INDONESIAN JOURNAL OF MULTIDISCIPLINARY SCIENCE

P-ISSN: 2808-5957
E-ISSN: 2808-6724
ijoms.internationaljournallabs.com

HIBISCUS SABDARIFFA ON FIBROBLAST GROWTH FACTOR 21 (FGF21) ON DIABETES MELLITUS TYPE 2 PATIENTS

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ARTICLE INFO

Published: May 27th, 2023

Keywords: *fibroblast growth factor 21, Hibiscus sabdariffa linn., diabetes mellitus type 2*

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ABSTRACT

FGF21 has a role in modulating the uptake of macronutrients in the body. It is produced by the liver in response to high carbohydrate intake and acts as a signal to the brain to reduce carbohydrate intake. Liver is the main site for FGF21 production under the regulation of Unfolding Protein Response (UPR) in hepatocytes. FGF21 has an important role in regulating peripheral glucose tolerance as well as lipid metabolism. FGF21 expression in the liver depends on the PKR-like ER kinase (PERK)–eukaryotic initiation factor 2α (eIF2α)–activating transcription factor 4 (ATF4) pathway. FGF21 can regulate the expression of glucose transporter 1, and increase glucose uptake. In addition, research shows that FGF21 can reduce blood sugar levels and also body weight in mice[1]. FGF21 can also increase insulin sensitivity by suppressing hepatic glucose production and increasing hepatic glycogen content, so that this can improve systemic glucose intolerance and insulin resistance. The researchers attempted to discover the influence of Hibiscus sadariffa on FGF21 on Diabetes mellitus type 2 patients. The method used was literature review with data generated from various sources such as Google Scholar, Scopus, and Pubmed. FGF21 has an effect on the function of α and ß cells in the pancreas organ. In the islets of the pancreatic organs of rats with DM, administration of FGF21 increased insulin levels, induced insulin secretion, and inhibited glucagon secretion.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease with an increase in blood glucose levels due to failure of blood glucose regulation. DM is classified into several subclassifications, including type 1 DM (DMT1) and type 2 DM (DMT2), maturity onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes (Sapra & Bhandari, 2022). Based on WHO, in 2019, DM is the leading cause of death in the world with rank -9, an estimated 1.5 million deaths due to DM. It is reported that the prevalence of DM is increasing rapidly, especially in people in developing countries (World Health Organization, n.d.). Southeast Asia is ranked 3rd with a fairly large prevalence, which is around 11.3%. Indonesia is ranked 7th out of 10 countries in DM disease, as many as 10.7 million people suffer from DM in Indonesia (InfoDATIN, 2020).

Fibroblast growth factor (FGF21) is a hormone that regulates important metabolic pathways. FGF21 is expressed in several metabolically active organs (Tezze et al., 2019). In healthy individuals, the main source of circulating FGF21 is the liver, especially during the fasting state. Meanwhile, adipose tissue is the main site of action of FGF21. In addition to the liver and adipose organs, tissue targets for FGF21 are the pancreas and the central nervous system (Matikainen,

2014). Based on recent data, it is known that FGF21 is also secreted by skeletal muscle tissue, both from rats and humans, especially when triggered by physical activity such as exercise and also in conditions where there is mitochondrial dysfunction (Tezze et al., 2019).. FGF21 has an important endocrine role in regulating carbohydrates, lipids, phosphates and vitamin D. Most FGFs require heparin to bind stably to the FGF receptor, where this heparin will work in an autocrine or paracrine manner, and is not released into the circulation. In the FGF21 signal transduction, apart from the need for a receptor, a co-receptor is also needed, namely the ß-klotho protein (Zhang et al., 2018).

FGF21 is expected to work when in a state of eating, when free fatty acids circulate in large quantities, this will stimulate the expression of FGF21 in adipose tissue, where there will be an increase in glucose uptake. In the liver, FGF21 will induce gluconeogenesis through the PGC-1α pathway and increase the availability of carbohydrates. In addition, in a fasting state, increased expression of FGF-21 will increase hepatic fatty acid oxidation, which will later use stored fat as an energy source (Matikainen, 2014)..

FGF21 has an effect on the function of α and ß cells of the pancreas organ. In the islets or islets in the pancreatic rats with DM, administration of FGF21 as one of the treatments increased insulin levels in the islets of the pancreas, induced glucose-induced insulin secretion, and also inhibited glucagon secretion. In addition, FGF21 can activate FGF1 in primates and research mice, FGF1 plays a role in regulating appetite, where the effect will induce hypophagia and produce weight loss (Matikainen, 2014).

It is thought that inflammatory conditions can inhibit ß-klotho expression by tumor necrosis factor-alpha (TNF-α), and this will cause disruption of FGF21 function in adipose tissue, causing glucose intolerance. Individuals with DMT2 usually experience an increase in C- reactive protein (CRP) which indicates an inflammatory process. In addition, T2DM patients usually experience an increase in free fatty acid levels in circulation, which is suspected as a trigger for increased FGF21. Increased FGF21 in serum also indicates resistance to FGF21 (Gao et al., 2019).

Hibiscus sabdariffa, known as the Rosella plant, has been known to contain flavonoids, quercetin, polyphenols, catechins, and anthocyanins. In addition, *Hibiscus sabdariffa* is known as an anti-obesity, because of its role in reducing body weight in research mice that were previously made obese. In obese mice, there is an increase in miR-34a expression which will trigger chronic inflammation. miR-34 has an important role in suppressing Klf4 expression so that it can cause macrophage infiltration. Macrophages will produce TNF-α which can induce proinflammatory cytokines through nuclear factor kappa B (NF-κB). The binding of TNF-α to its receptor will induce the production of proinflammatory cytokines, such as IL-Iß and IL-6 through an NF-κB-dependent mechanism. Research shows that by administering *Hibiscus sabdariffa*, this will increase FGFR and Klb. In addition, miR-34a will also be suppressed as a regulator of ß-klotho and FGFR expression through PPARγ expression and C/EBP expression. Reduced PPARγ and C/EBP expression is associated with reduced miR-34a loss. By increasing the expression of FGFR and ß-klotho, this can suppress the occurrence of chronic inflammation and increase the sensitivity of the FGF21 receptor (Kartinah et al., 2022).

Based on th statements, the researchers would like to analyze the influence of *Hibiscus sabdariffa* on Fibroblast Growth Factor 21 (FGF21) on Diabetes mellitus type 2 patients. The researchers hope that this study will contribute to enhancing the knowledge regarding *Hibiscus sabdariffa* and its effects on different aspects.

METHODS

A literature review was the approach taken in this paper. A literature review is a research approach that entails examining and evaluating theories, concepts, and findings in the corpus of academic literature in order to more fully express a fact. The information used was gathered from a variety of literary sources, including books, journals, working papers, reports, and other materials pertaining to using issues and completing research goals. Through websites like Google, Google Scholar, PubMed, and other databases, library resources were accessed in order to prepare this systematic review. The most recent sources to be published were used by the researchers.

RESULTS AND DISCUSSION

Diabetes Mellitus (DM)

Diabetes mellitus (DM) is a metabolic disease characterized by increased blood glucose levels due to failure of glucose regulation. DM is classified into several subclassifications, including type 1 DM (DMT1), type 2 DM (DMT2), maturity onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes (Sapra & Bhandari, 2022). Based on WHO, in 2019 DM is the main cause of death in the world by ranking 9th, an estimated 1.5 million deaths are caused by DM. It is reported that the prevalence of DM is increasing rapidly, especially in people in developing countries (World Health Organization, n.d.). Southeast Asia is ranked 3rd with a fairly large prevalence of around 11.3%. Indonesia is ranked 7th out of 10 countries with the highest DM disease in China, and as many as 10.7 million people suffer from DM in Indonesia (InfoDATIN, 2020).

Factors causing DM are sedentary lifestyle, lack of exercise, smoking, alcohol consumption, dyslipidemia, reduced beta cell sensitivity, and several other factors. Based on WHO data, around 90% of patients who are overweight tend to experience DMT2. In addition, consumption of foods that are low in fiber and high on the glycemic index is thought to be associated with an increased onset of DMT2. In addition, soft drinks that are high in fructose levels also have an effect (Alam et al., 2021).

Pathophysiology of Diabetes Mellitus Type 2 (DMT2)

In the islets of Langerhans in the pancreas, there are two main endocrine cells, namely beta cells which function to produce insulin and alpha cells which function to produce glucagon. These beta and alpha cells continuously regulate the secretion of their respective hormone products so that their levels will vary according to the glucose levels in their environment. If there is no balance between insulin and glucagon, glucose levels will not be balanced in the body. In the case of DM there is a regulatory disorder in the form of insulin that cannot be produced or does not work

(insulin resistance), so that these conditions can cause hyperglycemia (Amit Sapra & Priyanka Bhandari, 2021).

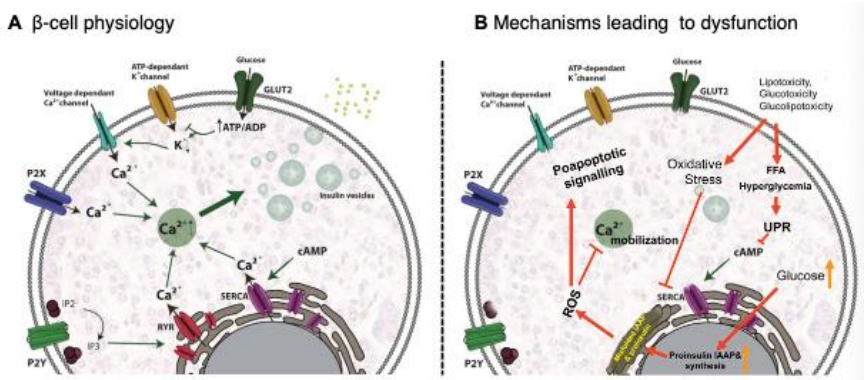

Figure 1. Signal Pathways of Normal and Abnormal Insulin Secretion (Galicia-Garcia et al., 2020)

Beta cells function in producing insulin, which is initially synthesized in the form of pre-proinsulin. In the process of maturation, pre-proinsulin will undergo conformational modifications with the help of the endoplasmic reticulum (RE) and the Golgi body to form immature secretory vesicles. These vesicles will later experience cleavage into peptide C and insulin. Furthermore, insulin will be stored in the form of granules until it is released when stimulated by the trigger. Insulin release is primarily triggered in response to high blood sugar levels. When the sugar level in the blood is high, beta cells will take glucose through the GLUT2 transporter which also works as a beta cell sensor for glucose. Glucose is further catabolized to increase the ADP/ATP ratio, which in turn induces the closure of ATP-dependent potassium channels in the plasma membrane. This event causes depolarization so that it opens calcium channels and calcium will enter the cell. Increased intracellular calcium will trigger priming and fusion of insulin-containing vesicle granules to the plasma membrane resulting in insulin exocytosis. The calcium signal will also amplify the RY receptor (RYR), then RYR will amplify the calcium signal again when the channel is sensitized by messenger molecules resulting from nutrient metabolism so that it will later play a role in amplifying insulin secretion activity. cAMP also plays a role in increasing the potential for insulin release. cAMP is an important messenger that can induce mobilization of insulin-containing vesicles by depleting the intracellular calcium reservoir, so that calcium levels in cells will increase (Galicia-Garcia et al., 2020).

Impaired beta cell function in cases of T2DM is associated with the death of beta cells in the pancreas. In addition, it can also be caused by complex interactions between the environment and its molecular pathways. Individuals with obesity, hyperglycemia and hyperlipidemia, will experience insulin resistance and chronic inflammation. Under these conditions, beta cells become the target of toxicity resulting in inflammation, endoplasmic reticulum disruption, oxidative/metabolic disturbances, and loss of integrity in the islets of Langerhans. (Galicia-Garcia et al., 2020).

Excessive free amino acids and hyperglycemia can induce RE disruption through activation of the apoptotic unfolded protein response (UPR) pathway. Lipotoxicity, glucotoxicity and glucolipotoxicity that occur in obesity can induce oxidative and metabolic stress which can damage pancreatic beta cells. Stress caused by increased free fatty acids can activate the UPR pathway by several mechanisms, including inhibition of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA), which functions in mobilizing calcium, activating IP3 receptors or directly disrupting ER homeostasis. Continuously increasing glucose levels can lead to an increase in proinsulin biosynthesis and also islet amyloid polypeptides (IAAP) in beta cells, which will lead to accumulation of IAAP, unfolding insulin and reactive oxygen species (ROS). These things will interfere with calcium mobilization and form a proapoptotic signal, degrade proinsulin mRNA, and induce the release of interleukin-1 beta IL-1ß, which will recruit macrophages and increase inflammation in the islets of Langerhans (Galicia-Garcia et al., 2020).

Prolonged stimulation of circulating nutrients will induce an inflammatory response under T2DM conditions. Increased levels of glucose and free fatty acids will activate the JNK and IKK pathways, which will result in NF-kappa-B translocation and increased expression of inflammatory mediators such as IL-1β and TNF which will in turn induce insulin resistance. These pro-inflammatory molecules will induce apoptosis of pancreatic beta cells and interfere with insulin secretion by activating the JNK and IKK pathways. In the end, the beta cells will fail to secrete the amount of insulin needed so that a condition of hyperglycemia occurs (Kong et al., 2021).

Fibroblast Growth Factor 21 (FGF21)

Fibroblast growth factor (FGF21) is a hormone that regulates important metabolic pathways. FGF21 is expressed in several metabolically active organs (Tezze et al., 2019). In healthy individuals, the main source of circulating FGF21 is the liver, especially during the fasting state. Meanwhile, adipose tissue is the main place for FGF21 to work. In addition to the liver and adipose organs, tissue targets for FGF21 are the pancreas and the central nervous system (Matikainen, 2014). Based on several studies, it is known that FGF21 is also secreted by skeletal muscle tissue, both in mice and humans, especially when triggered by physical activity such as exercise and in conditions of mitochondrial dysfunction (Tezze et al., 2019). FGF21 has an important role in the endocrine system in regulating carbohydrates, lipids, phosphates and vitamin D. Most FGFs require heparin to bind stably to the FGF receptor, where this heparin will work in an autocrine or paracrine manner, and is not released into the circulation. In addition to the receptor, the FGF21 transduction signal also requires a co-receptor, namely the ß-klotho protein. (Zhang et al., 2018).

FGF21 is thought to work in a state of eating (absorptive phase). When free fatty acids circulate in large quantities, they stimulate FGF21 expression in adipose tissue, which in turn increases glucose uptake. In the liver, FGF21 will induce gluconeogenesis through the PGC-1α pathway and increase the availability of carbohydrates. In addition, in a fasting state, increased expression of FGF-21 will cause an increase in hepatic fatty acid oxidation, which in turn will use stored fat as an energy source (Matikainen, 2014).

FGF21 has an effect on the function of α and ß cells in the pancreas organ. In the islets in the pancreatic rats with DM, administration of FGF21 as one of the treatments will increase insulin levels in the islets of the pancreas, induce glucose-induced insulin secretion, and inhibit glucagon secretion. In addition, FGF21 can activate FGF1 in primates and research mice, where FGF1 plays a role in regulating appetite, so that its effect can induce hypophagia and result in weight loss. (Matikainen, 2014).

It is also thought that inflammatory conditions can inhibit ß-klotho expression by tumor necrosis factor-alpha (TNF-α), this will disrupt the function of FGF21 in adipose tissue, causing glucose intolerance. In individuals with DMT2 there is usually an increase in C- reactive protein (CRP) which indicates an inflammatory process. In addition, T2DM patients usually experience an increase in free fatty acid levels in circulation, which is suspected as a trigger for increased FGF21. In addition, an increase in FGF21 in serum may indicate resistance to FGF21 (Gao et al., 2019).

FGF21 signaling

Activation of the FGFR1/ß-Klotho complex will trigger tyrosine receptor autophosphorylation, which will then be followed by activation of the MAPK (mitogen-activated protein kinase) pathway and activity of the mTORC1/S6K pathway. The mTORC1/S6K pathway triggers adiponectin secretion, glucose uptake, and UCP1 and FGF21 expression. Transcriptional regulation is the key to this process, FGF21 will upregulate UCP1, FGF2 mRNA, adiponectin and GLUT1 mRNA. FGF21 transcription will trigger phosphorylation of transcription regulators, including CRTC2, and CREB coactivators which will stimulate PGC1α transcription and mitochondrial biogenesis; MORC2a is required for 3T3-L1 preadipocyte differentiation and for the expression of genes involved in de novo lipogenesis; and NR3C1, a glucocorticoid receptor that regulates GLUT1 expression (Minard et al., 2016).

When FGF21 binds to its receptor, ß-klotho, and FGFR1, FGF21 will also have an effect on the pancreas organ, where later FGF21 will improve ß-cell function and cell survival by activating the Erk and Akt signaling pathways. In addition, it is stated that FGF21 can increase muscle glucose uptake through upregulation of GLUT4 (Fu & Kemper, 2016).

FGF21 on Gluconeogenesis

Peroxisome proliferator-activated receptor gamma (PPAR- γ) has an important role in fasting-induced hepatic gluconeogenesis. The effect of FGF21 will be mediated by inducing the expression of peroxisome proliferator-activated receptor coactivator protein 1 α (PGC1 α), a transcriptional coactivator that regulates gluconeogenesis gene expression (Ge et al., 2012).

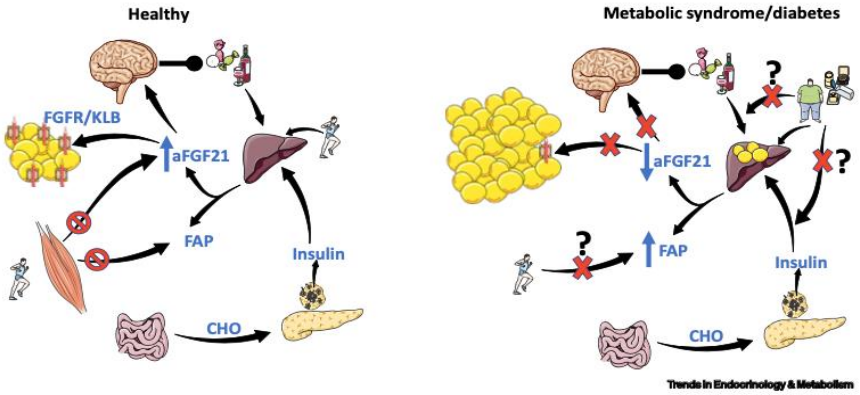

Figure 2. FGF21 signaling (Lewis et al., 2019)

FGF21 can regulate hyperglycemia by sensitizing the role of insulin. In studies with obese mice, FGF21 can reduce insulin and glucose levels, this study shows a role in increasing insulin sensitivity. Insulin can increase glycogen synthesis, lipogenesis, lipoprotein synthesis and inhibit gluconeogenesis, glycogenolysis and VLDL secretion (Emanuelli et al., 2014).

Hibiscus sabdariffa

Hibiscus sabdariffa, known as rosella, is an ideal plant to treat various diseases in developing countries, because it is relatively easy to grow. In China, the rosella seeds are used for oil while the plant and powdered seeds are used as food. In addition, rosella is also often used for medicine and the food industry (Da-Costa-Rocha et al., 2014).

Hibiscus sabdariffa is widely used for local treatment. In India, Africa and Mexico, water from the leaves is used for diuretic, choleretic, hypotensive effects, reducing blood viscosity and stimulating intestinal peristalsis. In Egypt, rosella is used to treat nervous and heart disorders, as well as increase urine production or diuresis. In North Africa, rosella is used to treat sore throats, coughs, and genital problems (Da-Costa-Rocha et al., 2014).

The Role of Hibiscus sabdariffa as an Anti-Inflammatory

Inflammation is a physiological response in the body that functions to fight damage or interference from external factors. Diabetes will trigger the release of inflammatory substances such as IL-6, TNF-α, and IL-18. *Hibiscus sabdariffa* polyphenolic extract can prevent diabetic nephropathy, inhibit albuminuria, and increase creatinine clearance, prevent fat storage, and glycation-end products (AGE) in the kidney (Riaz & Chopra, 2018). *Hibiscus sabdariffa* was reported to suppress C/EBP expression, which suppressed miR-34a expression. miR-34a can trigger chronic inflammation by inhibiting Klf4 expression, which can trigger macrophage infiltration which will produce TNF-α. TNF-α binds to its receptors to produce proinflammatory cytokines such as IL-1ß and IL-6 (Kartinah et al., 2022). In people with diabetes mellitus, it is known to experience an increase in miR-34a levels. miR-34a is frequently associated with the

regulation of several proteins, including Akt. Akt is important in the translocation of GLUT4 to the membrane moiety (Fomison-Nurse et al., 2018).

The Role of Hibiscus sabdariffa as an Antihyperlipidemic

One of the functions of insulin is to coordinate the conversion of food carbohydrates into energy stored in fat (triglycerides). VLDL and chylomicrons, which transport exogenous and endogenous triglycerides, are broken down by lipoprotein lipase. When there is a deficiency of insulin, or insulin that doesn't work, the activity of this lipoprotein lipase will be reduced, this is what causes hyperlipidemia in people with DM (Johansen, 1990).

Hibiscus sabdariffa has inhibitory lipase activity which can hydrolyze 50-70% of total dietary fat. This antihyperlipidemic effect is thought to originate from the anthocyanins and protocatehuic acid present in rosella extract. The isomer of hydroxytric acid (-)-HCA has an inhibitory effect on citrate lyase which can inhibit the formation of acetyl-CoA as well as triglyceride and cholesterol biosynthesis (Riaz & Chopra, 2018).

The Role of Hibiscus sabdariffa as an Antidiabetic

Atherogenic dyslipidemia has a triage of high LDL cholesterol, high triglycerides, and low HDL cholesterol, and this condition is part of the metabolic syndrome. It is known that hyperlipidemia is a risk factor that is quite strong in triggering cardiovascular disease, and also DMT1 and DMT2 disease. Excessive production of reactive oxygen species (ROS) by oxidative stress can occur in T2DM patients with hyperglycemia. *Hibiscus sabdariffa* has antioxidant substances, such as protocatechuic acid, catechin, and epigallocatechin gallate, which can fight harmful substances such as ROS (Wang et al., 2011).

In addition, in a state of hyperglycemia, the capacity of insulin to activate the Akt cascade will be impaired. In DMT2, the PI3K-Akt pathway is thought to be the center of insulin resistance. Hyperglycemia can also increase Akt phosphorylation and activity. In fact, oxidative stress is one of the important factors causing the disruption of Akt activation. In addition, TNF-alpha has been identified to trigger suppression of Akt phosphorylation (Wang et al., 2011).

Hibiscus sabdariffa which has an active metabolite that acts as an antidiabetic, because it contains organic acids, anthocyanins, flavonoids, and polyphenols, is thought to inhibit the PI3-K.Akt pathway, resulting in a decrease in Akt phosphorylation (Wang et al., 2011).

In addition, *Hibiscus sabdariffa* was reported to be able to reduce ROS levels, and TNF-induced nuclear factor kappa light chain enhancer of activated B cells , thereby creating an oxidative state and reducing inflammation. Carotenoids, which are the main metabolites in *Hibiscus sabdariffa*, are reported to have great antioxidant activity. In addition, anthocyanins are also reported to have antioxidant effects (Bule et al., 2020).

Figure 3. *Hibiscus sabdariffa* (R.A. Mans & Grant, 2017)

The Role of Hibiscus sabdariffa on FGF-21 Signaling

It has been reported in several studies that people with diabetes mellitus have high levels of FGF21, accompanied by impaired glucose regulation, this indicates the possibility of FGF21 resistance. In addition, a state of hyperglycemia is thought to suppress ß-klotho (So et al., 2013).

FGF21 resistance will trigger excess FGF21 secretion from the liver. So that FGF21 levels in people with diabetes will be higher than people without diabetes. From the research, it is known that administration of *Hibiscus sabdariffa* can overcome FGF21 resistance through increasing the expression of FGFR and Klb. *Hibiscus sabdariffa* is thought to suppress miR-34a as a regulator of FGFR and also ß-klotho expression (Kartinah et al., 2022).

The increase in ß-klotho and FGFR can be influenced by *Hibiscus sabdariffa*, which can also suppress the chronic inflammatory state experienced by T2DM sufferers. Several studies have shown that the polyphenols in *Hibiscus sabdariffa* can inhibit proinflammatory cytokines by suppressing NFkB. *Hibiscus sabdariffa* can also significantly reduce TNF-a by suppressing NFkB. In addition, polyphenols can increase FGFR1 and ß-klotho in research rats (Kartinah et al., 2022).

So, *Hibiscus sabdariffa* has the potential to regulate FGF21 resistance by suppressing miR-34a expression and also increasing the number of FGF21 receptors, such as FGFR1 and also its coreceptor, namely ß-klotho (Kartinah et al., 2022).

CONCLUSION

Diabetes mellitus (DM) is a metabolic disease with an increase in blood glucose levels due to failure of blood glucose regulation. In obese patients with Type 2 Diabetes Mellitus (DMT2), or in non-obese patients with DMT2, FGF21 levels are higher than individuals without T2DM. In T2DM and obesity, a condition occurs, namely the presence of FGF21 resistance where exogenous FGF21 is disrupted in obese mice. This is supported by reduced FGF21 receptors such as FGFR1c, FGFR2, and FGFR3, and their coreceptor ß-Klotho.

FGF21 is expressed in several metabolically active organs. In healthy individuals, the main source of circulating FGF21 is the liver, especially during the fasting state. Adipose tissue is the main site where FGF21 has an important role in the endocrine system in regulating carbohydrates, lipids, phosphates and vitamin D. FGF21 has an effect on the function of α and ß cells in the

pancreas organ. In the islets of the pancreatic organs of rats with DM, administration of FGF21 increased insulin levels, induced insulin secretion, and inhibited glucagon secretion. It is also thought that inflammatory conditions can inhibit ß-klotho expression by tumor necrosis factor-alpha (TNF-α), this will cause disruption of FGF21 function, causing glucose intolerance. In addition, individuals with T2DM usually have a chronic inflammatory process.

Hibiscus sabdariffa, known as rosella, is an ideal plant to treat various diseases in developing countries. *Hibiscus sabdariffa* was reported to suppress the PPARγ pathway and C/EBP expression, which suppressed miR-34a expression. miR-34a can trigger chronic inflammation by inhibiting Klf4 expression, resulting in macrophage infiltration which will produce TNF-α. *Hibiscus sabdariffa* which has an active metabolite that acts as an antidiabetic, because it contains organic acids, anthocyanins, flavonoids, and polyphenols, is thought to inhibit the PI3-K & Akt pathway, resulting in a decrease in Akt phosphorylation. In addition, *Hibiscus sabdariffa* was reported to be able to reduce ROS levels, and TNF-induced nuclear factor kappa light chain enhancer of activated B cells, thereby creating an oxidative state and reducing inflammation. So it can be concluded that, by increasing the expression of FGFR and ß-klotho, this can suppress the occurrence of chronic inflammation and increase the sensitivity of the FGF21 receptor.

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