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Impact of Gut Microbiome Dynamics on Epidermal Health

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The trillions of bacteria that reside on and inside the body constitute the human microbiome, which is essential to maintaining host health. The gut microbiome is one of these microbial communities that has attracted a lot of attention due to its effects on the skin and other physiological systems. An extensive synopsis of the complex connection between gut microbiota and epidermal health is given in this review. There are ways in which the gut microbiota influences the health of the epidermis. It has been demonstrated that gut microbe-produced metabolites, such as vitamins, secondary metabolites, and short-chain fatty acids, affect skin barrier function and immune response modulation. Furthermore, the complex interaction of immunological signalling pathways, which govern communication between the gut and skin, regulates the gut-skin axis. Rosacea, psoriasis, eczema and other dermatological disorders are related to dysbiosis of the gut microbiome. Gaining knowledge of mechanisms underlying this relationship could be extremely beneficial for the creation of novel treatment approaches targeted at enhancing health and treating or preventing a range of dermatological disorders. In order to maintain optimal epidermal health, future research endeavours should concentrate on clarifying the precise microbial taxa and metabolites that are essential to this complex interplay in gut-skin axis.

Keywords: Dysbiosis; Epidermal Health; Gut-Skin Axis; Gut Microbiome; Probiotics.

The 10-100 trillion symbiotic microbial cells that each individual carries, predominantly bacteria in the stomach, make up the human microbiota[1]. Numerous illnesses, such as inflammatory bowel disease, multiple sclerosis, diabetes (types 1 and 2), allergies, and asthma, have been linked to dysbiosis in the microbiome[2, 3, 4]. They enhance the immune system, provide pathogen defence, support metabolic activities, and through these vital tasks directly or indirectly affect most of our physiological systems[5]. The microbes in the gut which harbours around 1000 species of bacteria and around 5 million genes carry out many of the tasks necessary for human survival as well as physiology[6]. It is becoming widely recognized that the gut microbiome and human health are corelated. The healthy gut microbiota has specialized roles in the host's food metabolism, the metabolism of xenobiotics and drugs, the preservation of the immunomodulation and the structural integrity of the gut as mucosal barrier and pathogen defence[7]. The human body's largest organ is the skin, which

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behave like a protective barrier against wounds and microbial attack[8]. The host's health and longevity are directly related to the billions of microbial communities that make up the gut, which is known as a virtual organ. The homeostasis of both gut and skin tissues are both influenced positively and negatively by the gut microbiota[9, 10]. Skin symptoms of Gastro-Intestinal (GI) illnesses are frequently present., The gut microbiota seems to have an important role in the pathogenesis of many inflammatory conditions[11, 12]. The microbiome functions to conserve homeostasis by interacting bidirectionally with tissues and organs, making it a crucial immune system regulator. As a result, imbalance in the skin and gut microbiota is linked to a diversified immune response, which promotes the evolution of skin illnesses like atopic dermatitis, psoriasis, acne vulgaris, dandruff, and melanomas[13]. The diversified gut microbiome may influence the cutaneous flora, according to mounting evidence, although the precise mechanism by which this happens is unclear[14]. Studies have connected gut microbiome imbalance to inflammatory skin illnesses, making it possible to modulate gut microbiota to treat skin conditions. Natural products are becoming more popular as synthetic medicine substitutes today. In this regard, oral probiotics may be a straightforward, risk-free, and affordable therapeutic management strategy for skin irritation[15]. Consequently, the gut microbiota is a possible target for controlling the host's immunological reactions. Numerous skin conditions are characterized by persistent inflammation. The health of the skin may be impacted by imbalances in the gut microbiota that result in a condition of systemic inflammation. The generation of inflammatory chemicals, which can affect the skin's inflammatory response, is controlled by the gut microbiota. It is possible that an unhealthy gut microbiota will make skin inflammation worse. The gut microbiome aids in the maturation of immune cells and the gut is home to a sizeable percentage of the immune system cells. When the gut microbiota is in equilibrium, the immune system is better trained to distinguish between benign and hazardous substances. The capacity of immune system to stop inappropriate inflammatory reactions that can cause skin diseases is influenced by this equilibrium[10]. The epidermal barrier of the skin guards against infections. It is interesting to note that the gut microbiota has an effect on the expression of proteins necessary for skin barrier maintenance. While imbalances may jeopardize the integrity of the epidermal barrier, a balanced gut microbiota can support a healthy epidermal barrier. Numerous researches have looked into the relationship between skin allostasis and homeostasis with gastrointestinal health in recent years, and corroborating evidence suggests that the skin and gut have a strong bidirectional association[10, 16]. This is demonstrated by the existence of translocation of bacterial DNA, which has recently been linked to the gut microbiome composition and suggests that recent active plaque psoriasis breakouts may be related to circulating bacterial DNA in blood from the intestinal lumen[17]. The alterations in gut microbial metabolism and immunological responses are brought on by the imbalance of the diversity of the gut microbiome and its composition, which also results in intestinal microecological disturbance. These changes are crucial for maintaining human health, since they are strongly related to physiological and pathological processes. The structural diversity of gut microbiota resists pathogen invasion and lessens the feeding conflict between symbiotic and possibly hazardous microorganisms. The adult innate and adaptive immune systems are stimulated by the gut microbiota, which is important in the metabolism of bile acid, vitamins, amino acids, and short-chain fatty acids.[18]. Modifications in the microbiome are associated with the onset of cancer and may have an effect the immune system and treatment response. Recent research has demonstrated that the gut microbiota, in particular, can modify the response to melanoma immunotherapy[19]. However, the significance of the skin microbiota in the microenvironment of epidermal tumours has not been thoroughly researched, and the interrelation between the gut microbiome and skin microbiome in the advancement of melanoma has not been looked into[19]. The gut-brain-skin axis, which was initially proposed by Arck *et al*.[20], postulated that a number of gastrointestinal and skin disorders are caused by excessively shared signals and cellular protagonists, complex gut and skin innervation, and the predominance of neurogenic inflammation. The human microbiome project (HMP), which was started in 2007, aims to characterize the resident bacteria of the oral cavity,

skin, nose, vagina, and stool by examining the diverse microenvironments of the human body. The HMP identified the "normal" human microbiome in the end, with the help of samples taken from distinct anatomical environments at various times[21]. Previous restrictions have been overcome by more recent methods including metagenomic sequencing[22] and 16S ribosomal RNA (16S rRNA) amplification[21]. This review explores the intricate relationship between gut microbiota and epidermal health, elucidate their interconnections and their consequences for overall well-being.

Gut microbiome

The bacteria, viruses, and eukaryotic organisms living in and on our body make up the microbiome of humans. These bacteria have a great capacity to affect both the health and illness of our physiological system. They play a role in the metabolic processes, provide defence against pathogens, prepare the immune system, and through these fundamental processes affect the majority of our physiologic processes directly or indirectly[5]. It is becoming widely understood that the gut microbiota and human health are related. It is now well understood that a healthy gut microbiota has a significant impact in the host's overall wellbeing. *Bacteroidetes* and *Firmicutes* make up the majority of the normal human gut microbiota[7]. The Human Microbiome Project and the Metagenome of the Human Intestinal tract (MetaHIT) investigations predict that the human microbiome may contain about ten million genes that are non-redundant, if seen from the perspective of all bacterial genes[31]. The phyla *Actinobacteria* and *Verrucomicrobia* are then listed after this. Even while this basic profile does not change, the distribution of the gut microbiota shows temporal and spatial variations at the genus level and above. As one travels from the oesophagus and stomach to the rectum, there will be a discernible change in the variety and quantity of bacteria with values ranging from 10^1 per gram of contents in the former to 10^{12} per gram of contents in the latter and distal gut[7]. The microbiota of the gastrointestinal system is divided into two groups: transverse and longitudinal, and its composition is a reflection of the physiological characteristics of a particular area[32]. Chemical, nutritional, and immunological gradients in and along the gut are believed to have an influence on the density and constitution of the microbiota. High quantities of acids, oxygen, and antimicrobials with a quick transit time are normally seen in the small intestine[33]. Numerous environmental factors, such as geographic location, medical procedures, smoking, depression, and type of housing, whether it is urban or rural have been linked to forming the microbiota[34]. The microbial communities that live in different parts of the human gut have an impact on a variety of health-related factors. In a healthy state, they support the host's metabolism and immune system by providing nutrients and energy to the host through the large intestine's fermentation of dietary components that are indigestible.

Negative effects, however, may include being causes of infection and inflammation, being connected to gastrointestinal disorders, and perhaps making a difference in the development of diabetes mellitus and obesity[35]. In some circumstances, changes to the gut microbiome are noticeable years before a disease manifest itself, providing biomarkers for early disease risk detection and chances for preventive therapies. The growing body of information linking microbial causes of disease to specific pathogenic mechanisms, which in turn identifies new microbial targets for drug development, is fundamental to all of these observations. Following attempts to restore a disturbed gut microbiota through dietary intervention, microbial supplementation, or faecal microbiota transplant, positive effects have been seen for several disease indications[36].

Gut-Skin axis

The processes through which intestinal microbiota affect skin homeostasis are yet unknown, but they seem to be connected to the modulatory impact of gut commensals on systemic immunity[10]. According to recent research, the intestinal microbes may have a more direct influence on the physiology, pathology, and immune response of the skin due to the gut microbiota and their metabolites' skin metastasis[10, 37, 38]. The mechanisms via which the gut microbiota has an effect on the skin health is unknown[38]. Both the skin and the gut are active, intricate immunological and neuroendocrine organs that are frequently exposed to the outside world and support a diverse array of microbiomes[39, 40]. Gut-skin axis microbiota research have an influence to research and to acknowledge the link between the gut microbiome and alterations

to the skin microbiome as well as the ensuing epidermal illnesses such as atopic dermatitis, psoriasis, acne vulgaris and other disorders. These studies go beyond the aetiological factors such as environmental, nutritional, or medicinal exposures[41]. According to the study conducted by Liedtke[42], the management of dermatoses with probiotics and prebiotics as well as dietary and lifestyle changes point to the presence of a crucial gut-skin axis. It is essential to balance the gut microbiota in order to develop aesthetically healthy skin. In order to effectively treat inflammatory skin illnesses, treatments that raise or repair the intestine are necessary as adjuvant therapy. These procedures may also increase the efficacy of conventional dermal therapy. [43] The immune system and gut microbiome appear to interact as well as train the regulatory T lymphocytes, which can result in the inflammation in other parts of the body[43, 44]. Although the significance of the gut microbiome in autoimmune and inflammatory skin disorders is still being investigated, regulatory T cells appear to have a significant role in these conditions[45. 46, 47].

Psoriasis

A chronic inflammatory skin condition called psoriasis is characterized by whitish scale-covered, clearly delineated erythematous plaques[48]. Psoriasis is a chronic skin disorder that frequently has systemic symptoms. Although psoriasis can appear at any age, it usually first appears between the ages of 15 and 30. The clinical course is uncertain[49]. A first-degree relative who also has psoriasis affects about one-third of individuals. Research indicates that inheritance is complex[49]. Psoriasis risk and severity both rise with smoking. Alcohol misuse and obesity are also connected to psoriasis. These correlations may not be causal; psoriasis sufferers may be more prone to these patterns of alcohol misuse and obesity[50]. The most well-known and approachable human illness that is interceded by T lymphocytes and dendritic cells is psoriasis vulgaris. Interleukin-23 and interleukin-12 are released by inflammatory myeloid dendritic cells, which then stimulate T lymphocytes, Type 1 T helper (Th1) cells, and T helper 22 (Th22) cells to produce large amounts of the psoriatic cytokines IL-17, interferons, tumour necrotic factors, and IL-22. These cytokines influence keratinocytes in a way that intensifies psoriatic inflammation[51]. Many studies revealed that intestinal permeability, the immune system, and metabolism are all significantly influenced by gut bacteria[52, 53]. The psoriasis comorbidities metabolic syndrome, depression, cardiovascular disease, and inflammatory bowel illnesses have all been linked to the dysbiosis of the gut microbiome, also known as gut dysbiosis[54, 55, 56, 57]. Psoriasis and changes in gut microbial composition are significantly correlated, but there is significant variation among various researches[58]. Psoriatic flare-ups and microbiome imbalances, defined by modified diversity and organisation as well as blooms of opportunistic pathogens, are closely related[59]. Zakostelska *et al.*[60] demonstrated that imiquimod stimulates milder psoriasis-like skin inflammation in mice that were germ-free than in conventional mice by enhancing the Th17 response, indicating that gut dysbiosis acts as a probable pathogenic element for psoriasis. The intestinal microbiota promotes balance between Th17 effector cells and their equivalent regulatory T cells[61]. In a study conducted by Huang *et al.*[62], 35 psoriasis sufferers and 27 healthy controls had their faeces sequenced by 16S rRNA and then the results were examined using informatics techniques. It was discovered that the psoriasis group's microbiome was unlike that of the healthy group. The microbiome of people with severe psoriasis is different from those of people with more mild cases and also from healthy controls[62]. The microbiome has been shown to have a crucial role in the production of immunoglobulin A and the preservation of the equilibrium between effector and regulatory T lymphocytes in the gastrointestinal tract. Furthermore, chronic inflammatory skin diseases like psoriasis are linked to gut bacterial dysbiosis. Consequently, it may be said that the microbiota is a potent therapeutic target for curing this condition[63]. The composition of the human gut microbiome begins to form shortly after birth and stabilizes at the age of two, however significant changes can also be observed later in life due to food, lifestyle, comorbidities, antibiotic courses, and other factors.[64]. Gram-negative and Gram-positive anaerobic bacteria, such as those in the *Bacteroides, Bifidobacterium, Eubacterium, Fusobacterium,* and *Ruminococcus* genera, make up the great majority of the intestinal microbiome, outnumbering aerobic bacteria by

a factor of over a hundred. *Bacteroidetes* along with *Firmicutes* are the two phyla that make up the majority of the intestinal microbiome[65]. In a study performed by Arumugam *et al.*[66] three distinct gut microbiome clusters known as enterotypes were identified according to dominating genera. *Bacteroides*, *Prevotella*, and *Ruminococcus* are the three enterotypes. Enterotype three, which includes the *Ruminococcus* genus in addition to the *Akkermansia* genus, is the most prevalent. As studied by Polak *et al.*[64] the most remarkable discoveries regarding changed gut physiology in psoriatic patients appear to be microbiota dysbiosis, depletion in short chain fatty acid synthesis, an increase in generated trimethylamine-N-oxide, and dysregulation of pathways controlling the balance of lymphocyte populations[69].

The bacterial composition of the stomach may be impacted by the medications used to treat psoriasis. A different form of psoriasis called guttate psoriasis, which is more frequent in children and adolescents than in adults, is traditionally brought on by a streptococcal infection[69]. Guttate psoriasis exhibits rapid involution and extended remission than other kinds of psoriasis, although little is known about its clinical history[67]. Based on the finding that patients' gut microbiota profiles were dysbiotic when compared to healthy controls, abnormal cytokine levels are linked to abnormal cytokine profiles. As therapeutic targets or psoriasis biomarkers, it was anticipated that gut microbiota will be crucial in the clinical diagnosis and treatment of psoriasis[70]. The last 20 years have seen the discovery of causative immunological course of psoriasis that link up on adaptive immune pathways including interleukin (IL)-17 and IL-23[71]. Mice fed with *Lactobacillus pentosus* showed a decrease of psoriasis-related, pro-inflammatory, and Th17-associated cytokines like tumour necrosis factor (TNF)-, IL-17A, and IL-23[72]. The clinical value of the immune system's and microbiota's interaction is crucial. Secukinumab, ixekizumab, and guselkumab, monoclonal antibodies that target IL-17A and selective IL-23, respectively were all very successful in treating psoriasis, but their effects in treating inflammatory bowel disease (IBD) were inconsistent. IBD has become worse as a result of clinical studies for biologics that block IL-17A or its receptor[73, 74]. In a study done by Huang *et al.*[71] showed that the patients with psoriasis who received therapies with IL-23 and IL-17 inhibitors experienced different changes in the composition of their gut bacteria. According to significant changes within the comparative plethora of bacterial taxa between responders and non-responders, IL-23 and IL-17 inhibitors may work in conjunction with the gut microbiome to lessen cutaneous inflammation. It looks quite complicated how skin psoriasis and gut microbiota are related. Just about all studies of the gut microbiome found consequential changes in psoriatic sufferers. The complete therapeutic potential of the alterations in the gut microbiota in patients affected by psoriasis needs to be further investigated in the future[64].

Atopic dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a habitual relapsing seditious epidermal condition. Prevalence of atopic dermatitis has shot up two to three-fold within bucolic nations, impacting roughly 15 to 20 of children and one to three of grown-ups worldwide[75]. Although atopic dermatitis shows indications of skin barrier disfigurement and immunological divagation, the fundamental mechanism of action of eczema isn't recognised properly, and the therapy is frequently veritably delicate. There is substantial data that AD cases have an imbalanced microbial anatomy and decreased microbial diversity in their skin and gut in contrast to controls, which contributes to complaint onset along with atopic march[76]. As compared to healthy individuals, diversity of the gut microbiome reduced and the relative plethora of the beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* consequently decreased, in contrast, the magnitude of *Escherichia coli*, *Clostridium difficile* and *Staphylococcus aureus* was higher in people suffering from AD. Principally, the microbial colonization and adaptations were illustrated preceding any clinical manifestations in early life, stipulating gut microbial imbalance as one of the reasons for AD[77]. In addition, host-commensal interactions affect how children' immune systems grow and, as a result, how often illnesses like atopic dermatitis manifest. The cutaneous microbiota influences the onset and progression of skin diseases later in life. As a result, the severity of the condition and a rise in the colonization of harmful bacteria such *Staphylococcus aureus* are correlated in AD patients with a decrease in microbiome diversity[78]. More severe clinical signs

of AD are caused by skin microbiota, mainly *S. aureus* and Malassezia blooms in the lesions[79]. Diet, lifestyle choices, and psychological stress all have an impact on the dynamic and special ecosystem known as intestinal microecology. The alterations in gut bacterial metabolism and immunological reactions are brought on by the dysbiosis of gut microbial diversity and anatomy, which also results in intestinal microecological disturbance. These changes are crucial for maintaining human health since they are strongly related to physiological and pathological processes. The innate and adaptive immune response mature as a result of the gut microbiome's role in the metabolism of short-chain fatty acids, amino acids, vitamins, and bile acids[80]. The "gut-skin" axis has also been suggested as a new goal for the prevention and therapeutic modalities of AD[10]. In a study performed by Atarashi *et al.*[81] the relationship between the gut microbiota and the T and B lymphocytes might result in systemic effects which are distant from the gut location. Additionally, intestinal dendritic cells' migration of microbial antigens from the gut to the thymus caused gut microbial colonization to increase growth of microbiota and T lymphocytes in the thymus[82]. Myeloperoxidase and lipid hydroperoxide levels were considerably higher in a recent study of 56 children with atopic dermatitis. In contrast, a lower blood level of the total antioxidant potential value suggest that AD may be linked to an increase in oxidative stress reactions and a decrease in antioxidant defence[75]. As a result, changes in gut microbes are intimately related to immunological responses and are critical in the emergence of disorders involving abnormal immune activities[80].

Seborrheic dermatitis

A chronic relapsing erythematous scaly skin condition called seborrheic dermatitis affects 1 to 3% of the population in United States. It has two incidence peaks: the first occurs through the first three months of life, and the second starts throughout puberty and peaks between the ages of 40 and 60[84]. Malassezia yeasts, hormones (androgens), sebum levels, and immunological response are all recognized to have important contribution in the development of seborrheic dermatitis, despite the fact that the actual cause is still unknown. Seborrheic dermatitis may be made worse by additional elements such as medicines, cold weather and stress[85]. Seborrheic dermatitis and dandruff are frequently linked by a fungal component. The most prevalent yeast species in the skin's mycobiome, *Malassezia spp*. are lipophilic and dominating fungi that colonize the scalp of humans[86]. It is believed that *Malassezia spp.* increase oleic acid synthesis, disrupting the stratum corneum cells and causing an inflammatory reaction on the scalp[13]. When compared to a placebo treatment, a clinical trial on the consumption

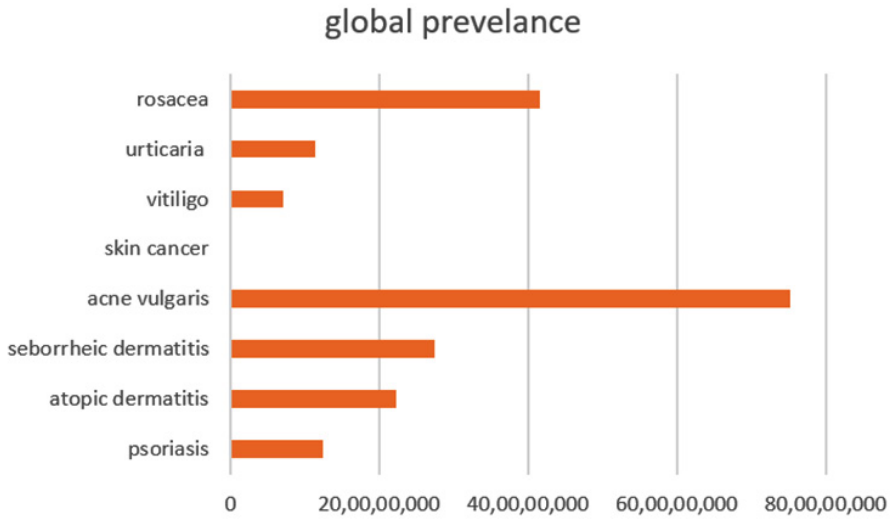

Fig. 1. Plot of the global prevalence of psoriasis, atopic dermatitis, seborrheic dermatitis, acne vulgaris, skin cancer, vitiligo, urticaria and rosacea[23, 24, 25, 26, 27, 28, 29, 30]

of probiotics (*Lactobacillus paracasei* strain) revealed significant reductions in the intensity and signs of moderate to severe dandruff. It is yet unclear, nevertheless, how the composition of the gut microbiota affects seborrheic dermatitis and dandruff[87]. It is debatable if gut dysbiosis and dandruff or seborrheic dermatitis are related. Patients with seborrheic dermatitis have intestinal mucosal abnormalities that have been identified[88].

Acne vulgaris

Inflammation, increased sebum production, hyperkeratinisation, and primarily Propionibacterium acnes (formerly known as *Cutibacterium* acnes) proliferation are the main causes of acne, which can leave behind crippling psychological scars[89]. As a follicular illness, acne is characterized by the impingement and distention of the follicles by a keratinous plug, which results in the initial comedown. Keratinocyte hyperproliferation and improper differentiation result in keratinous plugs. The production of antimicrobial peptides and cytokines by activated keratinocytes can have both a direct antimicrobial effect and result in the recruitment and regulation of immune cells[90]. There is currently little consensus on the precise processes through which the gut microbiota affects the start as well as progression of acne[91]. Endotoxemia and increased intestinal permeability have been linked to acne in studies conducted many years ago[92]. Due to increased serum reactivity to faecal coliforms in 66% of patients compared to 0% of controls in a complement fixation test, intestinal permeability may be higher in acne patients[92]. Gut flora and its metabolites can invade the bloodstream, collect in the epidermis, and affect skin homeostasis when intestinal barrier is compromised[40]. The link between gastrointestinal problems and acne may have its roots in the brain. The aggravation of acne brought on by stress lends credence to this hypothesis. Stress affects the normal gut microbiota, most significantly *Lactobacillus* and *Bifidobacterium* species, according to experimental animal and human investigations[93]. There is evidence that the Western diet and its accompanying intestinal flora cause inflammatory acne. For example, diets high in fat decrease the quantity of gut microbiota and raise the quantities of lipopolysaccharides which affect colonic epithelial integrity and barrier function, which reduces the thickness of the mucus layer and increases release of pro-inflammatory cytokines, all of which lead to systemic inflammation[94]. Additionally, Yan *et al.*[95] discovered that acne sufferers' levels of *Lactobacillus*, *Bifidobacterium*, *Butyricicoccus*, *Coprobacillus*, and *Allobaculum* were lower than those of controls offers fresh insight into the relationship between acne and changes in gut flora. Common probiotic species like *Lactobacillus* and *Bifidobacterium* regulate the intestinal microbiota by digesting unabsorbed oligosaccharides in the upper intestine[96]. Additionally, *Bifidobacterium* and *Lactobacillus* promote the development of regulatory dendritic cells and CD4+Foxp3+ T cells (regulatory T cells), which inhibits the response of T helper cells and B cells as well as the generation of cytokines[97]. In an earlier investigation, blood

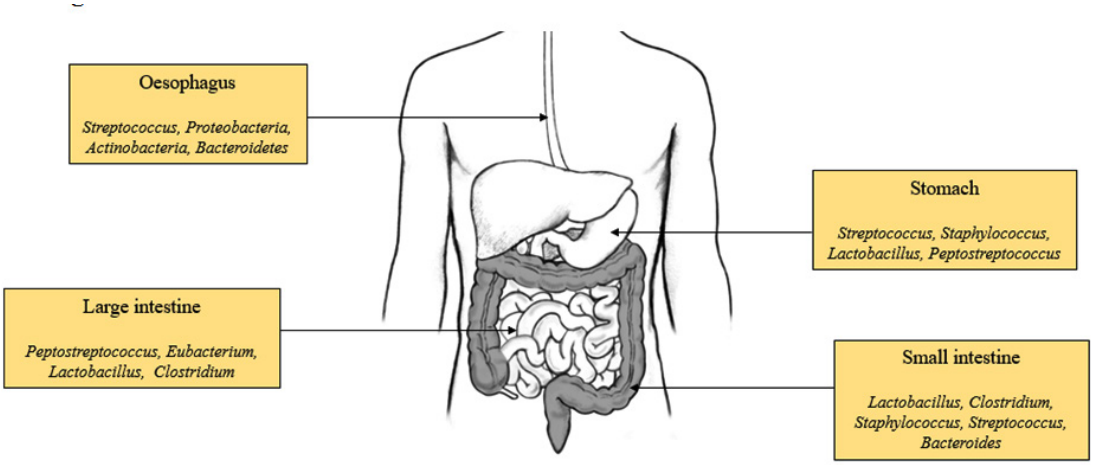

Fig. 2. Microbiome composition in organs of the gastrointestinal tract

serum complement fixation testing was utilized to determine whether patients had increased reactivity to bacterial strains isolated from stool[93]. Acne sufferers were more prone to have this enhanced reactivity. Comparatively to none of the control patients with no active skin disease, almost 66% of the 57 acne patients displayed positive reaction to stool-isolated coliforms[93]. It is important to conduct more research to understand the enteral microbiome of acne sufferers and the alterations in gut microbiota that occur after using oral antibiotics and isotretinoin[96].

Skin Cancer

The most prevalent group of malignant neoplasms in the white population is skin cancer. Melanoma and non-melanoma skin cancer incidence rates are rising globally[99]. In general, Caucasians have a lifetime risk of acquiring melanoma of 2.4%, Blacks have a risk of 0.1%, and Hispanics have a risk of 0.5% [100]. Age raises the likelihood of developing melanoma. At the time of diagnosis, the usual age is around 60. Males are around 1.5 times more likely than females to develop melanoma. It has been demonstrated that the incidence rate does not differ considerably until the age of 40, but after the age of 75, the incidence is nearly three times higher in men than in women[101, 102]. The methods by which the gut microbiome may raise or lower the risk of particular malignancies have been relatively thoroughly investigated, and they may also apply to the skin microbiome. Furthermore, through encouraging systemic inflammation, the gut flora may directly affect the risk of cancer in skin and other organs[103]. Alterations in the gut flora have been linked to carcinogenesis, immune evasion, and chronic inflammation, with particular bacteria being responsible for the emergence of particular tumours. Recently, it has come to light that the gut microbiota may be a novel element in the progression and management involved in malignant melanoma[104]. Indicators that the gut microbiome may be associated with the aetiology of melanoma were discovered by Vitali *et al.*[105]. In another study conducted by Luo[106] it was discovered that *Lactobacillus reuteri* FLRE5K1 could increase the formation of anti-oncogenic cytokines in mice, stop the migration of the melanoma cell line B16-F10, and delay start of skin cancer thus prolonging survival. According to research by Li *et al.*[107] introduction of 11 bacterial strains that are abundant in ubiquitin ligase RNF5 negative mice results in the establishment of anti-tumour immunity and limits the formation of melanoma in germ-free mice. Meanwhile, Pereira *et al.*[108] demonstrated that the microbiota and IL-6 of obese mice promote the progression of melanoma, and faecal transfer experiments from leptin-deficient (obesity) mice revealed tumour evolution in lean mice. These two experiments show an alternative

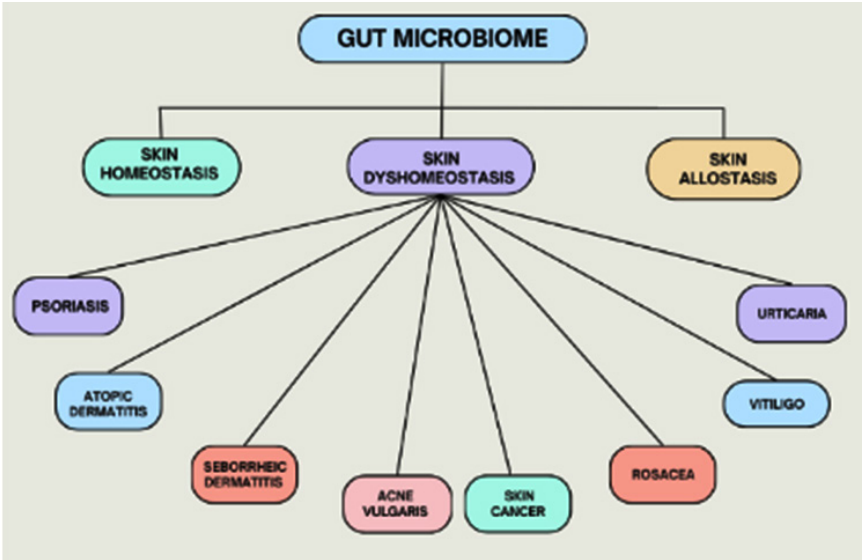

Fig. 3. Effect of gut microbiome on skin dyshomeostasis

melanoma treatment approach to the conventional methods now in use[104].

Vitiligo

An autoimmune condition called vitiligo is characterized by white patches of skin caused by the loss of melanocytes[109]. 0.5 to 1% of the global population is affected by this autoimmune skin disorder[110]. A loss of melanocytes that occurs over time in the skin and occasionally in the hair follicles is what defines vitiligo. The loss of melanocytic cells is now well established to be caused by CD8+ T lymphocytes drawn to the epidermis. In patients with vitiligo, Genome-Wide Association Studies found more than 50 loci are susceptible for the condition related to melanogenesis and the immune system[111]. Numerous inflammatory and autoimmune illnesses have been linked to gut and, to a lesser extent, skin dysbiosis. Surprisingly, there are still few microbiome investigations of vitiligo[109]. It is recognized that the primary factor in the degeneration of melanocytes is autoreactive CD8+ T lymphocytes. Additionally, a number of parameters, such as the heightened inflammatory environment brought on by excessive proinflammatory substances, affect how CD8 is activated. One such cytokine is IL-1. It has been shown that CD4+ T cells, such as Th1 and Th17 cells, aid CD8+ T cells' abnormal response in vitiligo[112, 113]. There may be a relation between vitiligo and intestinal microbiome, even though the relationship of the intestinal microbiome and the autoimmune state in vitiligo has never been studied. According to Hadi *et al.*[114], vitiligo patients frequently also have inflammatory bowel disease (IBD), another autoimmune condition linked to an abnormal gut microbiome[115, 116]. In an experiment conducted by Dellacecca *et al.*[117] link between gut dysbiosis and ampicillin-induced depigmentation has been suggested by the correlation between ampicillin treatment and faster depigmentation, decreased bacteria in faecal pellets, and altered T cell distribution in tissues and blood. According to a recent study by Ganju *et al.*[118] the skin lesions associated with vitiligo

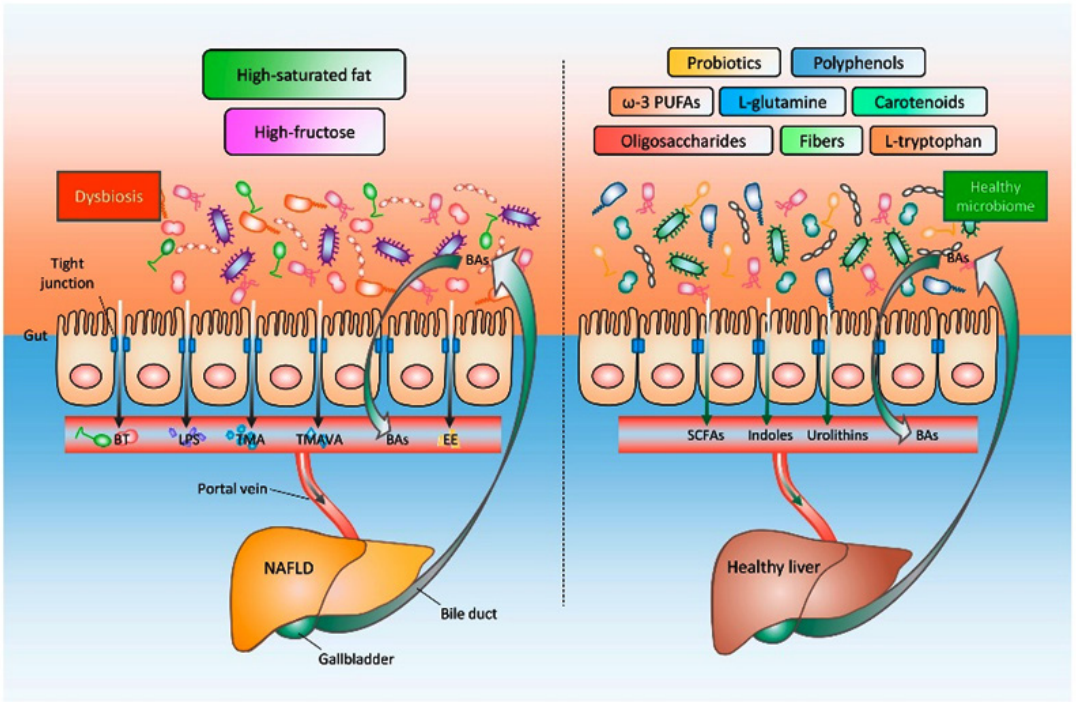

Fig. 4. Long-term consumption of a high-saturated-fat or high-fructose diet disrupts the balance of intestinal flora, which causes an increase in permeability and impaired gut barrier function. This is then followed by the entry of additional bacterial components and metabolites into the liver through the portal vein, such as lipopolysaccharides, trimethylamine, N, N, N-trimethyl-5-aminovaleric acid, and endogenous ethanol[68]

had a specific skin microbiome distribution. However, it is believed that the skin microbiome is very changeable and influenced by a variety of factors, including skin locations and various microenvironments. In contrast, the anatomy of the gut microbiome has a tendency to remain consistent since early childhood, despite the possibility of rapid changes in illness state, particularly for autoimmune disorders[111]. Probiotics-based therapy and preservation of the skin's microbiota may result in novel immune therapies for vitiligo[119].

Urticaria

A skin condition known as urticaria is distinguished by wheals (hives), angioedema, or both. The most common type of urticaria, the chronic spontaneous urticaria (CSU) is indicated by repetitive itchy wheals and/or angioedema that last for greater than six weeks without any known eliciting factors. It is defined as when a person has transient wheals that last longer than 6 weeks and occur almost every day[121]. Around 1% of the general population worldwide experiences CU at some or the other point in their lives, and in recent years, there has been a surge in prevalence [122]. The activation and degranulation of epidermal mast cells, thereafter followed by the release of histamine along with other mediators that cause sensory nerve activation, vasodilatation, plasma extravasation, and cellular recruitment, resulting in urticaria, a frequent and varied inflammatory skin condition[123, 124, 125]. It has been proposed that the pathophysiology of CSU may be influenced by pro-inflammatory responses brought on by changes in the gut microbiome and mediated by an imbalance of the cytokines Th1/Th2/Th17[126]. Although the gut microbiota of CSU patients has been examined in the past, only a small number of research have so far found a substantial distinction between the makeup of the gut flora in CSU participants and healthy controls[127, 128, 129]. In an experiment performed by Wang *et al.*[130], profiling of intestinal microbiome of CSU patients was performed using 16S rRNA gene sequencing. And metabolomics analysis was utilised to analyse metabolites of the patients. The major findings showed a significant increase in *Lactobacillus, Turicibacter,* and *Lachnobacterium,* whereas *Phascolarctobacterium* was decreased. The perturbed gut flora may further contribute to the progression of CSU via G protein coupled receptors. Thus, insinuating that CSU is potentially associated with the gut microbiome being disturbed. The findings of another study show that the *Enterobacteriaceae* family was found in the faecal samples of all patients and healthy controls, and that the quantities *of A. muciniphila, C. leptum,* and *F. prausnitzii* in healthy controls' stool samples were considerably higher than in patients with CSU[131]. There were some changes in the gut microbiota's phylum, order, family, genus, and species abundance between urticaria patients and healthy people. Patients with urticaria had a predominance of *Firmicutes, Bacteroidetes, Proteobacteria, Verrucomicrobia*, and *Actinobacteria* in their gut microbiomes[132, 133, 134]. Genus *Coprococcus* 3 and Genus *Defluviitaleaceae* UCG011[135] were discovered to have an increased risk against urticaria. A crucial genus of gut bacteria, *Coprococcus* is a member of the Phylum *Firmicutes*. According to earlier studies, *Coprococcus* was important for immunological responses[128] and was connected to the severity of atopic disease[136]. Additionally, Yun-Zhou *et al*.[135] discovered a connection between *Coprococcus* and urticaria and it was discovered that *Defluviitaleaceae* UCG011 was positively related with urticaria for the first time. *Defluviitaleaceae* and butyric acid levels have been discovered to have a positive association with *Defluviitaleaceae* [138] and a negative association with butyric acid levels[139] but the precise effect is yet unknown.

Rosacea

A widespread, chronic skin condition affecting the face known as rosacea is categorized by erythema, papules, pustules, telangiectasias, flushing, phymatous differences, and ocular clinical manifestations. Avoiding triggers, taking care of your skin, and getting treatments that target specific traits are all part of management[140]. Rosacea is a long-lasting inflammatory condition with a complex pathophysiology that includes genetic and environmental factors, as well as dysfunctionality of innate as well as adaptive immune system, neurovascular reactions, microbiome colonization or infection, leading to recurring inflammation. Inflammatory bowel illness, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease, *Helicobacter pylori* (HP) infection, as well as small intestine bacterial overgrowth (SIBO) are just a few of the gastrointestinal conditions that

have been linked to rosacea[141]. In comparison to healthy controls, rosacea patients had lower levels of the following genus-level bacteria: *Peptococcaceae* family, *Methanobrevibacter*, *Slackia*, *Coprobacillus*, *Citrobacter*, *Desulfovibrio*, *Lactobacillus*, *Hemophilus*, *Roseburia*, and *Clostridium*[142, 143]. One can speculate that the gut microbiota may be involved in the etiology of the disease given that rosacea has been connected to small intestine bacterial overgrowth and inflammatory bowel disease[144]. It has long been assumed that *Helicobacter pylori* has a role in the pathophysiology of the disease[145]. Pernicious chemicals may enter the bloodstream and harm peripheral sites if the gut mucosa is compromised, whether as a result of autoimmune illness or changes in the microbiome[146]. Improvements in inflammatory bowel disease and the clinical manifestations of rosacea with oral metronidazole treatment support the theory that resident gut flora may act as the underlying stimulant to an inflated immune response[147]. Several factors, such as the mode of birth, food, age, stress, and antibiotics, may affect the components of the gut microbiota and therefore, may cause rosacea[148]. Certain foods and beverages may behave as "triggers" for rosacea exacerbations. These may be split into heat-related, alcohol-related, capsaicin-related, and cinnamaldehyde-related[149]. Hot drinks in particular, such as hot coffee (33%) and hot tea (30%), served as a trigger. Another common trigger was alcohol, which included both wine (52%) and hard liquor (42%). Certain spices and peppers contain the compound capsaicin. Spices (identified as a trigger by 75% of respondents), spicy sauce (54%), cayenne pepper (47%), and red pepper (37%), were also often mentioned. Finally, foods that don't seem to have anything to do with each other, like tomatoes, citrus, cinnamon, and chocolate, contain cinnamaldehyde[150]. Another matter of concern is to the connection between rosacea and inflammatory bowel disease (IBD). In contrast to matched controls, a Taiwanese countrywide cohort experiment of more than 89,000 rosacea patients discovered an independent link with IBD incidence[151]. But the mechanisms underlying the contribution of gut bacteria to the pathophysiology of rosacea remain unclear. Dietary alteration may have a role in the management of rosacea[149].

Probiotics as a therapeutic agent

Probiotics are well recognized to be beneficial in certain illnesses, and numerous clinical surveys have shown that they can have peculiar influence on the epidermis, directly or indirectly, that can be significant from a variety of angles. Probiotic bacteriotherapy has the potential to be very effective in treating and preventing skin disorders such as atopic dermatitis, acne, and allergic inflammation; it can also be used as a cosmetic product and to treat skin hypersensitivity, UV-induced skin damage, and injury protection[152]. Studies show that probiotics can enhance the functioning of the epithelial barrier of the intestine and have antibacterial, competitive exclusion, and immunomodulatory properties. Probiotics' benefits for human health are becoming more well documented in science, and the information that is now available supports the benefits of probiotics against a number of illnesses[153]. In order to determine the probiotic strains' ability to stick to human skin and their antibacterial effectiveness against particular infections, Lopes *et al.*[154] conducted a study which showed the ability of probiotic strains' cell-free culture supernatants to stop or eliminate specific pathogens' ability to build established biofilms was also assessed by these investigators, who also looked for possible quorum-sensing antagonists. The scientists discovered that certain probiotic strains' CFCS had antimicrobial action against *Propionibacterium acnes, Escherichia coli,* and *Pseudomonas aeruginosa,* but none of them could stop *Staphylococcus aureus* from growing[154]. Five paediatric and 10 adult participants participated in a trial examining *Roseomonas mucosa* as a potential therapy for AD. With no negative side effects or consequences, treatment with *Roseomonas mucosa* was linked to considerable reductions in the severity of the disease, the need for topical steroids, and the *S. aureus* load. The study's preliminary findings encourage further assessment of *Roseomonas mucosa* therapy through a placebo-controlled experiment[155]. By decreasing mast cells and raising T-reg cytokines, topical use of *Vitreoscilla filiformis* and *Lactococcus* has been proven to be effective in the treatment of seborrheic dermatitis and atopic eczema[156]. It may also be hypothesized that topical probiotics, like gut

microbiome, may similarly lower the incidence of skin cancer by enhancing immune surveillance and decreasing chronic inflammation. Additionally, a topical probiotic may modify the tumour microenvironment by changing immune responses, which may have therapeutic effects, if it is injected into or administered to a cutaneous tumour[157]. Probiotics have been shown in numerous studies to be effective in treating long-term inflammatory diseases like rosacea while having few negative effects[150, 151]. Most studies have found that the initial beneficial effect of probiotics cannot be sustained upon discontinuation and that probiotics do not necessarily allow for recolonization of beneficial gut microorganisms[159]. The severity of dermatologic illnesses increases and treatment effectiveness is decreased as patients become resistant to antimicrobial medicines[160].

CONCLUSION

In conclusion, the complex relationship between the gut microbiota and skin health are an emerging field of study that has the potential to completely transform how we think about skincare and general well-being. The data highlights the significant function of the gut microbiota in regulating the immune system, nutritional absorption, and inflammatory responses—all of which have an immediate effect on the epidermal health. Imbalance in the stomach can cause a wide range of dermatological problems, from acne to eczema and beyond, and it is now abundantly obvious that they play a crucial part in preserving good skin. The creation of bioactive substances, immunological regulation, and inflammatory modulation are just a few of the many ways that the gut microbiome affects skin health. This discovery not only opens the door to novel therapeutic methods but also offers crucial insights into the underlying pathophysiology of skin problems. Although no therapeutic modalities have yet been discovered to provide persistent relief to these dermatological conditions, probiotics, prebiotics, and dietary modifications are becoming more and more effective weapons in the fight against these illnesses, giving patients additional options for controlling and even averting skin-related problems. But it's crucial to recognize that there is still a lot to learn and that the field of gut-skin health is still in its infancy. Subsequent investigations will surely deepen our comprehension of these complex relationships, possibly opening the door to innovative therapies and interventions for people with a variety of skin conditions. The more we learn about this interesting interplay between the gut and the skin, the more obvious it is that maintaining a diverse and well-balanced gut microbiota is essential to good health in general and is also a key component of a holistic skincare regimen. Once thought of as a remote environment, the stomach is now recognized as a vital component in the pursuit of healthy skin. Accepting this paradigm change gives people with skin problems hope for a better future by providing them with a more efficient and all-encompassing route to recovery and wellbeing.

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Conflict of Interest

There is no conflict of interest.

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