Chapter – II

Review of Literature
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2.0 Diabetes mellitus

Diabetes mellitus is a metabolic disease which, when not properly treated or untreated is characterized by chronic hyperglycemia and disordered carbohydrate, lipid and protein metabolism and is associated with the development of specific microvascular complications and of non-specific macrovascular disease (Fowler, 2008). Diabetes is now ranked among one of the most common non-communicable diseases in the world. Diabetes is a progressive condition initially characterized by insulin resistance, where muscle and adipose tissue become relatively insensitive to the effects of insulin. As the condition progresses, a decline in beta cell activity results in relative insulin deficiency and blood glucose levels rise above normal levels. (Hill, 2009). It is a systemic disease caused by an imbalance between insulin supply and insulin demand in the body by pancreas.

2.1 Relationship between pancreas and diabetes

Pancreatic islets, also called islets of Langerhans, are tiny clusters of cells scattered throughout the pancreas located behind the lower part of the stomach. Pancreatic islets (Figure 1) contain beta cells, which produce the hormone insulin to keep the supply and use of glucose in balance. Pancreatic cells in the islets of Langerhans continuously monitor blood glucose levels in the body. β cells in the pancreas are the key players in glycemic homeostasis. Glucotoxicity, lipotoxicity, endoplasmic reticulum (ER)/oxidative stress, inflammatory mediators, and incretins were reported to modulate β-cell function and survival (Leahy et al., 2010). Pancreatic polypeptide secretion was absent in chronic pancreatitis without endogenous insulin production. Sometimes pancreatic enzyme replacement therapy
Figure 1 Image of pancreas responsible for making insulin
(PERT) may be carried out in patient with chronic diabetes. Any form of extensive pancreatic damage may result in diabetes.

2.2 Classification of diabetes mellitus (Davidson’s, 1987, Smith, 1995 and Kahn, 1995)

Based on etiology, there are three main categories of diabetes namely

1. Primary diabetes
2. Secondary diabetes
3. Gestational diabetes

2.2.1 Primary diabetes

Primary diabetes, in general, has been classified into two types, viz., insulin – dependent (Type 1) and non-insulin dependent (Type 2). Type 1 diabetes formerly called as “Juvenile onset diabetes/childhood diabetes”, generally caused by destruction of insulin producing pancreatic beta-cell or decrease in the number of beta cells, usually leading to absolute insulin deficiency, often occurs in children and young adults. Type 1 diabetes people develop ketoacidosis due to insulin deficiency. It is necessary to administer insulin exogenously.

The non-insulin-dependent type 2 DM (NIDDM) was previously called as "adult onset diabetes/maturity-onset diabetes" (caused by aging, obesity, spiritual stress, or other environmental factors and it may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance). Usually about 10 and 90% of all people with diabetes accounts for type 1 and type 2 DM respectively.
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NIDDM is usually associated with normal β-cell morphology and insulin content. Type 2 diabetes mellitus has both genetic and environmental components (Ezenwaka et al., 2004). It has been characterized as hepatic and peripheral (muscle and adipose tissues) insulin resistance. Pancreas compensates by secreting more insulin but eventually beta cells will fail to sustain this and during this stage patient requires treatment (Cerasi, 2000). Type 2 diabetes affects many metabolic pathways in different tissues and many of which are considered to be target for drug treatment. Patient suffering from type 1 are therefore totally dependent on exogenous source of insulin, whereas, patient suffering from type 2, are unable to respond to insulin and can be treated by medications. According to Adisesiah (2005), the high-prevalence of type 2 diabetes resides with the age group of 45-64 years. The treatment system for type 2 diabetes may involve lifestyle modifications, physical exercise or oral medications (Hypoglycemic agents) or sometimes insulin injections.

2.2.2 Secondary diabetes

The factors considered for secondary diabetes includes, (i) genetic defects of beta-cell function; (ii) genetic defects in insulin action; (iii) diseases of the exocrine pancreas; Endocrinopathies; pancreatic dysfunction (iv) drug or chemical or surgically induced diabetes; (v) infections like viral; (vi) uncommon forms of immune-mediated diabetes; (vii) other genetic syndromes sometimes associated with diabetes; (viii) diseases such as cystic fibrosis, exposure to certain drugs; (ix) hormonal imbalances; (x) malnutrition and other unknown causes.
2.2.3 Gestational diabetes

Other categories of diabetes include gestational diabetes (a state of hyperglycemia which develops during pregnancy) (without previously known diabetes) and usually (but not always) resolving within 6 weeks of delivery. Several other diabetes subtypes beyond type 1 and 2 are Latent Autoimmune Diabetes of Adulthood (LADA) or type 1.5 diabetes and Maturity Onset Diabetes of the Young (MODY).

2.3 Causes

The causes of all type I diabetes include genetic factors, immunologic factors, environmental factors and infectious agents. Age, obesity, stress, depression, family history and ethnic group are the major cause associated with the development of type 2 diabetes. The focus of the management and control of diabetes is maintaining a healthy lifestyle by following the correct diet, exercising, and taking medication as prescribed by the physician. Aspects, which are considered essential to diabetic control, include urine and blood glucose self-monitoring, foot care, eye care, attendance of diabetic clinics and counselling. Despite the efforts to control the growing number of diabetes patients, yet, the number of adults with diabetes worldwide is increasing rapidly. It is observed that human and economic costs of diabetes are abnormally high. In every 10 seconds, diabetes causes one death and one amputation in every 30 seconds. Despite oral administration of anti-diabetic drugs and insulin injections, phytotherapy and metal based phytomedicine plays a crucial role in the management of diabetes mellitus.
2.4 Transition metal complexes in diabetes therapy

Many metal compounds play a vital role in living systems and found to elicit potential effect in the pathogenesis and complication of the disease. The metal, its oxidation state, the number and types of coordinated ligands, and the coordination geometry of the complexes can provide a variety of properties. A characteristic of metals is that they easily lose electrons to form positively charged ions, which tend to be soluble in biological fluids. It is in this cationic form metals play their role in biology. Metal ions are electron deficient, whereas, most biological molecules such as proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind to and interact with biological molecules and elicit pharmacological activity. These variables provide enormous potential diversity for the design of metallodrugs (Pattan et al., 2012).

The transition metal ions are responsible for proper functioning of different enzymes (Hariprasath et al., 2010). Chronic hyperglycemia may cause alterations in the status of trace elements in the body and thus the essential trace elements such as zinc, chromium and manganese are deficient in DM. Therefore, trace elements may play an important functions for glucose and lipid metabolisms, particularly insulin function in DM (Hiromura et al., 2008). The amount of metals present in the human body is approximately 0.03% of the body weight (http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/) and Bharti et al., 2009).

Metal based drugs to treat diabetes with metal complexes are first studied by Coulson and Dandona in the year 1980 and reported that ZnCl₂ stimulate lipogenesis in rat adipocytes similarly to the action of insulin (Tripathi et al., 2013). The idea of
using metal ions for the treatment of diabetes originates from the report in 1899. Vanadium, chromium, copper, cobalt, tungsten and zinc were found to be effective for treating diabetes in experimental animals. The orally active metal complexes containing vanadyl oxidovanadium (IV) ion and cysteine or other ligands were first proposed in 1990 (Sakurai et al., 2010). Many metal complexes have been synthesized and evaluated to overcome the problems of painful insulin injection and the side effects for type 1 or type 2 DM. So far chromium, manganese, molybdenum, copper, cobalt, zinc and vanadium ions have been reported to exhibit insulin-mimetic or enhancing insulin like properties under in vitro and in vivo condition (Bharti et al., 2009).

Metal compounds induce hypoglycemia by a wide variety of mechanisms. Possible mechanisms of antidiabetic insulin-like effects are due to the activation of insulin receptor signaling (chromium, magnesium), antioxidant properties (cobalt, manganese, tungstate, zinc), inhibition of phosphatases (vanadium), stimulation of glucose uptake, glycogen and lipid synthesis in muscle, adipose and hepatic tissues and inhibition of gluconeogenesis (chromium, cobalt) or stimulation of the activities of the gluconeogenic enzymes: phosphoenol pyruvate carboxykinase and glucose-6 phosphatase (manganese) (Bharti et al., 2009 and Wiernsperger et al., 2010). Table 1 depicts the metal and the complexes to induce hypoglycemia in diabetic patients (Sakurai et al., 2002).

**VANADIUM**

The human body is estimated to contain 50-200 μg of vanadium. In each organ, vanadium is present at very low concentrations, 0.01-1 μg, and is thought to
Table 1  Reports of metal ions and the complexes with antidiabetic activity in experimental animals and the subjects with diabetes mellitus

<table>
<thead>
<tr>
<th>Metal</th>
<th>Ionic form</th>
<th>Complex form</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Vanadyl sulfate (VOSO₄)</td>
<td>Bis(methylcysteinato) oxovanadium(IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bis(maltolato)oxovanadium(IV)</td>
</tr>
<tr>
<td></td>
<td>Sodium vanadate (NaVO₃)</td>
<td>Bis(picolinato)oxovanadium(IV)</td>
</tr>
<tr>
<td>Cr</td>
<td></td>
<td>Bis(picolinato)chromium(III)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chromium polynicotinate</td>
</tr>
<tr>
<td>Mn</td>
<td>Manganese chloride (MnCl₂)</td>
<td></td>
</tr>
<tr>
<td>Co</td>
<td>Cobalt chloride (CoCl₂)</td>
<td></td>
</tr>
<tr>
<td>Zn</td>
<td>Zinc chloride (ZnCl₂)</td>
<td>Bis(picolinato)zinc(II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bis(maltolato)zinc(II)</td>
</tr>
<tr>
<td>Se</td>
<td>Sodium selenite (Na₂SeO₃)</td>
<td></td>
</tr>
<tr>
<td>Mo</td>
<td>Sodium molybdate (Na₂MoO₄)</td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>Sodium tungstate (Na₂WO₄)</td>
<td></td>
</tr>
</tbody>
</table>
play a role in a wide variety of physiological processes. So far number of vanadium complexes have been developed; most of them have insulin-mimetic properties (Rafique et al., 2010).

In 1985, it was discovered that a simple vanadium salt, sodium orthovanadate, when added to drinking water, could reverse most of the diabetic symptomatology of experimentally-diabetic rats, was exceptionally enticing. Vanadyl complexes with maltol (3-hydroxy-2-methyl-4-pyrone) and kojic acid (3-hydroxy-2-hydroxymethyl-4-pyrone) which possess insulin mimetic activity and low toxicity profile, have been proposed for clinical use in humans. Oxovanadium(IV) with maltol/ethylmaltol has shown enhancing insulin mimetic activity in experimental diabetic animals in recent years (Bharti et al., 2009). Since 1990, a wide class of vanadyl oxidovanadium (IV) complexes involving bis(methylcysteinato) [VO(cysm)\textsubscript{2}]\textsuperscript{-} (1990), bis(L-tartrato) [(V2O4)(L-tart)\textsubscript{2}]\textsuperscript{-} (1990), bis(maltolato) [VO(ma)\textsubscript{2}]\textsuperscript{-} (1992), bis(pyrrolidine-N-dithiocarbamato) [VO(pdc)\textsubscript{2}]\textsuperscript{-} (1994), bis(picolinato) [VO(pa)\textsubscript{2}]\textsuperscript{-} (1995), and bis(1-oxy-2-pyridinethiolato) [VO(opt)\textsubscript{2}]\textsuperscript{-} (1999) have been found to improve the hyperglycemic state in streptozotocin induced diabetes in rats (STZ-rats). In particular, studies on VO(pa)\textsubscript{2} with a VO(N\textsubscript{2}O\textsubscript{2}) coordination environment and bis(3-hydroxy-4-pyronato) [VO(3hp)\textsubscript{2}]\textsuperscript{-}, bis(1,4-dihydro-2-methyl-4-oxo-3-pyridinolato)- and bis(1,2-dihydro-2-oxo-1 pyrimidinolato) oxidovanadium (IV) complexes with a VO(O\textsubscript{4}) coordination environment have been intensively performed to find more potent analogues than the parent complexes, leading to the discovery of the linear relationship between \textit{in vitro} insulin-mimetic activity and the partition coefficient of these complexes (Sakurai et al., 2010).
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The discovery that modification of the vanadium core by chelation could improve biodistribution and tolerability was found to be a crucial step in development of vanadium compounds for treatment of diabetes. Bis(maltolato) oxovanadium(IV) or BMOV is the first vanadium complexes shown superior activity over other inorganic vanadium sources (e.g. VOSO$_4$ or NaVO$_3$) both in vivo and/or in vitro studies (Bharti et al., 2009 and Thompson et al., 2006) (Figure 2).

Earlier reports have shown that VV-dipicolinato complex has more insulin enhancing effect compared to BMOV. New orally active $\beta$-diketonato complexes such as VO(acac)$_2$ and bis($\alpha$-furancarboxylato) oxovanadium (IV) have shown glucose lowering ability comparable to BMOV and possess high water solubility and less toxicity, when orally administered in diabetic rats. Vanadium complex, bis(pyridine-2-carboxylato) oxovanadium(IV) [VO(pic)$_2$] has shown higher insulin-mimetic activity than VOSO$_4$ (Bharti et al., 2009).

ZINC

Zinc, an essential trace element is an activator for more than three hundred enzymes in the body (Haase et al. 2008) and plays a major role in various metabolic pathways including glucose metabolism. The antidiabetic activity of zinc is currently thought to be its important role. In fact, zinc and diabetes interact at several points during metabolism in a cell. In the relevance of zinc to diabetes mellitus, zinc is known to be present in insulin, coordinated by three nitrogen atoms from histidines and three water molecules in an irregular octahedral environment, which is also believed to have a functional structure. Zinc is also known to keep the structure of insulin (Sun et al., 2009), and has a role in insulin biosynthesis, storage
Figure 2 Bis(maltolato)oxovanadium(IV), BMOV, the first purpose designed vanadium-based insulin enhancing pharmaceutical agent
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and secretion (Chausmer et al., 1998). There are several zinc transporters in pancreatic β cells (Smidt et al., 2009); like zinc transporter which has a potent role in insulin secretion (Rungby et al., 2010). Zinc promotes hepatic glycogenesis through its actions on the insulin pathways and thus improves glucose utilization. Surprisingly, zinc was found to have important physiological and pharmacological functions involving an insulin-mimetic activity. Diabetes is usually accompanied by zincuria. Higher zinc intake has also been associated with a slightly lower risk of type 2 diabetes in women (Rafique et al., 2010). For diabetes mellitus with an increased risk of zinc deficiency, more important clinical data would be needed because zinc has an insulin-mimetic effect and protects against oxidative damage associated with the disease (Yoshikawa et al., 2012).

Upon oral administration of Zinc(II) complexes containing bis(6-methylpicolinato) [Zn(6mpa)₂], bis(maltolato) [Zn(ma)₂], bis(1-oxy-2-pyridonato) [Zn(opd)₂]-, and bis(1-oxy-2-pyridinethiolato) [Zn(opt)₂], it has been found to exhibit anti-diabetic activity and ameliorate hyper insulinemia and massive hereditary obesity in experimental studies on mice. In addition, structure–activity relationships on zinc complexes with dithiocarbamates and pyridine-2-sulfonates made to create new potential zinc complexes such as bis(pyrrolidine-N-dithiocarbamato) Zn [Zn(pdc)₂] and bis(3-methylpyridine-2-sulfonato)Zn, respectively under in vitro insulin mimetic activity. Oral administration of Zn(3hp)₂-related complexes with a Zn(O₄) coordination environment helped to induce high quality anti-diabetic properties and also a few complexes exhibited not only anti-diabetic activity, but also anti-metabolic syndrome activity in respect to
hypoglycemic effect and adiponectin secretion enhancing effect, when it was given to Streptozotocin induced rats by daily intraperitoneal injections (Bharti et al., 2009).

Zinc seems to exert insulin-like effects by affecting the insulin signaling pathway at several levels, inducing phosphorylation of the β subunit of the insulin receptor as well as of Akt and leading to inhibition of GSK-3β probably as a consequence of Akt phosphorylation and by reducing the production of cytokines, which lead to beta-cell death during the inflammatory process in the pancreas. Zinc supplementation produced a significant improvement in glucose disposal (Pandey et al., 2012).

**COPPER**

Copper (Cu) is an essential metallo element that is required for a variety of molecules to maintain the normal structures and functions and for cells to live, grow and proliferate. Copper is found in the liver, gallbladder, lungs and heart and is needed for synthesis of hemoglobin, proper iron metabolism and maintenance of blood vessels (Siva et al., 2013). Copper plays an important role in electron transfer reactions (Pandey et al., 2012). Copper complexes have different pharmacological actions such as antiulcer, anticonvulsant, anticancer, and antidiabetic activity (Sorenson et al., 1989). Yasumatsu et al. (2007) proposed that copper (II)-picolinate [Cu (Pic)₂] may be a potent alternative antidiabetic agent and Cu (Pic)₂ complexes by single intraperitoneal injection, exhibited a higher hypoglycemic effect on treatment with STZ induced diabetic mice.

Copper ions are also involved in the pathogenesis of type II diabetes and copper chelating agent exerts a beneficial effect in the treatment of type II diabetes.
The treatment with copper chelating agent tetrathiomolybdate decreased both serum copper ion and ROS levels and consequently ameliorate glucose and lipid metabolism in diabetic mice (Barthel et al., 2007). Treatment with copper sulfate can exert beneficial effects in diabetes with preservation of β-cell function by reducing free radicals or through reduction in glucose levels (Tanaka et al., 2008).

**CHROMIUM**

Chromium is an essential element required for normal carbohydrate and lipid metabolism. Chromium, Cr (III) the most stable oxidation state, is considered as an essential micronutrient for humans by many nutritionists. In 1950s, Schwarz and Mertz conducted experiments on nutrient-deficient rats and suggested that a biological Cr (III) compound could act as a nutritional enhancement to glucose metabolism. The Cr (III) complexes with propionate, L-histidinate, D-phenylalaninato and nicotinato (niacinato or 3- pyridinecarboxylato) ligands as well as Cr (III)- enriched yeast have been proposed as safer antidiabetics (Pandey et al., 2012). Chromium supplementation significantly improves glycemia among patients with diabetes, but do not show any significant effect on glucose metabolism in healthy subjects (Balk et al., 2007). Chromium picolinate (CrPic) may have a possible antidiabetic effect in insulin-resistant 3T3-L1 adipocytes through the involvement of p38 Mitogen-activated protein kinase (MAPK). Treatment with Chromium picolinate (CrPic) could partially reduce hyperglycemia and insulin-induced insulin resistance (Horvath et al., 2008).
COBALT

Cobalt is one of the most important trace elements and has therapeutic value in pharmacological doses. In the form of vitamin B12 (Cobalamin), this metal plays a number of crucial roles in many biological functions. Vitamin B12 is the only metal-containing water-soluble vitamin that is stored in the liver and must come from the diet. Cobalamin is necessary for DNA synthesis, formation of red blood cells, maintenance of the nervous system, growth and development of children. Cobalt was found to boost the effects of insulin and its action. Cobalt chloride (CoCl$_2$) works by augmentation of GLUT-1 gene expression and found to decreases the glycemia of diabetic rats. Treatment of STZ diabetic rats with cobalt chloride showed significant decline in blood glucose, no effect on plasma insulin and significant increase in liver glycogen showing no effect on muscle glycogen. Since cobalt is toxic to patients in its single and pure form various cobalt complexes has been suggested, which could reduce the potential toxicity of cobalt without impacting on its effectiveness (Pandey et al., 2012). Glucosaminic acid-cobalt chelate has been reported to be effective as an antidiabetic agent (Talba et al., 2011). Cobalt therapy may prove effective in improving the impaired antioxidant status during the early state of diabetes and ascorbic acid supplementation at this dose potentiates the effectiveness of cobalt action (Yildirim et al., 2003 and 2009).

TUNGSTEN

The antidiabetic properties of sodium tungstate have been widely reported. Sodium tungstate has shown a remarkable normoglycemic effect in several animal models of diabetes and found to be low toxic in diabetic and healthy animals.
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(Muñoz et al., 2001 and Ballester et al., 2007). Administration of this metal enhances the insulin activity rather than increased insulin levels (Nagareddy et al., 2005) and also treatment with this metal found to increases extra-islet β-cell replication without modifying intra islet β-cell replication rates (Fernández-Alvarez et al., 2004). Tungstate improves pancreatic function through a combination of hyperglycemia-independent pathways and through its own direct and indirect effects, whereas the MAPK pathway has a key role in the tungstate-induced increase of beta cell proliferation (Altirriba et al., 2009).

MANGANESE

Manganese (Mn) seems to be particularly important for the proper functioning of enzymes and it plays an important role in a number of physiological processes as a constituent or activator of some enzymes needed for metabolism process. The human body does not require much of this element, but several biological uses of manganese for the proper functioning of the body, and it is often included in small doses in mineral supplements. These enzymes have a variety of different functions. Some aid in repairing damage to the body. Others are antioxidants. Additional enzymes make use of manganese to aid in the development of strong and healthy bones. It is an essential component of metalloenzymes such as Se–cys containing glutathione peroxidase, Cu/Fe cytochrome C oxidase or different types of superoxide dismutase, all of them important in intra- and extra-cellular antioxidant defense (Pandey et al., 2012). Synthetic manganese porphyrins can be used as potent therapeutic agent in diabetes. EUK-8 is a member of a new class of synthetic salen-manganese compounds with low toxicity that possess catalytic superoxide dismutase, peroxidase and catalase activity that can inactivate superoxide
and nitrogen oxides (e.g. peroxynitrite and nitrogen dioxide). EUK-8 administration inhibited the adoptive transfer of type II diabetes and completely inhibited spontaneous disease progression in pre-diabetic NOD mice with established cell autoimmunity (Olcott et al., 2004).

MOLYBDENUM

Molybdenum (Mo), an important trace element plays a key role for participation in the active sites of metalloenzymes. It is capable of forming complexes with many compounds of biological importance and excreted in the form of simple molybdate ion, \([\text{MoO}_4]^{2-}\). Molybdenum is essential for life and is much less toxic than many other metals of industrial importance. Most organisms including human beings require molybdenum for their existence. Various forms of molybdenum have shown insulin mimetic properties and being used as anti-diabetic agent. Sodium molybdate (Na₂MoO₄) and its complex compounds such as cis-MoO₂L₂ (L \(\equiv\) maltol (3-hydroxy-2-methyl-4 pyrone)) were found to reduce the levels of blood glucose significantly and also free fatty acids (Lord et al.,1999). Molybdenum/ascorbic acid complex showed some significant insulin-mimic and cardio protective effects (MacDonald et al., 2006).

TIN

Tin is an ultra trace element in humans and generates a wide variety of biological activities deriving from its chemical character. It has been suggested that the amount of tin found in a healthy diet should be the value used to describe appropriate intake. Vanga bhasma, an Ayurvedic preparation of tin is used
traditionally for treatment of diabetes. Vanga bhasma is purified and calcinated form of tin with additional herbs (Soni Chandan et al., 2011).

2.5 Transition metal complexes of embelin

Among all quinones, benzoquinones possess numerous biologically significant properties and are present in several living organisms. Number of natural products containing benzoquinones exhibited important biological properties such as anticoagulant, antidiabetic, antioxidative, anticancer activities, etc. One such natural benzoquinone compound is Embelin from *Embelia ribes* berries received great attention in pharmaceutical and research field. However, only few literatures are available with metal complexes of embelin.

2.6 Herbal medicines Vs diabetes

Medical plants are used to treat various diseases for number of years and this also play a crucial role in the management of diabetes mellitus especially in developing countries due to less side effects and low cost. The medicinal plants provide a useful source of oral hypoglycemic compounds for the development of new pharmaceutical leads as well as a dietary supplement to existing therapies. Some of the plants, which are being used for the treatment of diabetes, have received scientific or medicinal scrutiny and even the WHO expert committee on diabetes recommends that this area warrant further attention (WHO, 1980).

Plants containing alkaloids, flavonoids, indoles, phenolic compounds and terpenes in small amount can serve as a phytonutrient, which is needed for the body in small amounts. This phytonutrients may have antioxidant properties and helps to
enhance the metabolism. Plant containing active constituents have demonstrated biological activity and may reduce the risks of chronic disease.

In Ayurveda and other traditional system of medicine of India, a large number of herbal drugs have shown anti-diabetic activity. The active principles present in medicinal plants have been reported to possess pancreatic beta cells regenerating, insulin releasing and fighting the problem of insulin resistance. Many modern medicines have been extracted from natural sources. Even the discovery of widely used anti-diabetic drug, Metformin is derived from the plant *Galega officinalis*. Indian plants widely used to lower the blood sugar level are mentioned in the introduction chapter (Chapter I). The effects of these phytomedicine may delay the development of diabetic complications and correct the metabolic abnormalities. People are greatly concerned about the efficacy and side effects of many synthetic drugs, and hence choose herbal medicines for providing a safe and natural alternative treatment for diabetes. With a view to explore traditional medicines and to investigate their scientific application, an endemic medicinal plant *Embelia ribes* was selected for the present study.

2.7 Botanical source of embelin

*Embelia ribes* Burm. f. belongs to the family Myrsinaceae

2.7.1 Geographical distribution

It is a large shrub, which is found in the hilly parts of India from the central and lower Himalayas down to Sri Lanka and Singapore. In India, from the central and lower Himalayas to Konkan, Deccan, Western Ghats and South India.
2.7.2 Vernacular Names/ Nomenclature of *Embelia ribes* Burm. f.

Used locally by different regions of Indian people are listed below:

Latin name : *Embelia ribes*

English name : False Pepper, False Black Pepper

Assam : Vidang

Bengali : Vidang, Biranga, Bhai-birrung

Gujarati : Vavading, Vayavadang, Vyvirang

Hindi : Vayavidanga, Baberang, Bhabhiranga, Wawrung,

Vayvidamg

Kannada : Vayuvilanga, Vayuvidanga

Kashmiri : Babading

Malayalam : Vizhalari, Vilal

Marathi : Vavding, Karkannie

Oriya : Bidanga, Vidanga, Baibidanga

Punjabi : Babrung, Vavaring

Sanskrit : Krimighna, Tandula

Tamil : Vayuvilangam, Vayuvidangam, Vellal, Vidanga

Telugu : Vayuvidangamu, Vayuvidangalu, Vayuvilamgam, Vidanga

2.7.3 Botanical description

A large, scandent climber with long slender, flexible, terete branches bark studded with lenticles. Leaves are simple (Figure 3), alternate, elliptic-lanceolate, gland dotted, short and obtusely acuminate, entire, shiny above. Flowers are small, white or greenish, in both terminal and axillary panicles. Fruits are globose,
wrinkled or warty, dull red to nearly black, a short pedicel often present usually one seeded and the seeds are globose. On drying, the colour of the fruit changes to dark brown.

2.7.4 Parts used

Fruits (Berries), Leaves and Root-bar are used to cure various diseases.

2.7.5 Active constituents

Embelin (2, 5 dihydroxy-3-undecyl-1, 4 benzoquinone), an orange pigment was extracted from the plant in the year 1900 by Heffter and Feurstein and then by Du and Wie (1963). In addition to a quinone derivative embelin, an alkaloid christembine, a volatile oil and vilangin (Rao and Venkateswarlu,1961). Other phyto constituents include fatty ingredients (linoleic acid and palmitic acid), gallic acid, simple carbohydrates (glucose and fructose), quercitol, a resinoid, tannins and glycerol (Ibrahim Khan et al., 2010 and Lakshmanan,1990). Followed by its potential use, chemical synthesis of embelin was attempted by (Hasan & Stedman,1931, Fieser & Chamberlin,1948, and Dallacker & Lohnert,1972).

2.7.6 Traditional uses

In olden days, dried fruits were considered for anthelmintic, astringent, carminative and used as an alternative and stimulant. The fruit is bitter in taste, good appetizer, cures tumors, ascites, bronchitis, jaundice and mental disorders It was also effective for the treatment of ascariasis better than santonin and as good as oil of Chenopodium (Anonymus,1952).
2.7.7 Physicochemical properties of embelin

Structure:

CAS Registry number: 550-24-3
Chemical name: 2,5-dihydroxy-3-undecyl-2,5-cyclohexadiene-1,4-dione
Molecular formula: $\text{C}_{17}\text{H}_{26}\text{O}_{4}$
Molecular weight: 294.391g/mol
Melting point: 142°C (Chem ID plus)
Log p (octanol-water): 4.34 (Chem ID plus)
Solubility: Insoluble in water but soluble in organic solvents like DMSO and ether
Appearance: Orange solid
3DMET number: B03757

3D structure:

Purity: $\geq 95\%$
$\lambda_{\text{max}}$: 289 nm
Stability: 2 years
Storage: -20°C

2.7.8 Derivatives of embelin

Other than embelin, research on derivatives of embelin has been carried out globally. Spectral, thermal and magnetic studies complexes of embelin with Mn(II), Ni(II), Cu(II) and Zn(II) have been prepared and characterized by Rasheed et al. (1983). Dhar and Onkar Singh (1986) reported various metal complexes of embelin.
According to Dhar et al. (1989), embelin with some metal ions gives colour reactions. Synthesis and characterization of copper (II) complexes of embelin in the cavities of zeolite Y attempted by Abrahmn and Yusuff (2003) displayed catalytic activity. Cherutoi et al. (2005) prepared Cu (II) embelin and Zn (II) embelin complexes. Pyrano embelin derivatives were also available in the literatures (Jimenez-Alonso et al., 2008). Further, the following complexes potassium embelate, 5-Methyl embelin, Embelin-5-O-Alkyl ethers (2-hydroxy -5-methoxy-3-undecylcyclohexa-2,5-diene-1,4-dione,5-ethoxy-2-hydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione,2-hydroxy-5-propoxy-3- undecylcyclohexa -2,5-diene-1,4-dione,5-butoxy-2- hydroxy -3-undecyl benzo-1,4 –quinone,5- allyloxy-2- hydroxy -3-undecyl benzo-1,4 –quinone,5-benzyloxy-2- hydroxy -3-undecyl benzo-1,4 –quinone) were prepared by Kantham Srinivas (2010). According to Rani et al. (2010), the metal ions (Co, Ni, Cu and Zn ) form octahedral complexes with bidentate embelin molecules based on their stability constant values. Recently, Viault et al. (2011) reported synthesis of new derivatives of embelin by Suzuki-Miyaura reaction which lead to second generation of embelin. Synthesis and bioprofiling of Embelin, Embelin metal complexes and azo-metal complexes were studied by Aravindhan et al. (2014). In this study, metal complexes were prepared using pure embelin and d-block transition elements, namely Mn, Fe, Co, Ni, Cu, and Zn. Results of antioxidant profile studies suggested that upon complexation with metals, the free radical scavenging activity of embelin reduced significantly.
2.7.9 Biological and Pharmacological studies

Quinones and their substituted derivatives have long been known to possess numerous chemically and biologically significant properties with many important applications in several areas. Biological studies on embelin and its metal have received considerable amount of attention in recent years.

Antioxidant activity

In general, an antioxidant is a molecule or agent capable of inhibiting the oxidation of other molecules. Oxidation reactions generate free radicals and these radicals triggered the biochemical reactions, which finally damage cells. Antioxidants terminate these chain reactions by neutralizing free radicals intermediates and inhibit other oxidation reactions. Sumino et al. (2002) reported, embelin exhibited free radical scavenging activities towards diphenyl-picrylhydrazyl (DPPH) radicals with 50% inhibitory concentration of 23.3 ± 0.5 µM. Joshi (2007) studied free radical scavenging reactions and antioxidant activity of embelin and suggested that embelin can act as a competitive antioxidant effect in physiological conditions. Surveswaran et al. (2007) reported crude Embelia ribes displayed free radical scavenging activities when tested using DPPH assay. Uma et al. (2008a) reported aqueous extract of E.ribes berries administered orally showed antioxidant activity in streptozotocin induced diabetic rats and Venkateshwar rao et al. (2008) substantiates the antioxidant activity of embelin. Dharmendra Singh et al. (2009) reported the hepatic antioxidant capacity of embelin (from Embelia ribes) using different antioxidant tests and in that reports embelin exhibited a natural antioxidant activity at concentration of 25mg/kg body weight. The antioxidant potential of
embelin in streptozotocin-induced diabetes studied by Gupta et al. (2012) at the dose levels of 15, 25, and 30 mg/kg/day for 21 days. He has shown treatment with embelin proved that the potent antioxidant activity of this compound helps in the management of diabetes.

**Anti-inflammmatory activity**

Anti-inflammatory refers to a substance that reduces inflammation. Most of commercially available anti-inflammatory agents have side effects and embelin finds use as anti-inflammatory drug in traditional medicine. Kapoor et al. (1983) reported the whole *E.ribes* plant as anti-inflammatory drug. Embelin and its 2,5-isobutylmine salts have been reported to possess anti-inflammatory effect in carrageenan-induced paw edema (Handa et al., 1992). Chitra et al.(1994) reported embelin as anti-inflammatory agent using rat model. Quinn et al. (2002) reported embelin inhibits binding of MIP-1α to HEK cell membranes expressing human CCR1 receptor.

**Anthelmintic activity**

Anthelmintics or antihelminthics are drugs that expel parasitic worms (helminths) from the body by either stunning or killing them and without causing significant damage to the host. Honiberger (1852) reported *Embelia ribes* as a vermifuge and then Watt (1972) suggested powdered seeds of *E.ribes* in curdled milk in combination with castor oil was found to be effective in expelling tapeworms. In the year 1987, Ved Prakash and Mehrotra, *E.ribes* is one out of the 52 Indian medicinal plants identified for anthelmintic activity. Further, Embelin is effective against tapeworms and not round/hookworms according to herbal
monographs (Anonymous 2002). Jalalpure et al. (2007) reported *E.ribes* seed oil had shown effective activity against *Pheretima posthuma* compared to standard piperazine citrate.

**Antiandrogenic activity**

Antiandrogenic are agents to counteract the effects of androgens (male sex hormones) on various body organs and tissue. Agarwal and co-authors reported antiandrogenic property of embelin during the year 1986 and after this report, no reports were available till today.

**Antiulcer activity**

Antiulcer drugs are class of drugs, exclusive of the antibacterial agents, used to treat ulcers in the stomach and the upper part of the small intestine. Vyawahare et al. (2009) reported *E.ribes* as one of the important ingredient of amlant (capsule) which cures ulcer. The protective effect of embelin against acetic acid induced ulcerative colitis in rats may be due to its antioxidant and anti-inflammatory activities was reported by Thippeswamy et al. (2011).

**Antimicrobial activity**

Antimicrobial drugs are an agent that kills microorganisms or inhibits their growth. *In vitro* antibacterial activity fruits extract of *Embelia ribes* was reported by Khan et al. (2010). Chitra et al. (2003) reported antibacterial activity of embelin against three strains of the 12 bacterial species tested using disc diffusion method. Feresin et al. (2003) reported embelin inhibited methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus* with minimal MIC value of 250, 62 µg/ml
respectively. According to Rathi et al. (2009), petroleum ether extract of *Embelia ribes* showed lowest MIC value against *Candida parapsilosis* and 360 µg/ml against *Candida laurinitis*. Suthar et al. (2009) reported antifungal activity of *Embelia ribes* against *A. flavus* and *A. fumigatus*. In addition to this report, Tambekar et al. (2009) reported acetone fraction of *Embelia ribes* showed antibacterial activity against *Enterobacter* and *Klebsiella* pathogens. Radhakrishnan et al. (2011a) bacteriostatic and bactericidal activity against Gram-ve and +ve organisms. Rani et al. (2011) indicated that the seeds of *Embelia ribes* has potential antimicrobial constituents when tested against 4 different bacteria. According to Aravindhan et al. (2014), results of antimicrobial activity studies suggested that upon complexation with metals like Co and Ni, >80% growth inhibition were observed in comparison with embelin alone.

**Antihyperlipidemic activity**

Antihyperlipidemic agents lower abnormally elevated levels of lipids in the blood. They are also called as lipid lowering agents. Uma et al. (2008a) reported the antihyperlipidemic activity of aqueous extract of *E.ribes* berries in rats. Jagadeesh et al. (2009) reported that embelin exhibited antihyperlipidemic activity towards chemically induced hepatocarcinogenesis in wistar rats.

**Antispermatozoal activity**

Antispermatozoal compounds interfere with spermatogenesis process. Purandare et al. (1979) reported powdered berries of *Embelia ribes* administered orally 3 months at a dose of 100mg/day shown reduction in quantity and quality of semen. Seth et al. (1982) reported embelin significantly reduce the sperm count and
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motility in all the tested albino rats. Gupta et al. (1989) reported significant reduction in the sperm count with embelin.

**Anticonvulsant activity**

Anticonvulsant agents are used to treat convulsions and/or epileptic seizures. Mahendran et al. (2011) reported embelin significantly inhibited seizures induced by electric shock and shown effective against both grandma and petit mal epilepsy.

**Anticancer activity**

Anticancer drugs are an agent that inhibits or prevents the formation or growth of tumor. Chitra et al. (1994) reported anti tumor activity of embelin in albino rats. Nikolovska-Coleska et al. (2004) reported embelin as a lead compound for anticancer drugs that target the BIR3 domain of XIAP. Dai et al. (2011) reported embelin inhibits chemical carcinogen-induced colon carcinogenesis.

**Antidiabetic activity**

Antidiabetic drugs are used to lower blood glucose levels. They are also called as hypoglycemic or antihyperglycemic agents. Tripathi (1979) reported, antihyperglycemic activity of decoction of *E.ribes* berries in glucose-fed albino rats. Uma et al. (2008) reported the hypoglycemic activity of ethanolic extract of *E.ribes* berries in streptozotocin induced diabetic rats. And added that *E.ribes* treated rats showed 68% reduced blood glucose level versus control group. Mahendran et al. (2011) reported antihyperglycemic activity of embelin against alloxan induced diabetic rats at concentration of 25 and 50 mg/kg body weight administered orally and had shown reduction in blood glucose levels with a body weight gain. Gandhi et
al. (2013) showed that embelin could improve adipose tissue insulin sensitivity without increasing weight gain, enhance glycemic control, protect β-cell from damage and maintain glucose homeostasis in adipose tissue.

**Toxicity**

According to OSHA 29 CFR 1910.1200 as reported in (M/S Santa Cruz Company, USA) material safety data sheet (sc-2015555, 2010) embelin is not a hazardous agent. Despite this information, number of experimental studies have been undertaken to understand the nature of embelin using animal models and the results substantiate with the material safety data sheet. Gupta et al. (1991) observed no change in food intake, behavior, appearance and clinical signs in the experimental animals (rats) administered with embelin (subcutaneous) at a dose of 20mg/kg body weight /day for 30 days. Similarly, Prakash (1994) also observed no significant physical and morphological changes after the administration of embelin at a dose of 120 mg/kg body weight, except an increase in weight of the adrenals.

**2.8 Nanoparticles: An effective approach for the management of diabetes**

Literature survey reveals that so far no formulation is available using embelin and its metal complexes from *Embelia ribes* berries. Moreover, only pure active compound of embelin and its crude extract were reported for antidiabetic activity. In order to improve the efficacy of embelin and also to reduce the dose related side effects, a nanopreparation is designed, which can have a therapeutic value in human diabetics. However, few literatures on the preparation of metal nanoparticles have been reported. The present research study focuses mainly on metal-based nanoparticles and its therapeutic applications as an antidiabetic drug.
Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter) (Emerich et al., 2003 and Sahoo et al., 2003). When this science is applied specifically to the problems of medicine, it is called ‘Nanomedicine’ (Freitas, 2005 and Moghimi et al., 2005). Nanomedicine is a field with continuous progress, introducing novel applications in many health care areas. The underlying motivation is improvement of quality of life with economic and social benefits. Some of the most promising areas are the following (Jain, 2008 and Surendiran et al., 2009).

- Nanodiagnostics (molecular diagnostics, imaging using NP- based contrast materials, nanobiosensors)
- Nanopharmaceuticals (targeted drug delivery, nanotechnology- based drugs, implanted nanopumps, nanocoated stents)
- Reconstructive surgery (tissue engineering, implantation of rejection resistant artificial tissues and organs)
- Nanorobotics (vascular surgery, detection and destruction of cancer)
- Nanosurgery (nanolasers, nanosensors implanted in catheters)
- Regenerative medicine (tissue repair)
- Ultrafast DNA sequencing

To overcome the patient compliance, better and safer route of administration of herbal medicine is by nanoparticles. In this regard, application of nanotechnology in medicine revealed a solution to overcome the side effects of already existing
therapy. Nanomedicine shows great potential for the future diabetic management and at the moment, the suggested benefits in diabetic health care outweigh the possible dangers of nanoparticles use in medicine. Nanoparticles have the following characteristics:

1. High capacity for transporting drugs
2. Very large active surface for the reaction
3. Suitable small body to cross the blood levels
4. Ability of accumulation in the target tissue
5. And low toxicity

It has been expected that this technology effectively create a ‘closed-loop’ system that mimics the activity of the pancreas in a healthy person, and with respect to the present study on the release of embelin and its metal complexes in response to glucose level changes. All of this systems will improve stability, adsorption and drug therapy concentration in target tissue, in addition to those long-term redistribution and release of drug facilitated at the target site. The frequency drug administration is also reduced and improves patient comfort.

The design of nanoparticle-based drug delivery systems is tremendously increasing in research field due to their great therapeutic potential. Different types of materials have been explored as drug delivery carriers that include polymers, lipids, polysaccharides, and proteins. The selection of nanoparticle materials depends on many factors like (a) the size of nanoparticles, (b) properties such as aqueous solubility and stability of drugs, (c) drug release profile desired, (d) surface charge
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and hydrophobicity of nanoparticles, (e) biocompatibility and biodegradability of nanomaterials, and (f) antigenicity and toxicity of the product (Kreuter, 1994).

2.9 Chitosan as a carrier for drug delivery system

Most of the pharmaceutical drugs have problems of poor stability, water insolubility, low selectivity, high toxicity, side effects, and so on. Good drug carriers play a significant role in resolving these problems. Among all the carriers used in therapy, Chitosan has been widely used as a polymer carrier in most of the novel drug delivery system. Chitosan (β-(1→4)-2-amino-2-deoxy-D-glucose (Figure 4)) is a modified natural carbohydrate polymer prepared by partial N-deacetylation of chitin, a natural biopolymer. It is widely distributed in nature as a principal component of crustacean’s shells and insects (Chandra et al., 1998) and it is the second most abundant biodegradable polymer produced in nature after cellulose. It appears in nature as semi-crystalline powder. It is used in a variety of pharmaceutical applications because it has a low/tolerable level of toxicity, physicochemical stability, providing versatile route of administration, biodegradability and biocompatibility. Moreover, chitosan is lack of irritant and allergic effects (Dodane et al., 1998). Furthermore, it has the advantage of slow/controlled drug release and improves the drug solubility (Wang et al., 2011). The chitosan is characterized by its acetylation degree and by its molecular weight. These parameters also influence its viscosity and solubility. Depending on the source (shrimp, crab, mushrooms…), industrial chitosan has molecular weight varying from 5,000 to 1,000,000 g/mol and acetylating degrees from 2 to 60 %.
Figure 3 Image of leaves and berries of *Embelia ribes*

Figure 4 Chemical structure of chitosan
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Drug-loaded chitosan nanoparticles are decomposed into free chitosan and drug in vivo and as soon as the drugs enter into the cell and reaches the targeted tissues to exert therapeutic effects. Chitosan is mainly degraded by catalysis of lysozyme and bacterial enzyme in the colon. The kidney clears the chitosan absorbed into blood and the rest is discharged through other excretion process. Degree of deacetylation as well as molecular weight also influence degradation rate and degree of chitosan in vivo (Xu et al., 1996 and Yang et al., 2007).

2.9.1 In vivo metabolic process of chitosan nanoparticles

Usually any carrier enters into the body system will be recognized as a foreign matter and are absorbed by antibodies generated in the human body. Most of the proteins in plasma are also adsorbed onto the carrier (eg. Nanoparticles), accelerating the reorganization of the reticuloendothelial system. Carrier system is engulfed by macrophage and cleared from the body’s circulation (Mei et al., 2002). The bridge between nanoparticles and macrophage is formed because of plasma protein adsorbed on the nanoparticle surface, mainly due to the surface charge of the nanoparticles (Redhead et al., 2001). Nanoparticles with polarity and high surface potential as well as amphipathic or hydrophilic nanoparticles are engulfed less and have a longer circulating time in vivo. Nam et al. (2009) found that glycol–chitosan nanoparticles after hydrophobic modification is more distributed in all cells compared with unmodified nanoparticles. Yuan et al. (2010) reported chitosan–alumino-silicate nanoparticles has shown significant sustained/controlled-release effects.
2.9.2 Chitosan as carrier for different types of drugs

Literature has shown that chitosan nanoparticles can carry many numbers of drugs, which includes gene drugs, protein drugs, anticancer chemical drugs, and antibiotics. This carrier can be administered into the body system via different routes of administration including oral, nasal, intravenous, topical and ocular.

With regard to gene delivery, the main challenge for gene therapy is to find safe and effective vectors that are able to deliver genes to the specific cells and get them to express inside the cells. The carrier must enhance their physicochemical properties, improving transfection efficiency, reducing cytotoxicity as well as incorporating functional groups that offer better target ability and should have higher cellular uptake. Chitosan has been reported widely for gene delivery because of their availability, excellent non-cytotoxicity profile, biodegradability and ease of modification (Xu et al., 2010). It has been reported by Köping-Höggård et al. (2001) that chitosan is a nontoxic alternative to other cationic polymers and it forms a platform for further studies of chitosan-based gene delivery systems.

Chitosan was considered to be the most effective carriers with low cytotoxicity and good transfection activities at low charge ratios (N/P). It has also been identified as a safe and promising polycation vector for gene delivery (Oliveira et al., 2013).

Mansouri et al. (2006) used folic acid to modify chitosan for improving gene transfection efficiency. The results showed that folic acid-modified chitosan nanoparticles have lower cytotoxicity and help them as a nonvirus gene carrier with a good application potential.
2.9.3 Carrier of other drugs

Chitosan nanoparticles can able to load most categories of drugs including antivirus drugs, antiallergic drugs, hormone drug, and other classes of drugs either to increase the bioavailability, encapsulation efficiency or to have prolonged release.

Different methods for preparing chitosan-based nanoparticles were summarized in Table 2.

2.10 Emulsification and cross-linking method

This method is widely used for the preparation chitosan based nanoparticles and involves the preparation of a W/O emulsion using non-ionic surfactant. After the formation of emulsion, to cross link and separate the nanoparticles, subsequent addition of a cross-linking agent was carried out that has the function of hardening the formed droplets. The reactive amino groups of chitosan undergo a covalent cross-linking with the carboxylic groups of glutaric acid, which is added after the emulsion formation, and, consequently lead to the production of nanoparticle.

Earlier chitosan nanoparticles were prepared with glutaraldehyde. To overcome the problems of toxicity that are presented by glutaraldehyde, some biocompatible cross-linkers, such as natural di- and tricarboxylic acids, including succinic acid, malic acid, tartaric acid and citric acid, are used for intermolecular cross-linking of chitosan nanoparticles (Bodnar et al., 2005). By this method, the pendant amino groups of chitosan react in aqueous media with carboxylic groups of natural acids which were previously activated by a water-soluble carbodiimide, obtaining polycations, polyanions, and polyampholyte nanoparticles with an average
<table>
<thead>
<tr>
<th>Production Method</th>
<th>Matrix composition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsification &amp; crosslinking</td>
<td>Chitosan, glutaraldehyde</td>
<td>Ohya et al. (1994), and Songjiang &amp; Lixiang (2009)</td>
</tr>
<tr>
<td>Emulsion droplet coalescence</td>
<td>Chitosan</td>
<td>Tokumitsu et al. (1999), and</td>
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<td></td>
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<td>Shering (2011)</td>
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<tr>
<td>Reverse micellisation</td>
<td>Chitosan, glutaraldehyde</td>
<td>Mitra et al. (2001), and</td>
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<td></td>
<td></td>
<td>Banerjee et al. (2002), and</td>
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<td></td>
<td></td>
<td>Tang et al. (2007), and</td>
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<td></td>
<td></td>
<td>Manchanda &amp; Nimesh (2010)</td>
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<tr>
<td>Ionic gelation</td>
<td>Chitosan, tripolyphosphate</td>
<td>Calvo et al. (1997) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ma et al. (2002)</td>
</tr>
<tr>
<td>Polyelectrolyte complexation</td>
<td>Chitosan, alginate, arabic gum, carboxymethyl</td>
<td>Erbacher et al. (1998), Hu et al. (2002), Du et al. (2004), Sarmento et al.</td>
</tr>
<tr>
<td></td>
<td>cellulose, carrageenan, chondroitin sulfate,</td>
<td></td>
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<tr>
<td></td>
<td>cyclodextrins, dextran sulfate, polyacrylic acid, poly-γ-glutamic acid,</td>
<td></td>
</tr>
<tr>
<td>Modified ionic gelation with radical</td>
<td>Chitosan, acrylic acid, methacrylic acid,</td>
<td>Hu et al. (2002), Sajeesh and Sharma (2006a)</td>
</tr>
<tr>
<td>polymerization</td>
<td>polyethylene glycol, polyether</td>
<td></td>
</tr>
<tr>
<td>Desolvation</td>
<td>Chitosan</td>
<td>Mao et al. (2001), Agnihotri &amp; Aminabhavi (2007), and Atyabi et al. (2009)</td>
</tr>
</tbody>
</table>
size in the range of 270–370 nm depending on the pH. Since this method is versatile and is followed in the present study to prepare embelin and its metal complexes nanoparticles for antidiabetic efficacy.

2.11 Antidiabetic efficacy

2.11.1 In silico models - Docking studies

Few of the drugs have been tested for the antidiabetic efficacy under in silico models; however, computer aided docking studies on compounds from plants Vs proteins that mediate diabetes were even very less. This method of screening will help to reduce the cost and time of drug discovery. Moreover, docking studies are helpful to understand the interaction of ligand molecules with receptors with reasonable accuracy and speed (Akhila et al., 2012). Drug design is mainly based on protein-ligand interactions and the active site residues. The major driving force between protein-ligand interactions for binding appears to be hydrophobic interaction. In silico techniques helps identifying drug target via bioinformatics tools. They can also be used to explore the target structures for possible active sites, generate candidate molecules, dock these molecules with the target, rank them according to the binding affinities, and further optimize the molecules to improve binding characteristics.

The molecular modeling will show an energy binding affinity of the tested compound. There are several targets available to lower the glucose level in the body such as glucokinase (Angadi et al., 2013), pancreatic alpha amylase, aldose reductase, alpha glucosidase, etc. Among this enzymes, $\alpha$-Amylase and $\alpha$-glucosidase are significant enzymes, which cleave carbohydrates responsible for
absorption of glucose in the blood stream. Pancreatic α-amylase inhibitors offer an effective strategy to lower the levels of post-prandial hyperglycemia via the control of starch breakdown. According to Sivakumari et al. (2010) aldose reductase (AR) is an enzyme associated with retinopathy of both type 1 and type 2 diabetic patients.

Hence in the present study, the docking studies were performed using two receptors namely HPAA and HAR by using Discovery studio version 3.0. Discovery studio has the ability to predict the interaction energy of small molecule with molecular targets.

2.11.2 In vivo studies – Animal model

Experimental induction of diabetes mellitus in animal models is essential for understanding its pathogenesis. Several methods have been used to induce diabetes mellitus in laboratory animals with variable success and many difficulties. Surgical removal of the pancreas is an effective method; however, to induce diabetes, at least 90-95% of the pancreas has to be removed (Akbarzadeh et al., 2007). Since it is tedious and costly, alloxan or streptozotocin has been used usually to induce diabetes in the animal studies than other diabetogenic agents. Both the drugs, causes destruction of the beta cells of pancreas and thus gives permanent diabetes responsible for final observed rise in blood sugar level. These drug are toxic and affects other tissues than liver and pancreas. Alloxan is a uric acid derivative and is highly unstable in water. The hypoglycaemic phase may be quite severe and therefore alloxan should not be given to fasted animals. Because of this reason, alloxan is now replaced by Streptozocin. Streptozotocin (STZ; N-nitro derivative of glucosamine) is a naturally occurring, broad spectrum antibiotic and cytotoxic
chemical that is particularly toxic to the pancreatic, insulin producing beta cells in mammals (Szkudelski et al., 2001 & Hayashi et al., 2006). Induction of experimental diabetes in the rat and mice using streptozotocin is very convenient and simple to use (Brosky et al., 1969 & Ito et al., 1999). Streptozotocin can be injected either intravenously or intraperitoneally. In rats, it has been reported that a dose ranging from 25 to 100 mg/kg of streptozotocin injected intravenously was successful in inducing diabetes (Hayashi et al., 2006). Severity and onset of diabetes symptoms depend on the dose of streptozotocin. Clinically, symptoms of diabetes are clearly seen in rats within 2-4 days following single intravenous or intraperitoneal injection of 60 mg/kg STZ. In the present study, Streptozotocin was used to induce diabetes in Sprague-dawley rats.

In this chapter, diabetes mellitus and its treatment, transition metals in diabetic mellitus, embelin, nanoparticles and polymeric nanoparticles (chitosan) have been described briefly along with antidiabetic efficacy. Diabetes has many remaining problems; nanomedicine is likely to be a key technology for solving many of them and will be a core technology in diabetic research. With the advancement of science, the role of transition metal complexes as therapeutic compounds is becoming increasingly important and used in various therapies. Development of transition metal complexes as drugs is not an easy task; much effort is required to get a compound of interest. Besides all these limitations and side effects, transition metal complexes are still the most widely used therapeutic agents and make a large contribution to medical field. Based on the literature, structure of the present thesis is designed.


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Dhar, M. L., & Singh, O. 1986. Nature and composition of La (III), Ce (III), Pr (III), Nd (III), Sm (III), Gd (III), Dy (III) and Ho (III) complexes of embelin. Inorganica chimica acta, 117(2): 187-189.


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Honigberger GM. In: Thirty-five years in the East. Adventures, discoveries, experiments, and historical sketches, relating to the Punjab and Cashmere; in connection with medicine, botany,
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pharmacy, etc. Together with an original materia medica; and a medical vocabulary, in four European and five eastern language. Vol II, edited by H Baillière, London, 1852.


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**Web source**


http://faculty.virginia.edu/metals/cases/houck1.html

compound could act as a nutritional enhancement particularly essential for glucose metabolism. The Cr (III) complexes had better bioavailability and more beneficial influences on the improvement of controlling blood glucose and proposed to act as safer antidiabetics [2]. Supplementation of chromium significantly improves glucose level among patients with diabetes but fails to show any significant effect on glucose metabolism in healthy volunteers [21]. Treatment with Chromium picolinate (CrPic) improves glycemic control in diabetic patients [22]. Chromium picolinate is more bioavailable than other supplemental forms of chromium and therefore may be more efficacious.

**Cobalt**

Cobalt is one of the most important trace elements in the world of animals and humans and finds therapeutic application in pharmacological fields. In the form of vitamin B12 (cobalamin), this metal plays a number of crucial roles in many biological functions. Vitamin B12 is the only metal-containing water-soluble vitamin that is stored in the liver and must come from the diet. Cobalamin is necessary for DNA synthesis, formation of red blood cells and maintenance of the nervous system, growth and development of children. Cobalt is used to treat anaemia with pregnant women, because it stimulates the production of red blood cells. Cobalt was found to boost the effects of insulin and its action. Treatment with cobalt chloride (CoCl₂) decreases the glycaemia of diabetic rats which may be mediated by gene expression of GLUT-1 mRNA. Treatment with cobalt chloride showed significant decline in blood glucose in STZ induced diabetic rats but no observed change in plasma/serum insulin levels of normal or diabetic rats. Cobalt is the most important contributor to metal ion toxicity in nutrients both in single and pure form. Different forms of cobalt complexes have been reported to reduce the potential toxicity of cobalt without modifying its therapeutic effect[2]. The glycemic lowering effect of glucosaminic acid-cobalt chelate has been reported to be effectiveveagent for diabetes [23]. Cobalt therapy may prove effective in improving the impaired antioxidant status during the early state of diabetes and ascorbic acid supplementation at this dose potentiates the effectiveness of cobalt action [24,25].

**Tungsten**

Tungstate counteracts diabetes in the form of sodium tungstate. Studies in several animal models of diabetes have shown sodium tungstate to be an effective anti-diabetic agent and found to be less toxic both in diabetic and healthy animals [26, 27]. Administration of this metal enhances the insulin activity rather than increased insulin levels [28] and also treatment with this metal found to rise extra-islet β-cell replication without modifying intra islet β-cell replication rates [29]. Tungstate improves pancreatic function through a combination of hyperglycemia-independent pathways and through its own direct and indirect effects, whereas the MAPK pathway has a key role in the tungstate-induced increase of beta cell proliferation [30].

**Manganese**

Manganese (Mn) plays a key role in a number of physiologic processes and is considered to be essential for the carbohydrate, amino acid and cholesterol metabolism. The human body does not require much of this element, but several biological uses of manganese are critical to the proper functioning of the body, and it is often included in small doses in mineral supplements. Manganese seems to be particularly important for the proper functioning of enzymes. These enzymes have a variety of different functions. Some aid in repairing damage to the body. Others are antioxidants. Additional enzymes make use of manganese to aid in the development of strong and healthy bones. It is considered to be a key component of metalloenzymes such as S–Cys-containing glutathione peroxidase, Cu/Fe cytochrome C oxidase or different types of superoxide dismutase, which are in turn important for intra- and extra-cellular antioxidant defense mechanisms[2]. Synthetic derivative of manganese found to be used as potent therapeutic agent in diabetes. Two newly classified antioxidants namely EUK-8 and EUK-134 reported to reduce the serum levels of glucose [31].

**Molybdenum**

Molybdenum (Mo), an important trace metal plays a major role for participation in the active sites of metalloenzymes. Molybdenum is capable of forming complexes with many compounds of nutritional importance: carbohydrates, amino acids, flavins, porphyrins; but is probably taken up, transported, and excreted in animals as the simple molybdate ion, [MoO₄]²-. Molybdenum is essential for life and is much less toxic than many other metals of industrial importance. Most organisms including human beings require molybdenum for their existence. Molybdenum along with tungstate helps in the key transformations in the metabolism of nitrogen, sulphur, carbon, arsenic, selenium and chlorine compounds. This element plays a crucial role in the structure of certain enzymes involving redox reactions [32]. Molybdenum in different forms have shown to possess insulin mimetic properties and hence it used in the treatment of diabetes. Sodium molybdate (Na₂MoO₄·1·5H₂O) and its complex compounds such as cis-MoO₂L₂ (L = maltol (3-hydroxy-2-methyl-4-pyrone)) were found to reduce the levels of blood glucose significantly and also free fatty acids [33]. Combination of molybdenum and ascorbic acid exhibited significant insulin-like activities and also shown cardio protective effects [34].

**Tin**

Tin generates a wide variety of biological activities deriving from its chemical character. Tin is an ultra-trace element in humans. It has been suggested that the amount of tin found in a healthy diet should be the value used to describe appropriate intake. Vangabhasma, an Ayurvedic preparation of tin is used traditionally for treatment of diabetes. Vangabhasma is purified and calcinated form of tin with additional herbs[35].

**Siddha System Of Medicine**

Siddha system of medicine, one of the ancient medical systems has the great potential of treating many disease ailments. Siddha system of Medicine, many single and polyherbal formulations and higher medicines like Parpam, Chendooram Chunnamhave been practiced to cure or control diabetes mellitus from time immemorial. The familiar Siddha medicines prescribed for diabetes are AvaraiKudineer( decoction), MadhumegaChooranam(Fine powder), ThetranChooranam, SeenbhiChooranam, NaavalChooranam, Abrogaparpam, Vangaparpam etc. In Siddha, the management of a disease not only depends on the medicine but the modification of food, habits, and lifestyle also. In addition to this, yoga and exercise therapy also plays a key role for the management of diabetes. SiddhaKudineer, a polyherbal formulations equally referred to Khamayar in Ayurveda are more useful to prevent the diabetes and their associated complications.

Oral administration of Siddha formulation (Madhumegachooranum) ameliorated the plasma glucose and lipid levels in alloxan-induced diabetic rats reported by Vadivelan et al. [36-40]. It was studied that.Kovai KithuanghooChooranam found to possess remarkable anti-diabetic action in alloxan induced diabetic rats was reported by Parthiban et al. [36-40].

**CONCLUSION**

Metal complexes offer a platform for the design of novel therapeutic compounds. The metal compounds offer new properties that cannot be found amongst purely organic agents. Treatment of diabetes mellitus with metal complexes is a new therapeutic strategy. Although various metals like chromium, manganese, molybdenum, tungsten, copper, cobalt, zinc and vanadium were reported to exhibit insulin mimetic activity outside of these a wide class of vanadium, copper and zinc complexes was found to be effective for treating diabetes in experimental animals. Since metallotherapy overcome the problems of painful insulin injection and side effects for type 1 or type 2 DM, the encouraging results of preclinical and clinical studies with metal complexes as an agent of biologicals towards the development of metalloids for better healthcare.
CONFLICT OF INTERESTS
Declared None

REFERENCES
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