ) *and tumor-necrosis factor* (TNF-γ) cytokines can be increased by IL 12 and IL 12 contributes to the control of defenses against salmonella infection [15].

The first bacteremia occurs when *Salmonella typhimurium* bacteria enter systemically into the bloodstream after passing through the mesenteric lymph channels and then reach the *Reticuloendothelial System* (RES) located in the liver and spleen organs and body tissues.*Salmonella typhimurium* multiplies in mononuclear phagocytic cells in the lymph follicles of the small intestine,mesenteric lymph nodes, liver and spleen.When incubation is complete, *Salmonella typhimurium* will exit through the thoracic duct into the systemic circulation there is a second bacteremia until it reaches the organs.Emerging symptoms of infection are determined by virulence and number of *Salmonella typhimurium* as well as the immune response of infected humans . The bacteremic phase of typhoid fever is indicated by the spread of *Salmonella typhimurium* germs to various organs such as the liver, spleen, bone marrow, gall bladder, and Peyer's patch on the terminal ileum[16].

T CD4+

T CD4 + is one type of white blood cell that plays a role in the immune system that goes into the type of T lymphocytes or T cells.T CD4 + cells are made in the thymus gland and then circulate in the blood and lymphatic system throughout the body. Each B-cell has an Ag receptor on its surface to capture antigens. Then the Ag will be processed in the B-cell near MHC II and then the B-cell becomes APC. T-helper cells (Th) approach APC B cells and with the help of TCR and T CD4+[17].Th will interact with APC B cells and Th cells will be activated and release cytokines or lymphokines (IL-2, IL-4, IL-5 and IFN-β), these products will induce other B-cells to divide, proliferation and differentiation. Furthermore, T CD4 + cells are activated and produce IL-2 so that there is an increase in the ability to kill the antigen [4].

Interleukin 2

Interleukin 2 (IL-2) is a cytokine with 4 (four) helical α bundles that exerts its biological activity by binding to high-affinity IL-2 receptors (IL-2R). IL-2R is made up of three subunits of the α

chain (IL-2ra also known as CD25), the ß chain (IL-2rß also known as CD122) and the ɣ receptor cytokine chain (ɣc also known as CD132) which each contribute to The Binding of IL-2 . Regulatory T cells in a constant state always have IL-2 receptors even though they have not been activated and binding of IL-2 to receptors on the cell surface activates Treg T cells, therefore IL-2 is often referred to as T cell growth factor [18]. Interleukin 2 is the development of antigen-stimulated T cells and functions in the expansion of T cell clones after the antigen is known. IL-2 receptor expression is enhanced by antigen stimulation, so T cells that can recognize antigens are the primary cells that proliferate in specific immune responses. IL-2 increases the proliferation and differentiation of T cells, B cells and NK. IL-2 also eludes the immune response to its own antigen by increasing T cell apoptosis. The increase in IL - 2 in the body is followed by an increase in T CD4+, thus IL-2 also acts as an immunomodulator, namely the overall regulation of the immune system in the body, both in normal and abnormal conditions [6] .

Immune response of Salmonella

The body is infected with S. Typhi then the body will respond to the bacteria that is by way of macrophages will destroy the bacteria.Phagocytosis is the initial process for the formation of APC after contact with bacteria[19].Salmonella induces the release of Thelper1 and Thelper2.When APC is formed, the immune response changes from an innate immune response to a specific immune response.Once the APC is formed, Salmonella has proliferated in macrophages [20].Cytokines Th1 andth2 are elevated during salmonellosis, interleukins that come into play(IL-1,IL-2,IL4,IL-16,IL-8,IL-9,IL-10,IL-13,IL-15,IL-17) interferon-gamma comes into play also in the cellular immune response increased in the blood even after healing . Salmonella-specific T CD4+ cells plays a role in immunity to salmonella infection, T CD4+ cells provides protection both in tissue and in circulation, one of which is the liver.In previous studies after immunization with salmonella vaccine attenuated CD4+ effectively increased so as to provide protection to the liver [21].In mice that have been infected with salmonella then mice immunized with LVS the most appropriate location to check immunity chained CD4+ T cells in nonlimphoid organs is hepar [22].

Reference

[1] J. Bhandari, P. K. Thada, dan E. DeVos, “Typhoid Fever - StatPearls - NCBI Bookshelf,” *StatPearls*, no. November, 2021.

[2] World Health Organization, “Typhoid vaccine: WHO position paper - March 2018,” *Wkly. Epidemiol. Rec.*, vol. 13, no. 93, hal. 153–172, 2018, [Daring]. Tersedia pada: https://www.who.int/publications/i/item/typhoid-vaccines-who-position-paper-march-2018

[3] E. Yunandar, "Tutorial Word," 7 December 2017. [Online]. Available: www.tutorialword.com. [Accessed 1 March 2018].

[4] S. L. Swain, K. K. McKinstry, dan T. M. Strutt, “Expanding roles for CD4 + T cells in immunity to viruses,” *Nat. Rev. Immunol.*, vol. 12, no. 2, hal. 136–148, 2012, doi: 10.1038/nri3152.

[5] J. Song et al., "A mouse model for the human pathogen salmonella typhi," Cell Host Microbe, vol. 8, no. 4, hal. 369–376, 2010, doi: 10.1016/j.chom.2010.09.003.

[6] A. S. El-Radhi, J. Carroll, dan N. Klein, "Clinical manual of fever in children," *Clin. Man. Fever Child.*, hal. 1–318, 2009, doi: 10.1007/978-3-540-78598-9.

[7] M. F. Lubis, P. A. Zaitun Hasibuan, H. Syahputra, C. Surbakti, dan R. Astyka, "Saurauia vulcani (Korth.) as herbal medicine potential from North Sumatera, Indonesia: A literature review," Heliyon, vol. 8, no. 4, hal. 4–9, 2022, doi: 10.1016/j.heliyon.2022.e09249.

[8] I. N. Azizah dan A. Winanta, "In Vitro Immunomodulatory Activity of Fig Fruit Ethanol Extract (Ficus carica Linn) against Phagocytosis Macrophages and Lymphocyte Proliferation," *Maj. Obat Tradis.*, vol. 27, no. 2, hal. 85, 2022, doi: 10.22146/mot.70128.

[9] C. Ali dan A. Aminah, "223289-Perkembangan-Bunga-Dan-Buah-Pirdot-Saura," *J. Penelit. Hutan Tanam.*, vol. 14, no. 2, hal. 103–113, 2017.

[10] K. Gurning dan D. H. Sinaga, "Characterization and Screening of Phytochemical Secondary Metabolite of Seri (Muntingia calabura, L) Leaves which is Potential as an Anti-Diabetic based on Indonesian Herbal Medicine Standard," *J. Drug Deliv. Ther.*, vol. 10, no. 6-s, hal. 92–94, 2020, doi: 10.22270/jddt.v10i6-s.4458.

[11] Y. S. Pane, R. A. Ganie, D. Lindarto, dan A. Lelo, "The effect of gambier extract on the levels of malondialdehyde, superoxide dismutase, and blood glucose in type 2 diabetes mellitus patients," *Asian J. Pharm. Clin. Res.*, vol. 11, no. 10, hal. 121–124, 2018, doi: 10.22159/ajpcr.2018.v11i10.26620.

[12] H. Hayati, "Dampak Latihan Intensitas Berat Pada Fungsi Imun Tubuh," *Embrio*, vol. 4, hal. 50–56, 2014, doi: 10.36456/embrio.vol4.no0.a1234.

[13] R. A. Jatmiko, "Uji Aktivitas Antibakteri Ekstrak Biji Keluak (Pangium edule) Terhadap Bakteri Salmonella typhi," *Skripsi Fak. Kedokt. dan Ilmu Kesehat.*, 2020.

[14] J. Brainard *et al.*, "Typhoid fever outbreak in the Democratic Republic of Congo: Case control and ecological study," *PLoS Negl. Trop. Dis.*, vol. 12, no. 10, hal. 1–17, 2018, doi: 10.1371/journal.pntd.0006795.

[15] J. Kaur dan S. K. Jain, "Role of antigens and virulence factors of Salmonella enterica serovar Typhi in its pathogenesis," *Microbiological Research*, vol. 167, no. 4. hal. 199–210, 20 April 2012. doi: 10.1016/j.micres.2011.08.001.

[16] D. U. Muis, "Karakteristik Penderita deman Tifoid Rawat Inap Anak di RSUD Abdul Wahab SJahranie Samarinda," hal. 1–14, 2017.

[17] J. A. P. Sekar dan J. R. Faeder, "An introduction to rule-based modeling of immune receptor signaling," *Syst. Immunol.*, hal. 71–90, 2018, doi: 10.1201/9781315119847-5.

[18] A. K. Abbas, "The Surprising Story of IL-2: From Experimental Models to Clinical Application," *Am. J. Pathol.*, vol. 190, no. 9, hal. 1776–1781, 2020, doi: 10.1016/j.ajpath.2020.05.007.

[19] M. Moshinsky, *Peran Imunitas Pada Infeksi Salmonella*, vol. 13, no. 1. 1959.

[20] T. L. Hadfield, *Medical Microbiology 18th Edition*, vol. 155, no. 7. 1990. doi: 10.1093/milmed/155.7.a26.

[21] J. M. Benoun *et al.*, "Optimal protection against Salmonella infection requires noncirculating memory," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 115, no. 41, hal. 10416–10421, 2018, doi: 10.1073/pnas.1808339115.

[22] S. Lee *et al.*, "HHS Public Access," vol. 199, no. 4, hal. 1353–1361, 2018, doi: 10.4049/jimmunol.1601357.Duel.