REVIEW ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Hybrid drug combination: A new treatment strategy for type 2 diabetes- A review

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Article History:

Received on: 07.08.2019
Revised on: 03.11.2019
Accepted on: 15.11.2019

Keywords:

Diabetes mellitus, phytochemicals, polyphenols, antidiabetic effects

ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia arising from deregulation in insulin secretion, insulin action, or both. The current synthetic drugs have dose-dependent side effects which confined their uses. The phytochemicals are the natural compounds that have better therapeutic efficacy and interacts synergistically with oral hypoglycemic drugs. The addition of phytochemicals with OHDs may reduce the dose of synthetic drugs as well as their side effects and toxicity. A detailed outline about such combinations like Ferulic acid & THZ/Metformin, Ellagic acid & Pioglitazone (THZ), Chlorogenic acid & THZ/Metformin, Caffeic acid & THZ/Metformin, eugenol acid & THZ/Metformin, cinnamic acid & THZ/Metformin, p- coumaric acid & THZ/Metformin, Arecoline & Vanillic acid with the THZ/ Metformin have been illustrated. This review has also discussed the synergy and mechanism of phytochemical with the OHDs to combat hyperglycemia and other risk associated with it. A comprehensive review was conducted to pile up the information about polyphenols & synthetic drug combinations used for the treatment of diabetes mellitus, which has been carried out in-vitro or in-vivo and may contribute to identifying novel strategies in the treatment of T2D condition. This review shows the importance of the responsible bioactive agents present in medicinal plants in the drive to demonstrate their antidiabetic effects.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2131

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Diabetes mellitus (DM) is categorized as an endocrine disorder characterized by a lack of insulin action accompanied by the hyperglycemic condition. According to WHO, diabetes mellitus (DM) with their complications became the third greatest cause of mortality (Wild *et al.*, 2004; Hegazy *et al.*, 2013; Graf, 1992).In the year 2000, its impact on at the minimum 171 million people globally, and the entire figure of diabetes is projected to grow 366 million. In India, about 79.4 million patients have been diagnosed with DM by 2030 (Kaveeshwar, 2014). The prevalence of diabetes in India in middle-aged 20 years or older elevated from 5.5% in 1990 to 7.7% in 2016 (Tandon *et al.*, 2018). In the majority of the patient, current therapeutic strategies are failing to maintain the normal glycemic level due to their excess usage with a prolonged period leading dose-dependent side effects like gastrointestinal disturbance, weight gain, lactic acidosis, hepatoxicity, hypoglycemia are their major drawbacks (Mohler *et al.*, 2009).Therefore, there

is a vital need for novel treatment strategies for better therapeutic efficacy and decrease side effects. Earlier, Prabhakar and Doble (2011b) have shown that the combination of synthetic drugs and the phytochemical is a better strategy to treat diabetes when compared to single oral therapy. This could lead to a reduction in the dosage of OHD's, thereby minimizing the side effect and toxicity of the drug as well as enhance their therapeutic effect. (Prabhakar and Doble, 2009) According to Nankar and Doble (2017) have been considered that the drugs with a similar pharmacological effect, but the distinct mechanism may interact synergistically when merging together and reported that ellagic acid (phytochemical) and pioglitazone combination at a lower dose significantly reduces glucose level in Diabetic rats, comparison to the treatment of individual compounds (Nankar and Doble, 2017)Therefore, the current review stread light on possible hybrid drug Combination for the treatment of type 2 diabetes. The following are the list of Current pharmacotherapy for diabetes management Table 1.

MATERIALS AND METHODS

Role of Natural Compounds in the Treatment of Diabetes

Various studies have shown that medicinal plant has numerous bioactive compounds such as Tannins, phenolic acids, alkaloids, and flavonoids, also known as phytochemicals or polyphenols. These compounds have been reported for their antidiabetic activity like inducing beta- cell regeneration, and insulin secretion and prevention of insulin resistance (Kooti *et al.*, 2016). There have been several reports which have shown the risk of numerous degenerative diseases, including atherosclerosis, cardiovascular complications, diabetes, osteoporosis, and cancer can be reduced and prevented by the consumption of phenolic acid Scalbert *et al.* (2005). The presences of bioactive chemicals are mainly responsible for the antidiabetic action. Many experiments have shown the importance of these bioactive chemicals.

The plant Acacia arabica consists of polyphenols, flavonoids (quercetin), and tannins. Hegazy *et al.* (2013) gave an explanation for the anti diabetic activity of this plant is the presence of this antioxidant and reported 200 mg/kg and 100 mg/kg of Acacia arabica bark extract orally administered to STZ-induced diabetic rats for 21days. As a result, enhanced serum insulin, lipid profile, and reduced glucose serum and insulin resistance. Plasma glucose levels, oxidative stress, and metabolic disorders in the metabolism of lipids also improve by this plant extract (Hegazy *et al.*, 2013). Hence, these bioactive compounds may be considered as effective alternative medicines because of relatively fewer side effects and lower costs (Kooti *et al.*, 2016). Many trials have been done on these bioactive compounds shown in Table 2.

Mechanism of phytochemicals in Management of Diabetes Mellitus

If diabetes-associated hyperglycemia is not commanded, it gives rise to excess production of reactive oxygen species, which ensuing β-cell dysfunction and other secondary complications such as hyperlipidemia, coronary artery disease, renal failure, stroke, neuropathy, retinopathy, and blindness (Giacco and Brownlee, 2010). Moreover, the overproduction of ROS implicated in the evolution of insulin resistance, which is key pathophysiology in the development of the metabolic syndrome (Mathur *et al.*, 2007). Phenolic compounds are a class of phytochemicals having free-radical scavenging potential and high antioxidants that can inhibit the enzyme, which implicated in the ROS production (Thyagaraju, 2008). Phenolic acids have been reported to significantly lowered the blood glucose level via act on the function of glucose and insulin receptors, responsible for the evolution of diabetes. Phenolic acid markedly increases the GLUT2 and GLUT4 expression in pancreatic β-cells (Jung *et al.*, 2007) and stimulating the translocation of GLUT4 via PI3K/Akt and AMP-activated protein kinase (AMPK) pathway thereby increases the insulin sensitivity and also enhanced the glucose uptake in adipose tissue. The other, like chlorogenic acid (CGA) and ferulic acid (FA), evidenced stimulation of the same transporter (Prabhakar and Doble, 2011b). Chlorogenic acid, ferulic acid, eugenol, arecoline, and vanillic acids are the most abundant antioxidant in the diet widespread in daily eateries such as fruits, vegetables, cereals, chocolates, dry legumes and beverages like wine, tea, and coffee. These compounds have exhibited biological, medicinal, and therapeutic activity. They have been studied to alter glucose metabolism, increase glucose uptake and glycogen synthesis, and impacts on the activities of hepatic glucose-regulatory enzymes, which leads to enhanced glucose uptake by the cells in diabetes mellitus patients. (Jung *et al.*, 2007) they have been reported to interact synergistically with OHDs on the uptake of 2-deoxyglucose (2DG) in L6 myotubes Prabhakar and Doble (2009).

Table 1: Current pharmacotherapy for diabetes management

Therapeutic Class	Compound	Mechanism of action	Side effect
Sulfonylureas	Tolbutamide, Glibenclamide, Glipizide.	Enhance the secretion of insulin by inhibiting the K+ channel in β-cells and stimulate voltage-dependent Ca2+ channel.	Moderate Hypoglycemia, Headache, and Weight Gain.
Biguanides	Metformin, phenformin, and buformin.	Suppressed hepatic gluconeogenesis and enhanced muscle glucose uptake and utilization, as well as increase insulin sensitivity.	GI disturbance, diarrhea, bloating, and lactic acidosis.
Meglitinides	Repaglinide, Nateglinide.	Similar to sulfonylureas as well as suppressed postprandial hepatic gluconeogenesis.	Hypoglycemia and weight gain.
α-glucosidase inhibitors	Acarbose, Miglitol, Vocarbose.	Suppress hepatic gluconeogenesis and decrease the rate of intestinal glucose uptake.	GI discomfort, bloating, flatulence and diarrhea
Thiazolidinedione	Rosiglitazone, Pioglitazone.	Improves muscle insulin sensitivity via PPAR-γ receptors.	Oedema, hypoglycemia, weight gain/water retention, cardiac failure, anemia.
Dipeptidyl peptidase-4 (DPP-4) inhibitor	Sitagliptin, vildagliptin, saxagliptin, linagliptin.	Stimulate glucose-dependent insulin release and inhibition of raised glucagon levels act by inhibiting enzymes dipeptidyl peptidase-4.	Hypoglycemia, headache, dizziness, Nasopharyngitis.
SGLT2 inhibitors	Canagliflozin ,dapagliflozin and empagliflozin.	Selective inhibition of SGLT2 present in the renal uriniferous tubules causes decreases the glucose reabsorption and increases glucose excretion through urine.	Urinary tract infection, hypotension, dizziness.
GLP-1 Agonist	Exenatide, dulaglutide, albiglutide.	Potentiate GLP-1 receptor, which improves glycemic control.	Nausea, hypoglycemia.
Amylin analog	Pramlintide.	Significantly decreases the postprandial blood glucose.	Anorexia, nausea, vomiting, and hypoglycemia. Mohler *et al.* (2009)

Table 2: Clinical trial carried out using phytochemicals i.e., hybrid combination for the treatment of diabetes

S.No	Status	Study Title	Conditions	Intervention
1	completed	Effect of green tea (Epigallocatechin Gallate) on Albuminuria in patients with diabetic Nephropathy	Diabetic nephropathy Hypertension	Drug: Green tea extract
2	Completed	The FLAVO Trial: Dietary Flavonoids and Cardiovascular Disease Risk Reduction in Postmenopausal Women With Type 2 Diabetes	Cardiovascular Disease Diabetes	Dietary Supplement: Flavonoids enrichment (cocoa/soy compounds)
3	Completed	Effects of Cranberry (hydroxycinnamic acids) Extractive on the Lipid Profiles in Subjects With Type 2 Diabetes	Type 2 Diabetes	Dietary Supplement: cranberry
4	Recruiting	Metabolic Benefits of Drinking Blueberry Tea (phenolic acid) in Type 2 Diabetes	Type 2 Diabetes	Other: Blueberry Tea
5	Completed	A Comparison Chocolate With and Without High Cocoa Solids (phenolic acid) in Patients With Type 2 Diabetes in a Randomised Clinical Trial	Type 2 Diabetes	Other: Cocoa Polyphenols

RESULTS AND DISCUSSION

The combinational approach of polyphenols with synthetic derivatives in the management of diabetes.

The management of diabetes without any undesirable effects is still controversial. There is a frequent urge to control glycemia to lessen the impact of glucose-toxicity with the associated risk factors, include oxidative stress, dyslipidemia, mitochondrial dysfunction, vascular complications, etc. (Duckworth, 2001).Also, it is equally important to provide sustained glycemic control in the long term to prevent the development of further complications (Andersson and Svardsudd, 1995). Thus, combinational therapy becomes necessary to combat the multiple risk factors in diabetic patients. As the phytochemicals have the ability to alleviate hyperglycemia and also diabetes-associated risk factors like diminishing oxidative stress by inhibiting ROS, improves lipid profile, reduced hepatic gluconeogenesis so Drug–phytochemical interaction could be a more effective strategy for the management of diabetes mellitus and of the likelihood of high compliance. They are largely free from side effects, have better effectiveness, act on multiple target sites, and are of relatively low cost (Andersson and Svardsudd, 1995). There are a number of reports which describe the enhancement of the hypoglycemic activity of phytochemicals and synthetic drugs when administered in combination *in vitro* Table 3. Researchers have shown that Phytochemicals, when combined, interact synergistically with each other in *in-vivo* and *in-vitro* studies reported by Prabhakar and Doble (2011b). Hence, a judicious selection of suitable agents for combination therapy, which may provide the most metabolic benefits to the patient with type 2 diabetes, should be considered. This emphasizes that a synergistic combination of synthetic drugs with phytochemicals is definitely the way forward for effective and efficient therapy for T2D.

Combination of Ferulic Acid and Metformin / THZ

Ferulic acid

A strong antioxidant plant-derived chemical

Ferulic acid is a ubiquitous phytochemical present in daily eateries such as coffee, wheat, rice bran, vegetable, citrus fruit, and leaves and generally used in food additives, cosmetics, and pharmaceutical in certain countries. The presence of the carboxylic group in their structure binds to lipid bilayer and prevents lipid peroxidation (Graf,

1992; Srinivasan *et al.*, 2007), whereas Oxidative stress contributes significantly to the evolution of metabolic disorder. The free radical is responsible for the oxidative cell injury leads to the development of complications in type 2 diabetes(T2DM). On account of effectively scavenging deleterious radicals, FA at low concentration augment the activities of antioxidant enzymes and has shown inhibitory effect on atherosclerosis, hypercholesterolemia, diabetes, cardiovascular disease, and cancer. (Prabhakar and Doble, 2011b) FA is reported to exhibit very low toxicity even after treated with high doses in rodents (Kwok, 2004).

Antihyperglycemic activity of ferulic acid

In a study, FA acid has been shown antihyperglycemic activity in many in-vitro and invivo model. Treatment of STZ-induced diabetic rats, with the FA at a dose of 40 and 10 mg/kg BW for 3 weeks rendered to alleviate hyperglycemia, lipid profile, urea, creatinine, serum glutamic pyruvic transaminases (SGPT) and serum glutamic oxaloacetate transaminases (SGOT), and preserve islet mass (Andersson and Svardsudd, 1995) FA acid treatment almost normalized the Diabetes associated oxidative impairment such as elevation of ROS production, depletion of reduced glutathione and lipid peroxidation Thyagaraju (2008).

Synergistic effect of Ferulic Acid and Metformin / THZ

(Prabhakar and Doble, 2009) have shown in their in-vitro studied that Ferulic acid, in combination with THZ or Metformin, exhibits a synergistic effect on the uptake of 2-deoxyglucose (2DG) by L6 myotubes. The addition of 7.5μm Ferulic acid has shown a reduction in metformin dose by half and THZ dose by one third. The combination of FA with Metformin or THZ enhanced glucose uptake by 4.98-fold and 5.11-fold, respectively, compared to the control group via the mechanism of PI3K dependent pathway, and it also increases the expression of GLUT4. Resulting in, reduction in the doses of OHD's, which could lead to the reduction of the toxicity due to their prolonged used Prabhakar and Doble (2009).

Invivo study of the combination of both OHDs (Metformin/ THZ) with FA has shown to normalize the elevated blood glucose levels to the STZ induced rat. The addition of Ferulic acid with the dose of 10mg/kg BW significantly reduced the dose of both OHDs to the one-fourth folds i.e., metformin dose reduced from 50mg/kg BW to 12.5mg/kg BW and THZ dose of 10 mg/kg to 2.5 mg/kg BW. Consequently, the dose of metformin and THZ could be reduced by four-fold by adding 10 mg of FA/kg BW. The blood glucose levels also reported to reduced from 139.12 $\pm$ 2.08 mg/dl to 114.41 $\pm$1.25 mg/dl in the combination of FA (10 mg/kg) and MET (12.5 mg/kg)and in case of FA (10 mg/kg) + THZ (2.5 mg/kg) it reduced from 127.35 $\pm$ 0.42 mg/dl to 112.65 $\pm$ 1.25 mg/dl it emphasizes that the reduction of blood glucose levels is more in combination than comparing to alone. This report indicates that Ferulic acid in combination with both OHDs synergistically lowered the blood glucose levels in diabetic rats and the reduction of the number of doses of OHD's, so that it may reduce the dose-dependent side effect associated with OHDs. FA and THZ improved lipid profile individually, and in combination, the level of cholesterol found to be reduced up < 0.05 synergistically when compared to THZ (10 mg/kg BW) alone, but the FA and metformin combination didn't show any advantage over the treatment of the individual. Since, SGOT, SGPT, creatinine, and urea levels are high in diabetes patient but through the FA with the combination of Metformin or THZ, has shown a reduced level of all the four markers. This indicates that combination therapy of FA with both OHDs acts synergistically, but the combination of FA with THZ is greater significant to treat hyperglycemia as well as to improve blood lipid profile (Prabhakar *et al.*, 2013).

Ellagic acid

natural polyphenolic antioxidant

Ellagic acid (EA) is the strong natural antioxidant found in numerous fruits such as pomegranate, seeds, nuts, and in the beverages, foods based in fruit juice, jam, berries (Landete, 2011). The Chemical name of EA is 2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde] chromene 5,10-dione contains 2 pair of hydroxyl groups and 2 lactones in their structure. EA possesses the suppressing power of oxidative stress in biological systems. The antioxidant activity of EA is due to the four hydroxyl groups present in their structure. According to Zeb (2018) reported that oxidative stress induced by diabetes might alleviate by Ellagic acid. (Chao *et al.*, 2009) investigated the effect of 2% EA treatment for 3 months may counteract the risk of cardiac myopathy in diabetic mice Chao *et al.* (2009).

Antidiabetic activity of ellagic acid

The 2% EA treatment for 3 months of diabetic mice can mitigate the loss of Body Weight, enhanced insulin level in plasma, and glucose level suppressed on the plasma in the diabetic mice (p < 0.05). EA acid lowered diabetes-associated triglyceride level, oxidative stress, exhibit anti-coagulatory and anti-inflammatory protection in cardiac muscle cells of diabetic mice via increased cardiac mRNA expres-

sion like GPX1, SOD, and catalase in diabetic mice indicating that EA can be used for controlling Diabetes cardiac myopathy. (Chao *et al.*, 2009; Fatima *et al.*, 2017)documented that EA in Emblica Officinalis exhibit antihyperglycemic activity in STZ-induced non-obese type 2 diabetic rats via an act on pancreatic β-cells that enhances secretion of insulin and reduce glucose intolerance (Fatima *et al.*, 2017).

The synergy between Ellagic Acid and THZs in Diabetes mellitus

Pioglitazone drug belongs to the class of Thiazolidinedione (this). This agent enhances the insulin-sensitizing effects on peripheral insulin-responsive tissues via the activation of transcription factor PPAR-γ in a variety of different tissues. (Shah and Mudaliar, 2010; Nankar and Doble, 2017) investigated the synergistic effect of ellagic acid and pioglitazone on the activity of glucose uptake and expression of GLUT4 and PPAR-γ. They reported that insulin sensitivity in L6myotubes might enhance with the low dose of ellagic acid and pioglitazone. The addition of 1 μM of ellagic acid can reduce the dose of pioglitazone by 3times (from 3 to 1 μM) to achieve the same insulin-stimulated 2-NBDG uptake on L6 myotubes (Nankar and Doble, 2015).

Nankar and Doble (2015) investigated ellagic acid and pioglitazone effect on HFD/ STZ-nicotinamide induced rats. This model is best for the study of type 2 diabetes because HFD causes insulin resistance, and glucose intolerance leads to hyperinsulinemia. After that induction of STZ causes β-cell cytotoxicity leads to profound hyperglycemia, so the insulin resistance, hyperinsulinemia, hyperglycemia which characteristics of type 2 diabetes. They showed a reduction in blood sugar in diabetic rodents with a more significant combination of ellagic acid and pioglitazone ($p<0.05$) when contrasted with the therapy of individual compounds even at reduced doses. The addition of 10mg/kg BW ellagic acid may lower pioglitazone dose by two folds (from 10mg/kg to 5mg/kg BW) to produce the potential antihyperglycemic effect in HFD/ STZ-nicotinamide induced Wistar rat. Since the toxicity and side effects associated with pioglitazone abrogated significantly by reducing it by two folds. The level of HDL is significantly increased by involving 20mg of ellagic acid/kg BW with the Pioglitazone at a dose of 5mg/kg BW, while the amount of LDL, triglyceride, and cholesterol is reduced by the combination of 10 mg of ellagic acid/kg BW with 10 mg of pioglitazone/kg BW. (Chao *et al.*, 2009)This emphasizes that the interaction of ellagic acid with pioglitazone enhanced the lipid profile in diabetic rats in a synergistic manner. Combination of ellagic acid (20mg/kg BW) and pioglitazone (10mg/kg BW) has shown improvement on the kidney markers such as urea (26.11 ± 2.23 mg/dl), Creatinine (1.03 ± 0.02 mg/dl) as compared to control but it didn't show any significant improvement in Liver marker.

Chlorogenic Acid

Chlorogenic acid(CGA) is the most significant phenolic acid generally found in daily foods like fruits, cherries, eggplants, plums, and high concentrations in coffee. (Paganga *et al.*, 1999; Bassoli *et al.*, 2008)is reported that chlorogenic acid or CGA-rich coffee consumption has found to ameliorate the risk of DM.

20 g/d solids decaffeinated coffee for 14 days has shown the reduced glucose level and postprandial level of GIP and increment of GLP-1 in a healthy candidate. Scalbert *et al.* (2005) CGA inhibits G6Pase enzyme activity, so that inhibition of hepatic gluconeogenesis (Bassoli *et al.*, 2008).

Antidiabetic activity of Chlorogenic acid

Chlorogenic acid (CGA) enhances the glucose uptake via increases the expression of GLUT4 and PPARγ gene, as the PPARγ and PI3K is a key pathway for the transportation of Glucose in the cell. (Prabhakar and Doble, 2009)chlorogenic acid increases the cAMP synthesis and insulin secretion through stimulating the GLP production, and also its effects on Glucose absorption. (Mccarty, 2005)CGA has shown the reducing effect in lipid concentration on the 3T3-L1 adipocytes, so the risk associated with the increasing level of lipids also can be minimized. Thus, it can also combat the risk of secondary complications associated with diabetes. (Prabhakar and Doble, 2011b; Bassoli *et al.*, 2008)studied the chlorogenic acid effect on blood glucose, hepatic gluconeogenesis, and glucose tolerance. The Chlorogenic acid at a concentration of 0.5, 0.75 and 1.0mM has shown the inhibitory effect on hepatic G-6-Pase ($p< 0.05$) and at 0.25 mM ($p > 0.05$) gradually since, G-6-Pase is an enzyme found in hepatocytes, decomposes into glucose and phosphate which play an important step in the glucose release by the liver. In the oral glucose tolerance test, the oral administration of 3.5 mg CGA/kg BW has shown a reduction in the glycemic index of food by alleviating the intestine glucose absorption but did not significantly reduce the blood glucose. Bassoli *et al.* (2008) is reported that chlorogenic acid can improve glucose and lipid metabolism in diabetes patients (Fatima *et al.*, 2017).

The synergy between Chlorogenic acid and Metformin / THZ

Invitro cell-based study

The effect of chlorogenic acid with the combination

Table 3: List of various reported hybrid drug combinations

Author	Drug Combination	Target	Effect	Combination effects
Prabhakar *et al.* (2013)	Ferulic acid + THZ/ Metformin	GLUT4 & PI3K expression	Increases 2DG uptake on L6 myotubes, and in vivo studies, reduces BGL, improve the blood lipid profile and reduction in kidney markers.	Synergy with both of OHDs
Nankar and Doble (2017)	Ellagic acid + Pioglitazone (this)	expression of GLUT4 and PPARγ	Increase insulin sensitivity on L6 myotubes and in invivo, a significant reduction in BGL, TG, TC level and kidney marker	Synergy with both of OHDs
Prabhakar and Doble (2011b)	Chlorogenic acid + THZs	expression of GLUT4 and PPARγ	Reduce the expression of HMGCoA reductase & lipid concentration in 3T3-L1 adipocytes & Increases the glucose uptake in L6 myotubes	Synergy with both of OHDs
Prabhakar and Doble (2011b)	Caffeic + THZ/ Metformin	GLUT 4 translocations via PI3K pathway	Reduces the HMG-CoA reductase expression and FAS enzymes and stimulate the 2DG glucose uptake in 3T3-L1 adipocytes	Synergy with both of OHDs
Prabhakar and Doble (2011b)	Arecoline and eugenol + THZ/ Metformin	via GLUT4 expression and PI3K pathway	reduces triglyceride level and improves glucose uptake in L6 myotubes	Synergy with both of OHDs
Prabhakar and Doble (2011b)	Vanillic acid + THZ/ Metformin	unknown	improves glucose uptake in L6 myotubes	partly synergy with THZ and antagonistic activity with the metformin
Prabhakar and Doble (2011b)	P-coumaric acid	increase PI3K expression	Decrease the expressions of the fatty acid synthase and HMG CoA reductase, increases the 2DG uptake in 3T3-L1 adipocytes	Synergy with both of OHDs

of two OHDs on glucose uptake in L6 myotubes has been analyzed. It is reported that Chlorogenic acid at a concentration of 20mm with the combination of metformin (20μM) has shown a synergistic effect by increasing the 5.04 folds on the 2DG uptake by L6 myotubes. Similarly, 10μM of Chlorogenic acid with 20μM of THZ has shown a 5.28 fold increased in 2DG uptake compared to control. (Prabhakar and Doble, 2009) hence, the studies have shown that chlorogenic acid with a combination of both OHD acts in a synergistic manner.

Prabhakar and Doble (2011b)studied the interaction of Chlorogenic acid with a combination of Metformin / THZ on 2DG uptake in 3T3-L1 adipocytes. He reported that 15 μM chlorogenic acid reduced the dose of THZ by one-sixth to obtain a 2DG uptake of 263 ng/3.5 x 10^5 3T3-L1 adipocytes and 5 μM chlorogenic acid reduces the dose of metformin by half for the same 2DG uptake. The reduction in the expressions of regulatory enzyme fatty acid synthase and HMG CoA reductase both play a pivotal role in the mechanism of Insulin resistance. The current findings suggest that so chlorogenic acid with the combination could reduce the dose and limit the side effect and toxicity of the latter.

The Invivo experiment with the combination of OHD's needs to be performed to prove this hypothesis further.

Caffeic Acid

Caffeic acid is a major polyphenolic compound in coffee presents in many fruits like blueberries, apple, cherry, many beverages and vegetables (Vinayagam and Jayachandran, 2016) Caffeic acid [3,4-di(OH)- cinnamate having anti-inflammatory, anti-oxidative and anticoagulant effect and also found the suppressive effect in triglyceride level in the cardiac tissue of diabetic mice. (Chao *et al.*, 2009) The administration of caffeic acid ameliorates hyperglycemia and decreases plasma glucose in diabetes. At the concentration of 0.05-0.15%, caffeic acid counteracts or inhibit the development of cancer, but at a concentration of 0.5-2%, it may exhibit tumor activity in the kidney of rats or mice (Scalbert *et al.*, 2005).

Antidiabetic activity of Caffeic acid

The antioxidant effect of CA was analyzed in the cardiac tissue in STZ induced diabetic rats for 2 months. It is found that CA (10 mumol kg(-1) IP) can suppress the activity of SOD and CAT compared to an untreated diabetic group; this finding has shown that CA, through its antioxidant mechanism, can inhibit oxidative stress which arises as a consequence of diabetes. Additionally, it is known to have carcinogenic and mutagenic activity in STZ-induced diabetic activity. (Paganga *et al.*, 1999; Jung *et al.*, 2007)described the inhibitory effect of CA on hepatic gluconeogenesis and glucose generation on C57BL/KsJ-db/db mice. It significantly enhances the insulin level in plasma, leads to attenuate the damage of pancreatic islet. Moreover, it increases the expression of Adipocyte GLUT4 and hepatic GLUT2 and increases the SOD, CAT, GPx levels in the liver db/db mice. Hence, the caffeic acid exhibit the potential antidiabetic activity in db/db mice by the suppression of hepatic glucose production, boost insulin production, and their antioxidant property (Jung *et al.*, 2007).

The synergy between Caffeic acid and THZ/ Metformin

Invitro cell-based study

Prabhakar and Doble (2011b)investigated the Caffeic acid effect alone or with the combination of OHD's on the uptake of 2DG in 3T3-L1 adipocytes. He reported that Caffeic acid with a combination of hypoglycemic drugs interacts in a synergistic manner on the 2DG uptake. The CA acid at a concentration of 25 μM with the THZ (20 μM) increases the uptake of 2DG by 6.5- folds and with the Metformin (20 μM) increases by 6.3- fold compared to control. The mechanism of CA act through increases in the GLUT 4 translocation via the PI3K pathway. Also, it decreases the HMGCoA reductase expression and FAS enzymes, so it may reduce the lipotoxicity, which is associated with diabetes. So, CA can be combined with the OHDs to reduce the dose, thereby side effects of the latter (Prabhakar and Doble, 2011b).

Interaction of Eugenol, P-coumaric acid, arecoline & vanillic acid with the THZ/ Metformin.

The effect of eugenol, vanillic, and arecoline acid with the combination of THZ/ Metformin has been investigated on the 2DG uptake by L6 myotubes. It is reported that arecoline and eugenol acid with the combination of both OHDs has shown gradually increases glucose uptake with the increases of dose and time by the same mechanism via GLUT4 expression and PI3K pathway, whereas the vanillic acid has shown increased glucose uptake via an unknown mechanism. The arecoline and eugenol acid act in a synergistic manner with the combination of THZ/metformin but vanillic acid with the combination of THZ exhibit as a partly synergy and with the metformin it has shown antagonistic activity. (14) The p-coumaric acid in the combination of two OHDs has been analyzed in the 3T3-L1 adipocyte. The combination of coumaric acid with THZ/ metformin has shown the effect on the 2DG uptake in 3T3-L1

adipocyte in a synergistic manner via elevation of the expression of GLUT4 and PI3K (Prabhakar and Doble, 2011a). These phenolic acids have shown good bioavailability in the ADME analysis. Thus, they can use as a drug, and it may reduce the doses of the drug when it is used in combination.

CONCLUSIONS

This review gives insights about the new strategies for the better management of Diabetes in the form of Combinations therapy. The combination of Ferulic acid with Metformin or THZ has shown the synergistic effect on uptake of glucose in L6myotubes and in-vivo study, the combination significantly reduced the hyperglycemia, lipid profile, and SGOT, SGPT markers. Thus, there is synergy between the interaction of FA with both OHDs. So FA can be able to reduce the side effect of metformin i.e., GI disturbance, diarrhea, bloating, flatulence, anorexia, and lactic acidosis, by reducing the dose of it. The ellagic and pioglitazone combination has shown synergy on the glucose uptake by L6 myotubes as well as In-vivo, BGL, TGL, TC, and kidney markers and the pioglitazone concentration can be reduced by two-fold with the ellagic acid since reduced the side effect and toxicity of latter. The same can be hypothesized with the combination of ellagic acid & metformin. The Chlorogenic acid with both OHD's has shown a synergistic effect in in-vitro cell-based studies. The combination act via reduce the expression of HMGCoA reductase & lipid concentration in 3T3-L1 adipocytes & Increases the glucose uptake on L6 myotubes. The caffeic acid, in combination with OHDs, reduces the HMGCoA reductase expression and FAS enzymes and increases the 2DG glucose uptake in 3T3-L1 adipocytes in a synergistic manner. The other phenolic acids arecoline, eugenol, p-coumaric acid interacts synergistically with the THZ/ metformin, reduce the expressions of the fatty acid synthase and HMG CoA reductase, increases the 2DG uptake in 3T3-L1 adipocytes, further in-vivo data need to perform to prove this hypothesis. The reports suggested that the phytochemicals can be replaced with the OHDs and reduces the doses of the same leads to the side effect and toxicity associated with the drug could also be reduced.

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