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Hypoglycemic property of cocoa products: potential underlying mechanisms

Ayad S. Mubarak[1,2] and *Tang Yiquen[1]

[1]*Clinical Pharmacy Department, China Pharmaceutical University, Nanjing, China*
[2]*Fallujah Health Sector: Anbar Health Department, Iraqi Ministry of Health, Anbar, Iraq*

ABSTRACT
Cocoa powder and chocolate is most abundant flavonoids-plant product. Type 2 diabetes mellitus (T2DM) is health and epidemically serious metabolic disorder. The treatment and moreover preventing of T2DM is therapeutic target worldwide. This review focuses on antidiabetic mechanisms of cocoa products. Particularly, intensifying insulin sensitivity, which is a superior pathway for chronic glucose level control, and increasing insulin release for acute glucose level control. Accordingly, the hypoglycemic effect results in elevate synthesis and bioavailability of nitric oxide (NO). Subsequently, improve blood flow and capillary recruitment.

***Key Words*:** Cocoa flavanols, chocolate, nitric oxide, diabetes mellitus, hypoglycemic.

INTRODUCTION

Insulin resistance is a physiological conditions in which normally insulin-sensitive cells show weak response to insulin (Clark *et al.*, 2003) such as impaired glucose tolerance (IGT) (Association, 2010), in which reveal sustained hyperglycemia (Baron *et al.*, 1996, Kim *et al.*, 2006), with high incidence of type 2 diabetes mellitus (T2DM) occurrence (Osei *et al.*, 2004). T2DM is one of the most global health burden disorder and epidemically growing (Whiting *et al.*, 2011). Management and protection of T2DM patients from sudden and persistent increasing of glucose level in the blood is an essential aim of treatment (Genuth, 2003).

Natural flavonoids from plant source are a novel agent candidate for diabetes mellitus (DM) therapy (Hanhineva *et al.*, 2010). Flavonoids are polyphenolic compound abundantly found and detected in vegetables and fruits (Scalbert and Williamson, 2000). The regular intakes of polyphenolic rich diets or beverages bypass the deterioration prognosis of many disorders such as atherosclerosis and DM (Kosinska and Andlauer, 2012). Polyphenolic compounds have diverse health benefits for instance antioxidant, cardioprotective and anticarcigenic (Jaganath and Crozier, 2009). The production of raw cocoa powder or chocolate required many processing steps, namely, fermentation, roasting, grinding and alkalizing, subsequently influence the polyphenolic contents of final products (Wollgast and Anklam, 2000). Even so Cocoa powder and chocolate have remained one of the richest flavonoids plant products (Sanbongi *et al.*, 1998). Cocoa and chocolate polyphenols composed mostly of monomers (catechin and epicatechin) and oligomers (procyanidins) (Bravo, 1998; Tomas-Barberan *et al.*, 2007). Furthermore, methylxanthines, which are caffeine, theobromines, and theophylline, have been identified as well (Kelm *et al.*, 2006). This review points out the cocoa powder and chocolate potential hypoglycemic mechanisms, which are enhanced insulin release and sensitivity, antioxidant and angiotensin converting enzyme (ACE) inhibitor. Interestingly, boosting insulin sensitivity is mostly a predominant mechanism for chronic glucose level control through stimulation of insulin signaling mediators (Klover and Mooney, 2004; Cao *et al.*, 2007; Cordero-Herrera *et al.*, 2013; Zhang *et al.*, 2013; Cordero-Herrera *et al.*, 2014). Moreover, the augmenting of insulin release is likely to be acute glucose level control mechanism (Rabinowitz *et al.*, 1966; Brand-Miller *et al.*, 2003; Mhd Jalil *et al.*, 2009; Sarmadi *et al.*, 2012; Martin *et al.*, 2014). The evoked sensitivity and release of insulin result in amelioration of vasodilatation and/or capillary recruitment in which led to increase muscle blood flow (Steinberg *et al.*, 1994; Clark *et al.*, 2003) due to either direct vasodilatation effect of insulin (Schultz *et al.*, 1977; Chen and Messina, 1996) or insulin signaling mediators which led to boost nitric oxide NO production (Kim *et al.*, 2001).

HYPOGLYCEMIC EFFECT

Abbe *et al.* investigation arises short-term glucose control (at 60 and 90 min postprandial) of obese-diabetic (ob-db) rats supplemented with cocoa extract contains polyphenols, 3.55mg caffeine and 2.22mg theobromines /g cocoa extract (Mhd Jalil *et al.*, 2009). Consistent with this observation, cocoa supplementation boosted insulin release in blood of healthy adults (Brand-Miller *et al.*, 2003; Martin *et al.*, 2014). Noticeably, insulin has crucial hemodynamic impact, which affect muscle metabolism (Vincent *et al.*, 2004). It has direct vasodilator action through insulin receptors (IR) on vascular cells (Schultz *et al.*, 1977; Chen and Messina, 1996). In addition, the vasodilatation implicated nitric oxide (NO) synthesis by endothelial cells (Schultz *et al.*, 1977) through stimulation of signaling cascade that led to activation of endothelial nitric oxide synthase (eNOS) by IRS-1, phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) (Kim *et al.*, 2001). Furthermore, insulin modulates capillary recruitment in vivo (Baron *et al.*, 1993; Vincent *et al.*, 2004) through direct dilatation effect on blood vessels bed by enhancing NO generation from endothelial cells (Ziai *et al.*, 2005) or from skeletal muscles (Grassi *et al.*, 2008). Eventually, insulin-mediated elevation in muscle blood flow and/or capillary recruitment led to improve glucose uptake in healthy adult (Clark *et al.*, 2003), and inversely proportional to the blood pressure (Ruzaidi *et al.*, 2008).

***Corresponding Author**:
Tang Yiquen, Associate Professor
Clinical Pharmacy Dept., China Pharmaceutical University
Longmian Avenue 211198 Jianning District
Nanjing city, Jiangsu Province, China
E-mail: *tyq_cpu@sina.com*
Contact No.: 008613801590660

However, the amelioration of insulin plasma level is not only the sole mechanism of polyphenolic antidiabetic effect in T2DM (Lee *et al*., 2005), glucose-intolerant adult (Suzuki *et al*., 1995), and STZ-induced diabetic rats (Suzuki *et al*., 1995). Moreover, the cocoa supplementation shows long-term glucose control in both (ob-db) mice (Vincent *et al*., 2002), and streptozotocin (STZ)-induced diabetic rats (Shankar *et al*., 2000; Iwashita *et al*., 2001). Interestingly, medicines that ameliorate vasodilation, such as angiotensin-converting enzyme inhibitors (Amin *et al*., 2004; Tomaru *et al*., 2007), α-blockers (Fogari *et al*., 1998; Ruzaidi *et al*., 2005), are also attenuate the insulin-resistance. So that, the hypoglycemic effect of cocoa extract presumed to be owed to stimulate insulin release (Suzuki *et al*., 1995), and/or sensitivity (Suzuki *et al*., 1995; Andersson and Lithell, 1996). Subsequently, cocoa-polyphenols may have not restricted enhancement effect on insulin release only.

However, theobromines display no hemodynamic and electrophysiological impacts on healthy adults (Suzuki *et al*., 1992). While, caffeine intakes led to critical suppression of insulin sensitivity in sedentary subjects (Baron *et al*., 1999), and T2DM patients (Greer *et al*., 2001). Hence, caffeine has partly implicated in alleviating glucose uptake (Mhd Jalil *et al*., 2009).

The one more hypoglycemic potential mechanism of polyphenols is their impact on liver, muscles and intestine. The liver is one of the substantial organs, which regulate the blood glucose concentration within the normal ratio by controlling both gluconeogenesis and glycogenolysis for glucose supplementation during hypoglycemic condition and elevate glucose disposal from blood circulation to boost glycogen synthesis through hyperglycemia (Klover and Mooney, 2004). Whilst, diminishing in insulin's ability to elevate glycogen synthesis in the liver is one of hepatic insulin resistance characteristic features (Klover and Mooney, 2004).

Cocoa polyphenolic extract (CPE), and essential cocoa flavanol, (-)-epicatechin (EC), promote insulin sensitivity of hepatic cells (HepG2), by the suppression of alleviating levels and tyrosine-phosphorylated of insulin receptor (IR), insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) induced by high glucose concentration (Cordero-Herrera *et al*., 2014), which have a critical role in hepatic insulin resistance progression (Nakajima *et al*., 2000; Klover and Mooney, 2004). Furthermore, stimulation of IR, IRS-1and IRS-2 led to activation of AKT (PI3K)/PKB pathway (Klover and Mooney, 2004). CPE, EC and other naturally occurring polyphenols activate hepatic glycogen synthase (GS) by boosting the expression levels of PI3K/AKT and GSK3 in HepG2 cell line (Mhd Jalil *et al*., 2009) and liver of insulin-resistant rats (Brand-Miller *et al*., 2003; Martin *et al*., 2014). CPE and EC elevated 5-AMP-activated protein kinase (AMPK) phosphorylated level in induced insulin resistance HepG2 (Iwashita *et al*., 2001; Mhd Jalil *et al*., 2009) and cocoa liquor normalized P-AMPK in the liver of insulin resistance mice (Yamashita *et al*., 2012). However, AMPK alleviated in high glucose-induced insulin resistance hepatic cells (Zang *et al*., 2004). The concomitant scarcity of GLUT-2 levels with insulin resistance (Nakajima *et al*., 2000) can be reverted in HepG2 cells by treatment with CPE and EC (Cordero-Herrera *et al*., 2014). The increasing of gluconeogenesis owing to rise of phosphoenolpyruvate carboxykinase (PEPCK) levels (Klover and Mooney, 2004), which associated with induced insulin resistance of both HepG2 cell line and mouse liver, have been prevented by using of CPE, EC (Cordero-Herrera *et al*., 2013; Cordero-Herrera *et al*., 2014) and other natural polyphenolic compounds (Collins *et al*., 2007a; Pu *et al*., 2012). From the above results, we can conclude that CPE and EC reduced glucose synthesis and maintain or enhance glycogen production in induced insulin resistance liver or hepatic cells through improvement of AKT, AMPK, and GSK3, p-IRS-1, p-IRS-2 and GLUT-2 levels. Consequently, CPE and EC ameliorated liver insulin sensitivity and inhibited deterioration of insulin resistance liver. Interestingly, the using of N-acetylcysteine as antioxidant treatment led to repress synthesis of anti-inflammatory mediator rather than bolstering of insulin sensitivity (Setshedi *et al*., 2011).

Moreover, The treatment of L8 muscle cells with the Canna indicia root extract at doses of 0.1-0.5 mg/ml, which contains flavonoids and catechol, displayed rising in the amount of glucose transporter isoforms 1 (GLUT1) and 4 (GLUT4) at the muscle cell surface and boosted GLUT1 protein synthesis. In addition, it stimulates phosphatidylinositol 3-kinase (PI3K) as well (Purintrapiban *et al*., 2006).

Whilst, dietary polyphenols suppress the intestinal cell line glucose uptake (Johnston *et al*., 2005) by the repression of sodium-dependent glucose transporter (SGLT1) (Kobayashi *et al*., 2000), which is crucial for intestinal glucose active transport (Wright and Turk, 2004). Likewise, cocoa acetone-dry powder (AcDP) autolysis at PH 3.5 displayed higher α-amylase inhibition effect (Sarmadi *et al*., 2012). Accordingly, it sustained the carbohydrate degradation and decreased glucose absorption. Eventually, it reduced the postprandial plasma glucose raise (De Fronzo *et al*., 2004). As well as, in vitro study the autolysate yielded at PH 3.5 showed a high insulinotropic effect (Sarmadi *et al*., 2012) that led to increase insulin secretion, which is responsible for the hypoglycemic effect following protein ingestion (Rabinowitz *et al*., 1966). The yield of (AcDP) autolysis at PH 3.5 is mostly oligopeptides with hydrophobic amino acid residue (Amin *et al*., 2002). The comprising amino acids in peptides are not only responsible for their actions, but their structure and sequence also (Chen *et al*., 1998).

From all together previous observations, it can be assumed that the likely hypoglycemic effects of cocoa and chocolate is resulting from short-term glucose lowering action, where insulin secretion is increasing (Rabinowitz *et al*., 1966; Brand-Miller *et al*., 2003; De Fronzo *et al*., 2004; Mhd Jalil *et al*., 2009; Sarmadi *et al*., 2012; Martin *et al*., 2014), and long-term glucose level decreasing effect, which included boosting of insulin sensitivity (Suzuki *et al*., 1995; Andersson and Lithell, 1996; Klover and Mooney, 2004; Purintrapiban *et al*., 2006; Cao *et al*., 2007; Yamashita *et al*., 2012; Zhang *et al*., 2013; Cordero-Herrera *et al*., 2014) through immediate excitation of one or more of insulin signaling mediators cascade namely, AKT, AMPK, GSK3, p-IRS-1, p-IRS-2 and GLUT-2 in muscle cells and liver cells. Whilst, polyphenols decrease SGLUT1 levels in intestine cells to alleviate glucose absorption and subsequently decrease the glucose concentration in blood (Kobayashi *et al*., 2000; Johnston *et al*., 2005).

ANTIOXIDANT EFFECT

Vascular endothelial cells with High glucose levels show reactive oxygen species (ROS) production (Du *et al*., 2001). Consequently, aggravate oxidative stress condition (Kopprasch *et al*., 2002), where ROS interact with NO to yield peroxynitrate (Lee *et al*., 2003). Consequently, led to alleviate NO bioavailability (Beckman *et al*., 2001), and disturbs the balance of vasodilation and vasoconstriction factors (Beckman *et al*., 2001; Grassi *et al*., 2009). Therefore,

ROS inactivate endothelial NO and decrease it is vasodilation effect in diabetic adults (Kim *et al.*, 2006). Whilst, antioxidant impact of vitamin C infusion normalizes vasodilation of type1 and type2 diabetic patients (Ting *et al.*, 1996; Timimi *et al.*, 1998). Interestingly, insulin infusion boost glucose uptake of muscle cells through improving of blood flow and capillary bed recruitment of skeletal muscles (SkM) via amelioration NO bioavailability (Baron *et al.*, 1996; Clark *et al.*, 2003). Furthermore, insulin treatment results in enhancing of IR. PI3K and/or AKT in human umbilical vein endothelial cells (Zeng *et al.*, 2000), for optimization of glucose metabolism and blood flow (Muniyappa *et al.*, 2007). Hence, insulin sensitivity partly depends on NO bioavailability in vascular endothelial cells (Konopatskaya *et al.*, 2003), particularly in subjects with IGT (Hirai *et al.*, 2000). Subsequently, hypoglycemic agents who increase the insulin sensitivity such as thiazolidinediones are likely to reduce the blood pressure (Nolan *et al.*, 1994; Potenza *et al.*, 2006) and elevate glutathione level in SKM of T2DM (Lazich *et al.*, 2012). However, epicatechin-rich cocoa (ERC) treatment lead to retrieve the normal level of glutathione in SkM of T2DM and heart failure (HF) patients (Ramirez-Sanchez *et al.*, 2013). It has been demonstrated that flavanols boost the bioavailability of NO in endothelial cells through either it is insulin metabolic like effects, whereby interfering with vasodilation action of insulin (Schroeter *et al.*, 2006; Kim *et al.*, 2007; Steffen *et al.*, 2008), and/or ,in partly, it is antioxidant effects (Fisher *et al.*, 2003; Collins *et al.*, 2007b); this may be owe to protect of NO from destruction via ROS actions (Grassi *et al.*, 2009), stimulate the innate antioxidant enzymes superoxide dismutase (SOD), whereby superoxide anion converted to oxygen molecule and hydrogen peroxide in vitro (Malstrom *et al.*, 1975) and catalase ,whereby hydrogen peroxide converted to water and molecular oxygen (Bashan *et al.*, 2009), in thymus of young rats supplemented by cocoa-enriched diet (Ramiro-Puig *et al.*, 2007).The stimulation of antioxidant enzymes is likely through enhancement of SIRT3 (sirtuin), FOXO1 and PGC1α nuclear translocation and increasing their activating forms in skeletal muscles of T2DM and HF patients supplemented with ERC (Karim *et al.*, 2000). Furthermore, flavanols has ameliorating effects to endothelial nitric oxide synthase (eNOS) in blood vessel (Karim *et al.*, 2000; Xu *et al.*, 2004; Wallerath *et al.*, 2005). Thus, healthy adults consumption of flavanol-rich cocoa led to increase bioavailability of endothelial NO (Engler *et al.*, 2004; Fisher and Hollenberg, 2006), which is promoting for flow-mediate dilation (FMD) in elderly human (Fisher and Hollenberg, 2006), healthy subject (Fisher *et al.*, 2003), and conduit arteries and microcirculation, where bypassed by using L-N^G-mono-methyl-arginine as a NOS inhibitor (Schroeter *et al.*, 2006). In addition, alleviated endothelin (ET-1) levels may be one of flavanols antioxidant mechanisms (Corder *et al.*, 2001; Corder *et al.*, 2004), which ameliorate FMD in healthy volunteers treated with flavanol-rich dark chocolate (Grassi *et al.*, 2012).

RENIN-ANGIOTENSIN SYSTEM MODULATION EFFECT

Angiotensin I converting enzyme (ACE) is a glycoprotein peptidyldipeptide hydrolase, whose play substantial role in controlling of renin-angiotensin system, whereby angiotensin-I converted to angiotensin-II (Corvol *et al.*, 1995), is potent vasoconstrictor (Dzau, 2001). Interestingly, ACE inhibitors and Angiotensin receptor blockers significantly diminished peripheral vascular resistance and ameliorate vascular recruitment concomitant with improvement of insulin resistance (Koh *et al.*, 2005; Koh *et al.*, 2007) and supported antioxidant system of human body (de Cavanagh *et al.*, 2000). It was demonstrated that pure flavanols and procyanidins inhibit the ACE action (Actis-Goretta *et al.*, 2003). Moreover, chocolate extracts ACE quenching effects relay on flavanols content and the number of epicatechin units forming the procyanidin (Actis-Goretta *et al.*, 2006) and epicatechin tetramer possess the potent inhibition impact on ACE (Ottaviani *et al.*, 2006). In addition, the enhancing insulin resistance effect of ACE inhibitors is likely through stimulation of bradykinin-NO system which results in boosting of GLUT4 translocation and subsequently elevates glucose up take by peripheral tissues particularly in skeletal muscle of type 2 diabetic mice treated with temocapril (Shiuchi *et al.*, 2002).

CONCLUSION

DM is chronic, bad prognosis and widely spread disease nowadays. Considerable synthetic antidiabetic drugs are available. However, they are not safe, cheap and convenient like natural one. The polyphenolic rich plants are emerging hypoglycemic naturally occurring agent. Particularly, cocoa powder and chocolate rich with flavonoids owe to their prospective valuable beneficial application in medicine. Therefore, it is insistent to know and elucidate their antidiabetic mechanism for ultimate employing of cocoa products in manufacturing of pharmaceuticals and nutraceuticals.

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