CHAPTER II
LITERATURE REVIEWS

2.1 Diabetes Mellitus (DM)

Diabetes mellitus is a chronic metabolic disorder stemming from either insufficient pancreatic insulin production or the body's impaired insulin utilization, leading to hyperglycemia and progressive damage to various physiological systems, particularly the nerves and blood vessels (WHO, 2021). There are 4 types of DM divided by cause, Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), Gestational diabetes mellitus (GDM), and Specific types of diabetes due to other causes.

T1DM characterized by deficient insulin production requiring daily administration with unknown etiology and prevention (WHO, 2021). T1DM is results oocur by the β-cells in pancreas were destroys by autoimmune (Paschou et al., 2018). T2DM is the most common type, resulting from ineffective insulin use largely due to excess body weight and physical inactivity, with additional influences from race, ethnicity, and age. Undiagnosed or poorly managed diabetes significantly increases the risk of debilitating and irreversible complications, including severe damage to the heart, eyes, kidneys, and nerves, potentially leading to limb amputation, vision loss, and premature mortality. This condition represents a global epidemic, affecting over 420 million people worldwide, approximately 6% of the global population (WHO, 2021). GDM is highly insulin resistance during pregnancy but often disappear after pregnancy (Clinical Practice Guideline for Diabetes, 2017). Mother who used to had GDM increase risk in T2DM. (Jovanovic & Pettitt, 2001) GDM can be used in prediction in incoming T2DM (Farahvar et al., 2018). Specific types of diabetes due to other causes is notable cause DM such as Maturity-Onset Diabetes of the Young (MODY), DM cause by liver

disease, abnormal endocrine, drug, infection, autoimmune, and/or combination (Clinical Practice Guideline for Diabetes, 2017)

2.2 Obesity

Obese individuals develop insulin resistance, which is characterized by impaired insulin action in the liver and reduced glucose uptake in fat and muscle. Increased body mass index (BMI) and abdominal fat distribution linearly increases the risk of T2DM due to alterations in adipose tissue biology that links obesity with insulin resistance and beta cell dysfunction (Klein et al., 2022). Obesity is the most significant single risk factor for the development of fatty liver, Non-alcoholic fatty liver disease (NAFLD) is liver function impairments and tissue damage similar that not related with drinking alcohol, developed by steatosis to advanced fibrosis and cirrhosis (Festi et al., 2004).

2.3 Insulin signaling

Upon insulin binding, the insulin receptor undergoes autophosphorylation, initiating the phosphorylation of insulin receptor substrate (IRS) proteins. These phosphorylated IRS proteins then associate with phosphatidylinositol 3-kinase (PI3K) and engage protein kinase B (Akt), ultimately leading to the RAB10 protein-mediated translocation of glucose transporter 4 (GLUT4)-containing vesicles to the cell membrane, thereby enabling glucose entry into cells (Sano et al., 2003; Velez et al., 2014). Activated Akt additionally promotes glycogen synthesis (Sah et al., 2016) and mediates diverse tissue-specific insulin effects: in the liver, p-Akt upregulates glycogen synthesis, inhibits gluconeogenesis, and stimulates cell growth via mammalian target of rapamycin (mTOR) activation; in skeletal muscle, insulin drives glycogenesis; and in adipose tissue, insulin primarily regulates lipid transport and storage (Velez et al., 2014). Furthermore, in the post-prandial state, high insulin levels increase lipoprotein lipase activity, releasing free fatty acids from circulating triglyceride-containing chylomicrons, which are then captured by adipocytes via acylation-stimulating protein and re-esterified into triglycerides by diacylglycerol transferase (Velez et al., 2014).

2.4 Insulin resistance

Aberrations in the phosphorylation and dephosphorylation of key signaling proteins, from the insulin receptor itself to downstream effectors like Akt, can significantly impair insulin action, culminating in insulin resistance. At a cellular level, such impairments can manifest as down-regulation, deficiencies, or polymorphisms in the tyrosine phosphorylation of the insulin receptor, IRS proteins, or PI3K, as well as compromised Akt activation or functional abnormalities of GLUT4 (Wheatcroft et al., 2003; Sah et al., 2016). Furthermore, proinflammatory cytokines and endoplasmic reticulum stress contribute to insulin resistance through the activation of serine kinases, specifically c-Jun N-terminal kinase (JNK) and I kappa B kinase (IKK-β). These kinases promote the phosphorylation of IRS1 at serine residues (e.g., serine 302 and serine 307), which negatively regulate normal insulin signaling (Ropelle et al., 2010; Sah et al., 2016). Activated IKK-β also phosphorylates the inhibitory protein nuclear factor kappa b (NFkb), which typically sequesters the transcription NFkb. This phosphorylation targets NFkb, for proteasomal degradation, thereby releasing NFkb. Subsequently, NFkb translocate to the nucleus, where it promotes the expression of various target genes whose products contribute to the development of insulin resistance (Sah et al., 2016).

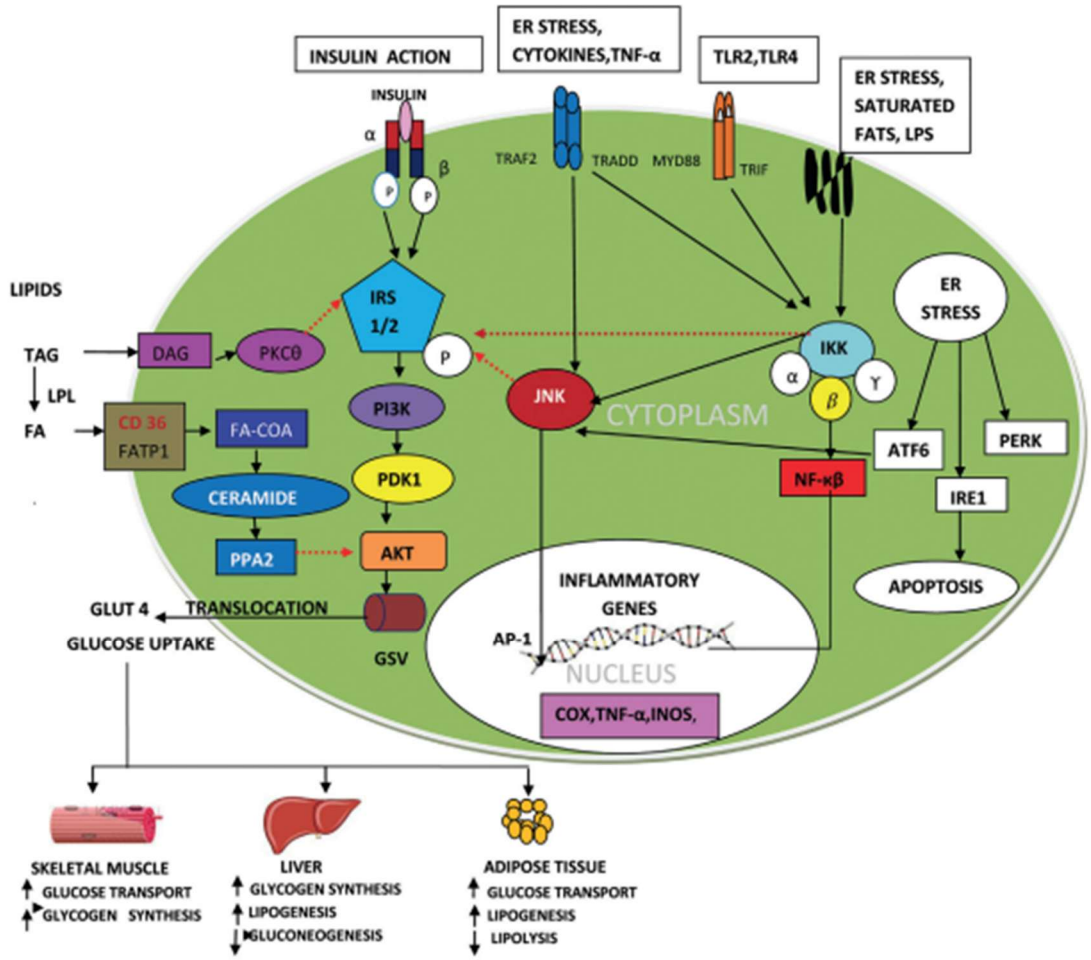

Figure 2.1 Pathophysiology of insulin resistance

(Source: Sah et al., 2016)

2.5 Hepatic steatosis

Accumulation of fat leads to liver steatosis, imbalance in free fatty acid availability, and impairment in the oxidative capacity of mitochondria ultimately causing mitochondrial dysfunction and further accumulation of fats in the cell. (Muoio & Newgard, 2008; Velez et al., 2014) Excessive concentrations of diacylglycerol also interfere with the phosphorylation of IRS proteins and activation of PI3K. This effect is mediated by serine kinases in the protein kinase C family that phosphorylate IRS proteins at serine residues impeding their ability to activate insulin signaling through PI3K. This effect impairs insulin signaling and prevents GLUT4 translocation (Roden, 2004; Velez et al., 2014)

2.6 Cafeteria diet (CAF)

The limitations of the high-fat diet model in accurately reflecting human obesity and its associated metabolic disorders (Yandell, 2015; Bortolin, 2018) have led to the introduction of the CAF model. Both high-fat diet and CAF effectively induce visceral obesity, glucose intolerance, and insulin resistance in mice (Lang et al., 2019). However, for optimal induction of hyperphagia and its metabolic consequences, the CAF model should incorporate a diverse range of palatable high-fat and high-carbohydrate (particularly sugar) food products, encompassing both salty and sweet tastes, as relying solely on high-fat or high-sugar items is less effective (Rodríguez-Correa et al., 2020; Lalanza & Snoeren, 2021).

Lang et al. (2019) conducted a 12-week study on male C57BL/6J mice, initiating dietary interventions at six weeks of age. Mice were assigned to one of four groups: standard chow diet, normal-fat diet, CAF, or high-fat diet. While both CAF and high-fat diet successfully induced visceral obesity, glucose intolerance, and insulin resistance, the CAF diet proved to be more potent in eliciting perivascular adipose tissue dysfunction and vascular dysfunction in the aortas. This suggests that the broader palatability and varied macronutrient composition of the CAF diet may more closely mimic the complex dietary patterns contributing to severe metabolic dysfunction in humans.

2.7 Pancreatic α-amylase

α-amylase (1,4--D-glucan-glucanohydrolase, EC 3.2. 1.1) is digestive enzyme that catalase the α-1,4 glyosidic linkage hydrolysis in starch, maltodextrins and maltooligosaccharides (Tundis et al., 2010). The cofactor of pancreatic α-amylase is calcium ion for structural integrity (Steer & Levitzki, 1973; Vallee et al., 1959) and chloride ion for activation (Levitzki & Steer, 1974), the optimum pH of pancreatic α-amylase is 6.9 (Ishikawa et al., 1990)

2.8 White kidney bean (*Phaseolus vulgaris*)

White kidney bean (*Phaseolus vulgaris*) is a notable source of dietary fiber and resistant starch, with research suggesting a negative correlation between starch intake and colorectal cancer risk, potentially attributed to the protective effects of resistant starch (Soral-Śmietana & Krupa, 2005). Beyond carbohydrates, bean seeds are remarkably rich in protein, constituting 17% to 39% of their dry matter, significantly higher than the 5-15% found in cereals (Bressani, 1993; Krupa & Soral-Śmietana, 2003; Soral-Śmietana et al., 2003). These proteins, primarily storage proteins, are deposited in membrane-bound organelles within cotyledonary parenchyma cells and serve as a crucial reservoir of amino acids, ammonia, and carbon skeletons for the developing seedling upon germination.

A key functional component of *Phaseolus vulgaris* is the α-amylase inhibitor (αAI), which exists in several isoforms: αAI-1, αAI-2 and αAI-3 (or αAI-L). αAI-1 and αAI-2. While αAI-1 and αAI-2 exhibit high amino acid sequence similarity, they differ in their specificity towards α-amylases. Specifically, αAI-1, prevalent in cultivated beans, effectively inhibits porcine pancreatic α-amylase, whereas αAI-2 is found in certain wild bean accessions. The αAI-L isoform, conversely, demonstrates no activity against tested α-amylases and is hypothesized to represent an evolutionary intermediate among plant defense proteins such as phytohemagglutinins and arcelins (Lee et al., 2002; Guzman-Partida et al., 2007; Obiro et al., 2008).

The biosynthesis and maturation of αAI-1, a typical bean lectin, involve several cellular compartments. It is synthesized in the rough endoplasmic reticulum, undergoes modification (signal peptide removal and N-glycosylation) in the Golgi apparatus, and is subsequently transported to protein storage vacuoles for proteolytic processing. Analysis of microsomal fractions via SDS-PAGE indicates that 30-35 kDa fractions are associated with the endoplasmic reticulum, while 14 kDa and 19 kDa fractions are linked to the Golgi body and storage vacuoles, respectively. αAI-1 becomes detectable in the cotyledons and axis of the plant seed approximately 17

days post-pollination, reaching a maximum concentration by 28 days that is maintained until maturity, though its dry weight content may slightly decrease during desiccation (Obiro et al., 2008). Mechanistically, **α**AI completely occludes the substrate-reducing end of the enzyme cavity and sterically hinders access to the other end. This inhibitor triggers substrate "mimetic" interactions with the enzyme's binding subsites, effectively targeting all catalytically competent components (Payan, 2004; Manatwiyangkool, 2014).

Figure 2.2 White beans (*Phaseolus vulgaris*)

2.9 Effect of white bean extract on vivo

Tormo et al. (2004) investigate the effect of orally administered with 50 mg/kg/days purified **α**-AI on male Wistar rats (week of age 10) for 3 weeks. They found that Acute effect purified **α**-AI lower postprandial glycemia. Chronic effect purified **α**-AI lower body weight, food intake, and glycemia. Fantini et al. (2009) investigate the effect of orally administered with 50, 200, or 500 mg/kg/days *P.valgaris* dry extract on male Wistar rats for 10 days. They found that Acute effect lower postprandial glycemia, and food intake, Chronic effect lower body weight, food intake, and glycemia. Oliveira et al. (2014) investigate the effect of orally administered with commercial phaseolamin on diabetic induced male Wistar rats, the experiment was start when rats had weight rage of 160-210g acclamation for 2 weeks, then rats were induced to diabetic with Streptozotocin, 10 days later rats were orally administered with 100, 500, 1500

mg/kg/days commercial phaseolamin for 20 days. They found that commercial phaseolamin lower glycemia, catalase and superoxide dismutase activity, and tissue damage caused by lipid peroxidation. Song et al. (2016) investigate the effect of orally administered with PVE on diet-induced obesity Male C57BL/6J mice the experiment was start when mice had 4 weeks of age and mice were acclamation for 1 weeks. Mice were induced to obesity with high-fat diet and start orally administered with PVE at the same time of obesity induction. The dose of PVE was 50 mg/kg/days and orally administered for 14 weeks. They found that PVE lower body weight, glycemia, hepatic steatosis, liver cholesterol, liver triglyceride, serum AST, serum ALT, serum glucose, and serum insulin; influence on the gut microbiota. Micheli et al. (2019) investigate the effect of orally administered with PVE on metabolic syndrome induced Male C57BL/6 mice. The experiment was start when mice had 20 gram of body weight and mice were acclamation for 1 weeks. Mice were induced to metabolic syndrome with high-fat diet and start orally administered with PVE at week 11 after the week of metabolic syndrome induction. The dose of PVE was 500 mg/kg/days and orally administered for 8 weeks. They found that PVE lower body weight, glycemia, blood glucose, blood cholesterol, blood triglyceride, blood LDL, plasma insulin, hepatic steatosis and liver lipid peroxidation. Ezzat et al. (2021) investigate the effect of orally administered with *P.vulgaris* fractions on diabetes induced rats the experiment was start when mice had 150-200 gram of body weight and rats were fast for 12 hour then rats were induced to diabetic with Streptozotocin. When Blood glucose level above 300 mg/dl after 48 house the administration with *P.vulgaris* fractions though orogastric tube were conducted for 30 days. The *P.vulgaris* fractions were prepared by *P.vulgaris* pods ethanolic extract and fractions (polar or non-polar). The dose of *P.vulgaris* fractions were 100, or 200 mg/kg/days. They found that the *P.vulgaris* fractions lower blood glucose (polar and non-polar), lower malondialdehyde, nitric oxide, cholesterol, and triglycerides, and increase HDL (non-polar).

In another study, Wang et al. (2020) allocated obese human subjects, balanced by gender, into a control group receiving placebo and an intervention group receiving

PVE. Subjects consumed two PVE capsules (total 2,400 mg/day) before each of three daily meals for a period of 35 days. At the conclusion of the study, the PVE group (n=56; 29 males, 27 females) demonstrated significant weight loss and reduction in subcutaneous fat compared to the placebo group (n=58; 28 males, 30 females), where baseline characteristics (height, weight, age, body fat) were not significantly different between groups ($p < 0.05$).

More recently, Jäger et al. (2024) conducted a randomized trial, assigning subjects to one of three groups: a high-dose PVE group (500 mg/capsule), a low-dose PVE group (350 mg/capsule), or a high-dose placebo group, following a two-week screening period. After 12 weeks of treatment, both PVE dosages significantly reduced body weight, BMI, and fat mass when compared to the placebo group ($p < 0.05$). These collective human studies provide compelling evidence for the beneficial metabolic effects of *Phaseolus vulgaris* extract.

Table 2.1 Reviews of *P. vulgaris* on animals

References	Animals	Induction of metabolic syndrome	Start of experiment (week of age)	Start induction after start of the experiment	Start administration of *P.valgaris* after start of induction	*P.valgaris* administered period	Dose of *P.valgaris* administered (mg/kg/days)	Product for feeding	*P.vulgaris* name	Effect	Main results
Tormo et al. (2004)	Male Wistar rats	-	10	-	-	3w	50	Purified α-AI	White kidney beans	Acute, chronic	[Acute] lower postprandial glycemia; [Chronic] lower body weight, food intake, and glycemia
Fantini et al. (2009)	Male Wistar rats	-	-	-	-	1w 3d	50, 200, 500	Dry extract	Kidney beans	Acute, chronic	[Acute] lower postprandial glycemia, and food intake; [Chronic] lower body weight, food intake, and glycemia
Oliveira et al. (2014)	Male Wistar rats	Streptozotocin	160-210g	2w	1w 3d	2w 6d	100, 500, 1500	Commercial phaseolamin	White beans	Chronic	Lower glycemia, catalase and superoxide dismutase activity, tissue damage caused by lipid peroxidation
Song et al. (2016)	Male C57BL/6J mice	High-fat diet	4	1w	0w	14w	50	Extract	White kidney bean	Chronic	Lower body weight, glycemia, hepatic steatosis, liver cholesterol, liver triglyceride, serum AST, serum ALT, serum glucose, and serum insulin; influence on the gut microbiota
Micheli et al. (2019)	Male C57BL/6 mice	High-fat diet	20g	1w	11w	8w	500	Extract	White kidney beans	Chronic	Lower body weight, glycemia, blood glucose, blood cholesterol, blood triglyceride, blood LDL, plasma insulin, hepatic steatosis and liver lipid peroxidation
Ezzat et al. (2021)	Male Albino Wistar rats	Streptozotocin	150-200g	12h fasted	Blood glucose level above 300 mg/dl after 48 hr of induction	4w 2d	100, 200	Pods ethanolic extract and fractions (polar or non-polar)	Green beans	Chronic	[polar and non-polar] Lower blood glucose [non-polar] Lower malondialdehyde, nitric oxide, cholesterol, and triglycerides; increase HDL

Table 2.2 Reviews of using of *P. vulgaris* human subjects

References	Subjects n (male/female)	Age (years)	BMI (kg/m^2)	*P. vulgaris* administration period	Dose of *P. vulgaris* (mg/days)	Effect	PVE effect
Spadafranca et al. (2013)	Placebo: 12 (6/6) PVE: 12 (6/6)	20 - 26	19.7 – 23.5	7 days of washout period	100	Acute	Lowered postprandial glucose, ghrelin secretion, and eating desire
Wang et al. (2020)	Placebo: 58 (28/30) PVE: 58 (28/27)	18 – 65	≥ 30	35 days	2,400	Chronic	Lowered body weight, BMI, and fat mass
Jäger et al. (2024)	Placebo: 36 (12/24) PVE Low: 18 (6/12) PVE High: 36 (12/24)	18 - 65	25 – 34.9	12 weeks	2100, 3000	Chronic	Lowered body weight, BMI, and fat mass

2.10 Reference

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