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Importance of natural products and their scope for future diabetic therapy

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Abstract: Diabetes, a metabolic disorder with one cardinal finding hyperglycemia, is characterized by either insulin resistance or pancreatic beta cell dysfunction or both. Maintaining consistent glycemic control is essential for delaying disease progression and preventing micro- and macrovascular complications. Unfortunately, many diabetic patients fail to achieve and maintain their glycemic status. As a result vascular disease remains the leading cause of morbidity and mortality in people with diabetes. It is also evident that existing therapies for diabetes with comorbidities have several adverse effects. This review focuses on the regulation of insulin resistance and hyperglycemia and their management by some common edible natural products such as apple and guava. The raw documents were obtained from online journals and books using popular search engines. Edible natural products have the reputation and potential to demonstrate efficacy with reasonable levels of safety and also provide important clues (such as SGLT1 inhibitor & GPCR mediated activation of Epac) for identifying and developing novel antidiabetic drugs. Although these products are not currently recognized as natural source for diabetes but these could provide some novel insights into the pathophysiology of diabetes and its management.

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Keywords: Apple, Guava, Type-2 diabetes, SGLT, Epac

INTRODUCTION

The number of people in the world with obesity and insulin resistance is driven by Type 2diabetes which has been increased markedly in the last decade and the trend continues with no attenuation insight (Asrafuzzaman et al., 2017; Guariguata et al., 2014). Asian populations, over 100

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million having diabetes have a steeper relationship between increasing obesity (higher BMI),less physical activity, increased sedentary time, abdominal and ectopic fat and insulin resistance, are the major contributors to the risk of Type 2 diabetes (Al-Aryahi et al.,2014; Sattar and Gill, 2014). Diabetes is identified and diagnosed by various parameters of hyperglycemia has devastating effects on micro- and macrovascular diseases as the largest single cause of premature mortality and multiple co-morbidities in modern populations other than cancer and accidents (Little et al.,2003; Little et al.,2013; U.P.D.S.,1998). The treatment of diabetes still today is insulin and mostly sulfonylureas and metformin which have resulted reduction of hyperglycemia but not in a reduction in macrovascular disease (Gray et al.,2017). So, the quest for the discovery of new antidiabetic agents from natural sources should get priority in research. From time immemorial, natural products played an important role for treatment of diseases including diabetes. Although all-natural products may not have higher levels of safety or compatible in long duration of therapy as required to treat chronic diseases like diabetes. Science has the capability of exploring and investigating in numerous appropriate models for the actions of natural products and chemical components derived therefrom. In this review we address the antihyperglycemic and other antidiabetic actions of multiple edible natural products and some chemical components present inthose natural medicines.

MATERIAL AND METHODS

Current review manuscript was developed with the help of different online journal articles and books by using some major key words like diabetes, natural product, Traditional medicine, Epac, SGLT, Phytochemicals and so on, through popular search engines like Google, Google scholar, Scopus, PubMed, sciencedirect, and researchgate.

RESULTS AND DISCUSSION

Importance of natural product as a traditional medicine in healthcare system: Traditional medicines have become attractive and are widely used as alternate and supplementary medicines in many countries around world particularly in primary health care (Islam et al.,2012; Marella, 2017; Matheka and Alkizim, 2012). However, WHO warns that traditional medicines are not as safe as it is claimed, that might have harmful and adverse effects in case of poor quality or if taken inappropriately or in conjugation with other medicines (Islam et al.,2012). Thus, random use of medicinal plants, based on folkloric reputation and ethno-botanical reports, must be validated through in-vitro or in-vivo proof of concept studies (Omeje et al.,2006). So, the purpose of the study of natural products is to validate and confirm their efficacy in the proposed target disease, diabetes and the validated natural products to be used in drug discovery (Arumugam et al.,2013).

Natural product for the management of diabetes: Medicinal plants are one of the important sources of human health problems, including diabetes. Ethnobotanical reports and Ethno-pharmacological studies showed nearly 800 plants possess antidiabetic activity (Arumugam et al.,2013; Chikezie et al.,2015; Ghorbani, 2013). Phytochemicals obtained from natural sources are more favourable to use in chronic diseases such as diabetes because they are commonly used to prevent morbidity and mortality in low- and middle-income populations (Fathy and Drees,2016). Currently, the research has been focused to understand the specific role and mechanism of individual food compounds involving in protection and reduction of human health risks (Hyson,2011). The antidiabetic effects of some plants have been experimentally evaluated and bioactive principles have been isolated and identified (Ansari et al.,2014; Chikezie et al.,2015; Hannan et al.,2015; Hasan et al.,2019; Mudi et al.,2017; Rokeya et al.,2004; Rokeya et al.,2011). Here we focus on natural products which are consumed as

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foodstuff not as a medicinal view point. Some of the chemical components of these foods play an important role in the activation of various molecular pathways to exert their antidiabetic effects.

Apple: Apple is the world second most eaten fruits after banana. The chemical constituents of apple are flavonoids, flavonols, polyphenols, phenolic acids, cyanidin, anthocyanidins, anthocyanins, chlorogenic acid, gallic acid, hydroxycinnamates, quercetin, carotenoids, vitamin C, minerals and soluble dietary fiber (Boyer and Liu,2004; Cuthbertson et al.,2012; Francini and Sebastiani,2013; Ferretti et al.,2014; Hyson, 2011; Masumoto et al.,2016; Vrhovsek et al.,2004). Apple polyphenols especially quercetin show strong antioxidant activity through strengthening endogenous antioxidant defence mechanism and occlude free radical mediated tissue damage, exhibits anti-inflammatory activity by impeding PGE2 production (Caco-2/12 cell line), it promotes relaxation of cardiovascular smooth muscle, hypocholesterolemic activity, secondary complication of diabetes, reduce the risk of non-communicable diseases and improve human health through blocking free radicals production and regulating glucose and gene expression, lipid metabolism, altering signalling transduction in target cells and tissues (Boyer and Liu,2004; Denis et al.,2013; Fathy and Drees,2016; Hyson,2011; Marella, 2017; Masumoto et al.,2016; Moon et al.,2003; Ravn-Haren et al.,2013; Shoji et al.,2017). Moreover, it shows a synergistic effect on glucose uptake in L6 myocytes cells in a dose dependent manner, promoted by GLUT4 translocation to the plasma membrane through PI3K, PPARγ, increases insulin sensitivity, Akt phosphorylation for glucose homeostasis (Manzano et al.,2016; Masumoto et al.,2009; Najafian et al.,2021; Orthan et al.,2013; Patel et al.,2015). α-Glucosidase inhibitory activity of apple in intestinal mucosa is in agreement with previous reports on wolf-apple flour (Alongi et al.,2018; Rocha et al.,2014). The inhibitory effect may be due to the apple dietary fiber and polyphenols such as quercetin, procyanidin, phlorizin, chlorogenic acid (Boque et al.,2013; Gonzalez-Abuin et al.,2015; Shoji et al.,2017; Manzano et al.,2016) . Another report claims that cloudy apple juice and its peel extract show antihyperglycemic effect as well as reduction of serum total cholesterol, triglyceride, LDL-C, VLDL-C and MDA level in diabetic model rats (Fathy and Drees,2016). The hypolipidemic effect of apple is due to its high phenolic compounds and the reduction of MDA level indicates that apple polyphenol may have antioxidant properties which protect β-cell (Fathy and Drees,2016; Peng et al.,2011). It was also confirmed that apple is safe and have no toxicity at average dietary level (Shoji et al.,2004). Therefore, we suggest that the reason of antihyperglycemic effect of apple are i) inhibitory effect of free radical production and inflammatory reaction resulting impede beta cell damage and sustain insulin secretion ii) improve the antihyperglycemic effect by delaying gastric emptying as well as forefending α-glucosidase, α-amylase, and SGLT1, and by iii) improving insulin sensitivity in skeletal muscle. It is suggested for future investigation for exploring AMPK status in skeletal muscle for insulin sensitivity, SGLT1 status in small intestine and kidney for glucose reabsorption capabilities.

Apple flavonoids maybe more available for absorption into the bloodstream, as procyanidincatechin showed significant antihyperglycemic activity which is related to insulin sensitive tissues by AMPK and Akt phosphorylation, enhanced β-cell function as well as decrease gluconeogenesis, β-cell apoptosis and hepatic lipogenesis but the oligomeric and polymeric flavan-3-ols are not absorbed into the small intestine (Gonzalez-Abuin et al.,2015; Marella, 2017; Monagas et al.,2010) because the majority of oligomeric structures reach to the large intestine and catabolized by the colonic microflora and then finally the phenolic acid absorbed into the circulatory system and excreted in urine (Aura,2008; Selma et al.,2009). Dietary fiber of apple may delay the gastric emptying and improve the glycemic abnormalities with the help of gut microbiota. Phloridzin and Phloretin-2-O-glucoside are specific, non-transported competitive

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inhibitor of sodium glucose transporter 1 (SGLT1) in the intestine and reduced of fasting and postprandial glucose level (Hyson, 2011; Najafian et al.,2012; Wright, 1998). Antihyperglycemic effect via reduced oxidative stress and intestinal glucose absorption are the specific which support the requirements of future research on different cellular target with apple polyphenols to control diabetes and its complication.

Sodium glucose like transporter 1 (SGLT1): In diabetic treatment, sodium glucose co-transporter, SGLT1 and SGLT2 have been in the spotlight for their physiology and therapeutic potentials (Spatola et al.,2018). Human SGLT1 is a protein having α-helical domains, encoded by the SLC5A1 gene on chromosome 22 at q13.1. and expressed in stomach, kidney, skeletal muscle, liver, lung, heart, trachea, prostate, cervix, stomach, mesenteric adipose tissue, pancreatic α-cell and brain possess high affinity for glucose (Song et al.,2016). SGLT1 is the main glucose transporter in the small intestine, expressed in the late renal proximal tubule of the kidney where it reabsorbs the glucose escaped from the upstream SGLT2 (Spatola et al.,2018) . However, this expression of both transporters is varying depending on some clinical factors and different degree of glycemic control, glomerular filtration rate as well as older age (Solisni et al.,2017; Spatola et al.,2018). Expression of SGLT1/GLUT1 is markedly increased more than fourfold in human kidney biopsy specimen than the SGLT2/GLUT2 and shows a significant correlation of SGLT1-mRNA expression with fasting, postprandial glucose and HbA1c level (Norton et al.,2017). Inhibition of intestinal SGLT1 by potent inhibitor such as LX2761 & LX4211 delays intestinal glucose absorption in animal as well as human subjects (Goodwin et al.,2017; Spatola et al.,2018; Zambrowicz et al.,2012). After oral delivery SGLT inhibitors are covalently attached with non-absorbable polymers in the GI tract in rats and inhibit intestinal SGLT1 and improve glycemic condition by lowering glucose excursions (Zambrowicz et al.,2012). Inability of glucose absorption through SGLT1 in GI tract also shows a flat blood glucose curve during OGTTs and may create some complexity in OGTT based diagnosis of diabetes (Zambrowicz et al.,2012).

Though, in human, administration of selective or non-selective inhibitors of SGLT1 are not accompanied by this adverse effect may be due to incomplete inhibition of SGLT1 (Spatola et al.,2018; Zambrowicz et al.,2012). Selective inhibitor of SGLT1 such as GSK-1614235 shows hypoglycemic effect without any adverse effect when administered 12 healthy subjects in a 20mg oral doses. Moreover, inhibitor GSK-1614235 concentration in plasma indicates very low level of active molecules with having rapid clearance ability and also impede 50% glucose reabsorption compared to placebo (Dobbins et al.,2015; Spatola et al.,2018). So effective dose determination of SGLT1 inhibitor may be more important to control glycemic abnormalities through SGLT1. LX4211 is a potent inhibitor of both transporter SGLT1 and SGLT2 in-vitro and in human study it improves measures of glycemic control such as decrease body weight, FBG, HbA1c, significantly reduced triglyceride level, which may be related to GLP-1 elevation, improve glucose tolerance as well as increases urinary glucose excretion as a dose dependent manner (Zambrowicz et al.,2012). GLP-1 and PYY act as an indicator of SGLT1 inhibition and delay glucose absorption. LX2411 partially inhibit SGLT1 and rises the circulating level of GLP-1 and PYY level after 28 days of human study and increased GLP-1 level may contribute to control the abnormal glucose level (Zambrowicz et al.,2012). Oral administration of glucose to mice stimulates incretin hormone (GLP-1, GIP) secretion from intestinal L and K cell (Moriya et al.,2009). Additionally, the luminal membrane of the duodenal L cell shows glucose induced GLP-1 secretion through α-gustducin coupled T1R3 taste receptors (Kokrashvili et al.,2009). So, it may be stated that, small intestine serves as the intestinal glucose sensor for the acute glucose induced secretion of incretin hormones. Incretin hormone act on pancreatic β-cell and enhance insulin secretion and GLP-1 also reduces appetite and glucagon secretion from pancreatic α-

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cell and regulates glucose homeostasis (Song et al.,2016). Impeding of SGLT1 in the small intestine rises the delivery of glucose to the more distal gut and colon which may induces a sustained enhancement of GLP-1 secretion through GPCR by gut bacterial fermentation of luminal glucose to short chain fatty acid and whereas GLP-1 promotes depolarization of cells by impeding ATP-sensitive K+ channels and effect at the exocytotic secretory apparatus, stimulates insulin secretion form pancreatic β-cell as well as reduces blood glucose level and play a potential role in diabetic treatment (Holz.2004; Kang et al.,2001; Song et al.,2016; Tolhurst et al.,2012). Therefore, this imaging role of SGLT1 in intestinal and renal glucose transportation as well as stimulation of incretin hormone secretion, makes it a potential target for developing a new approaches of antidiabetic therapy (Spatola et al.,2018).

Guava: Guava (Psidiumguajava L.) was acclaimed as poor man's apple, with a long history of traditional use for a vast range of diseases (Kamath et al.,2008). The fruit guava is found in tropical and subtropical countries and widely used as beverages, syrup, ice cream, jams for its taste and nutritional benefits as well as its medicinal value (Gutierrez et al.,2008; Wang et al.,2014). In traditional Chinese medicine, guava is considered as useful fruit for the management of diabetes and other chronic diseases (Pathare et al.,2017). In Bangladesh, the Garo communities use guava fruit with seed for the treatment of diabetes mellitus (Rahmatullah et al.,2009). The efficacy was proved by Cheng and Yang (1983), Chao et al.,2013 and others that water extract guava fruit can reduce plasma glucose level, triglyceride and LDL, in STZ-nicotinamide induced Type-2 diabetic model rats (Chao et al.,2013; Cheng and Yang,1983). In in-vivo acute study, guava fruit extract shows dose dependent anti-peroxidative effects of lipids, in chronic study (21 day) with water extract of guava fruit peel shows significant antihyperglycemic and hypoglycemic effect in STZ-induced and normal Wister rat (Chao et al.,2013; Rai et al.,2009). Importantly, guava fruit peel aqueous extract shows the reduction of oxidative stress through significantly lowering of MDA and protein carbonyl level while significantly increases the SOD and GSH activity in STZ-induced diabetic rats (Budin et al.,2013).

It is well known that GSH is an important host of antioxidant that reduces intracellular free radicals. Thus the antioxidant properties of guava fruit (polyphenols and other phenolic compounds) not only decreases the free radicles but also increases the activity of free radical scavengers (Budin et al.,2013). In histopathological study, Budin et al., 2013 also observed that, guava peel extract has no ability to regenerate the pancreatic β-cell those were damaged by STZ inductions in animal model (Budin et al.,2013). Additionally, guava fruits delays the intestinal absorption of glucose due to their enrich water soluble dietary fiber which reduce serum cholesterol, triglyceride and LDLc and thus improve glucose tolerance. Similar result was found in study in human subject, guava fruit shows the ability to impede α-glucosidase activity in the intestine (Kumari et al.,2016; Nahar et al.,1991; Rahman et al.,1994). Interestingly, there is lack of strong evidence of cellular mechanism regarding their antidiabetic or antioxidant activity of the fruit. So, we are suggesting the future investigation about the molecular pathway of antioxidant and antidiabetic properties of guava fruits. The role of polyphenols and phenolic compounds as an antioxidant that directly scavenge and impeding the formation of free radicals (Jimenez-Escrig et al.,2001; Gupta et al.,2011; Kamath et al.,2008; Kumari et al.,2016; Rai et al.,2007; Wang et al.,2014).

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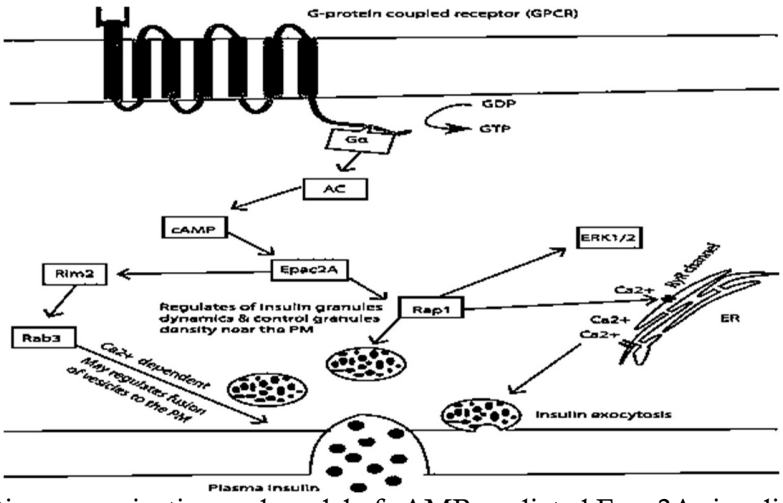

Figure 1: Schematic summarization and model of cAMP mediated Epac2A signaling pathway for insulin granules exocytosis from pancreatic β-cell.

In Figure 1, activation of GPCR on the β-cell membrane resulting activation of adenylcyclase pathway and thus increases intracellular cAMP level (Cullinan et al.,1994; Tsuboi et al.,2003). cAMP mediated activation of Epac2A-Rap1 opens RyR channels, release Ca2+ and thus insulin (Cullinan et al.,1994; Tsuboi et al.,2003). Epac2 also bind to Rim2 which regulates Ca2+ dependent fusion of insulin vesicles to the plasma membrane and responsible to mobilize insulin granules to fuse and enhance exocytic site to the plasma membrane (Kwan et al.,2007; Niimura et al.,2009; Ozaki et al.,2000). Interestingly, Epac2 has an affinity to bind with sulfonylurea and regulates pancreatic β-cell function in insulin secretion. For instance,Epac2-/- mice treated with glucose and sulfonylurea or sulfonylurea alone shows a reduction of insulin secretion as well as rising blood glucose level when compared with wild type C57BL/6 mice as a control whereas sulphonylurea is unable to stimulate insulin secretion in SUR1-/- mice (Zhang et al.,2009). Another study toward this research by exploring that sulphonylurea directly bind to Epac2 in-vitro study and activates Epac2/Rap1 signalling cascade and thus phosphorylate downstream signalling component such as ERK1/2 (Herbst et al.,2011). So, it was a novel clue that sulfonylurea induced insulin secretion required to bind both with SURs and Epac2. Sulfonylurea and receptor's role in insulin secretion is well established but little is known about sulfonylurea and Epac2 interaction. Additionally, in response to GLP-1 treatment intracellular Ca2+ oscillate in an INS-1 cell and potential for both Ca2+ induced insulin granules exocytosis through Epac2 and glucose induced insulin secretion by increasing glucokinase activity through Epac2-Rim2-Rab3 signaling (Doyle and Egan,2007; Schmidt et al.,2013).

Moreover, the effect on Epac2 in insulin secretion is mediated by Rim2 depends on intracellular Ca2+ as well as on cAMP (Kashima et al.,2001). So Epac2-Rim2 may show a link with intracellular Ca2+ as well as glucokinase pathway and play a role in glucose metabolism in the cell (Schmidt et al.,2013). Moreover, GLP-1 signal employs two common approaches of enhancing intracellular Ca2+ through PKA and Epac activation; first one is, by partial activation of the VDCC thereby causing them to open and permitting influx of Ca2+ and second one is, by increasing CICR from the intracellular store (Doyle and Egan,2007). Interestingly, it was suggested by the different research group that among the two main families (IP3R &RyR) of intracellular Ca2+ channels, GLP-1 mediated activation of IP3R is PKA dependent and activation of RyR is

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Epac dependent (Doyle and Egan,2007; Kang et al.,2003; Tsuboi et al.,2003). So we may suggest that GPL-1 exert a new approach to control abnormal glucose level by increasing Ca2+ induced exocytosis of insulin granules via cAMP mediated Epac2-RyR and Epac2-Rim2 signaling pathway.

Some work and key massage by our research group: Mushroom is an edible fungus that has been used in different cuisines and also as a remedy of diabetes around the world. But the underlining cellular mechanism was undefined. Recently, we reported the effect of Oyster mushroom powder (OMP) on expression of AMPK- and GLUT4-mRNA, and activation of AMP-activated protein kinase in STZ-induced diabetic rats (Asrafuzzaman et al.,2018).

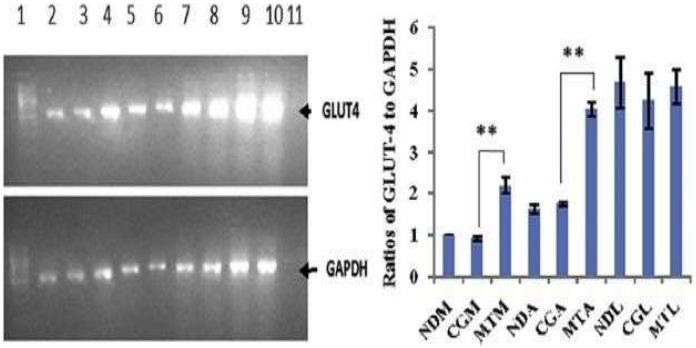

Figure 2.Effect of oyster mushroom powder on the expression of GLUT4 mRNA in type 2 diabetic model rats. 1- Marker; 2-Nondiabetic rat muscle; 3-Control group rat muscle; 4-Mushroom-treated rat muscle; 5-Non-diabetic rat adipose tissue; 6-Control rat adipose tissue; 7-Mushroom-treated rat adipose tissue; 8-Non-diabetic rat liver; 9-Control rat liver; 10-Mushroom-treated rat liver; 11-Negative control.

It was found that the expression of GLUT4- and AMPK-mRNA and activation of AMPK protein were increased more than two folds in mushroom-supplemented STZ-induced type 2 diabetic model rats compared to untreated diabetic model rats (Asrafuzzaman et al.,2018). Reduced hyperglycemia by oyster mushroom most likely through increased expression of GLUT4 and AMPK, and may also through increased activation of AMPK protein (Asrafuzzaman et al.,2018). Antidiabetic activity of aqueous leaf extract of guava with a target of exploring the underlining mechanism of insulin exocytosis from β-cell was performed. In first screening process on neonatal-STZ diabetic model rats it was found that the extract significantly ($p< 0.05$) increased serum insulin level compared to baseline value. It was also found that the extract significantly inhibited glucose absorption from upper intestine as well as enhanced glycogenesis and improved dyslipidemia (Rahman et al.,2019). Now the next step is to isolate their active chemical compounds and investigate the mechanism of insulin exocytosis with guava leaf using different advance research techniques.

CONCLUSION

This review focused on some edible foodstuffs, which are popular around the world including Bangladesh although these are not currently in the traditional medicines` portfolio. We have focused on the mechanisms of insulin resistance and hyperglycemia which are modulated by the selected food stuff. Apple and guava may activate multiple cellular mechanisms which are responsible for the control of glycemia and metabolic homeostasis. Polyphenols and phenolic compounds of the selected foods may exert their potential antioxidant activity and reduce cellular oxidative

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stress mediated cell damage specially β-cell, increase insulin sensitivity by the activation of AMPK and Akt as well as by delaying intestinal glucose absorption by impeding SGLT1, α-glucosidase and thus possibly stimulate incretin hormone secretion from intestine which can in turn increase insulin secretory effect from pancreatic β-cell through cAMP-Epac2 signalling pathway. Type 2 diabetes is a disease of enormous consequences to the health and wealth every societies– all avenues should be explored to get efficacious and safe medicines for the long term therapy of this chronic condition. In this review we have identified some hitherto overlooked products and their target mechanisms that might provide novel pathways for the development of new drugs in the management of Type 2 diabetes and its complications.

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DECLARATION OF CONFLICT OF INTEREST

No conflict of interest to declare.

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Appendices and Nomenclature

cAMP - Cyclic adenosine monophosphate, Epac -Exchange proteins directly activated by cAMP, PKA-Protein Kinase A, AMPK- 5'AMP-activated protein kinase, GLUT-Glucose transporter, STZ-Streptozotocin, CICR-Calcium induced calcium release, RyR-Ryanodine receptor, SGLT-Sodium glucose like transporter, MDA- Malondialdehyde, SOD-Serum superoxide dismutase, GSH- Glutathione, AC-Adenylcyclase, ERK1/2- Extracellular signal regulated kinase, GDP-Guanine diphosphate, GTP-Guanine triphosphate, ER-Endoplasmic reticulum

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