

Chapter 2

Immune-Mediated Disorders of Skin: Role of Dietary Factors and Plant Extracts?

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Key Points

- Since ancient time, many plant products are being used either to accentuate the beauty of skin or as soothing agents in various dermatological ailments.
- Recently certain dietary factors and plant extracts have been found to be responsible for triggering of some of the immune-mediated skin disorders.
- Autoimmune and hypersensitivity reactions are considered to be important mechanisms responsible for these diseases.
- Majority of these conditions can be prevented by knowing and avoiding these substances of plant origin.

Keywords Immune-mediated skin disorders • Diet • Plant extracts • Immunopathogenesis • Prevention

Introduction

The skin, which is the largest organ of the body, constitutes an important barrier between the body and environment. It is one of the most common sites exposed to various infectious and noxious agents. In fact, the skin serves as the first line of defense against the foreign invaders. Therefore, it has long been used as a vehicle for study and manipulation of the immune system. Whereas the role of cutis in the processing and presentation of antigens to the central lymphoid compartments is well recognized, its more complex immune functions remain to be understood. The skin has many characteristics which suggest that it can function as a relatively autonomous immune organ [1]. The cutaneous immunological repertoire involves a wide range of immune cells which act in concert to protect the internal milieu of the body. Any breakdown in cutaneous immunity therefore leads to the development of

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immune-mediated skin disorders (IMSD). A large number of environmental and genetic factors are believed to be important in maintenance of cutaneous health. Out of these the influence of dietary constituents/plant products has been a topic of extensive research in the modern times. This chapter focuses primarily on various IMSD with the possible role of diet or plant extracts in their etiology.

Classification of IMSD

Majority of the IMSD arise as a complex interaction of genetic, environmental, and immunological factors. Broadly they have been classified into those specific to skin and those occurring as a part of systemic disorders with dermatological manifestations (Table 2.1). In many of them the role of diet or plant extract has recently been observed. The diet-related IMSD (drIMSD) can further be divided into those in which the dietary factor has a predominant role in etiology and those in which the disease is a manifestation of deficiency or excess of particular element in diet. Finally, cutaneous disorders exist where the pathogenic interference of dietary factors has repeatedly been advocated, but without a convincing evidence. The literature on drIMSD is sketchy and scattered. However, in recent years enough epidemiologic, clinical, and experimental data has been collected warranting a systematic analysis of role of diet or plant extracts in drIMSD, especially in genetically predisposed individuals.

Skin as an Immune Organ

The common belief that the skin is not an active immune organ has been altered by the identification of an armamentarium of immune competent cells and their cytokines in the various layers of the skin. The epidermis, although not directly accessed by the blood or lymphatic circulation, is equipped with various immune competent cells like Langerhans or dendritic cells, the antigen-presenting cells (APC); Keratinocytes, the epithelial cells with immune properties; Epidermal T lymphocytes; and Melanocytes, the epidermal pigment cells with immune function. The dermis contains a network of

Table 2.1 Immune mediated skin disorders with suggested role of diet or plant extracts

Immune mediated skin disorders		Immune mediated systemic diseases with skin manifestations	
Causative	Preventive/therapeutic	Causative	Preventive/therapeutic/uncertain
Dermatitis	Discoid lupus	Gluten-sensitive	Systemic lupus
hepetiformis	erythematosus	enteropathy	erythematosus
Pemphigus	Scleroderma		Rheumatoid arthritis
Atopic dermatitis	Epidermolysis bullosa		Dermatomyositis
	acquisita		
Contact dermatitis	Lichen planus		Sjogren's syndrome
Psoriasis	Vitiligo		Systemic sclerosis
	Psoriasis		Behcet syndrome
			Vasculitis
			Autoimmune endocrinopathies
			Inflammatory bowel disease
			Autoimmune hepatitis
			Autoimmune paraneoplastic dermatosis

lymphatic and blood vessels rich in lymphocytes, other leukocytes, mast cells, tissue macrophages, and cytokines like interleukin 1 (IL-1). All these cells and their cytokines act together to initiate an immune response whenever the cutaneous barrier gets disrupted [2].

The first cell to encounter toxins or antigens in the skin is the APC which presents the antigen to other resident immune cells. The keratinocytes which are the reservoirs of IL-1 release it, which in turn initiates a multitude of local and systemic effects. IL-1 also increases the production of other cytokines by the keratinocytes, induces class II MHC antigen and adhesion molecule expression on keratinocytes and dermal endothelial cells, and thus facilitates leukocyte trafficking into the skin. The cutaneous melanocytes may also promote the immune response by secreting various soluble mediators of inflammation.

Mechanisms of drIMSD

The skin is continuously exposed to a tremendous diversity of antigenic stimuli which may initiate a series of immune responses in both the epidermal and dermal compartments. These immunological reactions may be antibody or T cell mediated in nature. Sometimes, an underlying genetic predisposition may also be present which serves to exaggerate this response resulting in pathological manifestations. The important mechanisms which may play a role in the pathogenesis of drIMSD include:

1. Autoimmunity triggered by dietary antigens
2. Hypersensitivity (HS) to dietary components
3. Idiosyncrasy to commonly used dietary compounds
4. Deficiency or excess of a specific nutrient present in the diet

Autoimmunity Triggered by Dietary Antigens

An autoimmune response to the dietary components has been implicated in etiology of many cutaneous disorders. The diet-related antigen is believed to resemble the skin protein. Therefore the antibody response directed against the diet proteins also damages the skin leading to various cutaneous manifestations. A role of autoimmunity has been suggested in autoimmune bullous disorders like dermatitis herpetiformis (DH) and pemphigus.

Dermatitis Herpetiformis

DH is an autoimmune disease characterized by intensely itchy blisters and hives on an individual's back or buttocks. The DH has been found to be associated with other autoimmune disorders also like celiac disease, rheumatoid arthritis, hypothyroidism, or Sjogren's syndrome. The role of diet in DH is now well established. The gluten proteins present in certain cereals activate the immune system, attacking the skin and proximal intestinal mucosa [3]. In this disease the immunoglobulin A (IgA) autoantibodies formed against gluten proteins are addressed toward an enzyme, type 3 epidermal transglutaminase, which has a marked homology with tissue transglutaminase. This homology is responsible for the cross antibody reaction in patients with gluten enteropathy. Avoidance of gluten in diet is the first and most important therapeutic solution [4]. The gluten free diet requires the strict avoidance of all foods that contain the alcohol soluble fraction of gluten, gliadin. This is present not only in cereals like wheat, rye, barley, buckwheat, and oats but also in thickeners, fillers, and additives contained in a wide variety of foods (Table 2.2) [5].

Table 2.2 Major dietary and plant products implicated in induction of IMSD

<i>Dermatitis herpetiformis</i>				
Barley	Buckwheat	Rye	Oat	Wheat
<i>Pemphigus</i>				
Black pepper	Garlic	Manioca	Radish	Red chilies
Coriander	Horseradish	Mustard	Red pepper	Tea
Cumin seeds	Leek	Onion		
<i>Atopic dermatitis</i>				
Almonds	Carob flour	Eggs	Hazelnuts	Peanuts
Cow's milk	Crustacea	Guar seed flour	Maize	Wheat
<i>Contact dermatitis</i>				
Anise	Carrots	Dill	Mace	Parsnips
Artichoke	Cashew nut oil	Edive	Mango	Parsley
Asparagus	Cassia	Horseradish	Mushroom	Potato
Basil	Cauliflower	Garlic	Mustard	Radish
Bay (Laurel) leaf	Celery	Ginger	Nutmeg	Tomato
Broccoli	Chamomile tea	Ginkgo fruit	Olive oil	Turnip
Brussel sprouts	Chicory	Jamaican pepper	Onion	Rosemary
Cabbage	Cinnamon	Kale greens	Orange	Spearmint
Capsicum	Cloves	Lettuce	Oregano	Turmeric
Caraway oil	Corn	Leek	Paprika	Vanilla
Cardamon	Cucumber	Lime and lemon	Peppermint	
<i>Contact urticaria</i>				
Apple	Chamomile	Flour	Mustard	Seaweed
Apricot	Chicory	Garlic	Oatmeal	Sesame seeds
Almond	Chicken	Grapefruit	Onion	Shallots
Amarith	Chives	Green pepper	Orange	Shellfish
Artichoke	Caraway seed	Honey	Paprika	Soybean
Arugula	Cayenne pepper	Kiwi lamb	Parsley	Spinach
Asparagus	Cinnamon	Lemon	Parsnip	Strawberry
Banana	Coriander	Lettuce	Peach	Sunflower seeds
Barley	Curry	Lime	Peanut	Thyme
Beans	Coffee bean	Litchi	Pear	Tofu
Beef	Corn	Liver	Pickles	Tomato
Beer	Cucumber	Lupin seed	Pineapple	Turkey
Brazil nut	Dill	Maize	Plum	Venison
Buckwheat	Egg	Malt	Pomegranate	Watercress
Cabbage	Endive	Mango	Pork	Watermelon
Carrot	Fennel	Melon	Potato	Wheat
Cauliflower	Fig	Milk	Rice	Wheat bran
Celery	Fish	Mushroom	Rutabaga	Winged bean
<i>Protein contact dermatitis</i>				
Almond	Celery	Fig	Liver (calf, chicken)	Parsley
Banana	Chicory	Fish	Meat (cow, pig, horse, lamb)	Parsnip
Barley Flour	Cheese	Garlic	Mesenteric fat (pig)	Peanuts
Bean	Cress	Gut (pig)	Mushroom	Pineapple
Blood (pig, cow)	Cucumber	Hazelnut	Onion	Potato
Caraway	Curry	Horseradish	Paprika	Rye
Carrot	Dill	Kiwi fruit		Skin (turkey, chicken)
Castor Bean	Eggplant	Lemon		Tomato
Cauliflower	Egg yolk	Lettuce		Wheat
	Endive			

(continued)

Table 2.2 (continued)

<i>Systemic contact dermatitis</i>				
Balsam of Peru	Cinnamon oil	Garlic	Raw cashew nuts	Vanilla
<i>Photo-allergic contact dermatitis</i>				
Bitter	Celery	Fig	Lemon	Parsley
Bergamot	Fennel	Grapefruit	Orange	Parsnip
Carrot				

Pemphigus

Pemphigus is an autoimmune bullous disease of the skin and mucosa. Histologically, it is characterized by acantholysis and immunologically by the presence of specific circulating autoantibodies. These are the immunoglobulin G (IgG) autoantibodies directed against the desmogleins. The desmoglein antigens are the cell–cell adhesion molecules expressed on the keratinocyte cell surface. Binding of circulating autoantibodies to these antigens on skin leads to widening of intercellular space between desmosomal junctions followed by splitting of desmosomes and finally complete epidermal cell detachment (acantholysis) [6]. Involvement of both environmental and dietary triggers in acantholysis has been suggested [7]. The important dietary factors implicated include allelic compounds found in plants of the genus *Allium* (garlic, onion, leek). The -SH group (thiolic) present in these compounds has been demonstrated to be acantholytic in in vitro experiments. These substances intervene in keratogenesis, modify the assembly of keratinocytes, weaken their mutual cohesion, and alter the biochemical structure of adhesion molecules. In vivo they stimulate the production of B cell clones that specifically generate histolesive autoantibodies.

Role of these food compounds in pathogenesis of pemphigus is supported by the high incidence of pemphigus in countries like India where meals contain lot of garlic and spices such as mustard, red and black pepper, coriander, and cumin seeds which are rich in thiols and isothiocyanates. The disease is especially prevalent in communities with practices of eating betel quid, a package of fresh betel leaves soaked in an infusion of citron and tobacco. Coastal communities with higher consumption of the nutrients like tannins, manioc, and thiocyanates are also predisposed.

Tannins are rich in drinking water in Amazon water basins due to nonstop rotting of huge amounts of tropical vegetation. They are polyphenolic compounds able to release cytokines with cytotoxic and acantholytic properties. Tannins can also be found in guarana, a plant that spontaneously grows in the Amazon area that is employed by indigenous people to prepare a very popular drink. Thus, in genetically predisposed individuals, the use of various foods containing thiols, phenols, or tannins may cause pemphigus, which is a rare disease in some countries but endemic in others. Most common treatment for pemphigus is steroid administration rather than diet free of these substances as seen in DH [4].

Psoriasis

Psoriasis is another autoimmune skin condition indicated by the rapid increase in skin cell proliferation. This leaves what is referred to as “plaque” where patches of raised skin appear. The patches are red and swollen and topped with dead silvery white skin cells. These lesions normally happen on the elbows, knees, lower back, and scalp.

The cause of psoriasis is not fully understood. It is believed that there is a hereditary component and many genes work together and involve immune system. This leads to T cell-mediated inflammatory changes. T cells demonstrating activated memory phenotypes are present within the dermis and epidermis of active psoriatic skin lesions [8]. Activated T cells within psoriatic lesions possibly respond to an autoantigen and elaborate many type 1 and proinflammatory cytokines, including Interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), IL-1, and IL-2. By contrast, cells within the

lesions express relatively low levels of type 2 cytokines such as IL-4 and IL-10. Keratinocyte hyperproliferation is believed to be a secondary biologic phenomenon, driven mainly by proinflammatory and type 1 cytokines produced locally by infiltrating T cells.

There is some evidence of association of disordered arachidonic acid metabolism in the pathogenesis. Studies have found that the skin of people with psoriasis contains high levels of inflammatory compounds called leucotrienes which are by-product of arachidonic acid metabolism [9]. Arachidonic acid is rich in diet containing animal fat.

In severe cases, the disease can also result in an inadequate nutritional status, which may be further compromised by nutrient drug interactions. Protein, folate, and iron deficiencies have been reported in such cases. Fasting periods, vegetarian diets, and diets rich in omega-3 polyunsaturated fatty acids from fish oils have been associated with improvement in the symptoms of the disease in some studies.

Scleroderma, a disease of connective tissue, is characterized by fibrosis and thickening of soft tissue. An association of intake of high fiber diet has been suggested with this condition. Improvement with vitamin E has been reported in these patients [10].

Disorders like discoid lupus erythematosus, dermatomyositis, epidermolysis bullosa, lichen planus, vitiligo, alopecia areata, etc. are few other autoimmune disorders; however the role of diet and plant extracts in these conditions is unclear.

HS to Dietary Components

HS reactions to diet-related antigens constitute the etiological basis for many cutaneous disorders collectively called “eczema” or “dermatitis.” The role of immunity has been demonstrated in some of them like atopic dermatitis (AD) and contact dermatitis (CD). Amongst the four types of HS reactions, type I and type IV responses are considered to be more important in diet-related cutaneous HS.

Atopic Dermatitis

AD is a chronic inflammatory skin disease that commonly begins in early infancy, runs a course of exacerbations and remissions, and is associated with a characteristic distribution and morphology of skin lesions. It results from a complex interplay between strong genetic and environmental factors. Genome screens of families with AD have implicated chromosomal regions that overlap with other skin diseases and with inflammatory and autoimmune diseases. This may be one of the reasons that AD is often associated with asthma, allergic rhinitis (hay fever), and food allergy.

Numerous trigger factors for AD have been identified over recent decades, including food allergens, inhalable respiratory allergens, irritative substances, and infectious microorganisms such as *Staphylococcus aureus* and *Malassezia furfur*. AD is regarded as the prototype of spontaneous HS. It manifests itself by means of the heightened capacity of the B lymphocytes to produce IgE antibodies against allergens which trigger off the immune response after contact [11]. This may be due to defective regulation of the T lymphocytes which is associated with inadequate function of the CD8+ lymphocytes in suppressing IgE [12, 13].

Normally the food antigens which are ingested enter the gut and encounter intestinal immune system (Gut-Associated Lymphoid Tissue—GALT). Here they are captured by the APC which then cause apoptosis amongst the antigen-specific T cells or differentiation in the suppressor T cells which produce suppressive Transforming Growth Factor-beta (TGF- β) [14]. A breach in the gut immunity and cross-reactivity of the IgE antibodies with skin antigens or direct interaction with specific IgE, Fc receptors on Langerhans cells, mast cells, monocyte basophilic granulocytes, or skin infiltrating T lymphocytes leads to skin allergy [15].

Cow's milk, eggs, wheat, maize, crustacea, hazelnuts, almonds, and peanuts are the most common allergens implicated in AD and may cause sensitization and an outbreak or worsening of skin changes. Some vegetable gums, carmine red, ethylvanillin, vanilla, and tartrazine can also trigger an IgE-mediated response. In addition to above, the way in which a food is cooked also influences its level of allergenicity. In general, allergens of animal origin continue their activity for longer, whereas vegetable allergens are more easily broken down by cooking or by other processes [16].

Breastfeeding for at least the first 6 months of life is considered to be an important measure in prevention of AD. During breastfeeding, atopic mother's diets should consist of frequently varied organic foods on the basis of their individual food intolerances. As a therapeutic measure also patients of AD should strictly use foods of strictly organic origin, particularly for fruit, vegetables, and whole grains. Frequent use of sunflower oil is also useful due to its high content of -3 and -6 polyunsaturated fatty acids. Topical corticosteroids are still a mainstay of treatment for AD.

Contact Dermatitis

CD occurs when skin comes in direct contact with an allergen. Food handlers, in particular, may acquire dermatoses resulting from occupational exposures. Bakers, chefs, housewives, and spice handlers are at an increased risk. These reactions occur frequently on the hands but may develop around the mouth or on the face. Various types of CD are known: allergic contact dermatitis (ACD), contact urticaria (CU), protein contact dermatitis (PCD), irritant contact dermatitis (ICD), phototoxic contact dermatitis (PTCD), photoallergic contact dermatitis (PACD), and systemic contact dermatitis (SCD). Of these, PTCD and ICD however are nonimmunological responses [17].

Allergic Contact Dermatitis

ACD is characteristically a delayed type of HS, although changes as early as 4–8 h after contact with the allergen can be seen histologically. ACD is a complex immune response, which is a cascade of nonspecific and antigen-specific T cell events. The food allergen that penetrates the stratum corneum after percutaneous contact with the epidermis interacts with APC expressing major histocompatibility complex (MHC) molecules. APC then bind, process, and present the allergen to trafficking lymphocytes in the epidermis. They also acquire the capacity to emigrate and trigger resting T lymphocytes in the lymphoid organs. It was previously thought that only antigen-specific CD4+ T cells and MHC class II restricted T lymphocytes are involved in the immune response, but studies have shown that CD8+ T lymphocytes via MHC class I molecule can also induce the contact HS response. Thus, both CD4+ and CD8+ T lymphocytes mediate the immune response in vivo. Lymphokines released from T cells activate the keratinocytes to up regulate the expression of Class I MHC molecules and expression of Class II MHC molecules along with the release of cytokines that in turn accelerate T cell activation, attract T cell migration into the epidermis, and further potentiate the immune response.

ACD to foods is most often caused by the oleoresins in the fruits and vegetables (Table 2.2). Mango dermatitis is a common reaction seen to the sap, fruit skin, leaf, or stem of the mango tree [18]. Urushiol, the allergen responsible for this reaction, is the same oleoresin present in poison ivy, poison oak, and other members of the Anacardiaceae family. The eruption commonly occurs within hours of contact with the allergen in previously sensitized individuals. The most common presentation is perioral dermatitis resulting from contact with the mango rind. Other members of the Anacardiaceae family, which may also be ingested, include cashew nut shell oil and ginkgo seed. Cashew nut oil is extracted from the cashew nut tree and contains cardol, a phenol similar to urushiol. Seed pulp of the female ginkgo tree (*Ginkgo biloba*) also contains urushiol and may cause perioral or perianal dermatitis upon ingestion. Peeled from its outer coat, the ginkgo seed is added to soups or roasted and eaten. Reportedly, only contact with the pulp will cause a reaction but may occur with the seed kernel as well

[19–21]. *Ginkgo biloba* taken orally for energy and memory is an extract obtained from the leaves. Many spices and their essential oils used in cooking are also reported to cause ACD [22]. Spice allergy usually presents as dermatitis on the palmar sides of the fingers or hands. Paprika, clove, Jamaica pepper, cinnamon, nutmeg, and ginger are the most commonly encountered spice allergens in food workers [23].

Contact Urticaria

CU is a transient wheal and flare reaction occurring in areas of contact with an allergen. This reaction can occur with or without sensitization. An immediate pruritic response develops with erythema and edema at the site of contact which usually subsides within 45 min. Two types of contact urticaria are recognized: nonimmunological contact urticaria (NICU) and immunological contact urticaria (ICU) [24]. The immunological reaction (ICU) occurs in sensitized persons as a type I HS response caused by mast cell degranulation within the skin. The antibodies of IgG1 or IgG3 subclass, directed against alpha subunit of the high-affinity IgE receptor (FcεRIα), effectively fix the complement and induce histamine release from basophils and mast cells that express FcεRIα. The reaction can be local, spread beyond the area of contact, or cause systemic symptoms including rhinitis, asthma, and anaphylactic shock. Food handlers and chefs are in constant contact with meats, fruits, and vegetables and their skin barrier is often compromised from repeated water exposure [25].

Protein Contact Dermatitis

PCD is a rare type of eczematous reaction occurring to large proteins in foods [26]. These proteins are thought to penetrate compromised skin to elicit an immediate urticarial and vesicular reaction. It is considered to be a combination of immediate Type I and delayed Type IV allergic responses. The majority of patients are food handlers. Meats are a well-known cause of PCD; therefore the butchers and slaughterhouse workers are most commonly affected. Different types of flour, including rye, wheat, and barley, as well as their additives such as the enzyme alpha amylase, have also been associated with PCD. Janssens et al. have described four principal groups responsible for PCD: fruits, vegetables, spices, and plants; animal proteins; grains; and enzymes [27].

Systemic Contact Dermatitis

SCD develops after oral or parenteral exposure to an allergen in a topically sensitized individual. This is believed to be resulting from the hematogenous spread of the allergen, provoking a cutaneous reaction. Systemic effects such as rhinitis, conjunctivitis, headache, gastrointestinal complaints, or anaphylaxis are commonly associated. SCD may be mediated by both type III and type IV HS reaction as both immediate and delayed reactions occur upon exposure. The foods that individuals become sensitized to topically and have the potential to cause SCD include flavoring agents such as oil of cinnamon, vanilla, and balsam of Peru, various spices, garlic, propylene glycol, and raw cashew nuts.

Photoallergic Contact Dermatitis

Phytophotodermatitis is the name given to phototoxic reactions occurring to plants, vegetables, or fruits. In PACD, the allergen is photoactivated by either sunlight or artificial light in the UVA range.

Hapten formation between the activated antigen and a skin protein is necessary to incite a delayed HS reaction. Garlic exposure has been suggested as an associated factor [28]. Psoralens (furocoumarins) are the responsible agents found in the Umbelliferae (carrot, celery, fennel, parsley, parsnip), Rutaceae (lemon, lime, bitter and bergamot orange, grapefruit), and Moraceae (fig) families [29].

Avoidance of allergen is the best and the only truly effective treatment for CD. Although exposure of patients to low levels of sensitizing chemicals may be permissible, strict avoidance is preferable. Physical barriers may provide protection; barrier creams are not generally useful. Antihistamines may provide some symptomatic relief and high-potency topical corticosteroids may hasten lesion resolution. Cases of severe CD may require systemic steroid treatment at relatively high doses. Adjunctive phototherapy with ultraviolet B light or PUVA may be indicated for such patients.

Idiosyncratic Susceptibility to Diet

Idiosyncratic susceptibility to dietary factors may sometimes be seen due to interactions with systemic medication, for example, severe alcohol induced flushing in some patients who take chlorpropamide and the reaction to cheese or pickles in patients taking inhibitors of monoamine oxidase [30]. There may be reactions due to anatomical abnormalities such as the flushing that accompanies the post-gastrectomy dumping syndrome. Some idiosyncratic reactions like the urticaria and bronchospasm caused by bisulfites used to keep fruits and vegetables fresh may be mediated by neural activity. The Chinese restaurant syndrome, in which similar symptoms occur after eating sodium glutamate, seems to be mediated by the transient release of compounds similar to acetylcholine [31].

Deficiency or Excess of Specific Dietary Nutrient

The skin functions normally when adequate nutrition is provided. Any dietary imbalance in the form of nutritional deficiency, specific nutrient inadequacy or excess, and toxic components can disturb the equilibrium of the skin. Although the cutaneous manifestations of deficiencies or excess of several vitamins, minerals, and fatty acids are well recognized their effect on immune system is not clear.

A deficiency of minerals like zinc leads to acrodermatitis enteropathica characterized by weeping dermatitis, delayed wound healing, secondary infection, alopecia, and nail defects. Lim et al. have hypothesized the involvement of dietary zinc in activating the nuclear factor-kappa B (NF B), expression of proinflammatory cytokines (IL-1b) and tumor necrosis factor- α , and neutrophil infiltration during the early stages of cutaneous wound healing [32]. Other foodstuffs which can block NF B-mediated activation of inflammatory cytokines include turmeric, red pepper, cloves, ginger, cumin, anise, fennel, basil, rosemary, garlic, and pomegranate that may also play a role in modulation of cutaneous immunity [33].

Vitamin deficiencies may also lead to various cutaneous manifestations, i.e., phrynodema (vitamin A), scurvy (Vitamin C), pellagra (niacin), etc. Majority of green vegetables and fruits are rich sources of one or other vitamins. Vitamins have been reported to induce increased production and activity of natural killer cells, increase IL-2 production, and stimulate humoral immune responses. Vitamin E has also been seen to decrease prostaglandin E₂ production, as a result of which the T cell proliferation and function may be enhanced. Besides these, some vitamins and minerals like Vitamin C, E, and selenium (found in wheat germ, garlic, Basil nuts, brown rice, whole wheat bread, eggs, and seafoods like Tuna and Salmon) are also required for their antioxidative properties. They prevent free radical damage of collagen and elastin, the fibers that support the skin structure and prevent wrinkles and other signs of ageing.

Carotenoderma, a condition caused by excessive intake of carotene-rich foods like oranges and carrots, manifests as yellowish to orange skin discoloration. Xanthelasma is a condition associated with high intake of fats and lipids. Phytanic acid is found in foodstuffs like dairy products, meat, and fish and its impaired oxidation leads to Refsum's disease causing a rough scaling skin over the extremities [34]. A high glycemic load in food with associated rise in insulin and Insulin Growth Factor-1 (IGF-1) levels has been associated with cutaneous disorders like acne and rosacea which are characterized by a heightened immune response and inflammation [35].

Conclusion

The relationship between diet and skin disorders has gained interest in recent years. There is abundance of literature linking almost every skin disorder with diet in one or other manner. Majority of these explain beneficial role of diet and plant products in dermatology. The literature on diet and plant extracts acting as etiological factors is still scanty and there is a gap in the understanding of their role in causation of IMSD. Futuristic studies may help not only in bridging the gaps in our current knowledge regarding drIMSD but also in developing specific therapies based upon the offending dietary antigens.

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