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Modulation of *Dilp2* and *Dilp5* Gene Expression by Pirdot Leaf Extract (*Saurauia vulcani* Korth.) in *Drosophila melanogaster* Hyperglycemia Model: A Literature Review

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ABSTRACT

Hyperglycemia is a pathological condition caused by impaired glucose metabolism that contributes significantly to the development of diabetes mellitus. The use of medicinal plants such as pirdot leaves (*Saurauia vulcani* Korth.) as an alternative therapy has become a focus due to their bioactive compounds with antihyperglycemic properties. This article presents a literature review on the potential of pirdot leaf ethanol extract in modulating the expression of *Dilp2* and *Dilp5* genes in the *Drosophila melanogaster* hyperglycemia model. *Drosophila melanogaster* was chosen as a model organism because it has insulin signaling pathways homologous to humans and produces *insulin-like peptides* (DILPs), including *Dilp2* and *Dilp5*, which play a crucial role in glucose regulation and energy metabolism. A high-sugar diet in this organism has been shown to disrupt glucose homeostasis and affect the expression of *Dilp2* and *Dilp5* genes. Pirdot leaf extract has been shown *in vivo* in mouse models to lower blood glucose levels and exhibit regenerative activity toward pancreatic cells. Although no direct studies have been conducted on the effects of pirdot extract on gene expression in *Drosophila*, previous studies indicate that plant compounds can influence metabolic pathways at the molecular level. Therefore, further research using *Drosophila melanogaster* is important to evaluate the potential of pirdot extract in gene expression-based hyperglycemia therapy.
Keywords: Dilp2, Dilp5, *Drosophila melanogaster*, hyperglycemia, pirdot.

ABSTRAK

*Hiperglikemia merupakan kondisi patologis akibat gangguan metabolisme glukosa yang berkontribusi besar terhadap perkembangan diabetes melitus. Penggunaan tanaman obat seperti daun pirdot (*Saurauia vulcani *Korth.) sebagai terapi alternatif menjadi fokus karena kandungan senyawa bioaktifnya yang bersifat antihiperglikemik. Artikel ini menyajikan tinjauan literatur terkait potensi ekstrak etanol daun pirdot dalam memodulasi ekspresi gen* Dilp2 *dan* Dilp5 *pada* Drosophila melanogaster *model hiperglikemia.* Drosophila melanogaster *dipilih sebagai organisme model karena memiliki jalur pensinyalan insulin yang homolog dengan manusia dan menghasilkan insulin-like peptides (DILPs), termasuk* Dilp2 *dan* Dilp5 *yang berperan penting dalam regulasi glukosa dan metabolisme energi. Pemberian diet tinggi gula pada organisme ini terbukti mengganggu homeostasis glukosa serta memengaruhi ekspresi gen* Dilp2 *dan* Dilp5*. Ekstrak daun pirdot telah terbukti secara in vivo pada model tikus dapat menurunkan kadar glukosa darah dan menunjukkan aktivitas regeneratif terhadap sel pankreas. Meskipun belum ada penelitian langsung mengenai pengaruh ekstrak pirdot terhadap ekspresi gen tersebut pada* Drosophila*, studi terdahulu menunjukkan bahwa senyawa tanaman dapat memengaruhi jalur metabolik secara molekuler. Oleh karena itu, kajian lebih lanjut menggunakan* Drosophila melanogaster *penting dilakukan untuk mengevaluasi potensi ekstrak pirdot dalam terapi hiperglikemia berbasis ekspresi gen.*
Kata kunci: Dilp2, Dilp5, *Drosophila melanogaster, hiperglikemia, pirdot.*

1. Introduction

Glucose is the end product of carbohydrate metabolism and plays a central role as an energy source for living organisms [1]. The use of glucose in the body is greatly influenced by the hormone insulin, which is responsible for regulating blood glucose levels. Imbalances in insulin production or sensitivity to insulin can lead to hyperglycemia, a condition in which blood glucose levels rise pathologically, and this is a characteristic feature of diabetes mellitus (DM) [2]. DM is a growing global health threat, with 537 million people affected in 2021 and projections reaching 783 million by 2045, with nearly half undiagnosed, particularly in low- and middle-income countries (LMICs) [3]. Chronic hyperglycemia in diabetes patients can damage various body systems, reduce quality of life, and increase the risk of death [4].

The use of medicinal plants as an alternative therapy for DM continues to grow due to their minimal side effects compared to synthetic drugs [5, 6]. One promising local plant in Indonesia is pirdot leaves (*Saurauia vulcani* Korth.), which are known to lower blood glucose levels [7, 8]. Pirdot leaf ethanol extract has been shown to contain various bioactive compounds such as flavonoids, saponins, glycosides, tannins, and steroids/triterpenoids that contribute to its antihyperglycemic effects [9].

As ethical considerations regarding the use of laboratory animals such as mice and rats in preclinical studies grow, alternative model organisms like *Drosophila melanogaster* have become a relevant choice [10]. This fruit fly has a genome and insulin signaling pathways homologous to humans, is easy to maintain, and is highly suitable for molecular research [11, 12].

2. *Drosophila melanogaster* as a Model Hyperglycemia

For over a century, *Drosophila melanogaster* has been widely used in various biomedical research studies due to its biological similarity to humans. This organism offers several advantages as a research model, including ease of maintenance, a short life cycle, and a relatively small genome [11]. Approximately 70% of the genes involved in human disease pathogenesis have homologs in the *Drosophila* genome, making it a relevant model organism for the study of metabolic diseases [13]. In the context of hyperglycemia, these flies can be dietetically manipulated using a high sugar diet (HSD) to induce a phenotype resembling type 2 diabetes (T2DM), such as increased blood glucose levels, insulin resistance, and triglyceride accumulation [14].

The main advantage of *Drosophila* lies in the similarity of its insulin signaling pathway to that of humans, which is controlled by *insulin-like peptides* (dILPs) to maintain glucose homeostasis. High doses of fructose and glucose can induce obesity and hyperglycemia, accompanied by increased insulin pathway activity through AKT phosphorylation as a marker of insulin response effectiveness [15]. Additionally, exposure to high concentrations of sucrose for 10 days has been shown to cause hyperglycemia accompanied by neurodegeneration in the eye tissue of *Drosophila* [16]. The metabolic disorders resulting from a high-sugar diet correlate with changes in gene expression, particularly in genes involved in lipogenesis and gluconeogenesis [17]. This pattern of genetic regulation shows similarities with human metabolic responses, making fruit flies a strong model system for understanding the molecular mechanisms of hyperglycemia and evaluating therapeutic interventions.

3. *Dilp2* dan *Dilp5* Genes as Molecular Markers of Metabolism

Despite not having a pancreas, *Drosophila melanogaster* has insulin-producing cells (IPCs) that are functionally homologous to the human pancreas. These IPCs produce *Drosophila insulin-like peptides* (DILPs), a hormone that plays an insulin-like role in the regulation of energy metabolism. Feeding a high-glucose diet or damaging IPC cells was shown to increase glucose and lipid levels in the hemolymph, resembling the condition of hyperglycemia in humans [10].

Among the eight types of DILPs that have been identified, *Dilp2* and *Dilp5* are the two most researched peptides due to their significant role in energy homeostasis and metabolism. These two peptides are secreted by neurosecretory cells in the brain and work in a complementary manner: *Dilp2* mainly regulates growth and glucose metabolism, whereas *Dilp5* is more active in the response to excess nutrients as well as the regulation of lipid metabolism and food intake [14], [18]. In addition, both also play a role in the regulation of hemolymph glucose levels, fat storage, developmental timing, body size, and longevity of *Drosophila* [19].

Dilp2 and *Dilp5* expression is highly responsive to changes in nutritional status. For example, feeding a high-sugar diet leads to increased expression of both genes as a form of adaptive response to carbohydrate overload. Further research revealed that *Dilp2* expression increases under conditions with adequate nutrient intake, while *Dilp5* is involved in the regulation of feeding behavior and energy metabolism [20]. A study by Nainu et al. showed that treatment of *Drosophila* with certain plant extracts can increase the expression of *Dilp2* and *Dilp5*, reflecting stimulation of insulin production as well as increased mitochondrial activity in cells [21]. In contrast, chronic hyperglycemia conditions induced by a high-sugar diet decreased the expression

of *Dilp2* and *Dilp5*. Therefore, changes in the expression of these two genes could potentially be used as molecular biomarkers in evaluating metabolic disorders and responses to antidiabetic agents.

4. Potential of Pirdot Leaf Extract on *Dilp2* and *Dilp5* Gene Expression

Saurauia vulcani Korth. known as pirdot has great potential to be developed as a raw material for medicines [22]. This plant contains various secondary metabolites that have antidiabetic, immunostimulant, antidiarrheal, anticholesterol, and hepatoprotective activities [23]. Pirdot has long been utilized in traditional medicine by the Karo and North Tapanuli communities in North Sumatra to treat diabetes mellitus (DM) [7], [8]. A number of *in vivo* studies in rats showed that the administration of pirdot leaf extract can significantly reduce blood glucose levels. Some of these findings are summarized in Table 1 which contains studies related to the antihyperglycemic activity of pirdot leaf extract.

Table 1. Summary of *In vivo* Studies on Pirdot Leaf Extract (*Saurauia vulcani* Korth.) with Antihyperglycemic Activity

No	Sample	Efficacy	Methods	Results	Reference
1	Ethanol extract of pirdot leaves	Antidiabetic	*In vivo*, *streptozotocin* (STZ)-induced rats	Pirdot leaf extract has a down-regulatory effect on *sRAGE* under diabetic conditions	[24]
2	Ethanol extract of pirdot leaves	Antidiabetic	*In vivo*, *alloxan-induced* rats	This extract can promote cell regeneration in the pancreas	[25]
3	Ethanol extract of pirdot leaf	Anti-hyperglycemic	*In vivo*, *alloxan-induced* rats	The results showed that pirdot leaf extract has potential as an antihyperglycemic.	[26]
4	Ethanol extract of pirdot leaves	Hypoglycemic	*In vivo*, *alloxan-induced* rats	After administration of the extract, blood glucose levels were lower compared to the diabetes mellitus control group	[27]
5	Ethanol extract of pirdot leaf	Hypoglycemic	*In vivo*, *streptozotocin* (STZ) and *nicotinamide* (NA) induced rats	The extract showed significantly reduced blood glucose levels and HbA1c levels (*$p < 0.05$), increased SOD levels and insulin secretion	[28]
6	Ethanol extract of pirdot leaves	Hypoglycemic	*In vivo*, *streptozotocin* (STZ)-induced rats	This extract has hypoglycemic activity ($p < 0.001$)	[8]

In a molecular context, pirdot leaf extract also has the potential to modulate *Dilp2* and *Dilp5* gene expression in *Drosophila melanogaster*, especially under hyperglycemia conditions. Although direct research on the specific effects of pirdot extracts on these two genes is still limited, a number of previous studies have shown that plant extracts and nutritional components can affect gene expression and associated metabolic pathways. To date, no studies have specifically evaluated the effect of pirdot extract on *Dilp2* and *Dilp5* expression in the *Drosophila* model. Therefore, considering the similarity of metabolic pathways as well as the ease of genetic manipulation, *Drosophila melanogaster* is a very relevant experimental model to explore the molecular effects of medicinal plants such as pirdot.

5. Conclusion

Pirdot (*Saurauia vulcani* Korth.) leaf extract has potential as a natural antihyperglycemic agent. *The Drosophila melanogaster* model is relevant because it has a human-like insulin pathway, including the *Dilp2* and *Dilp5* genes that play an important role in glucose regulation and metabolism. Although there has been no direct research, literature studies suggest plant extracts can affect the expression of both genes. Therefore, further research is needed to evaluate the molecular effects of pirdot extract on *Dilp2* and *Dilp5* expression as a basis for the development of antidiabetic therapy.

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