Recent Progression of Chromium and Its Salts for Combating in Kinds of Human Metabolic Disorder and Diseases

Dheeraj Bisht[1]*, Swati Patni Pant[1], Mohammad Rashid[2]*, Ankit Kumar[3], Aadesh Kumar[3], Rajeshwar Kamal Kant Arya[3], Latifah Hulayyil Alanazi[4], Rabah Warad AALAnazi[4], Thamer Sattam H Alshammari[4], Meshal Masad Almutairi[4], Majed Thabet A Almutairi[5], Awadh Fahad A Almutairi[5], Daliyah Mohammed Ali Alluqmani [6], Ahlam Ahmed H Alabdali[6], Abdullah Ruhaydin Khurayfish Aljohani[7]

[1]Devsthali Vidyapeeth College of Pharmacy, Veer Madho Singh Bhandari Uttarakhand Technical University, Lalpur-263148, Rudrapur, Uttarakhand, India
[2]Department of Pharmacognosy and Pharmaceutical Chemistry, College of Dentistry and Pharmacy, Buraydah Private Colleges, Buraydah-51418, Al-Qassim, Saudi Arabia
[3]Department of Pharmaceutical Sciences, Sir J. C. Bose Technical Campus Bhimtal, Kumaun University, Nainital-263136, Uttarakhand, India
[4]Riyadh Second Health Cluster, Post Box-3881, Riyadh-7499, Kingdom of Saudi Arabia
[5]King Fahad Specialists Hospital Tabuk, King Khalid Rd-8066, Alqadsiyyah, Tabuk-47717, Kingdom of Saudi Arabia
[6]King Fahad Madinah Hospital, Al-Jamiah-3177, Al-Madinah Al-Munawwarah, 42351, Kingdom of Saudi Arabia
[7]Prince Abdul Mohsen Hospital, Alula-43543, Kingdom of Saudi Arabia
*Corresponding author:
E-mail: dheeraj.bisht729@gmail.com (Dr. Dheeraj Bisht) & rashidpharm2008@gmail.com (Dr. Mohammad Rashid)
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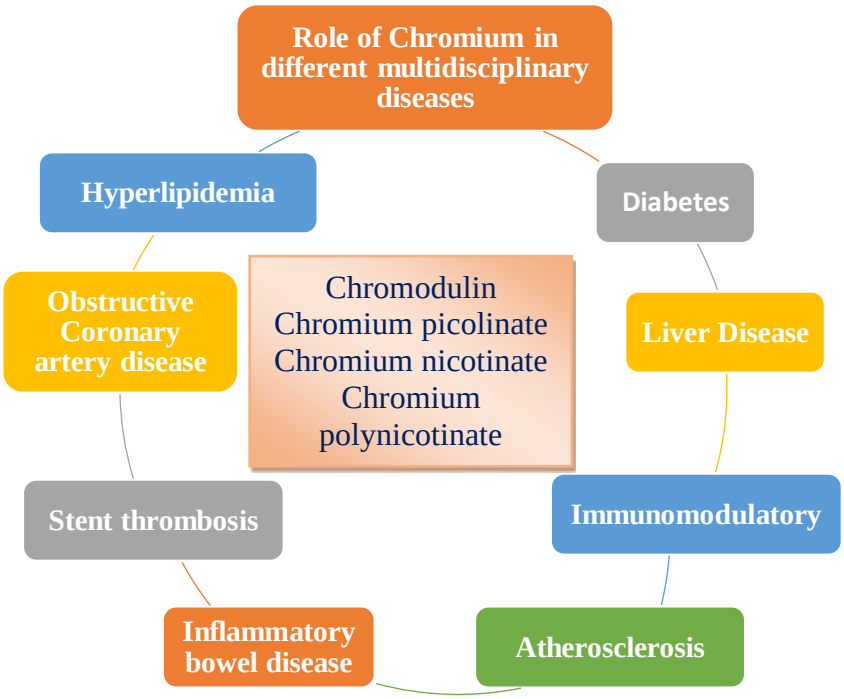
Abstract

Chromium is a glistening heavy metal that found in rocks, volcanic dust and gases, soil, animal and plants. Generally metallic chromium is mined to use in metal and steel industry. In veggies, barley, fruit, fish and meat little chromium is found. The hexavalent form of chromium is toxic, causing mutation and cancer. Other chromium salts like trivalent, chloride, acetate, chromium nicotinate, chromium picolinate, chromium polynicotinate, chromium proteinate, trichloride and

tripicolinate is being used in various human disease. Chromium is a vital mineral that seems to have a positive impact in the control of insulin, metabolism and cardiovascular disease also protect against injury to the liver. In a recent study the content of pro inflammatory cytokines (IL-12, TNF-α and IL-1β) has decreased by chromium and control values in the animal model for hepatic steatosis which recovered the anti-inflammatory cytokine (IL-10) values. Chromium has proven anti-inflammatory capabilities in our prior investigation in diabetic patients. Chromium has proven to improve the susceptibility of insulin in type II diabetes. Chromium supplementation also reduced liver damage in rats of chronic cholestasis. In future chromium would be the metal of choice in combating various human diseases after the study of therapeutic dosages and clinical trials.

Keywords: Chromium picolinate, Chromium nicotinate, Diabetes, Micronutrients, Hyperinsulinemia, Chromodulin, NAFLD, TBARS

Graphical Abstract



1. Introduction

Chromium is a heavy metal naturally occurring in the environment. The trivalent (Cr III) and hexavalent (CrVI) forms of chrome are available regularly in the environment [1]. This

glistening heavy metal is found in rocks, volcanic dust, and gases, soil, animal, and plants. Generally, metallic chromium is mined to use in the metal and steel industry. Several chromium-containing salts are used in the manufacturing of paints, leather tanning, and preserving wood. Somehow less toxic chromium is used in our daily need processes like xerox toner and flooring materials like tiles. The hexavalent form of chromium is toxic, causing mutation and cancer [2]. Other chromium salts like trivalent, chloride, acetate, chromium nicotinate, chromium picolinate, chromium polynicotinate, chromium proteinate, trichloride and tripicolinate are being used in various human diseases [1]. In veggies, barley, fruit, fish and meat little chromium is found [3].

Chromium (Cr) is a metal that is tough in touch, steel-grey in colour. It is recorded as one of 129 primary toxic waste announced by the USEPA (the United States Environmental Protection Agency). It is further indexed in 25 perilous materials that are supposed to have the most potential risk to human well-being at preference mentioned superfund sites. Metal Chromium is routinely found in groundwater and soil as a pollutant, specifically in integrated industrial areas. It is considered as second most copious inorganic groundwater pollutant at perilous garbage ground [4].

Chromium salts like chromium (III) and chromium (VI) penetrate the air, water, and soil., Chromium compounds are available in the form of fine dust particles within the air which ultimately settle over land and water. Chromium can adhere to silt and soil. A little amount is supposed to mix in water that will further leach to groundwater through the earth. Fish do not accumulate much chromium in their bodies [5]. Chromium is a metal of importance and it is widely used in combating various human diseases. In this review, we have focused to find out the various uses of chromium and its derivative in various human diseases. Different diseases are being discussed here, that have been treated and significant changes were found with the use of chromium and its derivatives. Chromium and its derivatives play a major role in lipid metabolism, glucose metabolism, carbohydrate metabolism, protein metabolism, and nucleic metabolism.

1.1. Metabolic pathway of Chromium

1.1.1. Carbohydrate metabolism and Lipid metabolism

The aftermath of chromium picolinate was studied by Sahin et al., (2007) on sugar and lipid pharmacokinetics with a rat model of type II diabetes. The findings of the study investigated that

chromium picolinate (CrPic**)** helps to improve insulin sensitivity by increasing intracellular insulin receptors. The results were reported that CrPic shows a significant beneficial effect against micro vascular complications. Treatment of rat model with CrPic for 02 weeks (80µg/kg of body weight), that was helpful in reduction of glucose level by63% ($P < 0.001$), total cholesterol by 9.7% ($P < 0.001$), and triglyceride by 6.6% compared to another group. Further continuing the dosing of CrPic up to 10 weeks, gives a significant change in metabolic risk factors that consisting favourable changes in the histopathology of various organs like the liver, kidney, and pancreas. The histopathology helps to prove the CrPic effect on the management of such metabolisms [6].

Chromium was found to enhance adipose fat synthesis and reduce net release. It is hypothesized that chromodulin is linked to the insulin-receptor and that the adipocyte increases glucose flow [7]. Cholesterol and triglyceride metabolism is also affected by chromium; however, the process was nevertheless not fully developed. The effect of the antidiabetic medicine metformin is anticipated to occur with procedures similar to chromium [8].

1.1.2. Glucose metabolism

Chromodulin is a molecule that binds with the low molecular weight of chromium and is thought to involve in glucose metabolism. Chromodulin is a naturally occurring oligopeptide consisting of cysteine, glycine, glutamate, and aspartate. In response to chromic ion influx mediated by insulins, chromodulin binds chromic ions and then the metal-saturated oligopeptide is linked to an insulin-stimulated receptor which activates the tyrosine kinase activity of the receptor [8].

Another study depicted that Chromium possibly affects glucose metabolism by increasing or, potentiating the action of insulin [9]. Metabolized form of chromium is termed GTF (Glucose Tolerance Factor) that has been isolated from brewer's yeast and kidney powder. GTF is an organic complex (low molecular weight) composed of trivalent chromium, nicotinic acid, and amino acids such as glycine, glutamic acid and cysteine [10]. GTF (Glucose tolerance factor) works as a carrier of chromium to the chromium-deficient proteins of the cell in the body. Chromium that is responsible for reducing blood glucose levels in type-II diabetes [11].

1.1.3. Nucleic acid metabolism

In trivalent form, chromium is meant to be a part of the integrity of the structure and genetic information expression. RNA is protected from heat denaturation by chromium. Chromium is a part of gene expression with the binding of chromatin, causing the initiation of loci to rise and therefore RNA synthesis to rise. An interaction between Chromium and DNA templates was observed which resulted in significant in-vitro stimulation of RNA synthesis. In-vitro investigations, a greater stimulation in the incorporation of amino acid into the liver is known to influence the metabolism of chromium [8].

1.1.4. Protein metabolism

It is reported that the intake of amino acid and glucose was increased with chromium-incubated rat skeletal muscles. The increase in consumption of these nutrients is connected with changes in chromium-dependent insulin characteristics. Chromium supplements have been reported to increase the tissue consumption of amino acids and also to intensify the integration of amino acids in the coronary proteins in rats [8].

2. Recent Progression of Chromium in combating of various human ailments

Today's life is so fast and hectic that proper nutrition is not available to meet the body's requirements. Due to deficiencies of essential minerals and micronutrients, there are chances of disorder and disease attack on the human body. Here we have a heavy metal for discussion that is being used and show the significant effect in the treatment of various human ailments.

2.1. Role of Chromium in Diabetes

Chromium, a fundamental mineral has been found to play a constructive performance in the supervision of insulin activity and its ramification on the metabolism of carbohydrates, protein, and lipid. Many research investigations depicted that patient suffering from type II diabetes were tends to face reduced blood concentration of chromium rather than those have no disease. Insulin defiance found commonly in the patient with a bunch of heart disorder liability aspects. It was found in the American population that 20% of people were suffering from metabolic syndrome and it influences 2 out of 5 persons of (60-70year age group) population. Several studies have now proved the effectiveness of chromium nutrition value that helps to increase the metabolism of insulin and also decrease the common hazard of heart disorders, specifically in obese patients. Chromium derivative named Chromium

picolinate is responsible for the reduction in insulin defiance. It is helpful by lowering the hazard of heart disorders and non-insulin-dependent diabetes [12].

Some studies claimed chromium as an imperative nutrition value that engaged in glucose, insulin, and cholesterol metabolism. Dietary intake of Chromium and its salts up to an optimum level would associate with the reduction in possible factors leading to heart disease and diabetes. From the last two decades, chromium has become a topic of study with the impact that has been shown to improve blood sugar levels. Chromium is also linked with the factors that are responsible for glucose prejudice in the patients suffering from due type-I, type -II diabetes along with gestational and steroid-induced diabetes [13].

Clinical Studies reported by Broadhurst et al, in which he discussed 15 clinical studies, among which 13studies (11 randomized and disciplines studies), that consist a sum up of 1,690 patients. A study on1, 505 subjects in the Chromium picolinate (CrPic) group proclaimed compelling development in partially one event of glycaemia domination. All mentioned 15 clinical studies represent healthful development as somewhat one criterion of diabetes control that includes dyslipidaemia. Decisive results were reported by CrPic to enrich diet, these were found as diminished blood glucose level, insulin, and lipid profile levels and also reduction in the demand for hypoglycaemic medication. CrPic was found to shown higher bioavailability correlated with others composed of Cr like niacin-bound Cr or $CrCl_3$, which expound its superiority of virtue in glycaemia with lipidemic management. Finally, the data from various studies focused on Chromium picolinate supplementation (specific for type-II diabetes patients) was merged and results proclaimed a significant decrease in hyperglycaemia and hyperinsulinemia, which correlates with a decrease in risk factors for complication in disease [14].

In another clinical study, the effects of chromium picolinate (CrPic) supplementation were evaluated on the glycaemic status and lipid profile in the subjects with T2DM (Type II diabetes mellitus). The study was performed on 52 patients with T2DM, was randomly allocated into 2 groups. One group was treated with 400 µg CrPic per day and a placebowas given to the other group. The intervention duration was set at 8 weeks. Anthropometric indicators and metabolic elements were measured at the starting, and end of the study. A

significant decrease was reported in blood lipid profile and insulin resistance. There were no significant changes reported in the concentration of FBG (Fasting blood glucose), triglyceride, and HDL-C (High-density lipoprotein cholesterol), as well as weight and BMI (Body mass index) [15].It was observed that CrPic supplementation in a patient suffering from type II diabetes who are treated with sulfonylurea, responds with improves insulin sensitivity and have better glucose control. Additionally, CrPic supplementation significantly vitiates body weight gain and visceral fat deposition in comparison with the placebo control group. Martin et al., (2006) achieve that 1mg dietary intake of Chromium picolinate for 6 months, momentous enhanced insulin subtlety and glycaemic management. In which the dose and the time of the study were higher than the current study [16]. Althuis et al., (2002) also reported a positive correlation between dietary intake of chromium and reduction of blood glucose level along with fasting insulin level [17].

2.2. Role of chromium in Hypertension

The response of various chromium salts on cardiovascular disorder was studied in the spontaneous hypertensive rats (SHR) model. The various salts of chromium that were kept under an investigation like chromium chloride, acetate, nicotinic acid-glycine-cystine-glutamic acid (NA-AA), picolinate and nicotinate. The rats were offered 5% and 10% w/v sucrose as for drinking water. It was noted that all chromium salts except NA-AA, restrain the glucose-generatedrise of systolic blood pressure. It was noted that acetate, picolinate and nicotinate salts of chromium, reduce the level of HbAlC (Hemoglobin A1C) compared to standard. Only acetate and nicotinate salts of chromium were reported to decrease in the level of TBARS (Thiobarbituric acid reactive substances) associated with liver and kidney. Chromium picolinate significantly reduced hepatic TBARS, while chromium chloride and NA-AA have no significant effect. Finally, it was summarised that chromium, somewhat a unique ligand, performs an important character in mitigating sucrose-prompt blood pressure ascent and also works as an antioxidant [18].

2.3. Immunomodulatory role of chromium

Chromium is a vital supplement required to promote the action of insulin in body tissues so that the body can metabolize the major nutrient molecules in living cells. Chromium is of importance in altering the immune response by immune

stimulatory or immunosuppressive processes as shown by its effects on T and B lymphocytes, macrophages, cytokine production, and immune responses that may induce hypersensitivity reactions [8]. The immune response is the process of recognition of potentially harmful agents by specialized cells of the immune system. It is expressed as cellular and humoral immunity. Several nutrients can modulate the immune response through the production of antibodies or cytokines (e.g., zinc, selenium, chromium). Moreover, the elements are required for immune cells proliferation or activation (e.g., iron). The elements are also required for the functioning of enzymes involved in the antioxidant system (e.g., selenium) of the immune cells. It has been shown, that nutrient supplementation may enhance but may also suppress immune function [19].

Chromium (VI) attracts the concentration of researchers due to its ample industrial utilization and proclaimed noxious effect. A Long-term Animal study was performed by Karaulov et al., (2019) on Wistar rats to find the effect of oral exposure of chromium for 135 days in the form of $K_2Cr_2O_7$. The exposed group (20 mg/kg/day) shows a decline in thymus mass and thymocytes count, which is found responsible to cause structural and functional changes in the lymph nodes and spleen. These changes are termed lymphoreticular hyperplasia and plasmacytic macrophage transformation. Scheduled cell denaturation was expanded in thymocytes and splenocytes and the comparative decline was seen in lymphocytes with the T-zones of the spleen and lymph nodes**.** A decrease in the count of myeloid cells and neutrophils was experienced with Cr (VI) administration, while increment was seen in the number of lymphoid and erythroid cells found in the bone marrow. Exposure to Cr (VI) results in decreased copper, nickel, and iron concentration associated with blood and liver. While increased Cr levels in blood, spleen, and liver were experienced with exposure to Cr (VI). The recognized variations in the array of immunological criteria considered to approach for the expansion of new way for the avoidance of low-level Cr exposure hazards [20].

The trivalent ion of chromium has been postulated as an essential element for mammals, with a role in carbohydrate and lipid metabolism. Dietary research with rodents, investigations on the effects of chromium on people on total parenteral nutrition, and investigations on the absorption and transport of chromium all supported a crucial function. During

the next few decades, nutritional supplements containing chromium have become so popular for weight loss and muscle growth that they are now second only to calcium in terms of sales among mineral supplements. However, the inability to identify the chromium-binding biomolecule (s) is a major setback its method of action, Specifically, a hypothesized species is known as glucose tolerance factor, as a result, the position of chromium has been questioned in recent years, and the subject of whether it is needed must be explicitly revisited. Concerns over chromium (III) safety arose at the same time as its use as a dietary supplement grew. While it has been proven that chromium has no favourable impact on body bulk or composition, it should be removed from the list of essential trace elements, compounds containing chromium (III) are generally nontoxic and in rodent models of insulin insensitivity, have beneficial pharmacological effects [21].

3. Effect of Chromium

3.1 Effect on Stress

The impact of chromium in alleviating stress has been thoroughly documented. Stress causes the hypothalamus to create a corticotrophin-releasing factor, which drives the pituitary to make adrenocorticotropic hormones, which then encourages the adrenal cortex to enhance corticosterone production and release. Corticoids lower serum protein concentrations and suppress immune system function. Insulin antagonists increase blood glucose levels and decrease glucose consumption by peripheral tissues, therefore acting as insulin antagonists. Chromium has been shown to affect corticosteroid secretion. Several studies have found that animals given chromium supplements have lower stress sensitivity as a result of lower cortisol levels in the blood. All-stress-producing stimuli have also been found to increase chromium excretion in the urine [8, 22].

3.2. Effect on Depression

A double-blinded, placebo-controlled study was performed by John P Docherty et al., (2005) to find out the exploratory effect of Chromium picolinate in atypical depression focussed on a population of adults suffering from atypical depression. Most of them were obese and overweight. Significant improvement was seen in the following Hamiton depression scale (HAM-D-29) items that include an increase in appetite with increased eating, carbohydrate craving, and stable changes of

perception. Overall HAM-D-29 score was found to be enhanced in a subpopulation of subjects with lofty carbohydrate craving, while patients treated with CrPic compared with placebo. It was found that a 600-µg dose of chromium produces a valuable response in patients with atypical depression. The effect of Chromium is not justified with the available studies so there is the need for further studies that would be helpful to evaluate the effect of chromium supplementation in depressed patients specifically selected for symptoms of increased appetite and carbohydrate craving. Those studies would be able to determine whether a higher dose of chromium affects mood change [23].

3.2.1. Role of Chromium Supplements in various disorders

Zn-pro supplementation improved feed consumption during the stress period. The final pH value of the muscle in stressed birds fed with the Cr-met diet was measured at the end of the experiment, the pH values of individuals treated with NC were higher, but the treatments did not affect pH. Malondialdehyde levels in the thigh muscle were reduced in diets with Nano-Cr and Zn-pro [24].

Supplementing with chromium can improve body composition and athletic performance in healthy, overweight people, or obese individuals have been predicated on the hypothesis that chromium increases insulin sensitivity, as well as a few trials that were not adequately controlled in terms of chromium consumption and physical activity [25]. Another study was performed by Navidad et al., to see the performance of broiler chicken after incorporation of chromium polynicotinate in diet, the blood lipid parameters like a fat deposition and plasma lipids profile were examined. It was found that dietary chromium content did not affect plasma triglycerides. The findings of this study indicated that using chromium polynicotinate supplements boosted growth and impacted blood cholesterol levels [26].

Cr as Chromium histidine (CrHis) had a better efficacy compared with Cr as CrPic, which is possible due to its better bioavailability. Finally, during hot seasons, CrHis can be added to broiler diets to combat oxidative stress-related declines in performance and well-being [27].

The effects of chromium-loaded chitosan nanoparticles (Cr-CNP) were studied by wang et.al., (2012) on finishing pigs for the growth, blood profile, immunological characteristics, and tissue chromium content. Cr-CNP supplementation raised the amount of chromium in the blood, muscle of longissimus,

heart, and liver upper body parts followed by kidney and pancreas in the lower region linearly [28].

The concentration of Cr in selected organs such as the liver heart, pancreas, and kidney along with blood and muscle was dramatically raised by the dietary supplementary complex Cr-CNP in the current investigation, which was similar to our prior findings with chromium nanocomposite in pigs. These findings indicate that dietary Cr supplementation could improve intestinal Cr absorption and tissue Cr accumulation. However, more research on the absorption of Cr from other sources, as well as the mechanisms of absorption, distribution, and control, is required [28].

3.2.2. Use of Chromium in different multidisciplinary diseases

Multichannel	Studies	References
Liver Disease	NAFLD stands for non-alcoholic fatty liver disease and is characterized by insulin defiance, oxidation, and swelling. Results advocate the role of chromium in the regulation of glucose and lipid metabolism, and it may responsible for the improvement in insulin sensitivity. Supplementing with chromium prevented the evolution of NAFLD, and the benefits were guided by a decrease in fatty liver development, an increase in the concentration of hepatic lipid catabolic enzyme, improved sugar and lipid metabolism, reduction in swelling, and settlement of oxidative stress, all of which were likely due to improved insulin signaling.	[29]

Hyperlipidemia	Serum total cholesterol levels in hyper lipemic animals and humans are known to rise. Following Cr supplementation, some researchers found a significant favorable effect on serum lipid levels. Moreover, Cr is well-suited for lipid-modulating therapy due to several variables.	[30]
Obstructive coronary artery disease	Coronary stents represent a compelling advancement in the treatment of obstructive coronary artery disease. Percutaneous coronary intervention (PCI) has been available since its inception. To increase stent safety and efficacy, novel medicines, polymers, and platforms for drug elution have been created since then. The creation of a new platinum chromium alloy with high radial strength and radiopacity has allowed the development of a new thin-strut, flexible, and highly trackable stent platform, while also increasing stent visibility.	[31]
Stent thrombosis	PtCr-EES (polymer platinum chromium everolimus-eluting stent) was found to be as safe and effective as CoCr-EES, with minimal rates of stent thrombosis and other side events. Patients with small arteries and lengthy lesions treated with PtCr-EES had acceptable 5-year event rates.	[32]
Inflammatory bowel disease	The goal of this study was to see how chromium-D-	[33]

	phenylalanine complex affected indomethacin-induced inflammatory bowel disease in rats. Cr complex caused a significant reversal of indomethacin-induced alterations at all dosages studied. Cr (D-phe)3 has been shown to protect against indomethacin in this investigation. Antioxidant and anti-inflammatory activities may be responsible for the observed protective effect of the Cr complex.	
Atherosclerosis	Atherosclerosis is an artery disease in which fatty plaques form on the inner arterial wall, obstructing blood flow over time. Genetics, nutrition, lifestyle, smoking, circulating lipid and cholesterol levels, and molecular and circulating signs of chronic arterial inflammation have all been identified as risk factors for atherosclerosis. GSPE (Grape Seed Proanthocyanidin Extract) had a significant influence on cholesterol and triglyceride levels, as well as oxidative lipid damage as evidenced by the generation of thiobarbituric acid reactive compounds, both alone and in conjunction with NBC (TBARS).	[34]

3.2.3. Other relevant studies on chromium salts

A study was performed by Wang J. et, al. to see if the amount of chromium polynicotinate (Cr-Nic) in the diet influences the growth and feed utilization of juvenile golden pompano. As a result of the findings of this study, the minimum Cr-Nic requirement for golden pompano has been established as 16

mg/kg and it is recommended to use of Cr-Nic in the diet of golden pompano fish [35].

The outcomes of chromium picolinate dietary intake were studied by Yazaki et al., (2010) in singleas well as a combination with dietary additives, on weight loss in apparently healthy overweight people. In this group of overweight adults, supplementing with 1 mg of chromium picolinate alone or in combination with nutritional education did not affect weight loss. The response to chromium was unaffected by central adiposity [36].

Yenice et al., (2015) studied the response of organic and inorganic Cr, Cu Mn, and Zn mixes diet at two different levels of concentration on the extent of these trace elements and Ca that reaches the systemic circulation in late-phase laying hens. The results of the study depicted that the addition of an organic mixture of Mn, Cu, Zn, and Cr helps to improve the bioavailability of Mn, Zn, Mn, Cu, and Ca compared with their inorganic sources. These findings show that dietary supplementation with an organic nutrients mixture increases micronutrients bioavailability when compared to inorganic sources. The lower concentration of vestige minerals in diet results in reduced mineral excretion, particularly in an organic system [37].

Chromium picolinate is a Cr dietary supplement that has one Cr(III) atom chelated with three molecules of picolinic acid. This form of the element has been demonstrated to have increased absorption and intracellular uptake. Supplementing with Cr(III) appears to be advantageous in the prevention of diabetes, cardiovascular disease, metabolic syndrome, and excessive cholesterol, according to some research, it has also been used as a weight reduction aid. Similarly, adding Cr(III) to nutritional solutions provided to individuals with digestive system impairments has been linked to improved glucose tolerance and other metabolic problems[38].

Conclusion

Chromium is a heavy metal responsible for therapeutic effects in different human diseases. CrPic, a chromium derivative plays a significant role in carbohydrate and lipid metabolism. CrPic is a Cr dietary supplement that has one Cr(III) atom chelate with three molecules of picolinic acid. This form has been demonstrated to have increased absorption and intracellular uptake. Chromodulin, a molecule that binds with the low molecular weight of Chromium and is involved in glucose metabolism. Cr (III) plays an important role in Nucleic acid

metabolism because being a part of the integrity of the structure in Nucleic acid. Chromium picolinate was found responsible to curtail insulin defiance and helps by lowering the hazard of cardiovascular disease and type-II diabetes. Various other Chromium derivatives were being used in the treatment of various human ailments like stress, depression, cholesterol, immunity-related issues, and inflammatory bowel diseases. Chromium would be the metal of choice in insulin activity, hyperlipidaemia, obesity, and various other human disorders with more clinical studies and Pharmacological activity performance. It is a metal of importance that has multidisciplinary action in combating human disorders.

Conflict of Interest

Authors declare they do not have any conflict of interest.

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