Chapter 22
Flavonoids:
Prospective Strategy for the Management of Diabetes and Its Associated Complications

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ABSTRACT

Diabetes Mellitus is one of the major healthcare problems faced by the society today and has become alarmingly epidemic in many parts of the world. Despite enormous knowledge and technology advancement, available diabetes therapeutics only provide symptomatic relief by reducing blood glucose level, thereby, just slows down development and progression of diabetes and its associated complications. Thus, the need of the day is to develop alternate strategies that can not only prevent the progression but also reverse already "set-in" diabetic complications. Many flavonoids are reported, traditionally as well as experimentally, to be beneficial in averting diabetes and lowering risk of its accompanying complications. In the present chapter we have convened different flavonoids beneficial in diabetes and comorbid complications and discussed their mechanisms of action. Further, we conclude that coupling current therapeutics with flavonoids might provide exceptional advantage in the management of diabetes and its complications.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder arising from variety of factors, genetic or environmental, resulting in hyperglycemia. Hyperglycemia leads to acute and chronic metabolic abnormalities, amongst which neuropathy, nephropathy, retinopathy, learning and memory impairment and cardiovascular complications are the major causes of morbidity (Goodman, 2011). Hyperglycemia is a consequence of either pancreatic β-cells destruction, thereby decreasing the level of insulin secretion

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(Type-1 Diabetes Mellitus; T1DM) or due to decreased responsiveness of target cells towards insulin with or without insulin secretory defects (Type-2 Diabetes Mellitus; T2DM) (American Diabetes Association, 2013). In 2013, 382 million people across the globe were reported to be diabetic amongst which 5.1 million lost their lives and therapeutic management of diabetes costs $548 billion. By the year 2035, diabetic population of the world is projected to increase by 55% and its management cost is expected to reach $627 billion. Major concern is that 46% cases of DM remain undiagnosed for longtime (International Diabetes Federation, 2013) and by the time clinical symptoms appear, damage has already been done. Majority of current diabetic research is focused on identifying various therapeutic targets with protective as well as restorative ability to reverse the diabetic damage. Currently available antidiabetic medications controls hyperglycemia by reducing dietary glucose absorption, disposing blood glucose into muscles, liver or adipose tissue and by increasing its excretion form the body thereby providing only symptomatic relief. None of the available treatments are capable of reversing the damage inflicted by diabetes and ceasing its progression (Tripathi, 2013; Verma, Itankar, & Arora, 2013). Hyperglycemia in diabetes generates excessive reactive oxygen/nitrogen species (ROS/RNS) by oxidation of glucose. These highly reactive ROS/RNS binds and disturb normal functioning of biomolecules such as proteins, ribonucleic acid (RNA), deoxy-ribonucleic acid (DNA), etc. and thus, directly or indirectly aids in the development of various diabetic complications (Rochette, Zeller, Cottin, & Vergely, 2014).Thus the use of flavonoids, which are natural antioxidants, may provide additional advantage over current antidiabetic therapy. Present chapter discusses various targets that are currently used for the management of DM and potential of various flavonoids to exploit them. It also provides the list of flavonoids that were reported to be effective in managing diabetes or diabetic complications with their possible mechanisms, which needs further exploration to fully understand their antidiabetic potential.

All the therapeutic interventions currently used clinically for the management of DM exploit primarily following biochemical processes of human body.

1. **Glucose Absorption:** Dietary polysaccharides are converted to glucose prior to their absorption in gastrointestinal tract by α-glucosidase and α-amylase. Therefore, inhibition of these enzymes reduces glucose absorption and ultimately lowers blood glucose level (Etxeberria, de la Garza, Campión, Martínez, & Milagro, 2012; Kim, Kwon, & Son, 2000; Kim, Nguyen, Kurihara, & Kim, 2010; Sales, Souza, Simeoni, Magalhães, & Silveira, 2012). Reduction in blood glucose level results in enhanced glycogenolysis and lipolysis for generating glucose to fulfill the energy requirements of body and thus provide beneficial outcomes in obesity and associated insulin resistance (InR). Both of these enzymes are important targets for antidiabetic therapy and compounds such as acarbose andglucsidase inhibitors are clinically used for the management of diabetes (Goodman, 2011).
2. **Glucose Disposal from Blood:** Insulin is a peptide hormone responsible for maintaining glucose homeostasis by disposing blood glucose into skeletal muscles (for energy), adipose tissue (lipogenesis) and liver (glycogenesis). Mechanistically, this is achieved through interaction of insulin with heterotetrameric insulin receptor (IR) which ultimately leads to the transcription and translation of glucose transporter-4 (GLUT4), responsible for glucose disposal. Insulin potentiators (sulfonylureas etc.), insulin analogues (beef and pork insulin preparations etc.) and insulin signaling modulators (peroxisome proliferator activated receptors-γ (PPAR-γ)) are extensively used clinically for the management of diabetes (Goodman, 2011; Tripathi, 2013). Further, glucagon like peptide-1 (GLP1) is responsible for disposing glucose from the blood by lowering glucagon and increasing insulin blood levels. GLP1 is degraded by enzyme dipeptidyl peptidase-4 (DPP4), inhibition of DPP4

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