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Review Article

ROLE OF PHYTOCHEMICALS IN DIABETES LIPOTOXICITY: AN OVERVIEW

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder caused by poor or ineffective insulin secretary response and it is characterized by increased blood glucose levels (hyperglycemia). Hyperglycemia associated with diabetes causes insulin resistance by increasing oxidative stress, formation of advanced glycation end products (AGEs), and flux through the hexosamine biosynthetic pathway. Increased plasma free fatty acid (FFA) stimulates gluconeogenesis, induces hepatic and muscle insulin resistance, and impairs insulin secretion in individuals. These FFA-induced disturbances are referred to as lipotoxicity. Conventional drugs treat diabetes by improving insulin sensitivity, increasing insulin production and/or decreasing the amount of glucose in blood. Apart from currently available therapy, herbal medicines recommended for treatment of diabetes throughout the world. Herbal drugs are prescribed widely because of their effectiveness, fewer side effects and relatively low cost. Phytochemicals are the bioactive compound contained in plants having biological properties such as antioxidant, anti-inflammatory, antidiabetic, anticancer, modulation of detoxification enzymes, stimulation of the immune system, etc. These compounds include vitamins, comprising of vitamin C, D and E, flavonoids, phenolic acids, terpenoids, polyphenols,etc. Furthermore, the latest discoveries and studies on the molecular mechanism of these phytochemicals suggested their potential positive effect in the prevention and treatment of type2 diabetes and other risk factors associated with it. They should be incorporated in food ingredients, dietary supplements, or drug preparations. Despite the availability of known antidiabetic medicines, remedies from phytochemicals are used with success to treat this disease. Use of antioxidants and phytochemicals can be a great help in tissue repair by quenching the free radicals generated due to oxidative stress. Hence, this article provides a comprehensive review of the available information on various aspects of phytochemicals, with special reference to their effectiveness in risk reduction of diabetes lipotoxicity.

Keywords: Diabetes, Lipotoxicity, Insulin Resistance, Phytochemicals, Polyphenols.

INTRODUCTION

Diabetes mellitus (DM) or type 2 diabetes (T2 D) is a health problem affecting millions of individuals worldwide. In the past few decades, the global incidence and prevalence of diabetes has increased dramatically in the developing countries of Africa, Asia, and South America. Among the total population of diabetic patients more than 90% suffer from Type 2 Diabetes (T2 D). India is one of the leading countries for the number of people with diabetes mellitus and it is estimated that diabetes will affect approximately 57 million people by the year 2025 (Zimmet et al 2001).

'Diabetes mellitus' describes a metabolic disorder of multiple physiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (Wang T et al 2007). The cause of type 2 diabetes is multifactorial and includes both genetic and environmental

factors that affect β-cell function and tissue (pancreas, muscles, liver, and adipose tissue) insulin sensitivity.

PATHOPHYSIOLOGY:

The free fatty acids (FFAs) play an important role in the development of insulin resistance (IR). FFAs released from intra-abdominal adipose tissue enter into circulation and these are involved in various organs (liver, muscles, etc.) of developing symptoms of IR. The excess of FFAs in the liver leads to stimulation of gluconeogenesis and hepatic glucose output, which contribute to the development of increased fasting plasma glucose, and the type 2 diabetes (Grundy et al 2005). Defective insulin secretion or β-cell dysfunction and insulin resistance contribute to more or less jointly to the development of pathophysiological condition. This defects cause the development of hyperglycemia, a major pathological feature of T2D (Laakso 2001). There is an assumption that the increased influx of FFAs into pancreatic β-cell through lipotoxicity mechanism contributes to the loss of their secretory capacity and definite sign of type 2 diabetes (Petersen and Shulman 2006).

The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy, nephropathy, and/or neuropathy with risk of foot ulcers, amputation, etc. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease (Gavin et al 1997). Hyperglycemia alone does not cause diabetic complications. It is rather the detrimental effect of glucose toxicity due to chronic hyperglycemia, which is mediated and complicated through oxidative stress. Diabetic hyperglycemia causes a variety of pathological changes in small vessels, arteries and peripheral nerves. Hyperglycemia-induced activation of protein kinase-C (PK-C) isoforms (Klein 1995), increased formation of glucose-derived advanced glycation endproducts (AGEs) (Kova & King 1998), and increased glucose flux through aldose reductase pathways, activation of hexosamine pathway and formation of glucosamine are some of the known biochemical mechanisms of hyperglycemia-induced tissue/organ damage(Brownlee 1995). Aldose reductase, the key enzyme of the polyol pathway, catalyses the reduction of glucose into sorbitol. Sorbitol does not readily diffuse cross the cell membrane and intracellular accumulation of sorbitol is responsible for cataract, in diabetic complications (Hori et al 1996).

Traverse et al. 1998 and Betteridge, (2000) reported that the imbalance of generation and scavenging of free radicals play an important role in determining tissue damage associated with diabetes. Lipid peroxidation is the primary cellular damage resulting from free radical reactions. The reactive oxygen species can induce lipid peroxidation particularly of those lipoproteins that contain unsaturated fatty acids. The hydroxyl radicals OH- and a product of the reaction between a superoxide anion and nitric oxide, known as peroxynitrite, are particularly powerful oxidant of low-density lipoproteins (LDLs) and DNA damage (Toborek 1992).

The major defect in T2D is the signaling pathway between the insulin receptor and stimulation of GLUT4 translocation. This defect is caused by insulin resistance. Insulin resistance is a generalized metabolic disorder characterized by inefficient insulin function in skeletal muscle, liver and adipocytes. Several pathogenic processes are involved in the development of diabetes. Hyperglycemia (glucotoxicity) and dyslipidemia (lipotoxicity) impair β-cell function and increase insulin resistance in peripheral tissues, such as muscle, liver, and adipose tissue. One major consequence of insulin resistance on lipid metabolism is the loss of the suppressive effect of insulin on fat mobilization from adipose tissue (Klimes 1998).

Both insulin resistance and type 2 diabetes are characterized by dyslipidemia, which is an important and common risk factor for cardiovascular disease. Diabetic dyslipidemia is a cluster of potentially anthrogenic lipid and lipoprotein abnormalities that are metabolically interrelated. These lipids include cholesterol, cholesterol esters (compounds), phospholipids and triglycerides. They are transported in the blood as part of large molecules called lipoproteins (McGarry and Dobbins 1999). The main lipid abnormalities in T2DM are reduced HDL cholesterol levels and elevated triglycerides. This leads to increases in total / HDL cholesterol. Besides, elevated levels of plasma FFAs are commonly observed in diabetic dyslipidemia.

Relationship between Glucotoxicity and Lipotoxicity

Glucotoxicity describes the slow and progressively

irreversible effects of chronic hyperglycemia on pancreatic β-cell function, which occurs after prolonged exposure to elevated glucose (D'Agostino et al, 2004) Lipotoxicity is also a diabetogenic outcome of increased circulating free fatty acids or increased cellular fat content. This condition is manifest in several tissues; most notably the liver, muscle, and pancreatic islets. The excess circulating glucose, fat, or both act on diverse cells and tissues to counteract insulin-mediated glucose uptake, hepatic regulation of glucose output, and insulin secretion (Sivitz, 2001). Like lipotoxicity, gluco-toxicity is manifest in the liver, muscle, and pancreatic islets Thus lipotoxicity and glucotoxicity may both be implicated in the pathogenesis of type 2 diabetes.

The cellular or biochemical mechanisms of glucotoxicity involve the process of glucose transport into cells. In insulin-responsive peripheral tissues (i.e. Fat, heart, and muscle), glucose entry into cells is regulated by insulin and glucose transporter -4 (GLUT-4). Chronic exposure to high glucose level, independent of insulin, impairs the mass-action effect of glucose to induce its own cell entry. Another possible way to account for glucotoxicity in diabetes involves with the activation of hexosamine pathway (Hresko et al 1998).

The mechanism of lipotoxicity can be explained with understanding Randle Cycle (Randle et al 1994). Accordingly, fatty acid and glucose oxidation can be thought of as competitive in that excess fat metabolism impairs the oxidation of glucose as a means of protecting the cell against excess fuel utilization .This explains that an excess of FFA may affect glycolytic pathways and glucose entry in cells by many ways. This occurs through the formation of acetyl CoA, a product common of both glucose and fat oxidation that is utilized by mitochondria in the tricarboxylic acid cycle to generate substrates for oxidative phosphorylation. However, in states of excess energy availability, acetyl CoA is converted to malonyl CoA, representing the first step in fat synthesis. Because malonyl CoA is a potent inhibitor of carrier mediated fatty acid transport into mitochondria, it mediates glucose inhibition competitively to that of fat oxidation. There is also evidence that fatty acids decrease glucose conversion into glycogen for storage.

Therefore, it appears that there is a kind of physiologic competition between fat and glucose for utilization as cellular fuel (Kelley and Mandarino, 2000). Thus glucotoxicity and lipotoxicity are closely interrelated, in the sense that lipotoxicity does not exist without chronic hyperglycemia.

Effect of Lipotoxicity on Liver, Muscles, Adipose tissue and Pancreas

In diabetes mellitus, an excess FFAs leads to impaired glucose consumption in muscle cells and also effects on the liver in which impaired glycolysis results in more hepatic glucose output from gluconeogenesis and glycogenolysis and both these alterations contribute to hyperglycemia.

The link between increased circulating FFAs and insulin resistance might involve accumulation of triglycerides and fatty acid-derived metabolites (diacylglycerol, fatty acyl-CoA and ceramides) in muscle and liver. Elevated FFAs are also associated with a reduction in insulin-stimulated IRS-1 phosphorylation and IRS-1-associated PI (3) K activity and failure to promote translocation of the GLUT4 glucose transporter to the plasma membrane in response to insulin stimulation (Boden, 1997). Triglyceride and FFA accumulation in the liver is associated with non-alcoholic steatohepatitis (NASH), characterized by an inflammatory response with evidence of hepatocyte damage and fibrosis that can progress to cirrhosis (Patti et al 1999).

Circulating FFAs derived from adipocytes are elevated in many insulin-resistant states and have been suggested to contribute to the insulin resistance of diabetes and obesity by inhibiting glucose uptake, glycogen synthesis and glucose oxidation, and by increasing hepatic glucose output. Many of the hormones that are secreted by the adipose tissue (TNF-α, IL-6, complement C3, adiponectin) are associated with insulin resistance, often independently of the degree of adiposity (Garg and Misra, 2002). Several prospective studies have shown a relationship between adipokines (IL-6 and adiponectin) and the risk of developing T2DM (Lindsay et al 2002).

Effect of Lipotoxicity on Beta cell

It has been suggested that hyperlipidemia alone is not detrimental for b-cells (Clayton et al, 2002). Hyperglycemia was proposed to be a prerequisite for fatty acid induced b -cell dysfunction and death. Like of adipose and muscle tissues, glucotoxicity and lipotoxicity also impair b -cell function and both the secretion and action of insulin

(Robertson et al, 1992). While these effects may occur through acute alterations in signaling pathways that lead to insulin secretion, there is also evidence that FFAs have effects on expression of PPARa, glucokinase, the GLUT2 glucose transporter, prepro-insulin, and pancreatic/duodenal homeobox-1 (PDX-1). In addition to FFA-induced b-cell dysfunction, accumulation of excess FFAs also causes b-cell apoptosis.

The decline in β-cell function found in the glucotoxic state is abnormal insulin gene expression as well as decreases in insulin content and insulin secretion (Tiedge et al, 1997). Hyperglycemia and elevated FFA levels contribute to ROS mediated generation of oxidative stress and damage to body molecules in diabetes .The β- Cells are particularly sensitive to ROS because they are low in free-radical quenching antioxidant- enzymes such as catalase, glutathione per-oxidase, and superoxide dismutase (El-Assad et al, 2003).The ROS may directly attack, caused damage and also changed the chemical as well as physical properties of these cells. Thus in diabetes, both glucotoxicity due to concurrent hyperglycemia and lipotoxic effects of diabetic dyslipidemia, may cause dysfunctions through generation of ROS and oxidative over load in these cells (Kahn, 2003).

Role of phytochemicals in diabetic Dyslipidemia:

Diabetes affects about 5% of the global population and management of diabetes without any side effects is still a challenge to the medical system. In India the treatment of this disorder takes three main forms: (i) Diet and exercise (ii) Insulin replacement therapy and (iii) the use of oral hypoglycemic agents. Currently available synthetic antidiabetic agents like sulfonyl ureas, biguanides, thiazolidinediones (TZDs), a glucosidase inhibitors etc besides being expensive produce serious side effects. Apart from currently available therapy, herbal medicines recommended for treatment of diabetes throughout the world. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost (Venkatesh et al, 2003). Numerous studies have confirmed the strong association between diet rich in plant foods and health the positive effects of these foods may rely on their content on phytochemicals, antioxidant, vitamins and fiber. Most of these dietary compounds contribute to a well redox balance by several mechanisms, such direct scavenging or neutralization of free radicals, modulation of enzyme activity and expression, and anti-inflammatory action. Phytochemicals are bioactive compounds contained in the plants that have the potential for offering protection against a range of non-communicable diseases like diabetes, cancer, cardiovascular disease and cataract.

Currently, it is known a huge amount of phytochemicals which mainly consists of flavonoids, glucosinolates (isothiocyanates and indoles), phenolic acids, phytates, phytoestrogens (isoflavones and lignans), fats and oils contained in vegetables, fruits, cereals, legumes and other plant sources (Surh,2002). Phytochemicals like resveratrol, found in nuts and red wine, has antioxidant, antithrombotic, and anti-inflammatory properties, and inhibits carcinogenesis. Lycopene, a potent antioxidant carotenoid in tomatoes and other fruits, monoterpenes in citrus fruits is thought to protect against prostate and other cancers, and inhibits tumor cell growth in animals (Rao, 2003). Camphene is bicyclic mpnoterpens and present in essential oil of ginger (Zingiber officianle), tulsi (Ocimum sanctum) etc. Camphene having antioxidant, antimicrobial, chemopreventive (Lai and Roy 2004) and antilipemic activity (Tang et al, 2008).

Polyphenols constitute the most abundant phytochemicals provided by food of plant origin, being widely distributed in fruits, vegetables, whole cereals, coffee, cacao, and tea. In recent years numerous in vitro and animal studies have provided evidence that polyphenols may be protective against oxidative-triggered pathologies, including CVD, metabolic disorders, cancer, and obesity. Polyphenols may have anti-obesity, anti-inflammatory, anti-diabetic, and anti-cancer properties through multiple mechanisms: they act by modulating inflammation and redox state, by regulating adipocyte differentiation and lipid metabolism, by inhibiting pancreatic lipase activity and intestinal permeability, and by interacting with gut microbiota. (Chattopadhyaya, 1996)

According to their chemical structure, polyphenols are classified into different categories: phenolic acids, stilbenes, flavonoids (flavonols, flavanols, anthocyanins, flavanones, flavones, flavanonols, and isoflavones), chalcones, lignans and curcuminoids. Ferulic acid, a phenolic acid present in whole wheat, chocolate, apples, oranges, oregano, and sage, has been proved to be effective against high fat-induced hyperlipidemia and oxidative stress, via regulation

of insulin secretion and regulation of antioxidant and lipogenic enzyme activities (Lacueva et al, 2011). Resveratrol, a primarily found in red grapes, apples, and peanuts, can be useful to counteract obesity, metabolic disorders, CVD, and cancer, through multiple actions: it increases mitochondrial activity, counteracts lipid accumulation, decreases inflammation, improves insulin signaling and modulates redox balance.

Several mechanisms have been proposed for the hypoglycemic effect of phytochemicals such as inhibition of carbohydrate metabolizing enzymes, β-cell regeneration and enhancing insulin releasing activity. Phytochemicals obtained from plant sources like catechin, ellagic acid, eugenol, kaempferol, berberin etc. have been roported to possess antidiabetic activity (Son et al 2011). Catechins are the most abundant flavonols contained in tea; they are also present in cocoa, grapes, and red wine. In streptozotocin-diabetic rats,establishes a hypoglycemic condition paralleled by a better lipid profile. Epicatechin-enriched diet reduces IGF-1 levels and prolongs lifespan in diabetic mice; similar results have also been found in Drosophila melanogaster (Engelhard, 2006). In humans, catechins have been proven to ameliorate blood pressure, LDL-cholesterol, obesity, and CDVD risk factors. Catechin-rich beverages (green tea containing about 600 mg catechins) improve obesity and glycaemia in type 2 diabetes patients (Ahmad, 1999). Daily supplementation of 379 mg green tea extracts reduces blood pressure, inflammatory biomarkers, and oxidative stress, and improves parameters associated with insulin resistance in obese, hypertensive patients. Mangifera indica L has been reported multiple biological activities such as antioxidant, anti-inflammatory, antitumor, antimicrobial (Muruganandan, 2005) Citral is a mixture of cis and trans isomers (gernial and neral). It is the main component of lemongrass (Cymbopogan citratus) oil and found in all citrus fruits and possesses, antimicrobial, antioxidant, anti inflammatory activities. Citral was found to possess anticancer effect against prostate gland tumor in various strains of rats (Carbajal,1989).

Epi-catechin isolated from Pterocarpus marsupim which was shown to possess preventive as well as restorative properties of b -cells (Si, 2011). Glycerrhizin is the active constituents of Glycerrhiza glabra have been reported to increase insulin level and improves glucose tolerance (Saxena, 2005). Curcumin, a principal curcuminoid extracted from turmeric (a spice derived from the rhizomes of Curcuma longa), has anti-cancer, anti-inflammatory, anti-obesity, and anti-diabetic properties (Shehzad et al, 2012). The underlying mechanisms of action seem to involve regulation of redox-sensitive transcription factors, inflammatory cytokines and growth factors. PPAR gamma is one of the most important targets for Curcumin extracted from Curcuma longa and 6-gingerol, derived from the root of ginger (Zingiber officinale Rosc) (Srivastava et al, 1996). Isoflavones (genistein, daidzein, and glycitein) are present in legumes, grains, and vegetables, but soybeans are the most important source of these polyphenols in human diet. (Cederroth, 2009)

Quercetin, a flavonol present in apples, onions, scallions, broccoli, apples, and teas, is known to have multiple biological functions, including anti-inflammatory, anti-oxidative and anti-mutagenic activities. Quercetin supplementation (10 mg/kg) lessens inflammatory state in the adipose tissue of obese Zucker rats and improves dyslipidemia, hypertension and hyperinsulinemia. Quercetin also lowers circulating glucose, insulin, triglycerides, and cholesterol levels in mice and rats fed a calorie-rich diet, and enhances adiponectin expression and secretion (Taesun and Yunyung, 2011). Capsaicinoids and capsinoids, alkaloids primarily found in red hot peppers and sweet peppers, exert pharmacological and physiological actions, including anti-cancer, anti-inflammatory, antioxidant, and anti-obesity effects (Luo et al,2011). It has been reported that capsaicinoid consumption increases energy expenditure and lipid oxidation, reduces appetite and energy intake, thus promoting weight loss. Capsaicin also attenuates obesity-induced inflammatory responses by reducing TNF-α, IL-6, IL-8, and MCP-1 levels (Choi et al, 2011), while enhancing adiponectin levels, important for insulin response ((Kang et al, 2011)). Several plant-derived flavonoids, apart from possessing their common antioxidant activity, have been reported to inhibit aldose reductase activity and impart beneficial action in diabetic complications (Thielecke and Boschmann, 2009). Recently, Lim et al (2001) have identified butein as the most promising antioxidant and aldose reductase inhibitor for prevention and treatment of diabetic complications. Further, there is an increasing body of

literature indicating that specific phytochemicals have discrete actions on kinase-mediated intracellular signaling processes that are disrupted in patients with chronic diseases. Tan et al (2008) demonstrated that an extract from bitter melon (Momordica charantia) had agonist activity for AMP-activated protein kinase (AMPK) in 3T3-L1 adipocytes and enhanced glucose disposal in insulin-resistant mice. In a retrospective sub-analysis of participants with higher cardiovascular disease risk, Lerman et al. found that the additional phytochemical supplementation was needed in order to adequately reduce multiple biomarkers associated with cardiovascular disease in this high-risk population (Lerman, 2010).

Compelling data on T2D treatment suggest that multiple targeting of the previous metabolic pathways is an acceptable, though not yet fully developed approach to reversing T2D. Pharmacological interference of these targets with anti-diabetic agents has undesirable side effects. Due to the richness and complexity of the compounds in plants, herbal therapy has always been thought to act on multiple targets in the human body. Even one single compound can have multiple targets, the multiple targets associated with anti-diabetic herbal medicine make clinical trials complicated, but such an approach is more likely to lead to an eventual cure for T2D.

CONCLUSION

Hyperglycemia, abnormal lipid metabolism and antioxidant profiles are the most usual complications in diabetes mellitus. Since to treat diabetes and related complications, a drug possessing antidiabetic, lipid lowering and antioxidant activities altogether are supposed to be more effective. Use of antioxidants and phytochemicals can be a great help in tissue repair by quenching the free radicals generated due to oxidative stress. If the mechanism for stress generated hyperglycemia is revealed, target driven therapeutic approach can be performed involving phytochemicals. More than 300 Indian medicinal plants are known to be antidiabetic but exact mechanism for hypoglycemic action of only few is known.

In conclusion T2D, a disease known to man for many millennia, causes serious morbidity and mortality in humans. Medicinal herbs, long used in alternative and complementary medicine systems, are an extremely rich source of T2D remedies. Many herbal medicines as single agents or in different oral formulations have been recommended for diabetes mellitus due to the fact that they have lesser repercussions than oral hypoglycemic agents such as sulfonylurea, metformin and triglitazone etc. Much interest has grown in the role and usage of natural antioxidants as a means to prevent oxidative damage in diabetes with high oxidative stress, therefore development of a drug from natural products possessing antidiaetic, antidyslipidemic and antioxidant properties will be a new approach and will be advancement in knowledge in development of antidyslipidemic drugs.

REFERENCES

1. Zimmet P, Alberti KG, Shaw J. (2001) Nature. 414: 782-787.
2. Wang T, Shankar K, Ronis M J, Mehendale H M. (2007) Critical Reviews in Toxicology. 37 (5): 413-459.
3. Grundy S M, Cleeman J I, Daniels S R, Donato K A, Eckel R H, Franklin B A, Gordon D J, Krauss R M, Savage P J, Smith S C, Spertus J A, Costa F. (2005) Circulation. 112:2735-2752.
4. Laakso M. (2001) International Journal of Clinical Practice. 121: 8-12.
5. Petersen K F, Shulman G I. (2006) American Journal of Medicine. 119: 10-16.
6. Gavin J R, Alberti K G M M, Davidson M B, DeFronzo R A, Drash A, Gabbe S G, Genuth S, Harris M I, Kahn R, Keen H, Knowler WC, Lebovitz H, Maclaren N K, Palmer J P, Raskin P, Rizza R A, Stem M P. (1997) Diabetes Care. 20:1183-1197.
7. Klein R. (1995) Diabetes Care. 18:258-68.
8. Koya D, King G L. (1998) Diabetes. 47:859-866.
9. Brownlee M. (1995) Annual Review of Medicine. 46:223-234.
10. Hori O, Yan S D, Ogawa S, Kuwabara K, Matsumoto M, Stern D, Schmidt A M. (1996) Nephrology Dialysis Transplantation. 11:13-16.
11. Traverse N, Menini S, Cosso L, Odetti P, Albano E, Pronazato M A, Marinar U M. (1998) Diabetologia. 41:265-270.
12. Betteridge D J. (2000) Metabolism. 49 (2):3-8.
13. Toborek M, Wasik T, Drozdz M, Klin M, Manger W, Kopieczna G E. (1992) Metabolism. 41(11):1229-1232.
14. Klimes I (1998). In: Vozar J, Krese A, Klimeš I Diabetes mellitus, (70-77), Slovak Academic Press, Bratislava
15. McGarry J D, Dobbins R L. (1999) Diabetologia. 42:128-138.
16. D'Agostino R B J, Hamman R F, Karter A J, Mykkanen L, Wagenknecht L E, Haffner S M. (2004) Diabetes Care. 27(9):2234-2240.
17. Sivitz. W I. (2001) Postgraduate Medicine. 109: 1-9.

18. Hresko R C, Helmberg H, Chi M M. (1998) Journal of Biological Chemistry. 273(32): 20658-68.
19. Randle P J, Priestman D A, Mistry S C. (1994) Journal of Cellular Biochemistry. 55:1-11.
20. Kelley D E, Mandarino L J. (2000) Diabetes. 49(5):677-83.
21. Boden G. (1997) Diabetes. 46(10): 3-10.
22. Patti M E, Virkamaki A, Landaker E J, Kahn C R, Yki-Jarvinen H. (1999) Diabetes. 48:1562-1567.
23. Garg A, Misra A. (2002) Journal of Clinical Endocrinology and Metabolism. 87:3019-3022.
24. Lindsay R S, Funahashi T, Hanson R L. (2002) Lancet. 360: 57-58.
25. Clayton P T, Eaton S, Aynsley-Green A. (2002) Journal of Clinical Investigation. 108:457-465.
26. Robertson R P, Zang H J, Pyzdrowski K L,Walseth T F. (1992) Journal of Clinical Investigation. 90: 320-325.
27. Tiedge M, Lortz S, Drinkgern J, Lenzen S. (1997) Diabetes. 46: 1733-1742.
28. El-Assad W, Buteau J, Peyot M L, Nolan C, Roduit R, Hardy S. (2003) Endocrinology. 144: 4154-4163.
29. Kahn S E. (2003) Diabetologia. 46(1):3-19.
30. Venkatesh S, Reddy G D, Reddy B M, Ramesh M, Appa Rao A V N. (2003) Fitoterapia. 74: 274-279.
31. Surh Y J. (2002) Food Chemistry and Toxicology. 40:1091-1097.
32. Rao B N. (2003) Asia pacific Journal of clinical Nutrition. 12(1): 9-22.
33. Lai P K, Roy J. (2004) Current Medicinal Chemistry. 11:1451-1460.
34. Tang G Y, Li X J, Zhang H Y. (2008) Molecules. 13:1189-1194.
35. Chattopadhyaya R, Pathak D, Jindal D P. (1996) Indian Drugs. 33: 85- 98.
36. Lacueva C A, Remon A M, Llorach R, Sarda U M, Khan N, Blanch G C, Ros Z R, Ribalta R M, Raventos R M L. (2011). In: Rosa LA, Parilla EA, Aguilar GAG Fruit and Vegetable Phytochemicals, Vol 1 (53-88). Wiley-Blackwel, USA
37. Son M J, Rico C W, Nam S H, Kang M Y. (2011) Journal of food Science. 76:7-10.
38. Engelhard Y N, Gazer B, Paran E. (2006) American Heart Journal. 151:100.
39. Ahmad F, Khan M M, Rastogi A K, Chaubey M, Kidwai J R. (1999) Indian Journal of Experimental Biology. 29:516-520.
40. Muruganandan S, Srinivasan K, Gupta S, Gupta P K, Lal J. (2005) Journal of Ethnopharmacology. 97: 497-501.
41. Carbajal D, Casaco A, Arruzazabala L, Gonzalez R, Tolon Z. (1989) Journal of Ethnopharmacology. 25:103-107.
42. Si H, Fu Z, Babu P V, Zhen W, Leroith T, Meaney M P, Voelker K A, Jia Z, Grange R W, Liu D. (2011) Journal of Nutrition. 141: 1095-1100.
43. Saxena S. (2005) Natural product radiance. 4(5): 358-367.
44. Shehzad A, Khan S, Sup Lee Y. (2012) Future Oncology. 8: 179-190.
45. Srivastava S K, Awasthi S, Wang C, Bhatnagar A, Awasthi Y C, Ansari M H. (1996) Current Eye Research. 15: 749-754.
46. Cederroth C R. (2009) Molecular and Cellular Endocrinology. 304: 30-42.
47. Taesun P, Yunyung K. (2011) Antiobesity Drug Discovery and Development. 1: 14-20.
48. Luo X J, Peng J, Li Y J. (2011) European Journal of Pharmacology. 650: 1-7.
49. Choi S E, Kim T H, Yi S A, Hwang Y C, Hwang W S, Choe S J, Han S J, Kim H J, Kim D J, Kang Y, Lee K W. (2011) Nutritional Research. 31:468-478.
50. Kang J H, Tsuyoshi G, Le Ngoc H, Kim H M, Tu T H, Noh H J, Kim C S, Choe S Y, Kawada T, Yoo H. (2011) Journal of Medicinal Food. 14:310-315.
51. Thielecke F, Boschmann M. (2009) Phytochemistry. 70:11-23.
52. Lim S S, Jung S H, Ji J, Shin K H and Keum S R. (2001) Journal of Pharmacy and Pharmacology. 53: 653-668.
53. Tan M J, Ye J M, Turner N, Ke C Q, Tang C P. (2008) Chemistry & Biology. 15:263-73.
54. Lerman R, Minich D, Darland G, Lamb J, Chang J, Hsi A. (2010) Journal of Clinical Lipidology. 4:59-68.

