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Chapter

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 (1.4×10^{-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

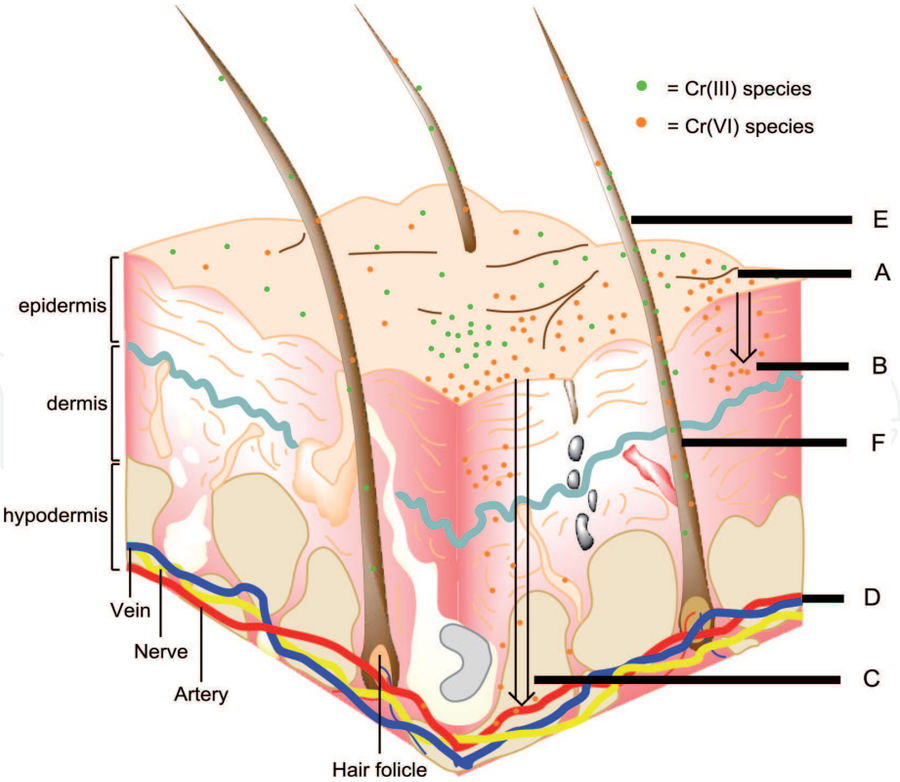

Figure 1.
Several pathways of dermal exposure: (A) deposition of Cr(VI) in the skin surface causes irritation or chemical burn; (B) penetration of Cr(VI) through transcellular and intercellular pathways induces cell apoptosis and contact dermatitis, while Cr(III) tend to suspended in the skin surface 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-1β (IL-1β) 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

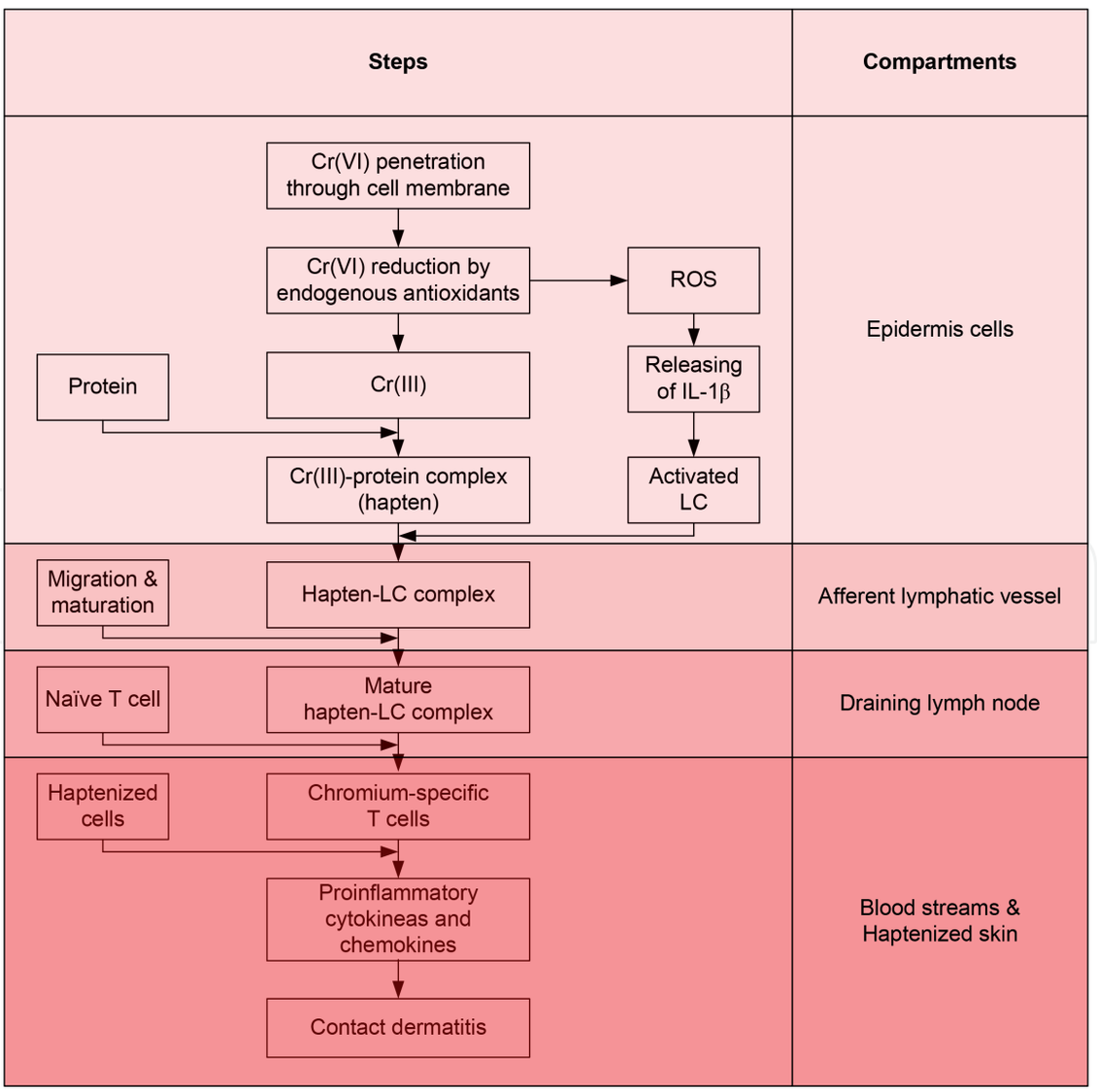

Figure 2.
Simplified elicitation mechanism of chromium-induced contact dermatitis adapted from several references [48, 49].

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.

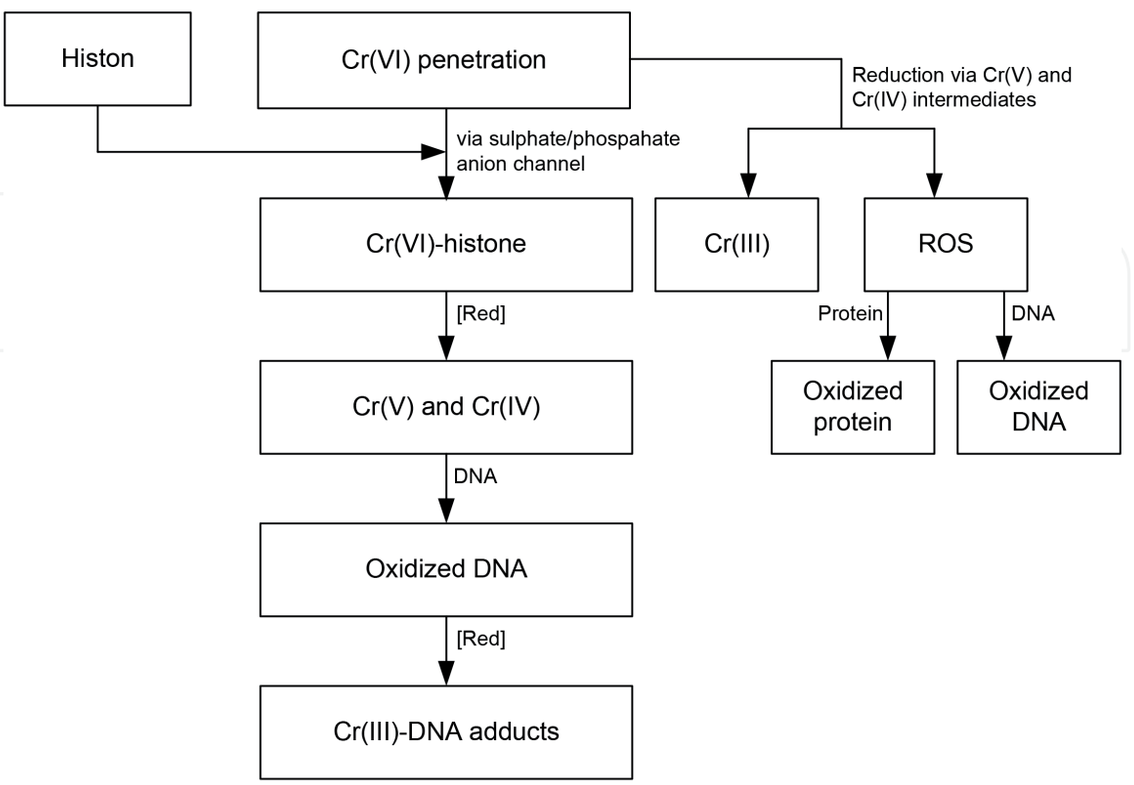

Figure 3.
Simplified mechanism of chromium carcinogenesis adapted from several references [86, 95].

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 = 100–200 μM) 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 1–5 × 10^{-5} mol/L) and chromium(VI) (dose range 1–4 × 10^{-5} 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 contradictive 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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References

[1] Lunk H-J. Discovery, properties and applications of chromium and its compounds. ChemTexts. 2015;**1**(6):1-17

[2] Anderson RA. Chromium as an essential nutrient for humans. Regulatory Toxicology and Pharmacology. 1997;**26**(1):S35-S41

[3] Pechova A, Pavlata L. Chromium as an essential nutrient: A review. Veterinární Medicína. 2007;**52**(1):1-18

[4] Wallach S. Clinical and biochemical aspects of chromium deficiency. Journal of the American College of Nutrition. 1985;**4**(1):107-120

[5] Vincent JB. New evidence against chromium as an essential trace element. The Journal of Nutrition. 2017;**147**(12):2212-2219

[6] Katz SA, Salem H. The toxicology of chromium with respect to its chemical speciation: A review. Journal of Applied Toxicology. 1993;**13**(3):217-224

[7] Terpilowska S, Siwicki AK. Pro- and antioxidant activity of chromium(III), iron(III), molybdenum(III) or nickel(II) and their mixtures. Chemico-Biological Interactions. 2019;**298**(25):43-51. DOI: 10.1016/j.cbi.2018.10.028

[8] Kondo K, Takahashi Y, Ishikawa S, Uchihara H, Hirose Y, Yoshizawa K, et al. Microscopic analysis of chromium accumulation in the bronchi and lung of chromate workers. Cancer. 2003;**98**(11):2420-2429

[9] Stearns DM, Belbruno JJ, Wetterhahn KE. A prediction of chromium(III) accumulation in humans from chromium dietary supplements. The FASEB Journal. 1995;**9**(15):1650-1657

[10] Hepburn DDD, Vincent JB. In vivo distribution of chromium from chromium picolinate in rats and implications for the safety of the dietary supplement. Chemical Research in Toxicology. 2002;**15**(2):93-100

[11] Wu LE, Levina A, Harris HH, Cai Z, Lai B, Vogt S, et al. Carcinogenic chromium(VI) compounds formed by intracellular oxidation of chromium(III) dietary supplements by adipocytes. Angewandte Chemie International Edition. 2016;**55**(5):1742-1745

[12] Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Menné T, Thyssen JP. Chromium allergy and dermatitis: Prevalence and main findings. Contact Dermatitis. 2015;**73**(5):261-280

[13] Yoshihisa Y, Shimizu T. Metal allergy and systemic contact dermatitis: An overview. Dermatology Research and Practice. 2012;**2012**:1-5

[14] Matthews NH, Fitch K, Li W-Q, Morris JS, Christiani DC, Qureshi AA, et al. Exposure to trace elements and risk of skin cancer: A systematic review of epidemiologic studies. Cancer Epidemiology, Biomarkers & Prevention. 2019;**28**(1):3-21

[15] McCarty M. High-chromium yeast for acne? Medical Hypotheses. 1984;**14**(3):307-310

[16] Hsieh Y-T, Hsu T-H, Wang H-C, Chen K-S, Lee W-M. Trivalent chromium restore dexamethasone-induced attenuation effect of insulin-like growth factor-1 and promote skin wound healing in mice. Pakistan Veterinary Journal. 2019;**39**(2):199-204

[17] Janson M. Orthomolecular medicine: The therapeutic use of dietary supplements for anti-aging. Clinical Interventions in Aging. 2006;**1**(3):261-265

[18] Junaid M, Hashmi MZ, Malik RN, Pe D-S. Toxicity and oxidative stress induced by chromium in workers exposed from different occupational settings around the globe: A review. Environmental Science and Pollution Research. 2016;**23**(20):20151-20167

[19] Saha R, Nandi R, Saha B. Sources and toxicity of hexavalent chromium. Journal of Coordination Chemistry. 2011;**64**(10):1782-1806

[20] Liang XW, Xu ZP, Grice J, Zvyagin AV, Roberts MS, Liu X. Penetration of nanoparticles into human skin. Current Pharmaceutical Design. 2013;**19**(35):6353-6366

[21] Filon FL. Penetration of metals through the skin barrier. In: Chen JK, Thyssen JP, editors. Metal Allergy: From Dermatitis to Implant and Device Failure. Cham: Springer; 2018. pp. 67-74

[22] Hostynek JJ. Factors determining percutaneous metal absorption. Food and Chemical Toxicology. 2003;**41**(3):327-345

[23] Rowbotham AL, Levy LS, Shuker LK. Chromium in the environment: An evaluation of exposure of the UK general population and possible adverse health effects. Journal of Toxicology and Environmental Health, Part B. 2000;**3**(3):145-178

[24] Gammelgaard B, Fullerton A, Avnstorp C, Menné T. Permeation of chromium salts through human skin in vitro. Contact Dermatitis. 1992;**27**(5):302-310

[25] Pan T, Wang P, Huang C, Chen C, Fang J. Elucidation of the percutaneous absorption of chromium compounds by functional proteomics. Proteomics. 2009;**9**(22):5120-5131

[26] Rytter M, Haustein U-F. Hapten conjugation in the leucocyte migration inhibition test in allergic chromate eczema. The British Journal of Dermatology. 1982;**106**(2):161-168

[27] Valko M, Morris H, Cronin MTD. Metals, toxicity and oxidative stress. Current Medicinal Chemistry. 2005;**12**(10):1161-1208

[28] Sinigaglia F. The molecular basis of metal recognition by T cells. Journal of Investigative Dermatology. 1994;**102**(4):398-401. DOI: 10.1111/1523-1747.ep12372149

[29] Smart GA, Sherlock JC. Chromium in foods and the diet. Food Additives and Contaminants. 1985;**2**(2):139-147

[30] Hamilton EM, Young SD, Bailey EH, Watts MJ. Chromium speciation in foodstuffs: A review. Food Chemistry. 2018;**250**:105-112. DOI: 10.1016/j.foodchem.2018.01.016

[31] Zhitkovich A. Chromium in drinking water: Sources, metabolism, and cancer risks. Chemical Research in Toxicology. 2011;**24**(10):1617-1629

[32] Basko-plluska JL, Thyssen JP, Schalock PC. Cutaneous and systemic hypersensitivity reactions to metallic implants. Dermatitis. 2011;**22**(2):65-79

[33] Vincent JB, Edwards KC. The absorption and transport of chromium in the body. In: Vincent JB, editor. The Nutritional Biochemistry of Chromium(III) [Internet]. 2nd ed. Amsterdam: Elsevier B.V.; 2019. pp. 129-174. DOI: 10.1016/B978-0-444-64121-2.00004-0

[34] Ducros V. Chromium metabolism. A literature review. Biological Trace Element Research. 1992;**32**(1-3):65-77

[35] Uter W, Werfel T, White IR, Johansen JD. Contact allergy: A review of current problems from a clinical perspective. International Journal of Environmental Research and Public Health. 2018;**15**(6):E1108

[36] Thyssen JP, Menne T. Metal allergy—A review on exposures, penetration, genetics, prevalence, and clinical implications. Chemical Research in Toxicology. 2010;**23**(2):309-318

[37] Wong CC, Gamboni SE, Palmer AM, Nixon RL. Occupational allergic contact dermatitis to chromium from cement: Estimating the size of the problem in Australia. The Australasian Journal of Dermatology. 2015;**56**(4):290-293

[38] Bregnbak D, Thyssen JP, Zachariae C, Johansen JD. Characteristics of chromium-allergic dermatitis patients prior to regulatory intervention for chromium in leather: A questionnaire study. Contact Dermatitis. 2014;**71**(6):338-347

[39] Hansen MB, Menne T, Johansen JD. Cr (III) and Cr (VI) in leather and elicitation of eczema. Contact Dermatitis. 2006;**54**(5):278-282

[40] Hedberg YS, Lidén C, Lindberg M. Chromium dermatitis in a metal worker due to leather gloves and alkaline coolant. Acta Dermato-Venereologica. 2016;**96**(1):104-105

[41] Hedberg YS, Erfani B, Matura M, Lidén C. Chromium (III) release from chromium-tanned leather elicits allergic contact dermatitis: A use test study. Contact Dermatitis. 2018;**78**(5):307-314

[42] Lim JH, Kim HS, Park YM, Lee JY, Kim HO. A case of chromium contact dermatitis due to exposure from a golf glove. Annals of Dermatology. 2010;**22**(1):63-65

[43] Thyssen JP, Jellesen MS, Møller P, Menne' T, Johansen JD. Allergic chromium dermatitis from wearing 'chromium-free' footwear. Contact Dermatitis. 2014;**70**(3):185-187

[44] Dikicier BS, Yaldız M, Çetinkaya R, Erdem T. Tattoo associated allergic contact dermatitis. Australian Journal of Dermatology. 2015;**2**(2):1037

[45] Seishima M, Oyama Z, Oda M. Cellular phone dermatitis with chromate allergy. Dermatology. 2003;**207**(1):48-50

[46] Tan S, Nixon R. Allergic contact dermatitis caused by chromium in a mobile phone. Contact Dermatitis. 2011;**65**(4):246-247

[47] Basketter DA, Angelini G, Ingber A, Kern PS, Menné T. Nickel, chromium and cobalt in consumer products: Revisiting safe levels in the new millennium. Contact Dermatitis. 2003;**49**(1):1-7

[48] Rustemeyer T, van Hoogstraten IMW, von Blomberg BME, Scheper RJ. Mechanisms of allergic contact dermatitis. In: Rustemeyer T, Elsner P, John S-M, Maibach HI, editors. Kanerva's Occupational Dermatology. Berlin, Heidelberg: Springer; 2012. pp. 113-146

[49] Buters J, Biedermann T. Chromium (VI) contact dermatitis: Getting closer to understanding the underlying mechanisms of toxicity and sensitization! Journal of Investigative Dermatology. 2017;**137**(2):274-277. DOI: 10.1016/j.jid.2016.11.015

[50] Saary J, Qureshi R, Palda V, Dekoven J, Pratt M, Skotnicki-grant S, et al. A systematic review of contact dermatitis treatment and prevention. Journal of the American Academy of Dermatology. 2005;**53**(5):845.e1-845.e13

[51] Lee Y-H, Su S-B, Huang C-C, Sheu H-M, Tsai J-C, Lin C-H, et al. N-Acetylcysteine attenuates hexavalent chromium-induced hypersensitivity through inhibition of cell death, ROS-related signaling and cytokine expression. PLoS One. 2014;**9**(9):e108317

[52] Bradberry SM, Vale JA. Therapeutic review: Is ascorbic acid of value in chromium poisoning and chromium dermatitis? Journal of Toxicology. Clinical Toxicology. 1999;**37**(2):195-200

[53] Lee I, Kim S, Shin I, Moon C, Park S, Kim S, et al. Protective effects of pine bark extract on hexavalent chromium-induced dermatotoxicity in rats. Phytherapy Research. 2012;**26**(10):1534-1540

[54] Wang B-J, Chiu H-W, Lee Y-L, Li C-Y, Wang Y-J, Lee Y-H. Pterostilbene attenuates hexavalent chromium-induced allergic contact dermatitis by preventing cell apoptosis and inhibiting IL-1β-related NLRP3 inflammasome activation. Journal of Clinical Medicine. 2018;**7**(12):E489

[55] Allenby CF, Goodwin BFJ. Influence of detergent washing powders on minimal eliciting patch test concentrations of nickel and chromium. Contact Dermatitis. 1983;**9**(6):491-499

[56] Wöhrl S, Kriechbaumer N, Hemmer W, Focke M, Brannath W, Götz M, et al. A cream containing the chelator DTPA (diethylenetriaminepenta-acetic acid) can prevent contact allergic reactions to metals. Contact Dermatitis. 2001;**44**(4):224-228

[57] Winnicki M, Shear NH. A systematic approach to systemic contact dermatitis and symmetric drug-related intertriginous and flexural exanthema (SDRIFE) a closer look at these conditions and an approach to intertriginous eruptions. American Journal of Clinical Dermatology. 2011;**12**(3):171-180

[58] Aquino M, Rosner G. Systemic contact dermatitis. Clinical Reviews in Allergy and Immunology. 2019;**56**(1):9-18

[59] Silvestri DL. Systemic contact dermatitis. Skin & Aging. 2012;(January):22-29

[60] Jensen CS, Lisby S, Larsen JK, Veien NK, Menné T. Characterization of lymphocyte subpopulations and cytokine profiles in peripheral blood of nickel-sensitive individuals with systemic contact dermatitis after oral nickel exposure. Contact Dermatitis. 2004;**50**(1):31-38

[61] Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions—New concepts. Clinical and Experimental Allergy. 2007;**37**(7):989-999

[62] Lachapelle J-M. The spectrum of diseases for which patch testing is recommended patients who should be investigated. In: Lachapelle I-M, Maibach HI, Ri I, editors. Patch Testing-Prick Testing: A Practical Guide. New York: Springer-Verlag Berlin Heidelberg GmbH; 2003. p. 7-26

[63] Häusermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: Is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Dermatitis. 2004;**51**(5-6):297-310

[64] Özkaya E. Current understanding of baboon syndrome. Expert Review of Dermatology. 2009;**4**(2):163-175

[65] Miyahara A, Kawashima H, Okubo Y, Hoshika A. A new proposal for a clinical-oriented subclassification of baboon syndrome and a review of baboon syndrome. Asian Pacific Journal of Allergy and Immunology. 2011;**29**(2):150-160

[66] Hubler WR Jr, Hubler WR Sr. Dermatitis from a chromium dental plate. Contact Dermatitis. 1983;**9**(5):377-387

[67] Shelnutt SR, Goad P, Belsito DV. Dermatological toxicity of hexavalent

chromium. Critical Reviews in Toxicology. 2007;**37**:375-387

[68] Fowler JF. Systemic contact dermatitis caused by oral chromium picolinate. Cutis. 2000;**65**(2):116

[69] Özkaya E, Topkarci Z, Özarmağan G. Systemic allergic dermatitis from chromium in a multivitamin/multimineral tablet. Contact Dermatitis. 2010;**62**(3):184-184

[70] Veien NK, Hattel T, Laurberg G. Chromate-allergic patients challenged orally with potassium dichromate. Contact Dermatitis. 1994;**31**(3):137-139

[71] Van Ulsen J, Stolz E, van Joost T. Chromate dermatitis from a homeopathic drug. Contact Dermatitis. 1988;**18**(1):56-57

[72] Pacheco KA. Allergy to surgical implants. Clinical Reviews in Allergy and Immunology. 2019;**56**(1):72-85

[73] Hedberg YS, Wallinder IO. Metal release from stainless steel in biological environments: A review. Biointerphases. 2016;**11**(1):018901. DOI: 10.1116/1.4934628

[74] Phedy P, Djaja YP, Boedijono DR, Wahyudi M, Silitonga J, Solichin I. Hypersensitivity to orthopaedic implant manifested as erythroderma: Timing of implant removal. International Journal of Surgery Case Reports. 2018;**49**:110-114. DOI: 10.1016/j.ijscr.2018.06.011

[75] Oleffe J, Wilmet J. Generalized dermatitis from an osteosynthesis screw. Contact Dermatitis. 1980;**6**(5):365-365

[76] Rostoker G, Robin J, Binet O, Blamoutier J, Paupe J, Lessana-Leibowitch M, et al. Dermatitis due to orthopaedic implants. A review of the literature and report of three cases. Journal of Bone and Joint Surgery. American Volume. 1987;**69**(9):1408-1412

[77] Balato N, Limbo G, Patruno C, Ayala F. Generalized dermatitis due to an osteosynthesis screw. Contact Dermatitis. 1991;**24**(4):310-310

[78] Gao X, He R, Yan S, Wu L. Case report: Dermatitis associated with chromium following total knee arthroplasty. Journal of Arthroplasty. 2011;**26**(4):665.e13-665.e16. DOI: 10.1016/j.arth.2010.06.002

[79] Thomsen M, Rozak M, Thomas P. Pain in a chromium-allergic patient with total knee arthroplasty: Disappearance of symptoms after revision with a special surface-coated TKA—A case report. Acta Orthopaedica. 2011;**83**(3):386-388

[80] Lampel HP, Silvestri DL. Systemic contact dermatitis: Current challenges and emerging treatments. Current Treatment Options in Allergy. 2014;**1**(4):348-357

[81] Wu G, Xiao X, Feng P, Xie F, Yu Z, Yuan W, et al. Gut remediation: A potential approach to reducing chromium accumulation using lactobacillus plantarum TW1-1. Scientific Reports. 2017;**7**:1-12. DOI: 10.1038/s41598-017-15216-9

[82] Sharma AD. Low chromate diet in dermatology. Indian Journal of Dermatology. 2009;**54**(3):293-295

[83] Ching HA, Choudhury D, Nine MJ, Osman NAA. Effects of surface coating on reducing friction and wear of orthopaedic implants. Science and Technology of Advanced Materials. 2014;**15**(1):014402

[84] Hallab NJ, Jacobs JJ. Biologic effects of implant debris. Bulletin of the NYU Hospital for Joint Diseases. 2009;**67**(2):182-188

[85] Burton L, Paget D, Binder NB, Bohnert K, Nestor BJ, Sculco TP, et al. Orthopedic wear debris mediated inflammatory osteolysis is mediated in part by NALP3 inflammasome activation. Journal of Orthopaedic Research. 2013;**31**(1):73-80

[86] Wang Y, Su H, Gu Y, Song X, Zhao J. Carcinogenicity of chromium and chemoprevention: A brief update. OncoTargets and Therapy. 2017;**10**:4065-4079

[87] Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: Nickel, arsenic, and chromium. Chemical Research in Toxicology. 2008;**21**(1):28-44

[88] Langard S, Andersen A, Ravnestad J. Incidence of cancer among ferrochromium and ferrosilicon workers: An extended observation period. British Journal of Industrial Medicine. 1990;**47**(1):14-19

[89] Langrrd S. One hundred years of chromium and cancer: A review of epidemiological evidence and selected case reports. American Journal of Industrial Medicine. 1990;**17**(2):189-215

[90] Birk T, Mundt KA, Dell LD, Luippold RS, Miksche L, Steinmann-steiner-haldenstaett W, et al. Lung cancer mortality in the German chromate industry, 1958 to 1998. Journal of Occupational and Environmental Medicine. 2006;**48**(4):426-433

[91] Deng Y, Wang M, Tian T, Lin S, Xu P, Zhou L, et al. The effect of hexavalent chromium on the incidence and mortality of human cancers: A meta-analysis based on published epidemiological. Frontiers in Oncology. 2019;**9**:24

[92] Program NT. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate (CAS NO. 7789-12-0) in F344/N Rats and B6C3F1 Mice. North Carolina; 2008

[93] Davidson T, Kluz T, Burns F, Rossman T, Zhang Q, Uddin A, et al. Exposure to chromium (VI) in the drinking water increases susceptibility to UV-induced skin tumors in hairless mice. Toxicology and Applied Pharmacology. 2004;**196**(3):431-437

[94] Uddin AN, Burns FJ, Rossman TG, Chen H, Kluz T, Costa M. Dietary chromium and nickel enhance UV-carcinogenesis in skin of hairless mice. Toxicology and Applied Pharmacology. 2007;**221**(3):329-338

[95] Lay PA, Levina A. Metal carcinogens. In: Reedijk J, Poeppelmeier K, editors. Comprehensive Inorganic Chemistry II [Internet]. 2nd ed. Amsterdam: Elsevier Ltd.; 2013. pp. 835-856. DOI: 10.1016/B978-0-08-097774-4.00333-8

[96] Rudolf E, Cervinka M, Cerman J, Schroterova L. Hexavalent chromium disrupts the actin cytoskeleton and induces mitochondria-dependent apoptosis in human dermal fibroblasts. Toxicology in Vitro. 2005;**19**(6):713-723

[97] Gibb HJ, Lees PSJ, Pinsky PF, Rooney BC. Clinical findings of irritation among chromium chemical production workers. American Journal of Industrial Medicine. 2000;**38**(2):127-131

[98] Boloorchi A, Sinna R, Benhaim T, Gobel F, Robbe M. Brûlure par acide chromique: Prévention systématique de la toxicité systémique. Annales de Chirurgie Plastique Esthétique. 2007;**52**:621-623

[99] Terrill PJ, Gowar JP. Chromic acid burns; beware, be aggressive, be watchful. British Journal of Plastic Surgery. 1990;**43**(6):699-701

[100] Lin C-C, Wu M-L, Yang C-C, Ger J, Tsai W-J, Deng J-F. Acute severe chromium poisoning after dermal exposure to hexavalent chromium. Journal of the Chinese Medical Association. 2009;**72**(4):219-221. DOI: 10.1016/S1726-4901(09)70059-0

[101] Laitung JK, Earley M. The role of surgery in chromic acid burns: Our experience with two patients. Burns. 1984;**10**(5):378-380

[102] Wang X-W, Davies JWL, Sirvent RLZ, Robinson WA. Chromic acid burns and acute chromium poisoning. Burns. 1985;**11**(3):181-184

[103] Ogawa M, Nakajima Y, Endo Y. Four cases of chemical burns thought to be caused by exposure to chromic acid mist. Journal of Occupational Health. 2007;**49**(5):402-404

[104] Mikulewicz M, Chojnacka K, Gedrange T, Górecki H. Reference values of elements in human hair: A systematic review. Environmental Toxicology and Pharmacology. 2013;**36**(3):1077-1086. DOI: 10.1016/j.etap.2013.09.012

[105] Bartlett RJ. Chromium cycling in soils and water: Links, gaps, and methods. Environmental Health Perspectives. 1991;**92**:17-24

[106] Testa SM. Sources of chromium contamination in soil and groundwater. In: Guertin J, Jacobs JA, Avakian CP, editors. Chromium(VI) Handbook. Florida: CRC Press; 2005. pp. 143-164

[107] Nocoń K, Kozłowska WR, Widziewicz K. Research on chromium and arsenic speciation in atmospheric particulate matter: Short review. E3S Web of Conferences. 2018;**28**:01026

[108] Horev L. Exogenous factors in hair disorders. Exogenous Dermatology. 2004;**3**(5):237-245

[109] Melnik BC, Plewig G, Daldrup T, Borchard F, Pfeiffer B, Zahn H. Green hair: Guidelines for diagnosis and therapy. Journal of the American Academy of Dermatology. 1986;**15**(5):1065-1068

[110] Bhat GR, Lukenbach ER, Kennedy RR, Parreira RM. The green hair problem: A preliminary investigation. Journal of the Society of Cosmetic Chemists. 1979;**30**(1):1-8

[111] Sarwar N, Imran M, Rashid M, Ishaque W, Asif M, Matloob A, et al. Chemosphere phytoremediation strategies for soils contaminated with heavy metals: Modifications and future perspectives. Chemosphere [Internet]. 2017;**171**:710-721. DOI: 10.1016/j.chemosphere.2016.12.116

[112] Salem HM, Eweida EA, Farag A. Heavy metals drinking water and their environmental impact on human health. In: Proceedings of International Conference for Environmental Hazards Mitigation (ICEHM 2000); Giza. 2000. p. 542-556

[113] Smart KE, Kilburn M, Schroeder M, Martin BG, Hawes C, Marsh JM, et al. Copper and calcium uptake in colored hair. Journal of Cosmetic Science. 2009;**60**:337-345

[114] Pierard GE. Toxic effects of metals from the environment on hair growth and structure. Journal of Cutaneous Pathology. 1979;**6**(4):237-242

[115] Trüeb RM. Systematic approach to hair loss in women. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2010;**8**(4):284-297

[116] Uhlenhake E, Yentzer BA, Feldman SR. Acne vulgaris and depression: A retrospective examination. Journal of Cosmetic Dermatology. 2010;**9**(1):59-63

[117] Marques AR, Silva C, Colmonero S, Andrade P. Diabetes mellitus and polycystic ovary syndrome: Beyond a dermatological problem. Diabetes Case Reports. 2016;**1**(3):10000113

[118] Sadeeqa S, Mustafa T, Latif S. Polycystic ovarian syndrome—Related depression in adolescent girls: A review. Journal of Pharmacy & Bioallied Sciences. 2018;**10**(2):55-59

[119] Gåfvels C, Hägerström M, Rane K, Wajngot A, Wändell PE. Depression and anxiety after 2 years of follow-up in patients diagnosed with diabetes or rheumatoid arthritis. Health Psychology Open. 2016;**3**(2):1-12

[120] Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. Nature Reviews Disease Primers. 2015;**1**:15029. DOI: 10.1038/nrdp.2015.29

[121] Zouboulis CC, Böhm M. Neuroendocrine regulation of sebocytes—A pathogenetic link between stress and acne. Experimental Dermatology. 2004;**13**(Suppl 4):31-35

[122] Roberts A, Matthews JB, Socransky SS, Freestone PPE, Williams PH, Chapple ILC. Stress and the periodontal diseases: Effects of catecholamines on the growth of periodontal bacteria in vitro. Oral Microbiology and Immunology. 2002;**17**(5):296-303

[123] Boyanova L. Anaerobe stress hormone epinephrine (adrenaline) and norepinephrine (noradrenaline) effects on the anaerobic bacteria. Anaerobe [Internet]. 2017;**44**:13-19. DOI: 10.1016/j.anaerobe.2017.01.003

[124] Borrel V, Thomas P, Catovic C, Racine P-J, Konto-Ghiorghi Y, Lefeuvre L, et al. Acne and stress: Impact of catecholamines on cutibacterium acnes. Frontiers in Medicine. 2019;**6**(July):155

[125] Fox L, Csongradi C, Aucamp M, Plessis J, Gerber M. Treatment modalities for acne. Molecules. 2016;**21**(8):E1063

[126] Amr N, Abdel-Rahim HE. The effect of chromium supplementation on polycystic ovary syndrome in adolescents. Journal of Pediatric and Adolescent Gynecology. 2015;**28**(2):114-118. DOI: 10.1016/j.jpag.2014.05.005

[127] Jamilian M, Bahmani F, Siavashani MA, Mazloomi M, Asemi Z, Esmaillzadeh A. The effects of chromium supplementation on endocrine profiles, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Biological Trace Element Research. 2016;**172**(1):72-78

[128] Russell KO. Method of administration of chromium and magnesium sulfate for treatment of acne. United States of America; US 9,642.877 B1. 2017

[129] Goodless DR. Composition and method for treatment of acne. Unites States of America; WO 2005/049060 A1. 2005

[130] Fitzjarrell EA. Method and composition for treating acne. United States of America; US00575.9559A. 1998

[131] Sardana K, Garg VK. An observational study of methionine-bound zinc with antioxidants for mild to moderate acne vulgaris. Dermatologic Therapy. 2010;**23**(4):411-418

[132] Rubin MG, Kim K, Logan AC. Acne vulgaris, mental health and omega-3 fatty acids: A report of cases. Lipids in Health and Disease. 2008;**7**(36):1-5

[133] Yousofvand N, Zarei F, Ghanbari A. Exogenous testosterone, finasteride and castration effects on testosterone, insulin, zinc and chromium in adult male rats. Iranian Biomedical Journal. 2013;**17**(1):49-53

[134] Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. Dermatoendocrinology. 2011;**3**(1):41-49

[135] Davidson JRT, Abraham K, Connor KM, McLeod MN. Effectiveness of chromium in atypical depression: A placebo-controlled trial. Biological Psychiatry. 2003;**53**(3):261-264

[136] Mcleod MN, Golden RN. Chromium treatment of depression. The International Journal of Neuropsychopharmacology. 2000;**3**(4):311-314

[137] Docherty J, Sack D, Roffman M, Finch M, Komorowski J. A double-blind, placebo-controlled, exploratory trial of chromium picolinate in atypical depression: Effect on carbohydrate craving. Journal of Psychiatric Practice. 2005;**11**(5):302-314

[138] Szöllősi AG, Oláh A, Bíró T, Tóth BI. Recent advances in the endocrinology of the sebaceous gland. Dermatoendocrinology. 2018;**9**(1):e1361576

[139] Hendrick V, Gitlin M, Altshuler L, Korenman S. Antidepressant medications, mood and male fertility. Psychoneuroendocrinology. 2000;**25**(1):37-51

[140] Partridge L. The new biology of ageing. Philosophical Transactions of the Royal Society B. 2010;**365**(1537):147-154

[141] Niccoli T, Partridge L. Ageing as a risk factor for disease. Current Biology. 2012;**22**(17):R741-R752. DOI: 10.1016/j.cub.2012.07.024

[142] Varani J, Dame MK, Rittie L, Fligiel SEG, Kang S, Fisher GJ, et al. Decreased collagen production in chronologically aged skin: Roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. The American Journal of Pathology. 2006;**168**(6):1861-1868

[143] Takema Y, Yorimoto Y, Kawai M, Imokawa G. Age-related changes in the elastic properties and thickness of human facial skin. The British Journal of Dermatology. 1994;**131**(5):641-648

[144] Hall GK, Phillips TJ. Skin and hormone therapy. Clinical Obstetrics and Gynecology. 2004;**47**(2):437-449

[145] Piérard GE. The quandary of climacteric skin ageing. Dermatology. 1996;**193**:273-274

[146] Mchugh D, Gil J. Senescence and aging: Causes, consequences, and therapeutic avenues. The Journal of Cell Biology. 2018;**217**(1):65-77

[147] Zhang S, Duan E. Fighting against skin aging: The way from bench to bedside. Cell Transplantation. 2018;**27**(5):729-738

[148] Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. Dermatoendocrinology. 2012;**4**(3): 308-319

[149] McCarty MF. Homologous physiological effects of phenformin and chromium picolinate. Medical Hypotheses. 1993;**41**(4):316-324

[150] Hao J, Hao C, Zhang L, Liu X, Zhou X, Dun Y, et al. OM2, a novel oligomannuronate-chromium (III) complex, promotes mitochondrial biogenesis and lipid metabolism in 3T3-L1 adipocytes via the

AMPK-PGC1α pathway. PLoS One. 2015;**10**(7):e0131930

[151] Loubet PE. Topical mixture and method for dermal application to remove excess iron and other heavy metals from cellular tissue. United States of America; US 2013/0344166A1. 2013

[152] Russell KO. Method and composition for inhibiting aged skin. United States of America; US 2018/0318184 A1. 2018

[153] Tsoukalas D, Fragkiadaki P, Docea AO, Alegakis AK, Sarandi E, Thanasoula M, et al. Discovery of potent telomerase activators: Unfolding new therapeutic and anti-aging perspectives. Molecular Medicine Reports. 2019;**20**(4):3701-3708

[154] Lai M-H. Antioxidant effects and insulin resistance improvement of chromium combined with vitamin C and E supplementation for type-2 diabetes mellitus. Journal of Clinical Biochemistry and Nutrition. 2008;**43**(3):191-198

[155] Cheng H-H, Lai M-H, Hou W-C, Huang C-L. Antioxidant effects of chromium supplementation with type 2 diabetes mellitus and euglycemic subjects. Journal of Agricultural and Food Chemistry. 2004;**52**(5):1385-1389

[156] Anderson RA, Roussel A-M, Zouari N, Mahjoub S, Matheau J-M, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. Journal of the American College of Nutrition. 2001;**20**(3):212-218

[157] Yanardag R, Peksel A, Yesilyaprak B, Doger MM, Arisan-Atac I. Effects of a combination of niacin and chromium (III)-chloride on the skin and lungs of hyperlipemic rats. Biological Trace Element Research. 2005;**103**(3):249-260

[158] Chen L, Zhang J, Zhu Y, Zhang Y. Interaction of chromium(III) or chromium(VI) with catalase and its effect on the structure and function of catalase: An in vitro study. Food Chemistry. 2018;**244**:378-385. DOI: 10.1016/j.foodchem.2017.10.062

[159] Panasci K. Burns and wounds. In: Paz JC, West MP, editors. Acute Care Handbook for Physical Therapists [Internet]. 4th ed. Missouri: Elsevier Inc.; 2014. pp. 283-311. DOI: 10.1016/B978-1-4557-2896-1.00012-3

[160] Lindenbaum E. Compositions and methods for stimulating wound healing. United States of America; US 10,292,997 B2. 2019

[161] Broughton G, Janis J, Attinger C. Wound healing: An overview. Plastic and Reconstructive Surgery. 2006;117(Suppl 7):1e.S-32e.S

[162] Cañedo-dorantes L, Cañedo-ayala M. Skin acute wound healing: A comprehensive review. International Journal of Inflammation. 2019;**2019**:ID 3706315

[163] Guo S, DiPietro LA. Factors affecting wound healing. Journal of Dental Research. 2010;**89**(3):219-229

[164] de Moraes SP, Chaves FR, Banci S, Rover PA, Georgetti F, Neto JA d R. Zinco e cromo na cicatrização de feridas em ratos normais e diabéticos. Revista do Colégio Brasileiro de Cirurgiões. 2000;**27**(6):394-399

[165] Peng Z, Qiao W, Wang Z, Dai Q, He J, Guo C, et al. Chromium improves protein deposition through regulating the mRNA levels of IGF-1 , IGF-1R, and Ub in rat skeletal muscle cells. Biological Trace Element Research. 2010;**137**(2):226-234

[166] Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T,

Wertheimer E. Glucose effects on skin keratinocytes: Implications for diabetes skin complications. Diabetes. 2001;**50**(7):1627-1635

[167] Snedeker JG, Gautieri A. The role of collagen crosslinks in ageing and diabetes—The good, the bad, and the ugly. Muscles, Ligaments and Tendons Journal. 2014;**4**(3):303-308

[168] Odukanmi OA, Salami AT, Koda K, Morakinyo OL, Olaleye SB. Trivalent chromium promotes healing of experimental colitis in mice by suppression of inflammation and oxidative stress. Journal of Bioscience and Medicine. 2017;**5**(8):108-126

[169] Lhotka CG, Szekeres T, Fritzer-Szekeres M, Schwarz G, Steffan I, Maschke M, et al. Are allergic reactions to skin clips associated with delayed wound healing? American Journal of Surgery. 1998;**176**(4):320-323

[170] Perfetto B, Stellavato A, Melito A, De Gregorio V, Cammarota M, Giuliano M. A time-lapse approach to examine chromium and nickel effects on wound healing in vitro. Journal of Immunotoxicology. 2012;**9**(4):392-400