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SELENIUM AND CHROMIUM AS ANTIDIABETIC TRACE ELEMENTS: AN OVERVIEW

B. Sarma and P. Saha *

Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Rd, Sahid Colony, Panihati, Kolkata - 700114, West Bengal, India.

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Correspondence to Author:
Dr. Prerona Saha

Associate Professor,
Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Rd, Sahid Colony, Panihati, Kolkata - 700114, West Bengal, India.

E-mail: prerona.saha@gnipst.ac.in

ABSTRACT: Trace elements are the dietary factors required by the body in small quantities for normal functioning of the body. The body's functional skill is negatively impacted by a diet with insufficient trace elements, which lowers the body's immune function. They are involved in catalyzing different enzymatic reactions. The permissible range of selenium is very narrow. Low levels of selenium have been reported in patients suffering from both acute and chronic kidney diseases. Reduced levels of selenium have also been reported in diabetic patients, while excess levels of selenium have been linked with inflammation and increased oxidative stress. Selenium at optimum amounts decreases oxidative stress by functioning as a cofactor of glutathione peroxidases and thioredoxin reductases. Insufficient intake of chromium leads to reduced insulin activity, hinder protein synthesis thereby leading to Type 2 diabetes mellitus. Chromium have been reported to boost enzyme activity and play crucial role in carbohydrate metabolism, increase sugar metabolism by initiation of insulin. This review aims to encompass the mechanism of action in prevention of diabetes mellitus of selenium and chromium.

INTRODUCTION: Diabetes mellitus can be defined as a group of metabolic disorders that have hyperglycemia as a common symptom. High levels of glucose present in the blood stream contributes to wide array of health risks. It is the leading cause behind kidney disorders, blindness, cardiovascular disorders, stroke and in some cases amputations [1]. Development of diabetes can be due to both genetic and environmental factors [2]. Different process are involved in development of diabetes, it can be due to resistance to insulin action or because of destruction of pancreatic β-cells which leads to deficiency of insulin.

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Due to diabetes, the body cells are unable to metabolize the glucose molecules properly because of insulin deficiency or insulin resistance. This triggers the body to metabolize its own fat, proteins and glycogen to produce sugar, leading to excess levels of sugar in blood. In long term complications arising from diabetes include retinopathy which can possibly cause loss of vision; peripheral neuropathy that can cause foot ulcers and amputations; nephropathy that can lead to failure of kidneys; and autonomic neuropathy that can possibly cause gastrointestinal and cardiovascular problems [3].

The most common forms of diabetes is: Type I DM and Type II DM. Gestational diabetes, is also a type of diabetes which can be defined as any degree of glucose intolerance after first detection of pregnancy. The various risk factors involved in predisposition of gestational diabetes includes advanced maternal age, family history of type 2 diabetes mellitus and ethnicity [4].

Management of diabetes is a complex and multidisciplinary process [5]. The currently available therapies for management of diabetes includes insulin and orally administered drugs such as sulfonyl ureas, biguanides and glinides. Majority of these drugs are associated with adverse side effects [5]. The World Health Organization (WHO) projects that by the year 2030, diabetes will be the seventh leading cause of death [6]. The therapeutic options for diabetes management such as oral hypoglycemic agents, insulin therapy and change in dietary habits have demonstrated limitations of their own [7].

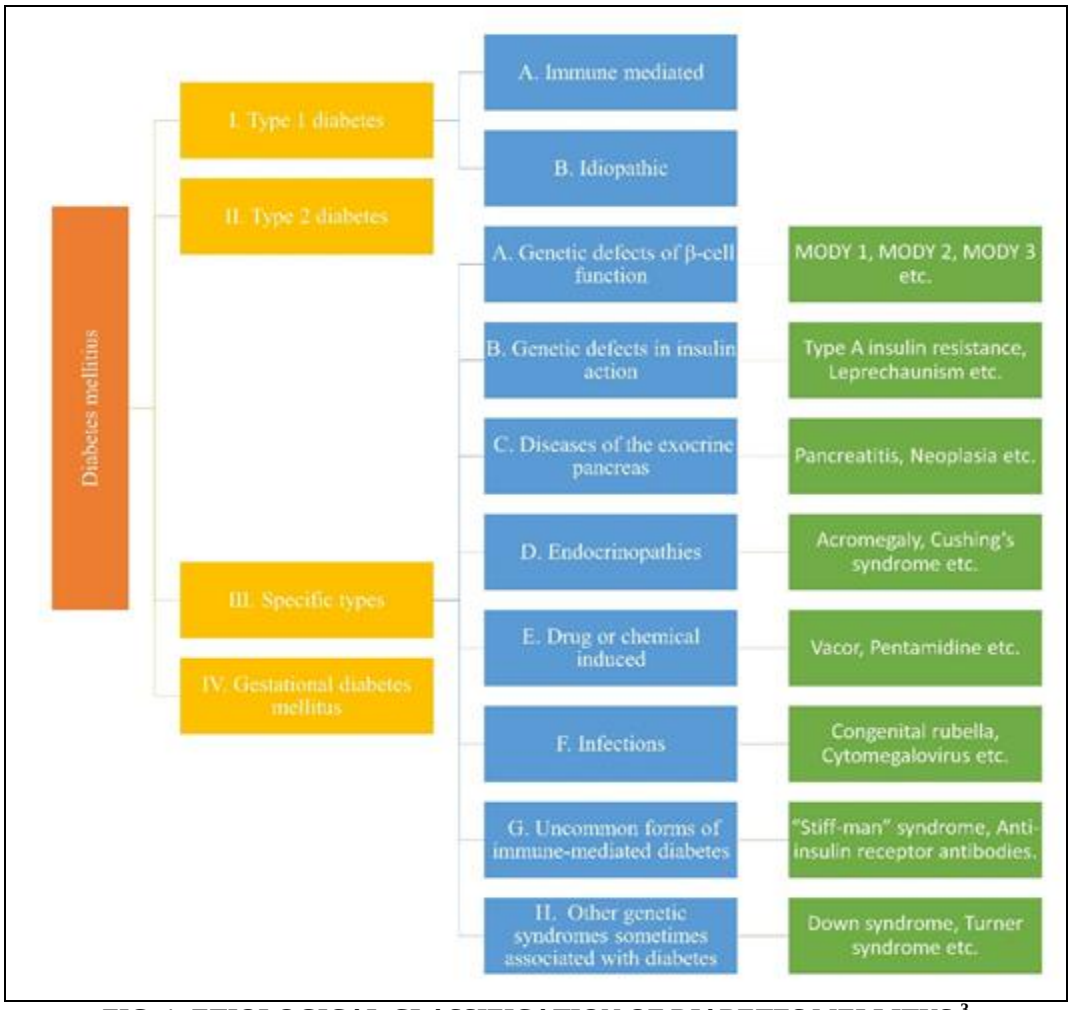


FIG. 1: ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS [3]

Micronutrients: Micronutrients are vital nutrients that are required by the body in very small quantities for homeostasis and proper functioning of various enzymes. They are responsible for activating cofactors and coenzymes that control metabolism, genetic transcription and also oxidative stress [8].

Micronutrients can be divided into four major classes i.e., vitamins, organic acids, macro minerals and trace elements. Macro minerals comprises of elements such as calcium, phosphorus, magnesium, manganese, sodium, potassium and iron. Whereas zinc, molybdenum, iodine, chromium, sulphur, copper, selenium, boron and cobalt falls under the category of trace elements [9].

Trace Elements as Antidiabetic agents: Trace elements have been identified as antidiabetic agents since a long time. Trace elements such as Zn, Se, Cr, V, Mg and Mn acts as cofactors for different antioxidant enzymes thereby reducing oxidative stress. Imbalance of some essential trace elements might adversely affect pancreatic islet and can possibly lead to development of diabetes. Trace elements such as zinc, chromium, vanadium, selenium etc. are essential for catalyzing many biochemical reactions and are also part of enzyme

prosthetic groups. For example, zinc acts as a cofactor to more than 100 enzymes. Trace elements are involved in activating insulin receptor signaling (Cr), possess antioxidant activities (Zn, Se) and inhibits phosphatases (Va) [10].

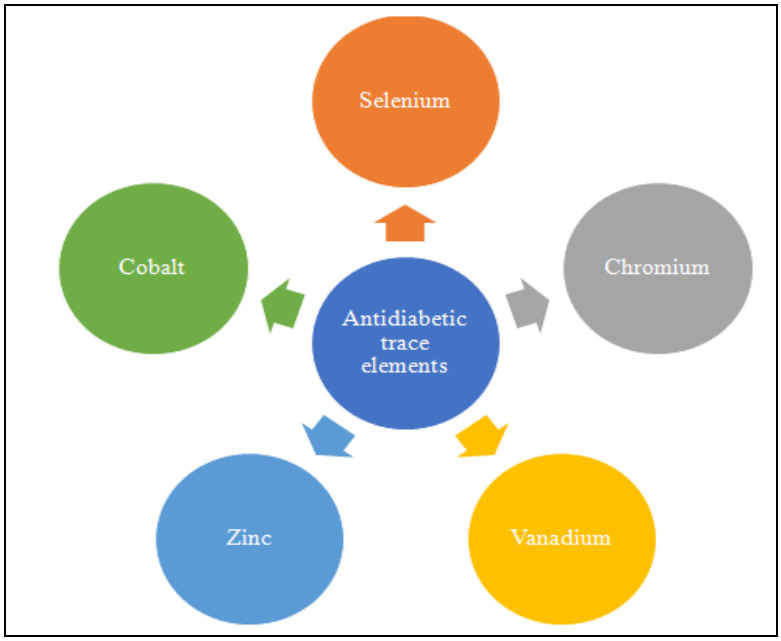


FIG. 2: DIFFERENT ANTIDIABETIC TRACE ELEMENTS

TABLE 1: MECHANISM OF ACTION OF DIFFERENT ANTIDIABETIC TRACE ELEMENTS

Sl. no.	Trace element	Antidiabetic mechanism of action
1	Chromium	a. Chromium supplementation improves blood sugar levels, triglycerides and HDL-C levels
		b. Chromium increases insulin receptor number and insulin binding to site of action [11, 12]
2	Vanadium	a. Vanadium acts as an insulin mimetic.
		b. Vanadium complexes inhibit PTPs thereby enhancing phosphotyrosinesignalling [13, 14]
3	Zinc	a. Important for functioning of number of enzymes [15]
		b. Stimulates postreceptor proteins
		c. Zinc possesses good antioxidant activity [16]
4	Cobalt	a. Deficiency of cobalt may lead to Type 2 DM [9]
5	Selenium	a. Selenoproteins function as antioxidant and Se supplementation prevents onset of metabolic disorders such as Type 2 D.M [17]

Objective: The objective of present review is to explore the role of Selenium and Chromium as antidiabetic trace element.

Selenium: The term Selenium is derived from the Greek word “Selene”. It was first described in the year 1817 as a by product from sulphuric acid production by Swedish chemist J.J Berzelius [18].

The endogenous level of selenium in humans varies across populations in different geographical areas and in different age groups residing in the same area, indicating there are environmental and internal factors at play [19, 20]. The common dietary sources of selenium include garlic, meat, fish, broccoli, black tea, mushrooms and soybeans [21]. The recommended dietary intake of selenium varies from country to country as the selenium levels in soil varies [22]. Although deficiency of selenium is rare, it can have detrimental effect on health by increasing the effect of other disease causing factors [23].

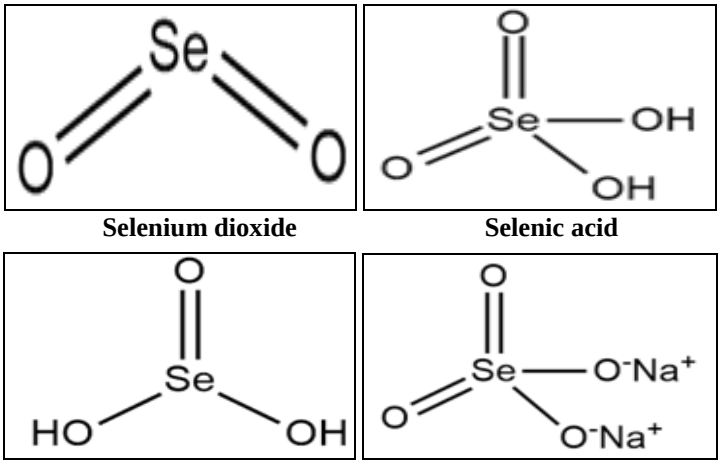
The World Health Organization recommends that daily intake of selenium must be 30µg to 40µg. Higher intake of selenium i.e., 400µg-700µg can have toxic effects on the body [24].

The range of selenium required by the body is narrow between deficiency, sufficiency and toxicity [25]. Selenium is present in different chemical forms and oxidation states that determines its bioavailability and toxicity. Selenium compounds having +4 and +6 oxidation states are

comparatively more bioavailable than compounds having 0 and -2 oxidation states [26]. Compounds having -2 and 0 oxidation states are reduced heavy metal selenides and elemental selenium and are insoluble in water; however, compounds with +4 and +6 oxidation states *i.e.*, inorganic alkali selenites and selenates are soluble in water and thereby more bioavailable.

TABLE 2: DIFFERENT FORMS OF SELENIUM AND THEIR RESPECTIVE OXIDATION STATE

Selenium form	Oxidation state
Elemental selenium and selenodiglutathione (dipeptide)	0
Sodium selenide and hydrogen selenide	-2
Sodium selenite, selenium dioxide and selenious acid	+4
Sodium selenate and selenic acid	+6



Selenium dioxide **Selenic acid**

Selenious acid **Sodium selenate**

FIG. 3: SOME SELENIUM COMPOUNDS HAVING +4 AND +6 OXIDATION STATE

Deficiency of selenium in diets have been reported in different countries, which is mainly due to low levels of the element in soil [22]. Selenium deficiency causes organ deterioration due to reduced expression of selenoproteins [27]. The deficiency of selenium has been linked with onset of Keshan disease and Kashin Beck disease [28, 29]. Keshan disease was first described in the year 1935, in the Keshan province of China. Keshan disease primarily affects women and child in the areas characterized by low levels of selenium in the soil. Keshan disease leads to cardiac dysfunction [30]. Kashin Beck disease was first described by a Japanese doctor by the name of T. Okano in the northern district of Korea. He reported KBD as a progressive polyarthritis condition. Presently the etiology of KBD is considered to be multifactorial based on the deficiency of iodine and selenium in the soil and presence of high concentrations of organic substances in the drinking water [31]. Chronic toxicity of selenium can lead to selenosis which manifests with symptoms such as hair loss, fragility of fingernails, infertility, skin rash and GIT upsets [32].

Selenium in Diabetes: In 1957, the therapeutic role of selenium as a micronutrient was described for the first time by Schwarz and coworkers. They reported that Selenium supplementation in lower doses prevented rat liver from necrosis [33]. Following this, there have been multiple studies on the beneficial effects of selenium. Osamu Ezaki was the first to show that selenate had insulin mimetic property. In the studies conducted by Ezaki, he reported that selenate stimulated glucose transport activity in rat adipocytes in a dose dependent manner. Ezaki further added that selenate increased glucose transport activity by translocation of GLUT-1 and GLUT-2 to membrane surface [34].

Different studies have reported that patients suffering from hyperglycemia exhibits low blood selenium level. A study conducted by Shang *et. al.*, used sodium selenite to treat alloxan induced diabetic mice. They reported that selenite reduced blood glucose levels [35]. A study performed by Satyanarayana *et. al.*, reported that half or single therapeutic dose of selenium (0.9 and 1.8 µg/200mg) had glucose lowering activity in alloxan induced diabetic animal. But a higher dose of (double dose) of 3.6 µg/200mg increased blood glucose level [36]. But increased intake of selenium (438 µg/kg/day) in the form of sodium selenite for

6 weeks showed higher levels of fasting blood glucose and postprandial blood glucose in rats. It also elevated gluconeogenesis in the liver which may be result of impaired glucose and insulin tolerance [37].

Mechanism of Action:

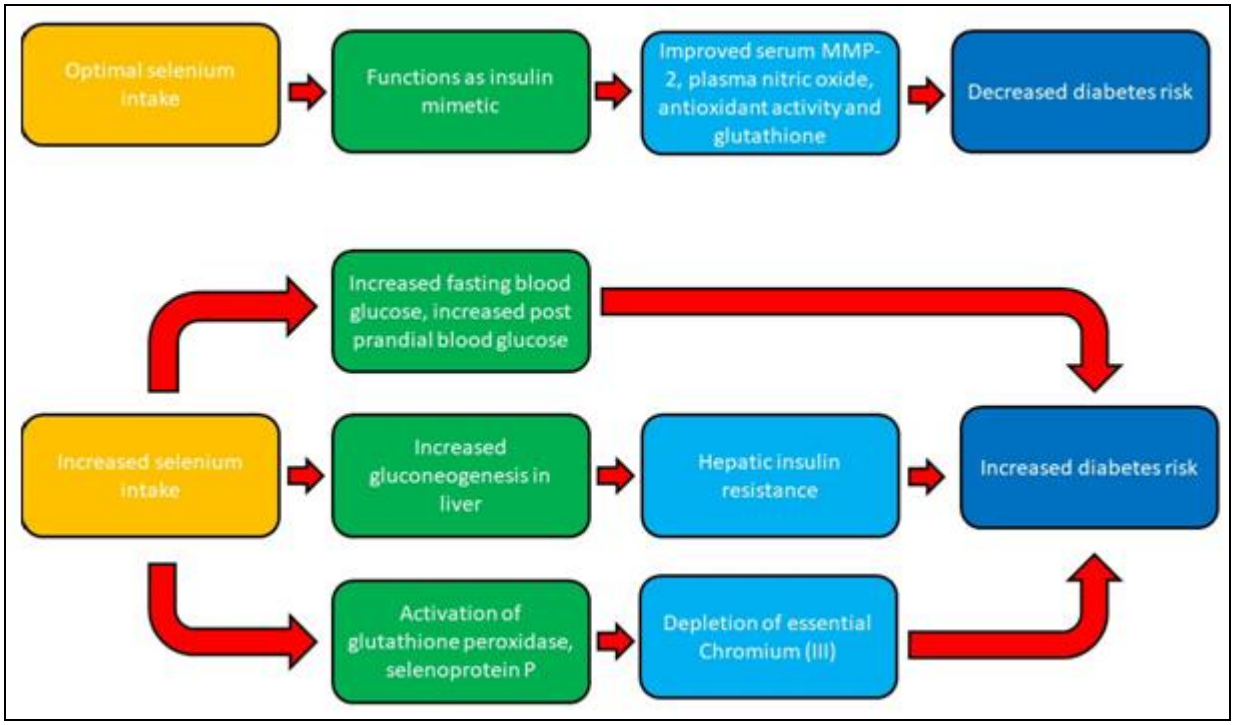


FIG. 4: MECHANISM OF ACTION OF SELENIUM IN DIABETES MANAGEMENT

Chromium: In the year 1955, chromium was discovered as an essential trace metal [38]. Chromium is involved in glucose metabolism. Chromium is an essential trace element that is required for metabolism of glucose, insulin and lipids. Improper intake of chromium in diet have been associated with onset of diabetes and cardiovascular diseases. Chromium exists in five different valence states: metallic chromium [Cr(0)], bivalent chromium [Cr(II)], trivalent chromium [Cr(III)], pentavalent chromium [Cr(V)] and hexavalent chromium [Cr(VI)]. Chromium (V) and chromium (VI) are carcinogens, while on the other hand chromium (III) is non-toxic and functions as a micronutrient by acting as cofactor in insulin action and plays an important role in glucose and lipid metabolism [12]. Chromium acts to prevent diabetes by increasing binding of insulin to cells, increasing insulin receptor numbers. Chromium potentiates the insulin action and thereby control the blood sugar levels. Chromium supplementation have been associated with increased binding of insulin to receptors because of the increase in numbers of insulin receptors. Chromium also improves insulin receptor enzymes by improving insulin sensitivity and β cell sensitivity [39]. Cr(III), present in the form of glucose tolerance factor (GTF), increases the insulin action in glucose metabolism. Glucose tolerance factor functions by improving the insulin action. Compared to simple compounds of chromium, GTF is easily absorbed, is safe and stabilizes blood glucose levels. Brewer's yeast contains the most common and naturally occurring form of GTF. A clinical investigation on diabetic patients showed increased insulin sensitivity on chromium supplementation via Brewer's yeast [40]. During pregnancy the requirements for different nutrient increases. During pregnancy, insulin resistance increases, which leads to greater insulin demand. If the pancreas is not able to produce enough insulin to meet this demand it leads to a state called as gestational diabetes. To prevent gestational diabetes or glucose intolerance, supplementation of nutrients in enough quantities is essential [41]. In 1969, Hambidge and Rogerson reported the decrease in chromium during pregnancy. They compared the concentration of chromium in hair of nulliparous women and parous

women. They reported that chromium concentration in parous group was significantly lower [42].

Chromium in Diabetes: Chromium plays an important role in glucose metabolism. Once in the tissue, chromium binds to chromodulin and improves the function of insulin. The conclusive evidence for essentiality of chromium was documented by Jeejeebhoy *et al.* in 1977, a patient on total parenteral nutrition had developed diabetic symptoms. On subsequent supplementation of 200µg chromium daily for next two weeks and the symptoms improved[43].Davis and Vincet in 1997, reported the beneficial effects of Cr(III) and it's relationship with diabetes. Chromium binds to insulin receptor and thereby increases the tyrosine protein kinase activity [44]. Jain *et al.*, in 2001, demonstrated the mechanism by which Cr(III) chloride functions to improve insulin sensitivity and glycemic control in cultured U937 monocytes. They reported that $CrCl_3$ supplementation inhibits the secretion of TNF-α, a cytokine which is involved in inhibition of insulin action [45].

In a study, oral administration of $CrCl_3$ on glucose and lipid metabolism in streptozotocin and neonatal-streptozotocin diabetic rats were studied. $CrCl_3$ treatment improved impaired glucose and insulin sensitivity of both groups. Lipid metabolism was also improved significantly by $CrCl_3$ treatment [46].

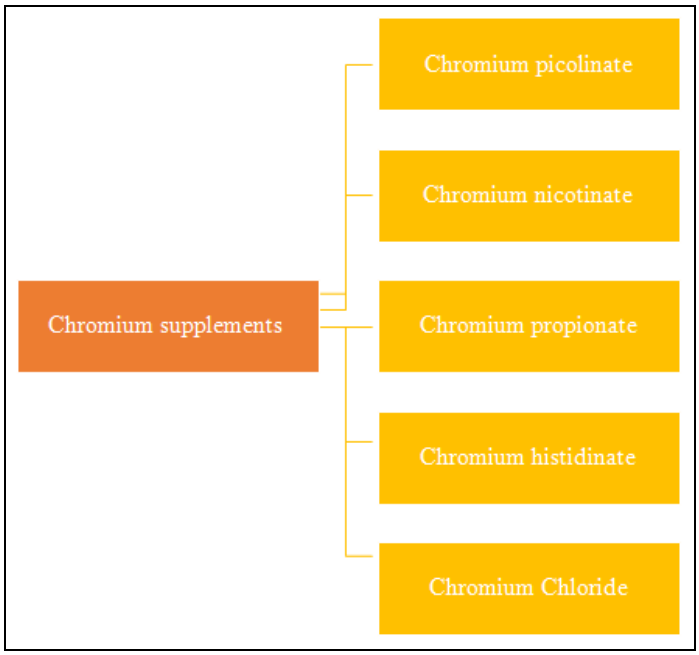


FIG. 5: DIFFERENT TYPES OF CHROMIUM SUPPLEMENTS

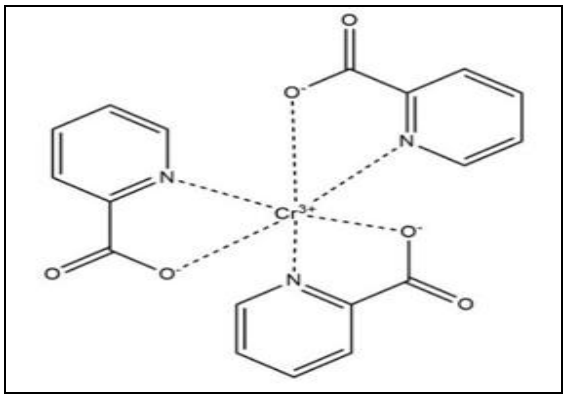


FIG. 6: CHROMIUM PICOLINATE

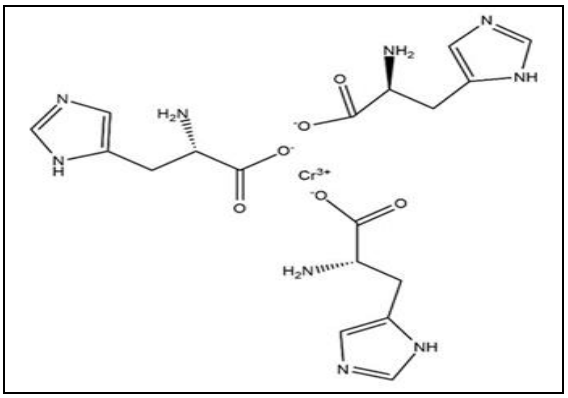


FIG. 7: CHROMIUM HISTIDINATE

Z. L. Wang *et al.* in 2006 reported that when chromium picolinate (80µg/kg body weight/day for 3 months) is administered to male JCR: LA-cp obese rats, it resulted in reduced plasma concentration of insulin and total cholesterol [47]. Another study reported that supplementation of

chromium picolinate (600µg/day) to type 2 diabetes patients reduced fasting blood glucose concentration and postprandial blood glucose concentration [48].

Mechanism of Action:

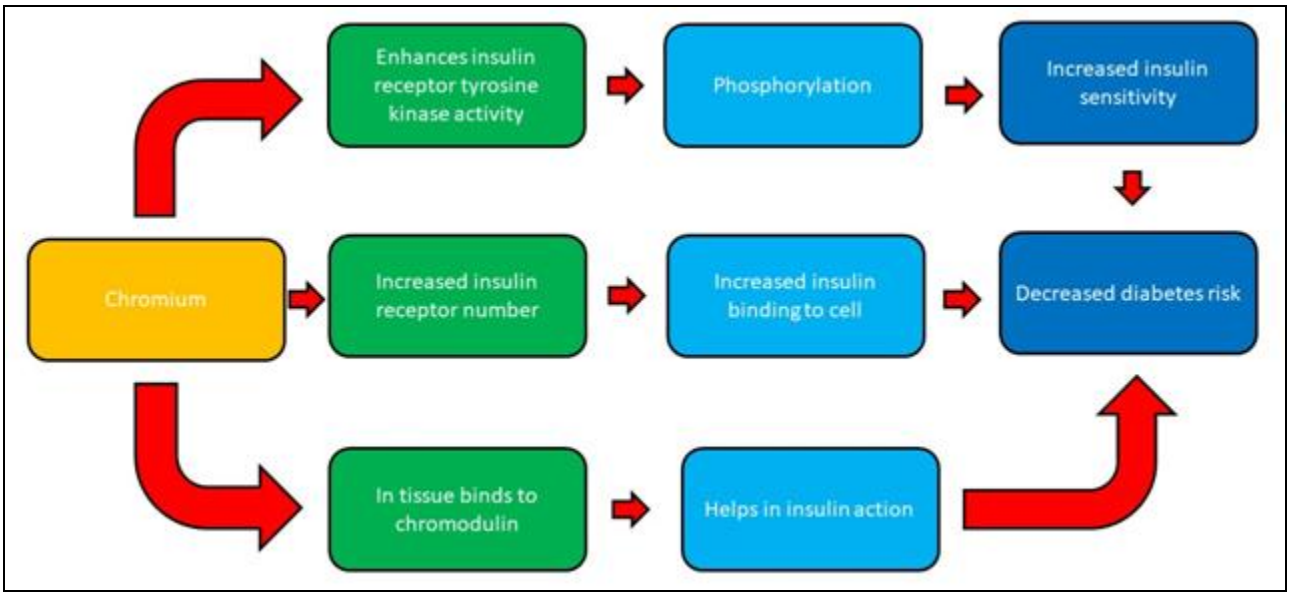


FIG. 8: MECHANISM OF ACTION OF CHROMIUM IN DIABETES MANAGEMENT

DISCUSSION: Development of diabetes mellitus can alter the concentrations of trace elements in body, and make one susceptible to health problems. Selenium is an essential element required by the body for normal physiological functions. Compared to other essential trace elements the amounts of selenium needed by the body is less (few µg), with a narrow concentration difference between deficiency, sufficiency and toxicity. Selenium is present in very low quantities in the food products daily. Therefore, it becomes imperative that food products containing selenium are consumed regularly. Searching for food sources that are enriched with selenium for consumption can help in prevention of diabetes mellitus.

Since trivalent Cr is commonly found in food and nutrient supplementations, is one of the least toxic nutrients. Anderson *et al* in 1997 showed that chromium chloride and chromium picolinate in rats at levels significantly higher than the upper limit were not toxic [39]. There was no toxicity reported by them in their study. Chromium has shown beneficial effects on metabolism of glucose, lipids and insulin. Supplementation of chromium increases insulin binding to cells because of increase in insulin receptor number. Increased intake of simple sugars increases the chances of chromium deficiency. Therefore, Cr supplementation can help in improvements in patients having diabetes.

CONCLUSION: In summary, essential nutrients selenium and chromium has notable beneficial effects on metabolism of glucose and insulin. It can be concluded that selenium and chromium have beneficial effects against diabetes as evidenced in different antidiabetic studies of trace elements. To understand the health benefits of these micronutrients in detail and understand the underlying pathways and mechanisms, more research is required in this field. Further, the safety levels of selenium and chromium should also be considered in the future research works for development of food supplements and nutraceuticals related to these micronutrients.

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