International Journal of Ecophysiology
Journal homepage: https://talenta.usu.id/ijoep

Potential of Pirdot Leaf (*Saurauia vulcani* Korth.) as Immunomodulator: JAK-STAT Pathway and Turandot A Gene Expression in *Drosophila melanogaster* Hyperglycemia Model

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ARTICLE INFO

Article history:
Received 5 May 2025
Revised 23 May 2025
Accepted 27 July 2025

E-ISSN: 2656-0674

How to cite:
Enisantaria Br Manik, Dwi Rita Anggraini, Mutiara Indah Sari, (2025). "Potential of Pirdot Leaf (*Saurauia vulcani* Korth.) as Immunomodulator: JAK-STAT Pathway and Turandot A Gene Expression in *Drosophila melanogaster* Hyperglycemia Model". *International Journal of Ecophysiology*, (7) 2, 110-115.

http://doi.org/10.32734/ijoep.v7i2.22256

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a global health issue characterized by chronic hyperglycemia, insulin resistance, immune system dysregulation, and increased mortality rates. Therapeutic approaches based on natural immunomodulators represent a potential strategy for managing this disease. *Saurauia vulcani* Korth. (pirdot), an endemic plant of Indonesia, is known to contain bioactive compounds such as flavonoids, saponins, and triterpenoids, which exhibit antioxidant, antidiabetic, and immunomodulatory activities. *Drosophila melanogaster*, which has a high level of genetic homology with humans, is used as a model for insulin resistance through the induction of a high-sugar diet. One of the key genes in the immune response of this organism is Turandot A (TotA), which is expressed in response to stress and regulated by the JAK-STAT signaling pathway.
Keyword: Hyperglycemia, TotA, JAK-STAT, Immunomodulators, *Saurauia vulcani* Korth., *Drosophila melanogaster*

ABSTRAK

Diabetes melitus tipe 2 (DMT2) merupakan masalah kesehatan global yang ditandai oleh hiperglikemia kronis, resistensi insulin, disregulasi sistem imun, dan peningkatan angka mortalitas. Pendekatan terapi berbasis imunomodulator alami menjadi strategi potensial dalam pengelolaan penyakit ini. Saurauia vulcani *Korth. (pirdot), tanaman endemik Indonesia, diketahui mengandung senyawa bioaktif seperti flavonoid, saponin, dan triterpenoid yang memiliki aktivitas antioksidan, antidiabetes, dan imunomodulator.* Drosophila melanogaster*, yang memiliki tingkat homologi genetik tinggi dengan manusia, digunakan sebagai model resistensi insulin melalui induksi diet tinggi gula. Salah satu gen penting dalam respons imun organisme ini adalah Turandot A* (TotA)*, yang diekspresikan sebagai respons terhadap stres dan diregulasi oleh jalur pensinyalan JAK-STAT.*
Keyword: *Hiperglikemia, TotA, JAK-STAT, Imunomodulator, Saurauia vulcani Korth., Drosophila melanogaster*

1. Introduction

Diabetes mellitus (DM) is one of the most significant global health problems, characterized by a continuous increase in prevalence. Based on recent data, more than 529 million individuals worldwide are living with the condition, and the number is predicted to increase substantially until 2050 [1]. Type 2 diabetes mellitus (T2DM) is the most common form of DM, which is commonly accompanied by serious microvascular and macrovascular complications, including retinopathy, nephropathy, cardiovascular disease and neuropathy.

These complications not only result in reduced quality of life, but also significantly increase the risk of mortality [2], placing a huge burden on healthcare systems globally.

Uncontrolled hyperglycemia is a major etiological factor in the onset and progression of T2DM, characterized by persistently elevated blood glucose levels. This hyperglycemic state has a strong correlation with chronic low-grade inflammation, which is one of the hallmarks of T2DM. Such inflammation exacerbates metabolic dysregulation and contributes to insulin resistance, which is one of the main markers of the disease [3]. In addition, hyperglycemia also has the potential to affect immune responses as well as inflammatory responses to pathogens [4], adding to the complexity of T2DM pathophysiology and emphasizing the need for innovative therapeutic strategies that target metabolic and immunological aspects simultaneously.

One promising approach in the management of inflammatory conditions and metabolic disorders is the use of immunomodulators, which are compounds capable of affecting the immune system either through stimulation (immunostimulant) or suppression (immunosuppressive) of humoral and cellular immune activity [5]. Pirdot leaf (*Saurauia vulcani* Korth.), a plant that is widely found in Indonesian regions such as Parapat, Balige, Samosir, and Tarutung [6]. Plants that have many potential bioactive chemicals such as flavonoids, glycosides, saponins, tannins, and steroids/triterpenoids that have antioxidant activity through a free radical capture mechanism [7].

In experimental studies, the selection of relevant animal models is very important to explore the mechanisms of disease pathophysiology. *Drosophila melanogaster*, an insect of the order Diptera and family Drosophilidae, is one of the model organisms widely used in biomedical research [8]. This species shares more than 70% genetic similarity with humans as well as highly conservative regulatory pathways of energy metabolism [9].

2. Pirdot Plant

High biodiversity makes Indonesia one of the countries with great potential in the development of plant-based medicines. The abundance of flora, especially medicinal plants, is interesting to be studied further in the context of health and medicine [10]. In recent years, interest in herbal plant research has shown a significant upward trend, along with the growing public interest in the use of natural ingredients in traditional medicine [11].

One of the plant species that has pharmacological potential is *Saurauia vulcani* Korth, known locally as pirdot. This plant belongs to the *Saurauia* genus and is widely found in Indonesia, especially in the Lake Toba catchment area, North Sumatra, such as Parapat, Balige, Samosir, and Tarutung [6][10]. The ethanolic extract of pirdot leaves has been reported to contain various secondary metabolite compounds, including flavonoids, glycosides, saponins, tannins, and steroid and triterpenoid class compounds, which play a role in its biological and pharmacological activities [7].

Various previous studies have revealed the therapeutic potential of pirdot leaves in several biological activities, such as antidiarrheal effects [7], antibacterial [12], anticholesterol [13], antidiabetes [14] [15], immunostimulant [16], immunomodulator [17], and hepatoprotective [18]. In particular, research on antidiabetic activity shows that ethanolic extract of pirdot leaves can reduce blood glucose levels in animal models induced with glucose, alloxan, and streptozotocin [19][20].

Furthermore, the potential of pirdot leaves as an immunomodulatory agent has also been reported. Pirdot leaf extract was shown to reduce nitric oxide production in RAW 264.7 cells and inhibit the expression of proinflammatory genes, such as TNF-α, IL-6, COX-2, IL-1β, and iNOS, which collectively play a role in immune and inflammatory responses [17]. These findings support the utilization of *Saurauia vulcani* Korth. as a potential candidate in the development of herbal-based therapies, both for diabetes mellitus management and immune system modulation.

3. *Drosophila* as a Model Organism in Metabolic and Immune System

Drosophila melanogaster, widely known as the fruit fly, has developed into one of the important alternative animal models in biomedical research. Its popularity as a model organism is supported by various biological and technical advantages, such as a short life cycle, small body size, and a relatively simple and thoroughly mapped genome. These characteristics make *Drosophila* highly suitable for testing the efficacy and safety of phytochemical compounds in various physiological processes, including metabolism, aging, and immune response [21][22].

In addition, *Drosophila melanogaster* has a low maintenance cost, a high reproduction rate, and the availability of many mutant lines with efficiently observable phenotypic characteristics. The combination of these factors makes it an ideal model for exploring the pathophysiology of various human diseases [23]. Genetically, about 70% of human disease-causing genes share homology with genes found in Drosophila,

including those involved in the regulation of metabolic energy homeostasis, making this model relevant for the study of metabolic diseases such as type 2 diabetes mellitus [9].

One approach that is widely used in mimicking hyperglycemia conditions in *Drosophila* is through the High Sugar Diet (HSD) model. This model was first introduced by Musselman et al. (2018) [24], by feeding wild-type *Drosophila* larvae a high-sucrose diet that exceeds the sugar composition of the control diet. The results showed that larvae reared on HSD had elevated levels of glucose and trehalose in the hemolymph, reflecting a condition of insulin resistance similar to that occurring in patients with type 2 diabetes. Insulin resistance in the HSD model is triggered by sustained high sugar consumption, leading to metabolic dysfunction in the form of chronic hyperglycemia, growth retardation, hyperinsulinemia, and excess fat accumulation [25].

4. Inflammatory Response and Immune System

Chronic hyperglycemia not only impacts metabolic regulation, but also triggers complex immune and inflammatory system activation. The inflammatory response that occurs is the result of immune system activation to high blood glucose levels as well as the production of inflammatory mediators by adipocytes and macrophages that accumulate in fat tissue. This chronic inflammation has a damaging effect on pancreatic beta cells, thus disrupting insulin production and worsening the condition of hyperglycemia [26].

At the molecular level, hyperglycemia and oxidative stress activate the IκB kinase (IKK) pathway, leading to the activation of nuclear factor κB (NF-κB), a key regulator of inflammation. In addition, cytokines can stimulate signal transducer and activator of transcription 3 (STAT3) via the Jak1/2 pathway, further enhancing the inflammatory response [27]. These signaling pathways amplify the production of proinflammatory cytokines, contributing to a vicious cycle of inflammation that exacerbates disease. In addition, hyperglycemia promotes the formation of advanced glycation end products (AGEs), which further exacerbates inflammation and insulin resistance, thus accelerating the progression of T2DM [28] [29].

The inflammatory process is initiated by priming signals involving Damage Associated Molecular Patterns (DAMPs) molecules, which activate pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), other immune receptors, and yet to be fully identified receptors. This activation triggers the production of inflammatory cytokine precursors such as pro-IL-1β as well as other inflammasome components. DAMPs also activate the inflammasome, which in turn activates caspase-1 through conversion from its proenzyme form (procaspase-1). The activated caspase-1 then converts pro-IL-1β into the active form of IL-1β, which will bind to its receptor on other immune cells and stimulate the production of further inflammatory cytokines [30]..

The immune system functions as the main biological defense to detect and neutralize pathogens or antigens that are potentially harmful to the body [5]. However, dysregulation or imbalance in the immune response can lead to various disorders, including allergic reactions, autoimmune diseases, immunosuppression, and immunodeficiency syndromes [31].

5. The Role of Turandot A (TotA) Gene and JAK-STAT Pathway in *Drosophila* on Immune System

The Turandot A (TotA) gene in *Drosophila* is one of the genes that plays an important role in the innate immunity system and in the response to physiological and environmental stress. This gene is expressed in the hemolymph and encodes a cryptic protein of 129 amino acids, whose expression regulation is activated in response to various forms of stress. TotA functions as part of the humoral response, activated primarily through activation of the JAK-STAT signaling pathway, and shows functional similarity (homology) to the NF-κB and Mekk1 pathways in vertebrates.

TotA expression is significantly increased in response to a variety of stressor conditions, such as bacterial infection, exposure to extreme temperatures, oxidative chemicals such as paraquat, and ultraviolet light. The main function of this gene is to increase cellular and tissue resistance to damage from these stressors [32]. TotA is also known to produce a group of small secreted proteins (eight proteins in total), which are expressed in a pattern similar to antimicrobial peptides (AMPs) during stressful conditions and immune system activation. These proteins act as protective humoral factors that protect host tissues, particularly the respiratory epithelium, from the destructive effects of AMPs, and contribute to resilience and immune homeostasis [33].

Regulation of TotA expression is mediated by Dome (Domeless) protein, a cytokine receptor homologous to the human IL-6 receptor, which functions in predicting cytokine-based signals. This pathway is activated by Unpaired (Upd) cytokine ligands, especially Upd3 produced by hemocytes, which further activates the JAK-STAT pathway to induce TotA expression [34].

The JAK-STAT signaling pathway is a signal transduction cascade originally identified in mammals in response to cytokines and growth factors. This pathway plays an important role in the regulation of the immune system, including the control of inflammation, wound healing, and the activation of neutrophils and

macrophages. JAK-STAT activation occurs when cytokine ligands such as Upd bind to the Dome receptor, which then recruits and activates Hop (homologs of Janus kinases in humans: Jak1, Jak2, Jak3, and Tyk2). This activation leads to autophosphorylation and cross-phosphorylation of JAKs and receptors, which form binding sites for STAT proteins. Once phosphorylated, STAT undergoes dimerization and translocation to the cell nucleus, where its DNA-binding domain recognizes promoters and enhancers of target genes to initiate transcription [35].

In Drosophila, the JAK-STAT pathway has been shown to be activated under stress conditions such as mechanical stress, dehydration, and heat exposure [34] [36]. In addition to being involved in cellular defense mechanisms, this pathway also plays an important role in developmental processes, embryo segmentation, as well as the progression of various pathologies such as chronic inflammation, lymphoma, leukemia, and other tumor types [37]. Thus, homologs between the JAK-STAT pathway in Drosophila and humans provide high translational value in the study of immunology and regulation of gene expression in response to physiological stress and pathogens.

6. Acknowledgements

The author would like to express sincere gratitude to Dr. dr. Dwi Rita Anggraini, M.Kes, Sp.PA, Dr. dr. Mutiara Indah Sari M.Kes, Prof. Dr. dr. Sry Suryani Widjaja, M.Kes., and Prof. apt. Firzan Nainu, S.Si., M.Biomed.Sc., Ph.D. for their valuable suggestions, active contributions, and guidance provided throughout the preparation of this article, as well as their willingness to share their knowledge and experience, which have been of great significance. The author also acknowledges SIE MELANOGASTER and the Unhas Fly Research Group for their support. Additionally, the author appreciates all assistance and contributions from various parties who, whether directly or indirectly, have supported the successful completion of this article.

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