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In Silico Analysis of the Potential for Gingerol to IRS-1, GLUT-4, PPAR Γ, and PI3K Activation in Insulin Resistance Condition

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ABSTRACT

Diabetes mellitus (DM) is one of the major threats to human health in the 21st century in both developing and developed countries. Diabetes mellitus is closely associated with the condition of insulin resistance. One of the management of non-pharmacological insulin resistance is the administration of ginger extract. The main content of ginger that plays a role in insulin resistance is gingerol. This study aims to determine the potential for gingerol to Insulin Receptor Substrate-1 (IRS-1), Peroxisome Proliferator Activated Receptor γ (PPARγ), Glucose Transporter 4 (GLUT-4) and Phosphatidilinositol-3 Kinase (PI3K). The method used is in silico by using Cytoscape Software. Based on the in silico results, it was shown that gingerol may affect the regulation of PPARγ, PI3K and GLUT-4 expression through the P53 pathway. The mechanism most likely to occur due to gingerol activity is PI3K pathway. IRS-1 can be induced to be phosphorylated via ATPase protein activation by gingerol. Although this mechanism did not occur directly and the chance of occurrence is small, IRS-1 activation process still allows passing through PI3K pathway. This study concludes that gingerol can influence the regulation of IRS-1, PPARγ, and GLUT-4 expression.
KEYWORDS: Gingerol, IRS-1, PPARγ, PI3K, and GLUT-4

INTRODUCTION

Diabetes mellitus (DM) is one of the major threats to human health in the 21st century in both developing and developed countries [1]. Indonesia ranks 7th out of 10 countries with the highest prevalence of DM in the world with the number of patients reaching 7.6 million [2]. Among cases of DM, almost 90-95% are type 2 diabetes mellitus (DMT-2). DMT-2 is a metabolic disease characterized by chronic hyperglycemia and hyperinsulinemia. Diabetes mellitus is closely associated with the condition of insulin resistance.

The causes of insulin resistance are closely related to PI3K, IRS-1 protein phosphorylation and GLUT-4 activity. Wilcox (2005) stated that the mechanisms responsible for insulin resistance include, for example, down-regulatory mechanisms, genetic deficiencies or polymorphisms of insulin receptor tyrosine phosphorylation, IRS or PI3K proteins, or GLUT-4 function abnormalities caused by various things [3]. The study by Carvalho et al (2001) also reported that there was a decrease in the expression of IRS-1 protein by about 65%, accompanied by a decrease in PI3K activity.

Efforts to improve insulin resistance in DMT-2 can be done pharmacologically and non-pharmacologically [4]. Pharmacologic improvement is done by administration of drugs to improve insulin sensitivity while non-pharmacological improvement is in the form of changes in lifestyle, physical exercise and nutritional therapy such as giving ginger extract. One of the most important ginger compounds in lowering blood glucose levels is gingerol.

Some phenol compounds including gingerol provide pharmacological and physiological activities such as antioxidant, anti-inflammatory, analgesic, anti-carcinogenic, and cardiotonic effects

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[5]. These compounds show a protective effect on β-pancreatic cells in DM mice and restore plasma insulin levels [6]. Gingerol compounds can lower blood glucose levels by decreasing apoptosis of β-pancreatic cells accompanied by the increased insulin production and sensitivity or by decreased intestinal glucose absorption in hyperglycemia [7].

Along with advances in technology, drug activity testing is not only through in vivo or in vitro but also in silico. In silico analysis can predict the likelihood which may occur such as the affinity of a particular target receptor compound, the properties of the compound toxicity, physicochemical characterization, and other pharmacokinetic parameters. Therefore, in silico assays can be used in the development and discovery of new drugs [8].

Based on the above explanation, in silico assay will be carried out to study the interaction of active compounds contained in ginger on protein activity in insulin resistance condition. The purpose of this study is to explain the effect of active compounds in ginger in the form of gingerol to the increased IRS-1 phosphorylation, GLUT-4 translocation, PPARγ activation, and PI3K phosphorylation on in silico assays.

METHODS

The method used is in silico. In silico method which terminologically means in silicon is one of the methods used to understand the natural phenomena through computer model simulation [9]. Analysis of the structure of active compounds of gingerol used in this study was obtained from the protein data bank (GDP) [10]. Using cytoscape software, the potential for gingerol against the reactions of IRS-1, GLUT-4, PPARγ, and PI3K proteins can be studied.

RESULTS AND DISCUSSION

The potential for gingerol against IRS-1, GLUT-4, PPARγ, and PI3K in this in silico assays was done by cytoscape software method. The image of pathway construction results can be seen in Figure 1 and the main mechanism analysis of the pathway can be seen in Figure 2.

In Figure 1, it can be seen that gingerol may affect the regulation of PPARγ, PI3K, GLUT-4 and IRS-1 expression. IRS-1 can be phosphorylated via the mechanism of ATPase enzyme activated by gingerol. From these results, the main mechanism influenced by gingerol is the expression of PI3K.

The results of the main mechanism analysis in Figure 2 show that PPARγ, PI3K, GLUT-4 and IRS-1 expression is highest through TP53. IRS-1 can be induced to be phosphorylated via activation of the ATPase protein by gingerol. The mechanism cannot occur directly and the chance of occurrence is small. IRS-1 activation process is still possible through PI3K pathway.

The image of functional pathway analysis of gingerol compound can be seen in Figure 3. Meanwhile, the top-five biological process influenced by gingerol can be seen in Table 1.

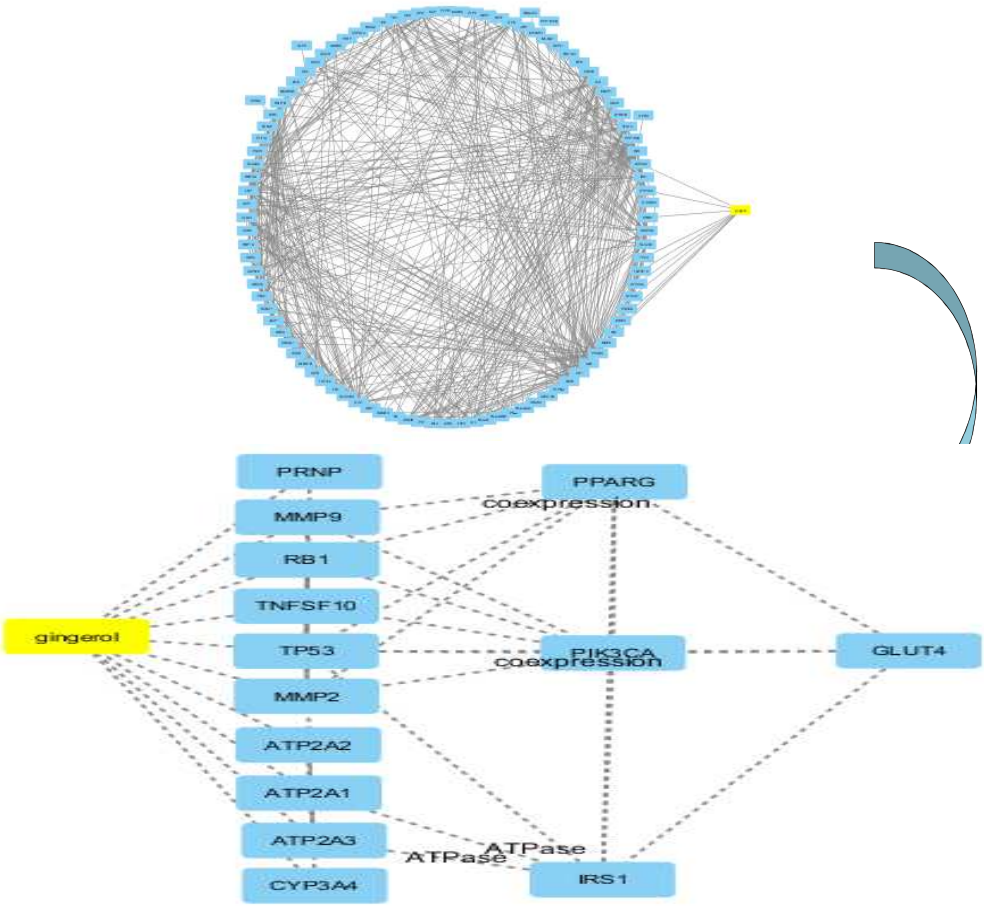

Figure 1. Pathway Construction Results of Gingerol Compound

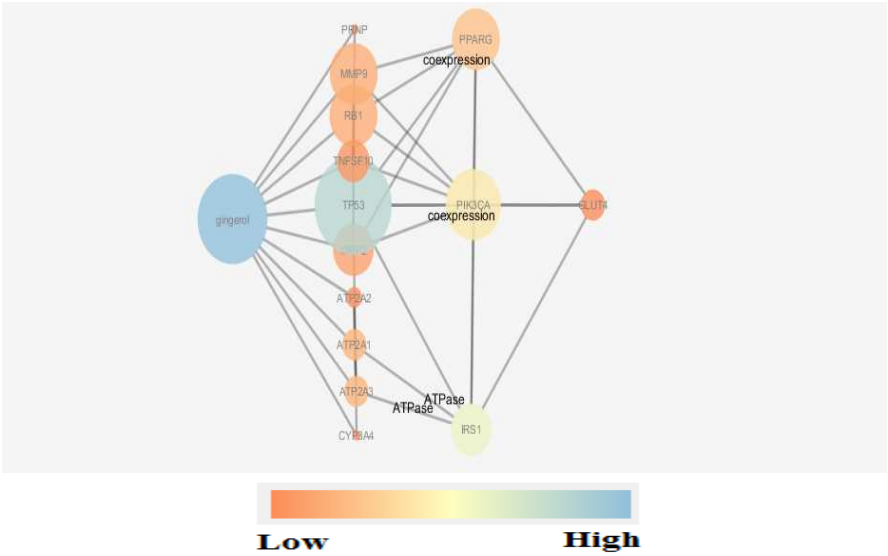

Figure 2. *Main Mechanism* Analysis of the Gingerol Compound Pathway

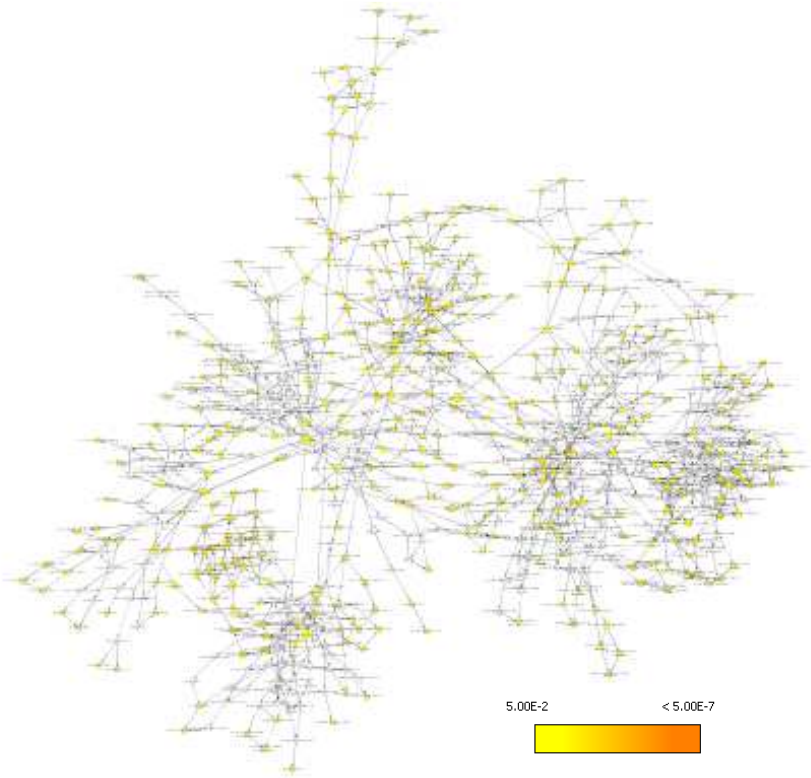

Figure 3. Functional Pathway Analysis

Table 1. Top-Five Biological Process Influenced by Gingerol

GO_ID	Description	p-value	Cluster Freq.
65008	Regulation of Biological Quality	P<0.05	64%
42592	Homeostatic Process	P<0.05	50%
48878	Chemical Homeostasis	P<0.05	42.8%
33500	Carbohydrate Homeostasis	P<0.05	21.4%
42593	Glucose Homeostasis	P<0.05	21.4%

Biological process influenced by gingerol compound which can be seen in Table 1 can also be known in this study. There are 5 biological processes influenced by this compound namely, regulation of biological quality, homeostatic process, chemical homeostasis, carbohydrate homeostasis, and glucose homeostasis. The highest frequency percentage of the five biological processes is the regulation of biological quality of 64%.

The results support previous study on the potential for gingerol against proteins that play a role in conditions of insulin resistance in silico. Several studies have shown that ginger is able to improve the condition of insulin resistance. Human studies demonstrated that ginger powder of 3 grams/day for 8 weeks in DM patients showed a significant decrease in GDP of 18.17 mg/Dl [11]. The study of Al Amin et al. examined the hypoglycemic potential of ginger in diabetic-induced mice by giving fresh ginger of 500 mg/kg daily for 7 weeks. The results showed that the dose was significantly effective in lowering serum glucose, cholesterol, and triacylglycerol levels [12]. Singh et al. has also studied the effects of ginger administration as anti-glycemic, lowering blood lipids, and as an antioxidant agent for DMT-2 [13].

CONCLUSION

This study concludes that gingerol can influence the regulation of IRS-1, GLUT-4, PPARγ, and PI3K expression. Expression of GLUT-4, PPARγ, and PI3K is through P53 pathway. The mechanism most likely to occur due to gingerol activity is the PI3K pathway. IRS-1 can be induced to be phosphorylated via activation of the ATPase protein by gingerol. This mechanism did not occur directly and the chance of occurrence is small. IRS-1 activation process is still possible through PI3K pathway.

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