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Dermatologic Toxicities and Biological Activities of Chromium

Jumina Jumina and Harizal Harizal

Abstract

Chromium is a versatile metal with various industrial applications and biological activities. However, as a transition metal, this element forms several species, i.e. oxidation states of -4 to $+6$, with different degrees of toxicities that affect ecosystems and organisms including human beings. The skin is the outermost organ that usually interacts directly with chromium species in nature. These contact and interaction induce the formation of several acute and chronic negative effects including contact dermatitis, skin cancer, allergy, etc. In this chapter, toxicity and biological activity of several chromium species, such as chromium zero-valent, trivalent, hexavalent, will be reviewed to obtain better comprehension in chromium toxicity. Sources and routes of exposure, toxicity and possible treatment, and biological activity on the skin are arranged and explained systematically.

Keywords: chromium, skin, toxicities, biological activities, treatments

1. Introduction

Chromium is a unique transition metal with relatively high abundance on earth crust ($1.4 \times 10^{-2}\%$). Chromium can form several species with different oxidation states from -4 to $+6$. Chromium with 0, $+3$, and $+6$ oxidation states are most commonly found and utilized in ambient conditions [1]. In industrial sectors, chromium-based materials have been used as coating material for corrosion resistant, pigments and dyes, wood preservatives, tanning agent, catalyst, and medical apparatus [1]. Chromium, especially for chromium(III), also showed certain biological activity especially in regulating carbohydrates and lipid metabolism [2, 3]. As an essential micronutrient, a low dietary of chromium will exhibit several adverse effects such as glucose intolerance, growth disorders, diminished longevity, etc. [3, 4].

Chromium toxicity has been a controversial problem due to its status as an essential micronutrient [5]. Various studies have shown that numerous acute and chronic adverse effects can be caused by any dermal or systemic exposure of chromium species in human organ systems [6]. The toxicity and biological activity of chromium seem to be correlated directly with the concentration of corresponding chromium species [7]. In this case, chromium species have its optimum concentration to produce beneficial effects. Meanwhile, accumulation of less toxic chromium species in relatively high concentration will still produce a negative effect in the accumulation site [8, 9]. Chromium picolinate, for instance, has been mainly used as food supplement. Chromium(III) in this compound tend to accumulate in male

Sprague-Dawley rats' cells over the period of investigation [10] and may be oxidized to more carcinogenic chromium(V) and chromium(VI) within the cells [11].

As the outermost organ that protects the human body from various pollutants, the skin is usually exposed to various sources of chromium, and it causes many dermatological acute and chronic negative effects such as contact dermatitis [12], systemic contact dermatitis [13], and possibly skin cancer [14]. In the same way, any topical or systemic administration of chromium compounds also can exhibit a beneficial effect for the skin such as antiacne [15], rapid wound healing [16], and anti-aging [17]. In this chapter, both toxicity and biological activity of chromium species in the skin are described starting from the source and route of exposure, toxicity and its possible treatment, and biological activity.

2. Source and exposure route of chromium in the skin

In modern life, chromium has been used in many forms and applications with Cr(0), Cr(III), and Cr(VI) as the main oxidation states. Various sources of chromium that affect or may affect the skin have been identified and tabulated in several review [12, 18, 19]. In general, exposure route of chromium that comes from these sources can be classified into two pathways including dermal and systemic pathways. In these cases, direct dermal exposure would cause contact dermatitis, irritation, and skin cancer, while systemic administration would elicit systemic contact dermatitis and skin tumor.

Dermal exposure (**Figure 1**) is initiated from direct contact of chromium sources on the skin. Chromium species are then accumulated on the skin surface or penetrated into the skin layers mediated by sweat or other biological fluids. The penetration of chromium species either as particulate or soluble forms occurred via three possible routes including transcellular by crossing the cell, intercellular by partitioning into the lipid matrix, and transappendageal by entering hair follicle and sebaceous glands [20, 21]. There are many factors involved in the penetration process including concentration of chromium species, medium (solvent and pH), intrinsic properties of chromium species (molecular volume of chromium species, counter ion, nature of chemical bond and polarity, solubility, and valence), reactivity towards protein, previous penetration or accumulation, skin characteristics (gender and race, age skin, density of sebaceous gland, thickness of skin, and anatomy of skin), and environmental factors (temperature, humidity, and UV radiation) [21, 22]. In a normal skin condition, Cr(VI) ions tend to have higher solubility [23] and percutaneous permeability than Cr(III) ions [24, 25]. However, Cr(III) have higher protein affinity to form metal-protein complex which tends to make it retain in the skin epidermis [26]. After penetrating the skin, Cr(VI) species are reduced by proteins or endogenous antioxidants to form Cr(III) [27] which then react further with any DNA or protein to form Cr(III)-protein complex as the actual allergen (haptens) [28].

In systematic exposure, chromium mostly enter the human body via oral consumption of certain chromium sources such as food or food supplement [29], foodstuff [30], and drinking water [31] or from applications of chromium-based implants [32]. In the digestive system, most of Cr(III) consumed are excreted to feces and some of it (~2%) is absorbed by epithelial cells covering the stomach and enterocytes covering the intestines through passive absorption (diffusion) [33]. This absorption was affected (increased or decreased) by the presence of various ligand such as amino acids, vitamins, carbohydrates, plasma proteins, certain metals, and other chelating agents [34]. After the absorption, Cr(III) complex would be accumulated inside the cells or actively transported to the blood stream by still an

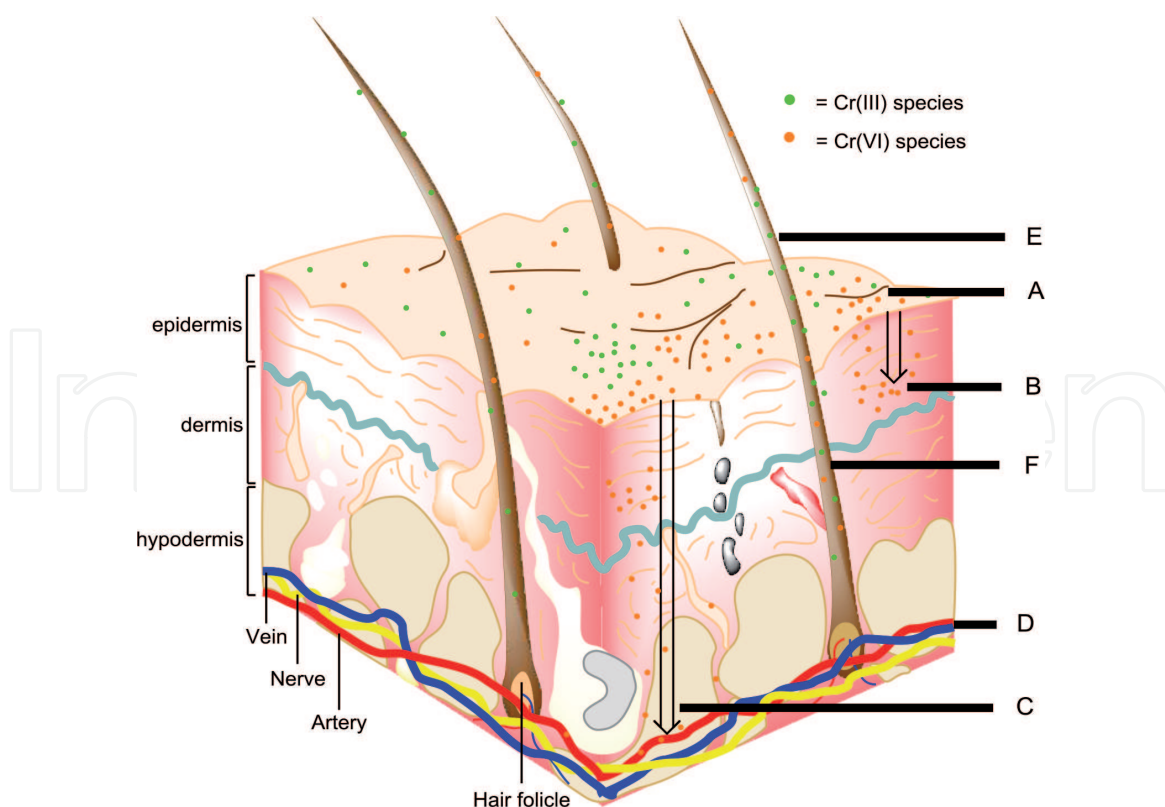


Figure 1. Several pathways of dermal exposure: (A) deposition of Cr(VI) in the skin surface causes irritation or chemical burn; (B) penetration of Cr(VI) through transcellular and intercellular pathways induces cell apoptosis and contact dermatitis, while Cr(III) tend to suspended in the skin surface due to strong affinity to skin protein; (C) deeper penetration to blood stream causes organ disruptions, (D) Cr species from systemic administration trigger systemic contact dermatitis, (E) deposition of Cr species on hair causes hair discoloration; (F) penetration of Cr species into hair follicle induces rapid hair fall. Figure is drawn using ChemBioDraw Ultra version 14.0 software.

unknown transporter. Cr(III) ions then bound to transferrin (siderophilin) or other plasma proteins in the blood stream and travel to the whole body [33, 34].

3. Toxicities of chromium

3.1 Contact dermatitis

Contact dermatitis is a common skin disease caused by repeated dermal contact with certain allergens (haptens) leading to delayed-type hypersensitivity effect [35]. Many haptens have been identified to cause contact dermatitis such as metals, fragrances, and flavors, preservatives, plastics, rubber, pharmaceutical, cosmetics, woods and plants, textile, etc. [35]. Chromium-induced contact dermatitis is characterized by the presence of certain clinical manifestations in feet and hands. Acute dermatitis is usually indicated by the formation of erythema, oedema, papules, vesicles, and weeping, while chronic dermatitis tends to form scaly, dry, and fissured skin [36]. Various chromium-induced contact dermatitis cases have been reported involving different chromium sources such as cement [37, 38], leather [38–43], tattoo ink [44], cellular phone [45, 46], etc. Concentration threshold for soluble chromium in each chromium-containing product should not exceed 1 ppm to minimize elicitation of contact dermatitis [47].

In general, chromium-induced contact dermatitis is formed through several steps which can be described as the following (**Figure 2**) [48, 49]: initially, after penetrating the skin, Cr(VI) ions are reduced by endogenous antioxidant to form Cr(III)

and oxygen reactive species (ROS). Cr(III) as the real allergen is bound to certain proteins to form the hapten, while ROS induces the releasing of interleukin-1 β (IL-1 β) which then activates antigen-presenting cells (Langerhans cells (LC)). Activated antigen-presenting cells bind with the hapten, mature, travel to the regional lymph nodes, and stay in paracortical T-cell areas. After that, activated antigen presenting cells-hapten complex activates naïve T cells by helping in vigorous blast formation and proliferation to become chromium-specific T cells. Activated chromium-specific T cells then travel through blood stream and recirculate to give hypersensitivity effect detecting a lower concentration of hapten in different parts of the skin.

Treatment of chromium-induced contact dermatitis could be conducted in several approaches including avoiding direct contact to chromium source and topical application of chelating agent and barrier creams to prevent any cutaneous permeation, corticosteroid to relieve inflammation, and antioxidant to reduce oxidative stress [36, 50]. Various antioxidants have been tested in treating chromium-induced contact dermatitis such as *N*-acetylcysteine [51], ascorbic acid [52], pine bark extract (pycnogenol[®]) [53], and pterostilbene [54]. Two chelating agents, ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA), also have been examined for preventing contact dermatitis, but both of these ligands showed a low effectiveness as a protecting agent [55, 56]. The developments in

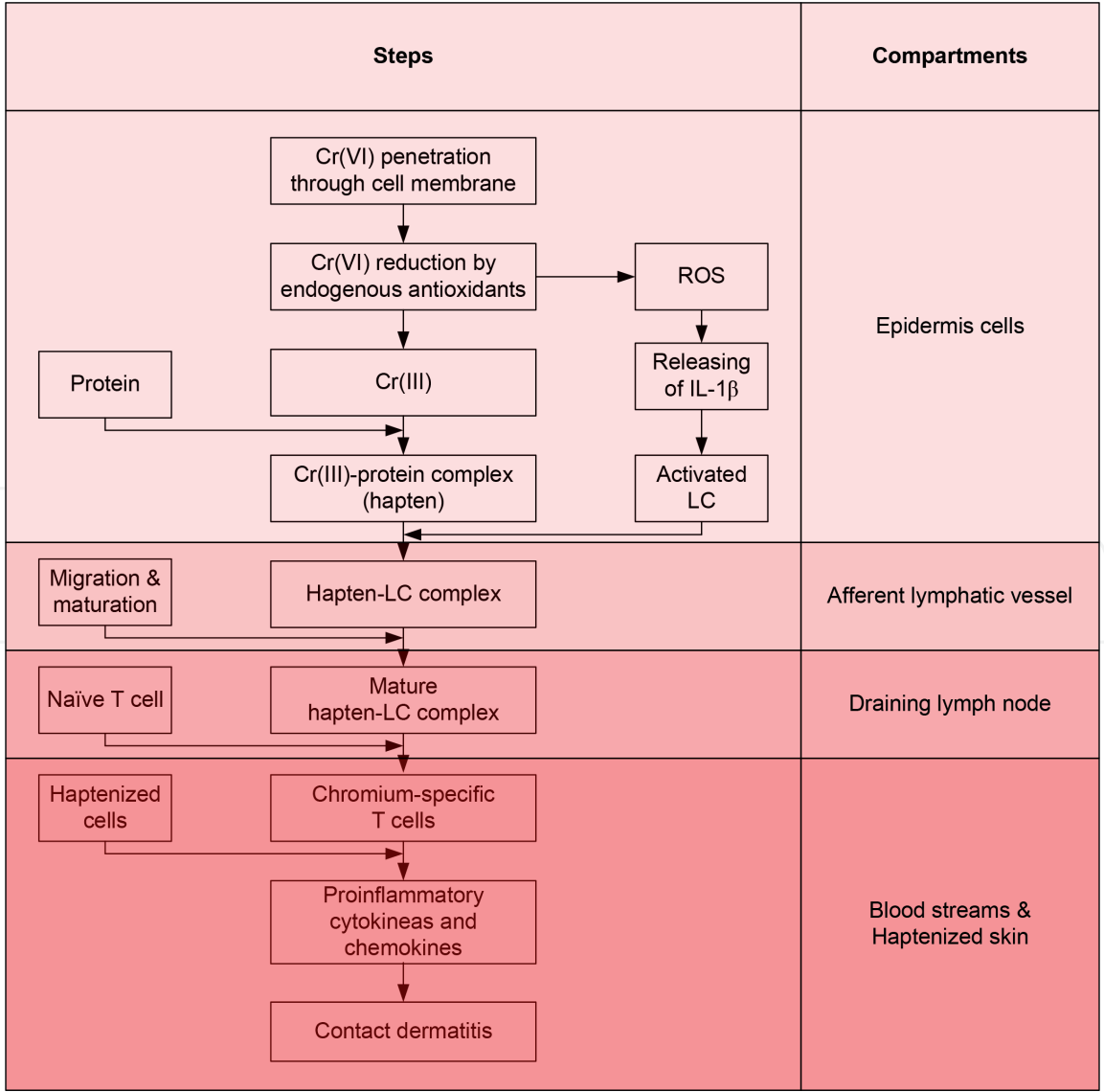


Figure 2. Simplified elicitation mechanism of chromium-induced contact dermatitis adapted from several references [48, 49].

chromium-induced contact dermatitis are still widely opened. These developments could be focused on finding natural antioxidant and chelating agents that effectively relieve oxidative stress and reduce the reactivity of chromium ions, respectively.

3.2 Systemic contact dermatitis

Systemic contact dermatitis is a kind of dermatitis elicited by systemic administration of certain allergen that previously sensitizes the skin through direct dermal contact [57]. Several groups of allergens have been identified to cause this inflammatory disease such as metals, medications, food, plants and herbals, and certain chemicals [57, 58]. Systemic administration of these allergens is also described in various routes including oral, subconjunctival, intramuscular, pulmonary inhalation, intranasal, intrauterine, endocardial, arthroplastic, intravenous, intraarticular, subcutaneous, intradermal, dental, intratubal, and endovascular [59]. The pathophysiology of this disease still remains unclear, but several mechanisms have been proposed [60–65]. Moreover, the theory suggesting type 3 immune response (antigen-antibody complexes) involved in systemic contact dermatitis (SCD) has not fully been proven [58].

Chromium as a metal allergen has been found to cause systemic contact dermatitis either through oral, dental, or arthroplastic routes [13, 66, 67]. Consumption of Cr(III)-based supplements in the form of chromium picolinate [68] and chromium chloride [69] has been shown to cause SCD. Oral ingestion of potassium dichromate previously used as a homeopathic drug also induces dermatitis as clinical manifestation of SCD [70, 71]. In certain case, SCD is also induced by various metal alloys applied in orthopaedical, cardiac, neurological, and abdominal associated devices [72]. In these cases, chromium-containing alloys such as stainless steel SAE 316 L, cobalt-chromium-molybdenum steel, and Vitalium™ release metal ion [73] are reported to cause SCD [74–79]. These reported SCD cases are identified with the presence of several manifestations including erythroderma [74], and localized/generalized eczema or urticarial [76–78]. These findings suggested that any chromium sources applied in systemic routes could elicit SCD with certain clinical manifestations and degrees of severity.

Treatment of chromium-induced systemic contact dermatitis may be conducted in several approaches including managing diets and lifestyles by gut remediation and avoiding the food and sources that contain chromium; systemic or topical treatment using immune-suppressants such as corticosteroid; phototherapy; and hyposensitization therapy [80, 81]. Sharma developed a guideline for the preparation of low chromate diet that could help in controlling daily chromium consumption from food and ameliorating skin condition [82]. In case of SCD from arthroplastic routes, revision or removal of implant needs to be conducted by considering the time of hypersensitivity incidence after surgery and degree of severity [74]. Revision of implant could be conducted by using less allergenic implant such as titanium-based implant or chromium-based implant coated with certain biocompatible materials such as polytetrafluoroethylene, ZrN multilayers, diamond-like carbon, titanium nitride, graphite-like carbon, and tantalum [74, 79, 83]. Revision or removal of implants may not produce rapid disappearance [76] probably due to the presence of soluble or particulate debris of implant that produce inflammations [84, 85].

3.3 Skin cancer

Chromium, especially Cr(VI), is a potent human carcinogen. In a human cell, carcinogenesis of chromium(VI) (**Figure 3**) occurs through the penetration of chromium(VI) species into the cell via sulphate/phosphate anion transport system,

reduction of chromium(VI) by endogenous antioxidant to produce ROS and chromium(III), and alteration of DNA directly by chromium(VI) or indirectly by ROS [86]. The alteration of DNA then produces different types of products including Cr-DNA adducts, DNA-protein and DNA interstrand cross-links, DNA breaks, and DNA base damage [87]. Carcinogenicity of chromium(VI) has induced lung cancer in workers from various chromium-based industries [88–90] and has been associated to incidence of other cancers [91]. However, the meta-analysis study showed that the correlation between exposure of chromium(VI) and the high mortality in skin cancer is not significant [91]. This study indicated that there is no supporting data confirming the chromium species as carcinogen in inducing skin cancer in human.

Several studies, however, showed that chromium species could induce skin cancer in rats and mice either as single carcinogen or cocarcinogen. Oral administrations of drinking water containing sodium dichromate dehydrate to male F344/N rats for 2 years showed that the sample developed various types of skin cancer [92]. Two other studies using hairless SK1-hrBR mice also exhibited that chromium(VI) could act as cocarcinogen in promoting UV-induced skin tumor [93, 94]. Davidson and co-workers [93] showed that oral administration of chromium(VI)-containing drinking water and UV irradiation to hairless mice have synergistic effect in promoting skin tumor. Exposure of chromium(VI) or UV radiation alone did not induce skin tumors [93]. Uddin and co-worker also conducted the same experiment and found that systemic administration of exogenous antioxidant (vitamin E and selenomethionine) did not improve skin condition [94]. It indicated that chromium(VI) cocarcinogenicity may be occurred in different mechanisms without involving ROS [94]. These three studies indicate that acute or chronic oral administration of chromium(VI) species has a great potency in promoting skin cancer in mammals including humans.

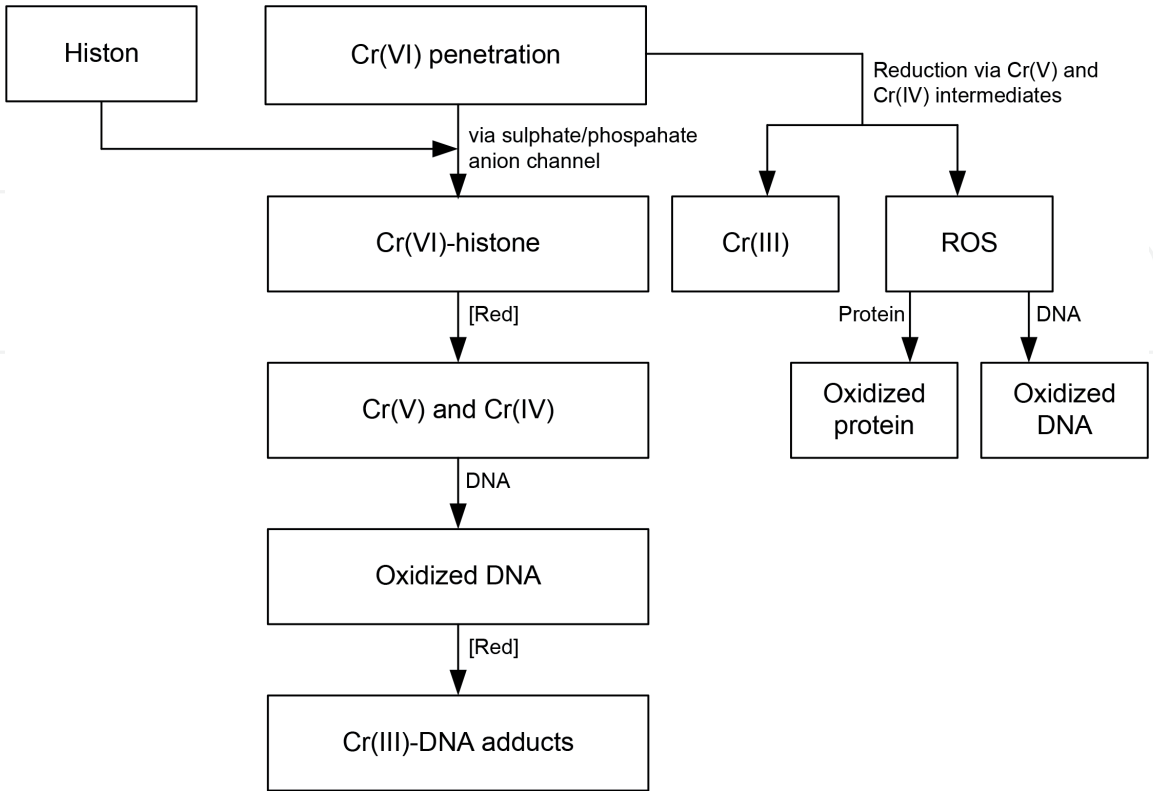


Figure 3.
Simplified mechanism of chromium carcinogenesis adapted from several references [86, 95].

3.4 Irritation and chromium burn

Irritation and chemical burn are caused by dermal exposure of chromium(VI) particle, solution, or mist in large quantities. Solid deposition of chromium(VI) would develop to “chromium ulcers” or “chrome holes” [67], while high concentration of chromium(VI) solution would lead to chromium burn. A mechanism for this ulcer formation is still unclear, but it may be related to the disruption of actin cytoskeleton by chromium(VI) leading to mitochondria-dependent apoptosis in skin fibroblasts cells [96]. Several reports exhibited these irritation and burning effects from different chromium species such as solid CrO_3 [97], chromic acid solution [98–100], hot chromium(III) sulphate solution [101, 102], and chromium acid mist [103].

Management of irritation is conducted by considering preventive and treatment approaches. Prevention of irritation is conducted by using barrier creams, moisturizers, etc., while treatment could be done by using moisturizers and corticosteroids [50]. For chromium burn, treatment is conducted by combining mechanical excision, hemofiltration, and systemic administration of chelating agent and antioxidant [100].

3.5 Hair disorders

Human hair is naturally exposed to a certain amount of chromium [104] that come from various sources [105–107]. Excessive and repeated exposures of chromium in certain environmental condition cause discoloration of blond, dyed-blond, and white hair (to become green) [108–110] and cause rapid hair fall [111, 112]. The mechanisms of these two effects are still unclear. Hair discoloration is probably the result of interaction between chromium ions (and also copper and nickel) and protein in hair (keratin) [113], while rapid hair fall may be related to several mechanisms such as promoting premature end of hair cycle [114] or disruption of hair shaft formation [115].

4. Biological activities of chromium

4.1 Acne vulgaris (antiacne)

Acne vulgaris is a common dermatological condition that affects physical and psychological aspects of patients [116]. Several diseases that show the presence of a certain degree of acne also relate with depression and emotional stress such as type-2 diabetes, rheumatoid arthritis, and polycystic ovarian syndrome (PCOS) [117–119]. Pathophysiology of this disease involves several key mechanisms including excessive sebum production due to hormonal and environmental conditions, alteration of fatty acids composition due to sebum metabolism by *Cutibacterium acnes*, hyperkeratinization within the follicle that clogs up the pore in the form of whitehead or blackhead comedones, inflammation induced by bacterial colonization, and malfunction of locale innate and adaptive immune system [120]. The presence of acne vulgaris is also correlated to the clinical depression in patients [116]. In this case, depression or stress can influence the regulation of sebaceous gland as the main part in sebum production [121]. Catecholamines (epinephrine and norepinephrine) as the main stress hormones also affect the growth of certain *Cutibacterium acnes* strains [122–124]. Catecholamine-treated *C. acnes* strain also can stimulate a limited but significant increase of lipid production in sebaceous

gland. However, the increase of intrinsic cytotoxicity or inflammatory potential of *C. acnes* is statistically significant [124].

Several reports exhibited that certain chromium(III) compounds have high activity in improving acne vulgaris. Initially, chromium has been used in the form of high-chromium yeast or chromium GTF (glucose tolerance factor) by consuming 400 µg chromium daily which exhibited comparable improvement in acne conditions [15]. This form of treatment, recently, is considered as a complementary and alternative medicine (CAM) for the treatment of acne vulgaris [125]. Further improvements used different chromium compounds including chromium picolinate [126, 127] and chromium salt such as chromium (III) chloride [128].

In most cases, the usage of chromium compound as antiacne is usually combined with other active compounds such as vitamins, certain minerals, and herbal medicine sources in the form of oral [129–131] or topical [128] formulation to get more effective treatment results. Application of topical formulation containing chromium (III) chloride and magnesium sulphate showed total improvement in acne vulgaris with temporal mild to moderate irritation as a side effect [128]. Oral capsule containing methionine-bound zinc complex, chromium, and vitamins also exhibited 80–100% improvements for mild to moderate acne vulgaris [131]. In another study, a combination of several nutrients with potential antiacne and anti-depressant properties (eicosapentaenoic acid, epigallocatechin-3-gallate, zinc gluconate from green tea extract, selenium, and chromium) may also improve inflammatory acne lesions and mood aspect of patients [132].

Treatment of acne vulgaris in polycystic ovary syndrome (PCOS) showed mix results. A study by Amr and Abdel-Rahim showed that using 200 µg/day oral consumption for 8 weeks has no significant improvement in acne and hirsutism [126]. In a different study, chromium supplementation by women with polycystic ovary syndrome (PCOS) in a randomized, double-blind, placebo-controlled trial exhibited that the treatment gives beneficial effects on acne and hirsutism using 1000 µg/day oral consumption for 6 months [127]. These two studies indicated that the treatment of acne vulgaris in PCOS patients needs greater dose and longer duration.

Action mode of chromium in ameliorating acne vulgaris has not been fully elucidated yet, but there are two mechanisms proposed including (1) by decreasing serum testosterone concentration and (2) lowering the depression of patients. In the first mechanism, chromium can decrease serum testosterone level possibly due to the reduction of testicular steroidogenic enzymes activities [133]. In this case, a lower level of serum testosterone reduces sebum production in sebaceous glands [134]. The second mechanism explains that chromium as an anti-depressant [135–137] may reduce sebum production [138] and affect *C. acnes* growth in sebaceous glands [122–124]. It is clearly showed that these two mechanisms may have direct or indirect synergistic effects [139] in ameliorating skin condition with acne vulgaris.

4.2 Cutaneous ageing (anti-ageing)

Aging is a complex multifactorial process of damage accumulation that causes the deterioration of fitness [140, 141]. Aging has been the main risk factor for several deadly diseases such as cancer, cardiovascular disease, diabetes, and neurodegeneration [141]. In the skin, aging is identified by the presence of folds and wrinkles due to the declining and degradation of collagen [142], loss of elasticity [143], and decreasing of various skin functions [144]. At least, there are seven factors that may produce these clinical manifestations including passage of time, genetics, radiation such as ultraviolet and infrared radiations, lifestyle, chronic debilitating diseases, dysfunction of hormonal system, and gravitational

force [145]. Several mechanisms have been proposed to explain the effect of these factors on aging including oxidative stress, telomere shortening, epigenetic dysregulation, DNA damage, genetic mutation, inflammation, mitochondrial dysfunction, and accumulation of glycation end product [146, 147].

Treatment for skin aging can be conducted through three approaches including adjusting lifestyle by routine exercise, calorie restriction, and maintaining mental health; gene therapies; and medications. Among other approaches, medication could be the simplest approach in fighting skin aging such as by using topical or systemic agents [148]. Chromium as dietary supplement (50–200 µg) has been used in preventing skin aging by controlling and regulating blood sugar and lipid levels [17]. Either in topical or systemic applications, chromium is usually combined with different vitamins and minerals to obtain optimum results based on certain parameters such as improving insulin function using chromium picolinate [149], promoting mitochondrial biogenesis and lipid metabolism using oligomannuronate-chromium(III) complexes [150], replacing or removing excess iron production using chromium(III) chloride or chromium picolinate [151, 152], and activating telomerase [153].

Antioxidant activity of chromium may also contribute to its anti-aging properties since oxidative stress has a certain role in the damaging process. Supplementation of chromium(III) in adult male and female with type-2 diabetes mellitus minimized the increase of oxidative stress (thiobarbituric acid reactive substances—TBARS) and increased total antioxidant status [154, 155]. Several combinations have been made by formulating chromium(III) with zinc [156], niacin [157], and vitamin C/E [154] and showed a protective effect against skin damage against oxidative stress.

Antioxidant activity of chromium(III) is correlated to the dose applied as shown in several experiments. Incubation of BALB/3 T3 clone A31 cells and HepG2 cells with chromium(III) chloride concentration higher than 400 µM would induce the formation of oxidative stress, while lower optimized concentration ($M = 100\text{--}200\text{ }\mu\text{M}$) would increase superoxide dismutase and catalase antioxidant activities [7]. In vitro study on the effect of chromium(III) and chromium(VI) on catalase activity also showed this dose-dependent activity in which treatment of cell-free catalase using chromium(III) (dose range $1\text{--}5 \times 10^{-5}\text{ mol/L}$) and chromium(VI) (dose range $1\text{--}4 \times 10^{-5}\text{ mol/L}$) separately increased the catalase activity [158]. These two studies clearly describe that either chromium(III) or chromium(VI) has a certain optimum concentration to exhibit their beneficial effects.

4.3 Cutaneous wound (rapid wound healing)

Cutaneous wound is the skin defect or skin opening that is caused by external forces [159]. Formation of this wound triggers a set of complex biochemical processes to repair the damage that are called as wound healing or wound repair. In normal condition, there are five consecutive phases occurred in wound healing process including (1) homeostasis phase (immediately) through the migration of thrombocytes and formation of fibrin clot to stop the bleeding; (2) first inflammatory phase (day 1–day 6) by sensing the injury, sending the danger signal, and initializing the inflammation; (3) second inflammatory phase (day 1–day 6) through elimination the pathogens and cleaning the wound; (4) proliferation phase (day 4–day 14) through epithelialization, angiogenesis, granulation tissue formation, and collagen deposition to repair the damage and initialize the tissue remodeling process; and (5) remodeling phase (day 8–year 1) through the deposition of collagen to reach maturation of tissue structure [160–162]. Several internal and external factors have been identified to affect the wound healing process including oxygenation, infection and foreign body, lifestyle, hormonal effect, age, and gender [163].

Several studies have shown that chromium(III), in a certain condition, could improve cutaneous wound either in normal or diabetic Wistar rats using a single dose of a combination of zinc(II) (1.5 mg/kg weight) and chromium(III) (0.02 mg/kg weight) [164] and C57BL6/J mice using chromium(III) chloride (80 µg/kg weight/day) for 21 days [16]. The mechanism of this effect has not been fully elucidated yet, but it may be related to chromium(III) activity in increasing insulin sensitivity, insulin-like growth factor 1 (IGF-1) serum concentration, and protein deposition [16, 165]. In this case, high glucose concentration could inhibit proliferation and differentiation of skin keratinocytes [166] and increase the stiffness of collagen [167] which further inhibits wound healing. In healing acetic acid-induced colitis wound, chromium(III) also acted as an anti-inflammatory agent by inhibiting several inflammatory markers and downregulating pro-inflammatory cytokine genes and antioxidant by suppressing oxidative stress without any significant side effect [168].

In different situations, the use of chromium-based skin clips [169] and orthopedic implant [74] gave an adverse effect by delaying surgery wound healing process. These cases represented a hypersensitivity effect as a manifestation of systemic contact dermatitis. In vitro study using human skin keratinocyte cell line (HaCaT cells) in a medium containing chromium(III) solution (10^{-6} M) showed that chromium(III) ions can decrease wound closure rate and be further decreased when the medium was replaced with another chromium(III) ion-containing medium [170]. Chromium(III) ions also caused downregulation of toll-like receptor-2, -4, and -9 messenger ribonucleic acids (TLR-2, -4, and -9 mRNA), upregulation of matrix metalloproteinase 2 and 13, and upregulation of intercellular adhesion molecule 1 messenger ribonucleic acid (ICAM-1 mRNA) [170].

There's no exact explanation for these opposite effects. However, it may be related to the local concentration of chromium species in wound location. An enhancing effect of wound healing was obtained by applying a relatively small concentration of chromium species via oral administration. In human, for instance, there is only 2% of oral chromium(III) that will be absorbed through stomach and intestine and distributed throughout the body. In the same time, an adverse effect was obtained when local chromium concentration was high due to a particulate and soluble chromium released from the implants.

5. Conclusions

Chromium as versatile heavy metals showed contradictory properties dealing with its dermatologic toxicity and biological activity properties. The main factors that probably correlate to these properties are concentrations and species of chromium. Significant increment of local chromium concentration (more than 1 ppm for chromium[VI] species) either from dermal or systemic administration would increase the risk of dermatologic toxicities, while topical or oral administration of small recommended dietary concentration of chromium (50–200 µg for chromium picolinate) would give several beneficial effects. More studies need to be conducted to know the exact effect of the local concentration of corresponding chromium species in many systems.

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Conflict of interest

The authors state that there is no conflict of interest.

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