INNERHEALTH

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

Conditions presenting with skin irritability are not uncommon. Australia and New Zealand have some of the highest incidences of eczema in the world[1,2] with the latest statistics showing at least 20% of children under the age of 2 years have eczema, whilst some reports showing incidence being as high as 1 in 3 (38.5%) in infants[3,4,5,6]. Further to this, 10% of children with eczema will continue to experience the condition into adulthood.[7]

Acne vulgaris is also a skin condition with high prevalence, with reports of it affecting 9.4% of the global population, making it the 8th most prevalent disease state in the world.[8,9] This is more prevalent in Western countries (Australia, New Zealand, England, The United States), particularly in adolescents,[10,11,12] though still highly occurring in adults, with reports in more than 40% of males and 50% of females aged 20-29.[13,14]

The aetiology of inflammatory conditions can be multifactorial (Figure 1)[15], with dysbiosis of the skin and gut microbiome being one causative factor.[16,17,18] For this reason, specific probiotics may be used to support gut health, and ultimately, skin health.

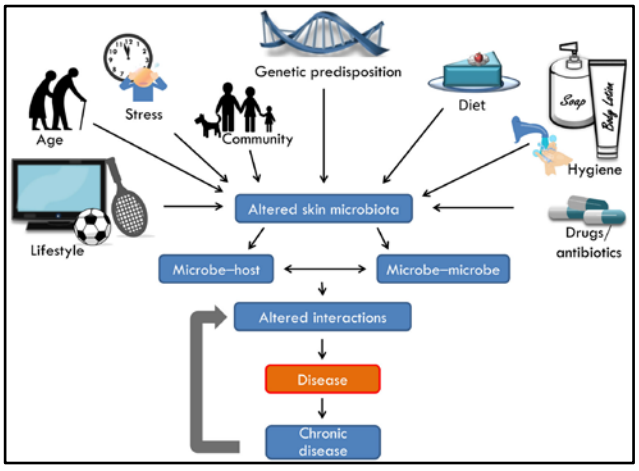

Figure 1: Factors that influence the skin microbiome

Probiotic Strains and Nutrients That May Assist

Lactobacillus rhamnosus (LGG®)

Bifidobacterium animalis ssp *lactis* (BB-12®)

Cholecalciferol (Microencapsulated Vitamin D)

Clinical Applications

- Support Skin Health
- Reduce Skin Irritation
- Reduce Mild Eczema Symptoms
- Reduce Occurrence of Acne Symptoms

*Microencapsulation is a process which coats the ingredient particles – in this instance it prevents an interaction between the vitamin D & supports stability of the probiotic strains (ensures viable live bacteria)

LGG® and BB-12® are trademarks of Chr. Hansen A/S

Vitamin D status is also something to consider when addressing skin health, particularly irritated conditions. Some people are more susceptible than others to developing vitamin D deficiency, defined as a level below 50ng/mL.[19] Risk factors for susceptibility include geographical location, polymorphisms of receptor genes, obesity, smoking, Fitzpatrick skin phototype, insufficient sun exposure, and age.[20] Inadequate vitamin D is related to a variety of skin conditions that present with irritated skin, including psoriasis, acne,[21] eczema.[22,23] Research conducted by the Australian Bureau of Statistics has shown that incidence of vitamin D deficiency can be as high as 49% of the population, across all age groups, particularly in the Winter months.[24] Further to this, vitamin D status, as well as polymorphisms of the vitamin D receptor (VDR) gene, are associated with the health and regulation of the gut microbiome.[25,26] It is for these reasons that vitamin D status is important to consider in those experiencing irritable skin conditions.

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

This document will investigate & explain:

1) Skin Health and the Gut
   a. The Immune System Response
   b. Gut and Skin Integrity
   c. Vitamin D and the Microbiome
   d. Vitamin D and the Skin
2) The Benefits of Skin Shield for Skin Health
   a. Modulating the Immune System to Regulate Inflammation
   b. Modulating the Immune System to Reduce Atopic Response
   c. Supporting Gut Integrity
   d. Supporting a Healthy Microbiome
      i. With Probiotics
      ii. With Vitamin D
3) Clinical Evidence to Support the Use of Probiotics and Vitamin D in Eczema
4) Dosage Considerations
5) Safety Information
6) References

1) Skin Health and the Gut

The link between the gut and the skin, otherwise known as the gut-skin axis, has long been established,[27] even if it is not yet completely understood.[28] Dysbiosis of the gut is implicated as a large contributing factor to disorders of the skin, particular inflammatory conditions.[29] The main bases of this relationship are the way the microbiota interacts with the immune system to modulate inflammation, as well as barrier integrity in both the skin and the gut[30].

a. The Immune System Response

Given that over 70% of the body's immune system is in the gut,[31] it makes sense to look to the health of the gastrointestinal tract (GIT) to support balanced systemic immunological responses. Research indicates that supporting the microbiome is essential for immune development, maturation, and maintenance.[32]
The composition of the gut microbiota modulates T helper cell activity by influencing two key mediators, dendritic cells (DCs) and T regulatory cells (Tregs).[33] DCs reside in an immature state throughout the gut mucosa, and mature in response to stimuli presented by specific proteins on the outer surface of gut microbes.[34] After maturation, DCs enhance the production of Tregs and further up-regulate anti-inflammatory cytokines, transforming growth factor beta (TGF-β), interleukin 4 (IL-4) and IL-10, whilst down-regulating proinflammatory cytokines, tumour necrosis factor alpha (TNF-α), IL-6 and interferon gamma (IFN-γ). As a result, these cytokines regulate T helper 1 (Th1) activity against infection as well as antibody-inducing activities of T helper 2 (Th2) cells.[35] In addition to this, immunoglobulins produced by B cells, specifically, secretory immunoglobulin A (sIgA) are a key player in the mucosal immune response within the GIT; functioning as part of the first line of defence against the external environment.[36,37] In a process known as immune exclusion, sIgA clears pathogenic microorganisms and other antigens from the luminal environment. It does so by blocking access to epithelial receptors (preventing pathogenic adherence to the mucosal lining), entrapping pathogens in mucosal secretions, and promoting their

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

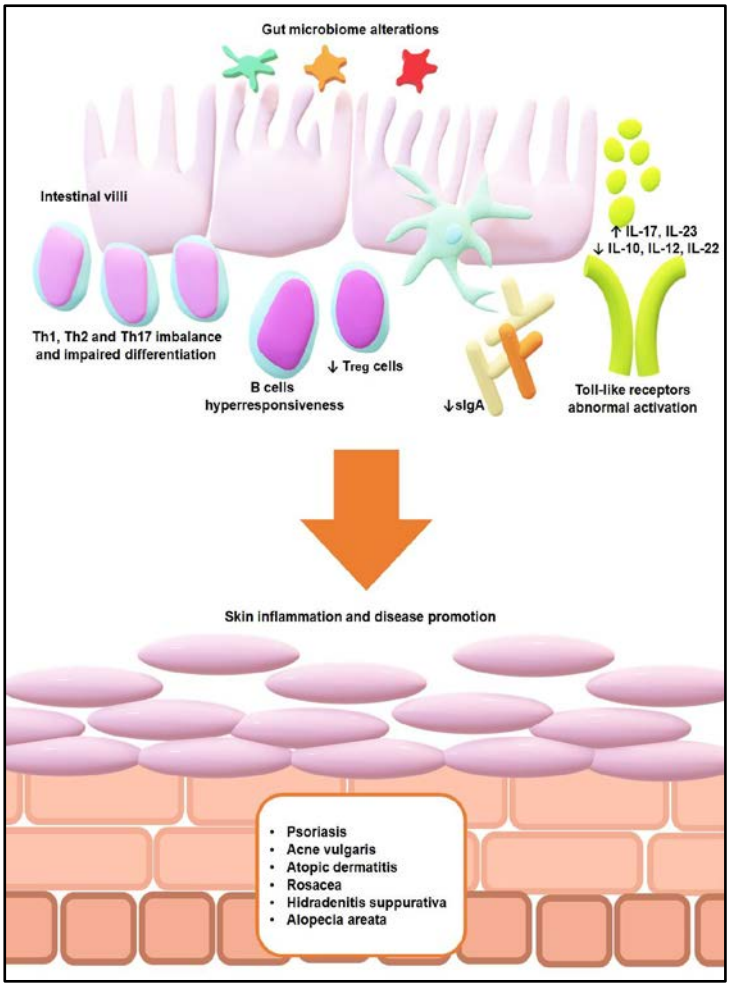

Figure 2: The interaction between gut microbiota alterations and immune mechanisms taking part in selected skin diseases pathophysiology.

removal via peristalsis.[38] Importantly, sIgA also regulates immune tolerance to benign antigens, such as food antigens and commensal flora[39], contributing to a protective yet tolerant mucosal immune response to a range of stimuli. Intestinal bacteria also influence this antigen recognition and differentiation via pattern recognition receptors, known as toll-like receptors (TLRs). Dysregulation of this function of sIgA, or of the commensal microbiome, could mean that usually benign antigens have the potential to illicit an allergic response, which is instead an immunoglobulin E (IgE)-mediated response, leading to release of inflammatory mediators into many systems, including the skin.[40]

As an allergic condition, eczema presents with an imbalance in the ratio of Th1 and Th2 immune cells and consequently, an imbalance of the inflammatory cytokines expressed by these cells.[41] These factors result in irregular immune system activity that skews towards a Th2/IgE response, and a tendency to be overly sensitive to allergens.[42] Conversely, as an autoimmune condition, psoriasis presents with an imbalance skewed towards the Th1 response.[43]

It is this imbalance that supplementation with probiotics and vitamin D aims to correct (Figure 2).[44]

b. Gut and Skin Integrity

Gut barrier integrity is important to protect against bacterial translocation (when enteric bacteria can cross the intestinal mucosal barrier and be found in remote tissues) as well as prevent immune dysregulation.[45] The integrity of the intestinal barrier depends on a complex of proteins that make up different intercellular junctions, including tight junctions (TJs).

Disruption of TJs by proinflammatory factors elevates TJ permeability (Figure 1),[46] thus increasing the likelihood of a systemic cycle of immune activation and inflammation,[47] as antigens, food, and microbes cross the mucosal barrier and cause an allergic response, aggravating the conditions associated with this response, such as eczema.[48]

The production of short-chain-fatty-acids (SCFA) by commensal flora helps to strengthen these TJs,[49] making a healthy gut microbiome essential for barrier integrity.

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

It has been reported that poor intestinal barrier function has led to the presence of intestinal bacteria as well as their metabolites being able to accumulate in the skin after being transported through the blood stream, and thus cause dysbiosis in the skin microbiome as well as the gut.[50] For example, an increased level of cresol, an amino-acid metabolite produced by *Clostridium difficile* in the gut, has been shown to be reflected by increased levels in the circulation and also in the skin, resulting in small corneocytes and reduced skin hydration,[51] and therefore a compromised skin barrier. Given that poor integrity of the skin barrier is one of the proposed mechanisms for eczema flares,[52] it is important to protect gut barrier integrity so as not to further exacerbate disease pathogenesis.

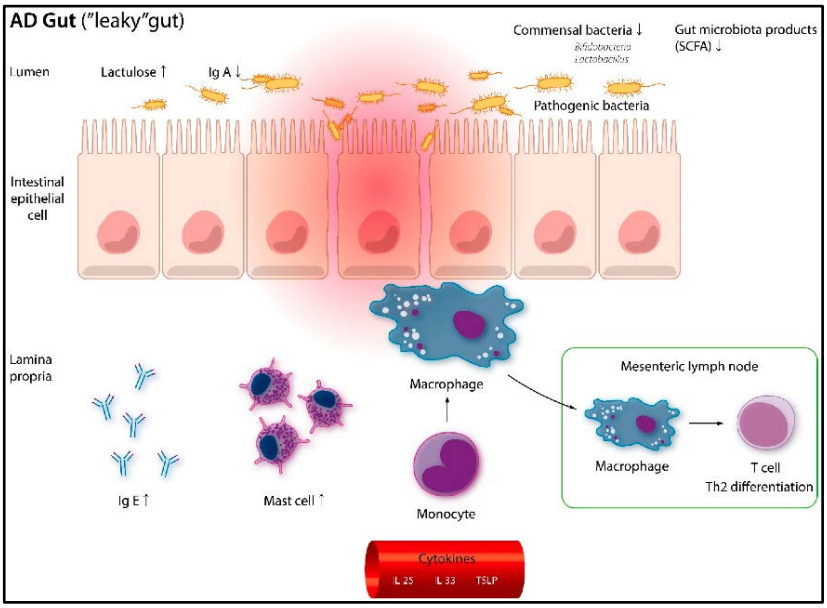

Figure 3: Disruption to TJs due to dysbiosis and consequent lack of SCFAs. Monocytes migrate and differentiate into macrophages due to a response to inflammatory cytokines. T cells mature into Th2 cells due to an increased exposure to luminal antigens. Cytokines also stimulate an increase in expression of IgE and a decrease in IgA.

It is also important to note that the skin of eczema sufferers have increased colonisation of certain bacteria,[53] and that this dysbiosis could also be reflected in the gut microbiome. Dysbiosis of the skin microbiome is due to an under-expression of antimicrobial peptides (AMPs) either by keratinocytes, sebocytes or white blood cells in the skin or a lack of commensal flora that would otherwise excrete AMPs themselves.[54] This can result in a local immune/inflammatory response that, like that initiated in the gut, can have systemic implications.[55]

Therefore, not only does the integrity of barrier of the gut impact the skin, but vice versa.

c. Vitamin D and the Microbiome

Vitamin D status directly impacts the microbiome. Research has discovered that the composition and function of the bacterial community comprising the gut microbiome is dependent on vitamin D status, and conversely, the presence of an unhealthy microbiome can predispose an individual to vitamin D deficiency due to reduced capacity to absorb vitamin D adequately.[56] This can be explained, at least in part, by the fact that VDR gene polymorphisms have been shown to alter the gut microbiota at a genetic level, specifically decreasing levels of *lactobacilli* and other butyrate-producing bacteria.[57] Additionally, supplementation with probiotics has been shown to increase vitamin D levels as well as VDR expression and activity.[58]

d. Vitamin D and the Skin

For most people, solar UVB radiation (wavelengths 280-315 nm) is the main natural source of Vitamin D3 (cholecalciferol). Sun protective factors and high skin pigmentation can reduce the UVB-mediated production of D3 – for example, SPF15 factor sunscreen can reduce D3 production by 99%.[59] Whilst there is no absolute causative

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

relationship between **vitamin D** status and severity of eczema, there is correlation between **vitamin D** status and responsiveness to treatment.[60] Interestingly, some studies have found that this link between **vitamin D** and eczema is more likely the result of the interactions between **vitamin D** and the skin specifically, as opposed to the allergic response.[61] This link between **vitamin D** and the skin specifically is further supported by evidence that insufficient **vitamin D** results in extended time between skin injury and complete wound healing,[62,63] as well as a propensity for hypertrophic[64] and keloid scarring.[65] Additionally, **vitamin D** levels directly regulate levels of antimicrobial and anti-inflammatory peptides in the skin, such as LL-37, which is under-expressed in the skin of eczema sufferers and overexpressed in the skin of individuals with psoriasis.[66] Vitamin D status also impacts acne sufferers due to a lack of vitamin D increasing sebum production and this encouraging the growth of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), the bacteria responsible for acne.[67,68]

2) The Benefits of LGG®, BB-12® for Skin Health (Figure2)

a. Modulating the Immune System to Reduce Inflammatory Responses

The microbiome is essential for the development and ongoing modulation of immune responses,[69] signalling TLRs in the intestinal epithelium, as well as in the skin itself,[70] and balancing between Th1 and Th2 responses,[71] and in this way, the composition of the gut microbiota can impact inflammatory responses.

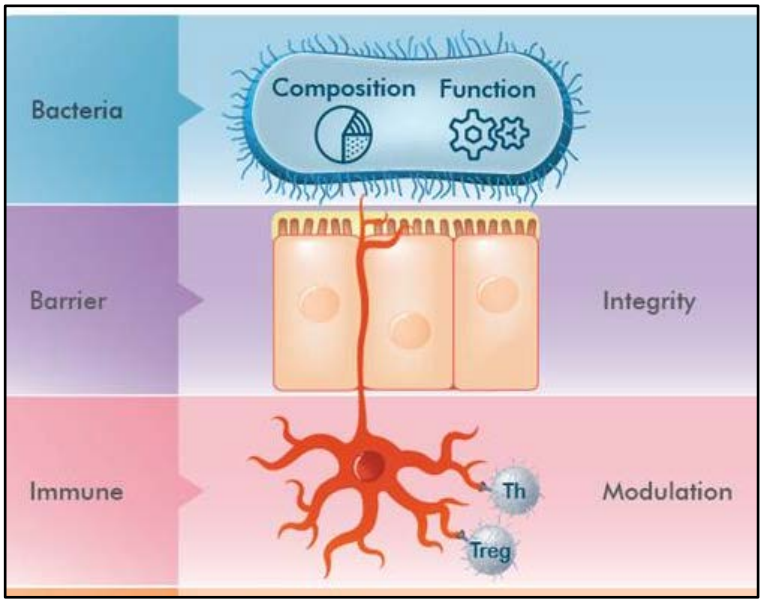

Figure 4: Key mechanisms of probiotics that are of benefit for skin health

A growing body of evidence indicates that some probiotic strains can modulate the immune system at both the systemic and the mucosal levels.[72] Specific strains of probiotics may be used to support the induction of Tregs, in turn supporting the balancing of the Th1 and Th2 pathways,[73] as well as provide additional anti-inflammatory support via the stimulation of the production of immunoglobulin A (IgA),[74] and suppression of IgE.[75] Specifically, **LGG®**[76] and **BB-12®**[77] possess considerable immunoregulating properties, with studies highlighting these strains to be of particular benefit for eczema relief.

Lactobacillus species help to promote immune regulation by interacting with DCs residing in gastrointestinal-associated lymphoid tissue (GALT) throughout the digestive tract, as well as stimulating Tregs and increasing production of regulatory cytokines, all of which maintain healthy immune function.[78] Specifically, the range of **LGG®** immune-regulating mechanisms is extensive; **LGG®** increases IL-10,[79] and TGF-β2,[80] cytokines and down-regulates TNF-α, IL-6, and IFN-γ, thus promoting Th1/Th2 balance.[81] **LGG®** has also been shown to increase IgA levels[82], as well as decrease circulating levels of IgE.[83]

In addition to this, **BB-12®** also plays an important role in modulating the intestinal immune system. Studies have shown **BB-12®** to induce maturation of DCs and increase IL-10, whilst lowering IL-1β, IL-6, IL-12, TNF-α and IFN-γ, supporting healthy immune activity.[84]

b. Supporting Gut Integrity

There is evidence to suggest that there is dysbiosis in both the gut and the skin microbiome in inflammatory skin conditions[85]. As evinced above, dysbiosis in the gut can lead to an imbalance in immune response to stimuli, not just in the gut but systemically. Similarly, dysbiosis of the microbiota of the skin can also elicit an inflammatory response locally, and systemically.[86]

Gut barrier enhancement is one of the central and most accepted mechanisms of probiotic function. Human trials have demonstrated the ability of LGG® to reduce intestinal permeability[87,88] and an *in vitro* study investigating the effects of BB-12® on cell junctions found that supplementation significantly enhanced the integrity of transepithelial junctions.[89] This is because LGG® and BB-12® can increase the formation of SCFAs such as acetate, propionate and butyrate.[90] These help to supply energy to the enterocytes and support gut barrier integrity via the preservation of transepithelial resistance (TER), and proteins such as occludens, E-cadherin, and β-catenin in the intercellular junctions. These points support the role of strain- specific probiotics in enhancing intestinal barrier function.[91]

c. Supporting a Healthy Microbiome

i. With Probiotics

The gut microbiota in non-allergic individuals has been shown to differ from allergic individuals.[92,93] Studies have shown that numbers of *Clostridia* are higher, whereas numbers of *bifidobacteria* and *lactobacilli* groups are lower in allergy sufferers,[94,95] suggesting that these latter species in particular offer benefits to the host that may lower allergy incidence. The gut microbiome of acne sufferers has also been shown to be altered compared to healthy controls,[96]and a higher incidence of gastrointestinal symptoms in these individuals also supports this gut-skin axis link.[97]

Also, as previously mentioned, the production of SCFAs by commensal flora is believed to exert strong immunomodulatory effects[98] and strengthen enterocyte health.[99]

It therefore makes sense to supplement probiotics that support the commensals that promote SCFA production, as well as promote microbial balance and diversity.

LGG® promotes the growth and biodiversity of *bifidobacterium*[100] and *lactobacillus/enterococcus*[101,102] therefore contributing to increased microbial diversity to support SCFA production, mucosal barrier function[103] and thus a lower incidence of allergy. BB-12® supplementation in infants has also been shown to increase faecal levels of *bifidobacteria,*[104] which is particularly significant as bifidobacteria cross-feed other important commensal species within the gut microbiota.[105] Further, two *in vitro* studies have also highlighted the positive effect of BB-12® on pathogen inhibition. In one of the studies, BB-12® proved antagonistic against eight of the 12 pathogens tested, including C. *difficile* and *E. coli*.[106] The second study investigated the antimicrobial action of a BB-12® and prebiotic combination against *E. coli* and C. *jejuni*. The results suggest that acetate and lactate producing BB-12® conferred a direct anti-microbial effect.[107]

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

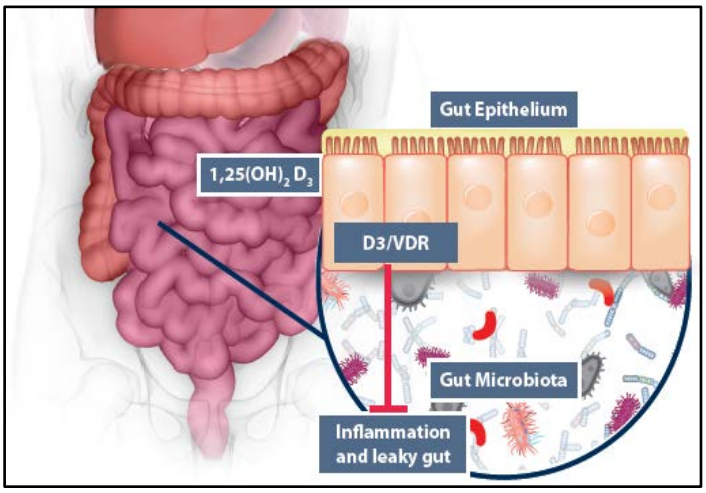

Figure 3: Vitamin D, VDR and the microbiome in the intestine

ii. With Vitamin D

As previously mentioned, **vitamin D** deficiency is one causative factor linked to the disruption of a healthy microbiome.[108] It has also been shown that individuals with allergic, and or inflammatory disease states, including eczema, are more likely to have insufficient levels of **vitamin D**[109,110,111,112,113,114] and VDRs[115,116,117]. **Vitamin D** and VDRs regulate host-bacterial interactions and innate immune responses of the gut microbiota, including the production of antimicrobial peptides,[118] as well as maintain gut tolerance and barrier function,[119,120] to help to control microbial dysbiosis,[121] and inhibit inflammation in the gut (Figure 3).[122] Further, probiotics have been shown to increase **vitamin D** and VDR in the gut.[123]

3) Clinical Evidence to Support the Use of Probiotics and Vitamin D for Skin Health

4) Summary of Key Evidence to Support Probiotic Use to Support Skin Health					
Study	**Population studied**	**Ingredient**	**Supplement duration**	**Equivalent daily dose**	**Outcome**
Miyazawa, et al, 2018[124]	Randomized, double-blind, placebo-controlled study. 96 healthy adults (22 males, 74 females, aged 20 to 59 years old) from Japan with a tendency of dry skin	**LGG®**	4 weeks	14 billion live bacteria	Hydration was higher in the **LGG®** group than in the placebo group ($p<0.01$). After week 4 in the **LGG®** group, the trans-epidermal water loss (TEWL) was lower than before intake. A questionnaire indicated improvements in the **LGG®** group compared to the placebo group (Skin is firm - $P<0.05$; Have pimples/breakouts - $P<0.01$; Skin has a fine texture - $P<0.05$).
Summary of Key Evidence to Support Probiotic Use to Reduce Symptoms of Eczema					
Isolauri E, et al. 2000	27 exclusively breastfed infants (mean age 4.6 months) with early onset atopic disease, were weaned to Extensively hydrolysed whey formula (EHWF), EHWF with **BB-12®**, or EHWF with **LGG®**.	**LGG® and BB-12®**	2 months	30-80 billion live bacteria – dose was dependent upon amount of formula consumed by child	A significant change in the SCORAD scores was seen in 9/9 of the patients receiving **BB-12®**, 9/9 in the **LGG®** group as compared to 4/9 in patients receiving the EHWF. ($P=0.002$)
Kirjavainen PV, Salminen SJ, Isolauri E. 2003[125]	Double-blind placebo-controlled trial ($n=35$) of infants with atopic eczema, allergic to cow's milk – mean age 5.5 months. Groups received either extensively hydrolysed casein formula (EHCF), EHCF + viable **LGG®** or EHCF + heat-inactivated **LGG®**.	**LGG®**	7.5 weeks	Formula contained **LGG®** concentration equivalent to 10^9CFU/g. Dose varied with amount consumed by child.	Eczema symptoms were significantly alleviated in all the groups; the SCORAD scores decreased in the **LGG®** group. The decrease in the SCORAD scores within the viable **LGG®** group tended to be greater than within the placebo group. ($P=0.02$)
Matsumoto et al. 2014[126]	44 Japanese men and women with eczema (24 men, 20 women, average age 33.8 years old)	**BB-12®**	8 weeks	6 billion live bacteria	Symptoms of eczema, specifically itching, improved significantly in probiotic group versus placebo group ($P<0.05$), at both 4 weeks and 8 weeks.
Sofrankova et al 2015[127]	Pilot study of 39 children ($n=22$ allergic, $n=17$ not allergic) aged 3 months to 3 years. Eczema sufferers had a higher lactulose/mannitol (L/M) ratio at baseline compared to controls. A higher L/M	**LGG®**	6 weeks	1 billion live bacteria	Positive correlation between reduction in atopic severity using the Scoring Atopic Dermatitis (SCORAD) index, and reduction in IP using L/M ratio ($P<0.05$) post **LGG®** intervention.

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

	indicates increased intestinal permeability.				
Schmidt et al 2019[128]	Randomised, placebo-controlled trial of 290 (n=144 probiotic group, n=146 placebo) children aged 8-14 months, to observe incidence of developing eczema.	**LGG® and BB-12®**	6 months	1 billion live bacteria of each **LGG®** and **BB-12®**	Receiving probiotic intervention significantly lowered eczema incidence (P= 0.036)
Summary of Key Evidence to Support the Use of Probiotics to Reduce Occurrence of Acne Symptoms					
Fabbrocini et al. 2016[129]	Pilot, randomised, double-blinded, placebo-controlled study. 20 adult subjects (14 females and 6 males; mean age: 33.7±3.3 years) with acne. Probiotic group (n=10) Placebo group (n=10)	**LGG®**	12 weeks	3 billion live bacteria	Patients in the probiotic group were rated by physicians as improved/markedly improved (vs worsened/unchanged) compared with the placebo group. (P<0.05). Skin biopsies also showed improvement in markers of skin health such as insulin-like growth factor 1 (IGF-1) (P<0.001)
Summary of Key Evidence to Support Vitamin D Use to Reduce Skin Irritation					
Amon et al. 2018[130]	Cross-sectional study (n=1532; patients n=1461, control n= 71)	**Vitamin D**	12 months	**Vitamin D** levels checked	Significantly reduced serum **vitamin D** levels in inflammatory skin conditions versus healthy controls (P<0.0001).
Cho et al. 2019	Cross-sectional study of 486 patients with burns in hospital.	**Vitamin D**	49 months	**Vitamin D** levels checked	**Vitamin D** deficient patients had significantly higher levels of TEWL (P=0.007), final distensibility (P<0.001), and gross elasticity (P<0.001)
Navarro-Trivino et al. 2019[131]	Review	**Vitamin D**	N/A	**Vitamin D** levels checked	Increased Psoriasis Area and Severity Index (PASI) correlates with lower serum levels of **vitamin D**.
Summary of Key Evidence to Support Vitamin D Use to Reduce Symptoms of Eczema					
Camargo et al. 2014[132]	Randomised, double-blind, placebo-controlled, trial of 107 children aged 2-17 years with atopic eczema that worsens in winter.	**Vitamin D**	1 month	1000IU	Eczema Area and Severity Index (EASI) score for children receiving **vitamin D** was decreased significantly more than scores of those receiving placebo (P=0.01)
Van der Schaft 2016[133]	Cross-sectional study (n=210)	**Vitamin D**	17 months	**Vitamin D** levels checked	69.5% of eczema patients have insufficient/deficient vitamin D (P=0.031) and such patients should use supplementation.
Di Filippo et al 2015[134]	59 children (eczema n=39, n=20 nonallergic) in a controlled intervention, measuring inflammatory markers and SCORAD indicis	**Vitamin D**	3 months	1000IU	SCORAD indicis were significantly reduced in the eczema group following intervention (P<0.001)
Summary of Key Evidence to Support the Use of Vitamin D to Reduce Occurrence of Symptoms of Acne					
Yildizgoren et al. 2014[135]	Cross-sectional study of patients with newly-diagnosed nodulocystic acne (n=43) and healthy controls (n=46)	**Vitamin D**	N/A	**Vitamin D** levels checked	Those with acne had significantly lower serum vitamin D levels when compared to controls (P<0.05)
Lim S-K et al. 2016[136]	Case-control study combined with randomised controlled trial. **Vitamin D** levels assessed in 160 participants (acne n=80, control n=80). 39 participants assessed as deficient were then randomised to be supplemented with **vitamin D** (n=20), or placebo (n=19).	**Vitamin D**	2 months	1000IU	The prevalence of vitamin D deficiency was higher in patients compared to controls (P=0.019). The level of vitamin D was inversely associated with the severity of acne, and there was a significant negative correlation with inflammatory lesions (P<0.001). Improvement in inflammatory lesions was noted after supplementation (P<0.05).
Abd-Elmaged et al. 2018	Cross-sectional study of patients with acne vulgaris (n=135) and healthy controls (n=150).	**Vitamin D**	N/A	**Vitamin D** levels checked	Significant decrease in the serum and tissue levels of vitamin D levels in acne patients when compared with the healthy controls (P<0.05).
El-Hamd et al. 2019[137]	Cross-sectional study of patients with acne vulgaris (n=90) and healthy controls (n=60)	**Vitamin D**	N/A	**Vitamin D** levels checked	Significant inverse relationship between **vitamin d** levels and severity of acne (P=0.001).
Kemeritz et al. 2020[138]	Cross-sectional study of patients with acne vulgaris (n=134) and healthy controls (n=129)	**Vitamin D**	N/A	**Vitamin D** levels checked	Serum **vitamin D** levels were significantly lower in acne patients than in controls (P < 0.001).

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

4Dosage Considerations

Not recommended for use in children under 4 months of age, unless advised by a healthcare professional.

5) Safety Information

Contraindications

- **Calcipotriene:** Calcipotriene is a vitamin D analogue used topically for psoriasis. It can be absorbed in sufficient amounts to cause systemic effects, including hypercalcemia. Theoretically, combining calcipotriene with vitamin D supplements might increase the risk of hypercalcemia. Avoid concurrent use.[139]
- **Calcitriol:** Calcitriol is a vitamin D analogue and when used in conjunction with vitamin D supplements may have an additive effect and increase risk of vitamin D toxicity and hypercalcemia. Avoid concurrent use.[140]

Cautions – Moderate level

- **Aluminium / aluminium-containing phosphate binders:** The protein that transports calcium across the intestinal wall can also bind and transport aluminium. This protein is stimulated by vitamin D, which may therefore increase aluminium absorption. This mechanism may contribute to increased aluminium levels and toxicity in people with renal failure, when they take vitamin D and aluminium-containing phosphate binders long term.[141] In patients with renal failure it is recommended to exercise caution when taking this combination and to only do so under medical supervision.
- **Calcium channel blockers:** Hypercalcaemia, due to high doses of vitamin D, can reduce the effectiveness of calcium channel blockers in atrial fibrillation. Monitor and avoid vitamin D doses above 2000 IU (50 μg) daily.[142,143,144]
- **Digoxin:** Hypercalcaemia induced by high doses of vitamin D (i.e. doses > 2000 IU/day or 50 μg/day) can increase the risk of fatal cardiac arrhythmias with cardiac glycosides. Use under medical supervision only and avoid vitamin D doses above 2000 IU (50 μg) daily.[145,146,147,148]
- **Hypercalcaemia:** Vitamin D doses above 2000 IU (50 μg) daily may cause hypercalcemia and should be avoided due to the risk of increased calcium accumulation.[149] For doses under 2000 IU, use caution and only under medical supervision.[150,151]
- **Hyperparathyroidism:** Vitamin D doses above 2000 IU (50 μg) daily may cause hypercalcemia and should be avoided due to the risk of increased calcium accumulation. For doses under 2000 IU, use caution and only under medical supervision.[152,153]
- **Renal failure and/or chronic kidney disease:** Vitamin D doses above 2000 IU (50 μg) daily may cause hypercalcemia and should be avoided due to the risk of increased calcium accumulation. For doses under 2000 IU, use caution and only under medical supervision.[154]
- **Sarcoidosis or other granulomatous disease:** The synthesis of vitamin D is altered by granulomatous inflammation, resulting in increased production of 1, 25-dihydroxyvitamin D.[155] Vitamin D doses above 2000 IU (50 μg) daily should be avoided due to the risk of increased calcium accumulation. For doses under 2000 IU, use caution and only under medical supervision.[156,157]
- **Thiazide diuretics:** Thiazide diuretics decrease urinary calcium excretion, which could lead to hypercalcemia if vitamin D supplements are taken concurrently. This has been reported in people being treated with vitamin D for hypoparathyroidism, and in elderly people with normal parathyroid function who were taking a thiazide, vitamin D, and calcium-containing antacids daily. Use combinations of thiazides and vitamin D with caution and monitor serum calcium levels.[158,159]

- **Verapamil:** Hypercalcaemia induced by high doses of vitamin D (i.e. doses > 2000 IU/day or 50 μg/day) can reduce the effectiveness of verapamil in atrial fibrillation. Avoid vitamin D doses above 2000 IU (50 μg) daily and monitor serum calcium levels in people taking vitamin D and verapamil concurrently.[160,161]

Cautions – Low level

- **Immunosuppressants:** Theoretically, Lactobacillus could cause infection in patients taking medications that suppress the immune system. These include cyclosporine (Neoral, Sandimmune), tacrolimus (Prograf), azathioprine (Imuran), and cancer chemotherapeutic agents like cyclophosphamide (Cytoxan) and cisplatin (Platinol-AQ), and others.[162,163] Use only under medical supervision in these patients.
- **Severely ill and/or immunocompromised patients:** Lactobacillus bacteraemia and sepsis have been reported in severely ill and/or immunocompromised patients consuming probiotics such as lactobacillus, though this is a very rare finding.[164,165] Based on these occurrences, a theoretical concern of bacteraemia and sepsis extends to bifidobacteria probiotics.[166,167] Use lactobacilli and bifidobacteria strains only under medical supervision in hospitalised patients.
- **Short-bowel syndrome:** Patients with short-bowel syndrome might be predisposed to pathogenic infection from lactobacillus. This might be due to impaired gut integrity in patients with short-bowel syndrome. Use only under medical supervision in patients with this condition.[168,169]

Pregnancy

- Likely safe. While there is evidence to support the use of these ingredients during pregnancy,[170,171,172,173,174,175] and a review did not identify concerns for use, Practitioner discretion is advised.

Breastfeeding

- Appropriate for use.[176,177,178,179,180]

Children

- Appropriate for use.[181,182,183 184,185]
    - NB: Infants from 0-12 months should not exceed the UL of 25 μg (1000 IU) of vitamin D per day. Children aged 1-18 years should not exceed the UL of 80 μg (3200 IU) per day;[186] however, much higher doses are often needed for the short-term treatment of vitamin D deficiency. Some research shows that giving vitamin D 14,000 IU/week for a year in children aged 10-17 is safe[187,188]; though intakes of 2000 – 3000 IU per day may cause toxicity symptoms in some children, as may doses of 1000 IU / day in hypersensitive infants.[189]

Prescribing Tips and Notes

- **Antibiotics:** Concomitant administration of antibiotics might decrease the effectiveness of lactobacilli and bifidobacterium. However, concomitant use of probiotics reduces the likelihood of gastrointestinal and genitourinary side effects and co-administration is considered beneficial. Separate administration of antibiotics and lactobacillus/bifidobacterium preparations by at least two hours.[190,191,192]

6) References

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH

[1] Martin PE. The epidemiology of infantile eczema. Uni of Melb. 2011 Dec.
[2] Robertson CF, Dalton MF, Peat JK, Haby MM, Bauman A, Landau LI. Asthma and other atopic diseases in Australian children. Med J Aust. 1998;168(9):434-8.
[3] Australasian Society of Clinical Immunology and Allergy (ASCIA). Eczema (atopic dermatitis) [Internet]. 2019 [cited 2019 Jul 3]. Available from: https://allergy.org.au/images/pcc/ASCIA_PCC_Eczema_2019.pdf
[4] Eczema Association of Australasia (EAA). Facts about eczema [Internet]. Unknown publication year [cited 2019 Jul 3]. Available from: https://www.eczema.org.au/eczema-facts/
[5] Page SS, Weston S, Loh R. Atopic dermatitis in children. Aust Fam Physician. 2016;45(5):293-6.
[6] Jenner N, Campbell J, Marks R. Morbidity and cost of atopic eczema in Australia. Australas. J. Dermatol. 2004; 45:16–22.
[7] BHC Medical Centre. How common is eczema in Australia? 2015 Dec 31 [cited 2020 Feb 11]. Available from: https://bhcmedicalcentre.com.au/uncategorized/how-common-are-eczema-and-psoriasis-in-australia/
[8] Harris VR, Cooper AJ. Modern management of acne. MJA. 2017 Jan 16;206(1):41-5.
[9] Tan JKL. Bhate K. A global perspective on the epidemiology of acne. Brit J Dermatol. 2015 Jan;172(Suppl 1).
[10] Kilkenny M, Merlin K, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school students: 3. Acne vulgaris. Brit J Dermatol. 1998; 139:840-5.
[11] Freyre EA, Rebaza RM, Sami DA, Lozada CP. The prevalence of facial acne in Peruvian adolescents and its relation to their ethnicity. J Adolescent Health. 1998; 22:480-4.
[12] Hassan J, Grogan S, Clark-Carter D, Richards H, Yates VM. The individual health burden of acne: appearance-related distress in male and female adolescents and adults with back, chest and facial acne. J Health Psychol. 2009;14(8):1105-18.
[13] Perkins AC, Maglione J, Hillebrand GG, Miyamoto K, Kimball AB. Acne vulgaris in women: prevalence across the life span. J Womens Health. 2012;21(2):223-30.
[14] Collier CN, Harper JC, Cantrell WC, Wang W, Foster KW, Elewski BE. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58(1):56-9.
[15] Schommer NN, Gallo RL, Structure and function of the human skin microbiome. Trends Microbiol. 2013 Dec;21(12):660-8.
[16] Schommer NN, Gallo RL, Structure and function of the human skin microbiome. Trends Microbiol. 2013 Dec;21(12):660-8.
[17] Polkowska-Pruszyńska B, Gerkowicz A, Krasowska D. The gut microbiome alterations in allergic and inflammatory skin diseases - an update. J Euro Acad Dermatol Venereol. 2019;34(3):455-64.
[18] Bowe W, Patel NB, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine. Beneficial Microbes. 2014;5(2):185-99.
[19] Royal Australasian College of Pathologists. [Internet] Surry Hills NSW: Position statement: Use and interpretation of vitamin D testing 2013 [reviewed 2019 May; cited 2020 Nov 19] Available from: https://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Use-and-Interpretation-of-Vitamin-D-Testing
[20] Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. Am J Clin Dermatol. 2018 Apr;19(2):223-235.

[21] Abd-Elmaged WM, Nada EA, Hassan MH, Elsadek BEM, Abdelrahim EA, Ahmed NS, et al. Lesional and circulating levels of interleukin-17 and 25-hydroxycholecalciferol in active acne vulgaris: correlation to disease severity. 2018;1-6.
[22] Sharma R, Abrol S, Badgal A, Chowdhary S. Vitamin D and its role in dermatology: a review of the literature. J of Evolution of Med and Dent Sci. 2015 Feb;4(10):1689-93.
[23] Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. Am J Clin Dermatol. 2018. 2018 Apr;19(2):223-235.
[24] Australian Bureau of statistics [Internet]. Feature article: vitamin D. 2014 (cited 2019 Jun 20). Available from: https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4364.0.55.006Chapter2002011-12
[25] Sun J. Dietary vitamin D, vitamin D receptor, and microbiome. Curr Opin Clin Nutr Metab Care 2018;21.
[26] Shang M & Sun J. Vitamin D/VDR, probiotics, and gastrointestinal diseases. Curr Med Chem. 2017; 24(9): 876-887.
[27] Perry HO, Cutaneous Manifestations of gastrointestinal disease. Postgrad Med [Internet] 1967. [cited 2020 Sep 28];41(5):501-508. Available from: doi:10.1080/00325481.1967.11696953
[28] Salem I, Ramser A, Isham N, Ghannoum MS. The gut microbiome as a major regulator of the gut-skin axis. Front. Microbiol. 2018 Jul; 9:1459
[29] O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: a paradigm with therapeutic implications. Bioessays [Internet] 2016 [cited 2020 Oct 12]; 38:1167–1176. Available from: doi: 10.1002/bies.201600008
[30] O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: a paradigm with therapeutic implications. Bioessays [Internet] 2016 [cited 2020 Oct 12]; 38:1167–1176. Available from: doi: 10.1002/bies.201600008
[31] Gill HS. Probiotics to enhance anti-infective defenses in the gastrointestinal tract. Best Pract Res Clin Gastroenterol. [Internet] 2003 [cited 2020 Sep 28]; 17(5):755-73. Available from: https://doi.org/10.1016/S1521-6918(03)00074-X
[32] Gottschick C, Raupach-Rosin H, Langer S, Hassan L, Horn J, Dorendorf E, et al. Cohort profile: The LoewenKIDS Study - life-course perspective on infections, the microbiome and the development of the immune system in early childhood. Int J Epidemiol. 2019 Aug 1;48(4):1382-1383.
[33] Blander JM, Longman RS, Iliev ID, Sonnenberg GF, Artis D. Regulation of inflammation by microbiota interactions with the host. Nat Immunol. 2017 Aug;18(8):851
[34] Rescigno M. Dendritic cells and the complexity of microbial infection. Trends Microbiol. 2002 Sep;10(9):425-61.
[35] Zeuthen LH, Christensen HR, Frøkiaer H. Lactic acid bacteria inducing a weak interleukin-12 and tumor necrosis factor alpha response in human dendritic cells inhibit strongly stimulating lactic acid bacteria but act synergistically with gram-negative bacteria. Clin Vaccine Immunol. 2006;13(3):365
[36] Mantis NJ, Rol N, Corthésy B. Secretory IgAs complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol. 2011 Nov 1;4(6):603-11
[37] Corthësy B. Secretory immunoglobulin A: well beyond immune exclusion at mucosal surfaces. Immunopharmacol immunotoxicol. 2009 Jun 1;31(2):174-9
[38] Mantis NJ, Rol N, Corthésy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol. 2011 Nov 1;4(6):603-11
[39] Mantis NJ, Rol N, Corthésy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol. 2011 Nov 1;4(6):603-11
[40] Tan RA, Corren J. The relationship of rhinitis and asthma, sinusitis, food allergy, and eczema. Immunol Allergy Clin North Am. 2011 Aug 1;31(3):481-91
[41] Di Filippo P, Scaparrotta A, Rapino D, Cingolani A, Attanasi M, Petrosino MI, et al. Vitamin D supplementation modulates the immune system and improves atopic dermatitis in children. Int Arch Allergy Immunol. [Internet] 2015 [cited 2020 Oct 7]; 166:91-96. Available from: https://www.karger.com/Article/FullText/371350
[42] American Academy of Allergy, Asthma & Immunology (AAAAI). Atopy definition [Internet]. 2019 [cited 2019 Jul 4]. Available from: https://www.aaaai.org/conditions-and-treatments/conditions-dictionary/atopy

[43] Sharma R, Abrol S, Badgal A, Chowdhary S. Vitamin D and its role in dermatology: a review of literature. J Evol Med Dent Sci. 2015;4(10):1689-93.
[44] Polkowska-Pruszyńska B, Gerkowicz A, Krasowska D. The gut microbiome alterations in allergic and inflammatory skin diseases - an update. J Euro Acad Dermatol Venereol. 2019; 34(3):455-64
[45] Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. Gastroenterol Hepatol (N Y). 2005;2(9):416-422
[46] Kim JE, Kim HS. Microbiome of the skin and gut in atopic dermatitis (AD): Understanding the pathophysiology and finding novel management strategies. J. Clin. Med. [Internet] 2019 Apr [Cited 2020 Nov 11]; 8(4):444-467. Available from: https://doi.org/10.3390/jcm8040444
[47] Chelakkot C, Ghim J, Ryu SH. Mechanisms regulating intestinal barrier integrity and its pathological implications, Exp. Mol. Med [Online] 2018 [Cited 2020 Nov 12]; 50(103). Available from: DOI 10.1038/s12276-018-0126-x
[48] Johnson-Henry KC, Donato KA, Shen-Tu G, Gordanpour M, Sherman PM. *Lactobacillus rhamnosus* strain GG prevents enterohemorrhagic *Escherichia coli* O157:H7-induced changes in epithelial barrier function. Infect Immun. 2008 Apr;76(4):1340-8.
[49] Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: The role of butyrate on colonic function. Aliment Pharmacol Ther. 2008; 27:104–119
[50] O'Neill, C. A., Monteleone, G., McLaughlin, J. T., and Paus, R. The gut-skin axis in health and disease: a paradigm with therapeutic implications. Bioessays. (Online) 2016 (cited 2020 Oct 12) 38, 1167–1176. Available from doi: 10.1002/bies.201600008
[51] Miyazaki K, Masuoka N, Kano M, Lizuka R. Bifidobacterium fermented milk and galacto-oligosaccharides lead to improved skin health by decreasing phenols production by gut microbiota. Benef Microbes 2014; 5:121–8
[52] Salem I, Ramser A, Isham N, Ghannoum MS. The gut microbiome as a major regulator of the gut-skin axis. Front. Microbiol. 2018 Jul; 9:1459
[53] Gallo RL, Structure and function of the human skin microbiome. Trends Microbiol. 2013 Dec;21(12):660-8.
[54] Gallo RL, Nakatsuji T. Microbial Symbiosis with the innate immune defence system of the skin. J Invest Dermatol [Internet] 2011 Oct [Cited 2020 Nov 3];131(10):1974-1980. Available from: doi: 10.1038/jid.2011.182
[55] Prescott SL, Larcombe DL, Logan AC, West C, Burks, W. et al. The skin microbiome: impact of modern environments on skin ecology, barrier integrity, and systemic immune programming. World Allergy Organ. J. [Internet] 2017 [Cited 2020 Nov 12];10: 29. Available from: https://doi.org/10.1186/s40413-017-0160-5
[56] Ananthakrishnan AN. Advances in IBD: vitamin D and inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2016;12(6):513-5.
[57] Sun J. Dietary vitamin D, vitamin D receptor, and microbiome. Curr Opin Clin Nutr Metab Care 2018;21.
[58] Shang M & Sun J. Vitamin D/VDR, probiotics, and gastrointestinal diseases. Curr Med Chem. 2017; 24(9): 876-887.
[59] Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81(3):353-73. 1.
[60] Van der Schaft J. Serum vitamin D status in adult patients with atopic dermatitis: recommendations for daily practice. J Am Acad Dermatol. 2016 Dec; 75(6):1257-9.
[61] Cheng HM, Kim S, Park G-H, Chang SE, Bang S, Won CH. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. J Allergy Clinical Immunol. 2014;133(4):1048-55.
[62] Cho YS, Seo CH, Joo SY, Song J, Cha E, Ohn SH. The association between postburn vitamin D deficiency and the biomechanical properties of hypertrophic scars. American Burn Association. 2019 Apr 26;40(3):274-80
[63] Smart H, Al Ghareeb AM, Smart S-A. 25-hydroxyvitamin D deficiency: impacting deep-wound infection and poor healing outcomes in patients with diabetes. Adv Skin Wound Care. 2019; 32:321-8.
[64] Correia-Sa I, Serrao P, Marques M, Vieira-Coelho MA. Hypertrophic scars: are vitamins and inflammatory biomarkers related with the pathophysiology of wound healing? Obesity Surgery. [Internet] 2017 [cited 2020 Nov 26] 27(12):3170-3178. Available from: DOI: 10.1007/s11695-017-2740-4.
[65] Damanik VI, Putra IB, Ginting O. Correlation between serum 25-hydroxyvitamin D levels with keloid severity. OA Macedonian J Med Sci. 2019 Jan 15;7(1):65-7.
[66] Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. Am J Clin Dermatol. 2018; 19(2):223-35
[67] Abd-Elmaged WM, Nada EA, Hassan MH, Elsadek BEM, Abdelrahim EA, Ahmed NS, et al. Lesional and circulating levels of interleukin-17 and 25-hydroxycholecalciferol in active acne vulgaris: correlation to disease severity. 2018;1-6.
[68] Lim S-K, Ha J-M, Lee Y-H, Lee Y, Seo Y-J, Kim C-D, et al. Comparison of Vitamin D Levels in Patients with and without Acne: A Case-Control Study Combined with a Randomized Controlled Trial. PLoS ONE. 2016;11(8): e0161162.
[69] Prakash S, Rodes L, Coussa-Charley M, Tomaro-Duchesneau C. Gut microbiota: Next frontier in understanding human health and development of biotherapeutics. Biologics. 2011; 5:71-86.
[70] Schommer NN, Gallo RL, Structure and function of the human skin microbiome. Trends Microbiol. [Internet] 2013 [cited 2020 Oct 12) Dec;21(12):660-8. Available from: doi: 10.1016/j.tim.2013.10.001
[71] Salem I, Ramser A, Isham N, Ghannoum MA. The gut microbiome as a major regulator of the gut-skin axis. Front Microbiol. 2018 Jul 10. doi.org/10.3389/fmicb.2018.01459
[72] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 773-4; 781-2.
[73] Cuello-Garcia CA, Brożek JL, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Terracciano L et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. J. Allergy Clin. Immunol. 2015 Oct 31;136(4):952-61.
[74] Dang D, Zhou W, Lun ZJ, Mu X, Wang DX, Wu H. Meta-analysis of probiotics and/or prebiotics for the prevention of eczema. J. Int. Med. Res. 2013 Oct 1;41(5):1426-36.
[75] Cuello-Garcia CA, Brożek JL, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Terracciano L et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. J. Allergy Clin. Immunol. 2015 Oct 31;136(4):952-61.
[76] Zeuthen LH, Christensen HR, Frøkiaer H. Lactic acid bacteria inducing a weak interleukin-12 and tumor necrosis factor alpha response in human dendritic cells inhibit strongly stimulating lactic acid bacteria but act synergistically with gram-negative bacteria. Clin Vaccine Immunol. 2006:13(3):365.
[77] Jungersen M, Wind A, Johansen E, Christensen JE, Stuer-Lauridsen B, Eskesen D. The science behind the probiotic strain *Bifidobacterium animalis* subsp. *lactis* BB-12®. Microorganisms. 2014 Mar;2(2):92-110.
[78] Zeuthen LH, Christensen HR, Frøkiaer H. Lactic acid bacteria inducing a weak interleukin-12 and tumor necrosis factor alpha response in human dendritic cells inhibit strongly stimulating lactic acid bacteria but act synergistically with gram-negative bacteria. Clin Vaccine Immunol. 2006;13(3):365.
[79] Schultz M, Linde HJ, Lehn N, Zimmermann K, Grossmann J, Falk W, et al. Immunomodulatory consequences of oral administration of *Lactobacillus rhamnosus* strain GG in healthy volunteers. J Dairy Res. 2003;70(2):165-73.
[80] Cuello-Garcia CA, Brożek JL, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Terracciano L et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. J. Allergy Clin. Immunol. 2015 Oct 31;136(4):952-61.

[81] Schultz M, Linde HJ, Lehn N, Zimmermann K, Grossmann J, Falk W, et al. Immunomodulatory consequences of oral administration of *Lactobacillus rhamnosus* strain GG in healthy volunteers. J Dairy Res. 2003 May;70(2):165-73.
[82] Piirainen L, Haahtela S, Helin T, Korpela R, Haahtela T, Vaarala O. Effect of *Lactobacillus rhamnosus* GG on rBet v1 and rMal d1 specific IgA in the saliva of patients with birch pollen allergy. Ann Allergy Asthma Immunol. 2008 Apr;100(4):338-42.
[83] Cuello-Garcia CA, Brożek JL, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Terracciano L et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. J. Allergy Clin. Immunol. 2015 Oct 31;136(4):952-61.
[84] Jungersen M, Wind A, Johansen E, Christensen JE, Stuer-Lauridsen B, Eskesen D. The science behind the probiotic strain *Bifidobacterium animalis* subsp. *lactis* BB-12®. Microorganisms. 2014 Mar;2(2):92-110.
[85] Kim JE, Kim HS, Microbiome of the skin and gut in atopic dermatitis (AD): Understanding the pathophysiology and finding novel management strategies. J. Clin. Med. [Internet] 2019 Apr [Cited 2020 Nov 11]; 8(4):444-467. Available from: https://doi.org/10.3390/jcm8040444
[86] Prescott SL, Larcombe DL, Logan AC, West C, Burks, W. et al. The skin microbiome: impact of modern environments on skin ecology, barrier integrity, and systemic immune programming. World Allergy Organization J. [Internet] 2017 [cited 2020 Nov 11];10: 29. Available from: https://doi.org/10.1186/s40413-017-0160-5
[87] Francavilla R, Miniello V, Magistà AM, De Canio A, Bucci N, Gagliardi F et al. A randomized controlled trial of *Lactobacillus* GG in children with functional abdominal pain. Pediatrics. 2010 Dec;126(6): e1445-52
[88] Gupta P, Andrew H, Kirschner BS, Guandalini S. Is *Lactobacillus* GG helpful in children with Crohn's disease? Results of a preliminary, open-label study. J Pediatr Gastroenterol Nutr. 2000 Oct;31(4):453-7.
[89] Commane DM, Shortt CT, Silvi S, Cresci A, Hughes RM, Rowland IR. Effects of fermentation products of pro- and prebiotics on trans-epithelial electrical resistance in an in vitro model of the colon. Nutr Cancer. 2005;51(1):102-9.
[90] Flint HJ, Duncan SH, Scott KP, et al. Links between diet, gut microbiota composition and gut metabolism. Proc Nutr Soc. 2015 Feb;74(1):13-22
[91] Castoldi A, Favero de Aguiar C, Moraes-Vieira PM, Camara NOS. They must hold tight: junction proteins, microbiota and immunity in intestinal mucosa. Curr Prot Pept Sci. 2015; 16:655-71.
[92] Prakash S, Rodes L, Coussa-Charley M, Tomaro-Duchesneau C. Gut microbiota: Next frontier in understanding human health and development of biotherapeutics. Biologics. 2011; 5:71-86.
[93] Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol [Internet] 2001 Jan [cited 2020 Nov 10];107(1):129-34. Available from: https://doi.org/10.1067/mai.2001.111237
[94] Sjogren YM, Jenmalm MC, Bottcher MF, Bjorksten B, Sverremark-Ekstrom E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. Clin Exp Allergy. 2009; 39:518–526.
[95] Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol [Internet] 2001 Jan [cited 2020 Nov 10];107(1):129-34. Available from: https://doi.org/10.1067/mai.2001.111237
[96] Bowe W, Patel NB, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine. Beneficial Microbes. 2014;5(2):185-99.
[97] Bowe W, Patel NB, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine. Beneficial Microbes. 2014;5(2):185-99.
[98] Prakash S, Rodes L, Coussa-Charley M, Tomaro-Duchesneau C. Gut microbiota: Next frontier in understanding human health and development of biotherapeutics. Biologics. 2011; 5:71-86.
[99] Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: The role of butyrate on colonic function. Aliment Pharmacol Ther. 2008; 27:104–119.
[100] Pärtty A, Lehtonen L, Kalliomäki M, Salminen S, Isolauri E. Probiotic Lactobacillus rhamnosus GG therapy and microbiological programming in infantile colic: a randomized, controlled trial. Pediatr Res. 2015 Oct;78(4):470-5.
[101] Rinne M, Kalliomaki M, Arvilommi H, Salminen S, Isolauri E. Effect of probiotics and breastfeeding on the bifidobacterium and lactobacillus/enterococcus microbiota and humoral immune responses. J Pediatr. 2005;147(2):186-91.
[102] Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Papaero L, Aitoro R, et al. *Lactobacillus rhamnosus* GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME J. 2016 Mar;10(3):742-50.
[103] Lee Y, Salminen S. *Lactobacillus rhamnosus* GG. In: Handbook of Probiotics and Prebiotics. 2nd ed. Hoboken: John Wiley & Sons. 2009:469-473
[104] Fukushima Y, Kawata Y, Hara H, Terada A, Mitsuoka T. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. Int J Food Microbiol. 1998; 42:39-44.
[105] Turroni F, Milani C, Duranti S, Ferrario C, Lugli GA, Mancabelli L, et al. Bifidobacteria and the infant gut: an example of co-evolution and natural selection. Cell Mol Life Sci. 2018 Jan;75(1):103-118.
[106] Martins FS, Silva AA, Vieira AT, Barbosa FH, Arantes RM, Teixeira MM, et al. Comparative study of *Bifidobacterium animalis*, *Escherichia coli*, *Lactobacillus casei* and *Saccharomyces boulardii* probiotic properties. Arch Microbiol. 2009 Aug 1;191(8):623-30.
[107] Jungersen M, Wind A, Johansen E, Christensen JE, Stuer-Lauridsen B, Eskesen D. The science behind the probiotic strain *Bifidobacterium animalis* subsp. *lactis* BB-12®. Microorganisms. 2014 Mar;2(2):92-110.
[108] Yamamoto EA, Jorgensen TN. Relationships between vitamin D, gut microbiome, and systematic autoimmunity. Front. Immunol. 2020; 10:3141.
[109] Sanchez-Armendariz K, Garcıa-Gil A, Romero CA, Karam-Orante M, Balcazar-Antonio D, Domınguez-Cherit J. Oral vitamin D3 5000 IU/day as an adjuvant in the treatment of atopic dermatitis: a randomized control trial. Int J Dermatol. 2018 Dec; 57(12):1516-1520

[110] Arumugam M, Jamil A, Nor N, Baseri M, Thevarajah S, Mustafa N. Sun Exposure, Dietary Vitamin D and Vitamin D Status in Adult Atopic Dermatitis: A Case Control Study. Mal J Med Health Sci. 2020 Jan;16(1): 66-69.
[111] Cheng HM, Kim S, Park G-H, Chang SE, Bang S, Won CH. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. J Allergy Clinical Immunol. 2014;133(4):1048-55.

[112] Rosendahl J, Fogelholm M, Pelkonen A, Mäkelä MJ, Mäkitie O, Erkkola M. A history of cow's milk allergy is associated with lower vitamin D status in schoolchildren. Horm Res Paediatr. 2017;88(3-4):244-250.
[113] Silva CM, Silva SAD, Antunes MMC, Silva GAPD, Sarinho ESC, Brandt KG. Do infants with cow's milk protein allergy have inadequate levels of vitamin D? J Pediatr (Rio J). 2017 Nov - Dec;93(6):632-638.
[114] Elsori DH., Hammoud MS. Vitamin D deficiency in mothers, neonates and children. J. Steroid Biochem. Mol. Bio. 2018;175, 195–199
[115] Kılıç S, Sılan F, Hız MM, et al. Vitamin D Receptor Gene BSMI, FOKI, APAI, and TAQI Polymorphisms and the Risk of Atopic Dermatitis. Journal of Investigational Allergology & Clinical Immunology. 2016 ;26(2):106-110.
[116] Heine G, Hoefer N, Franke A, Nothling U, Schumann RR, Worm M. Association of vitamin D receptor gene polymorphisms with severe atopic dermatitis in adults. Dermatology. 2013;168(4):855-8.

[117] Daniluk U, Filimoniuk A, Kowalczuk-Krystoń M, Alifier M, Karpińska J, Kaczmarski M G, et al. Association of antioxidants and vitamin D level with inflammation in children with atopic dermatitis. Int. J. Dermatol. 2019 Sep;58(9):1056-61
[118] Xiang J, Wang H, Li T. Comorbidity of vitamin A and vitamin D deficiency exacerbates the severity of atopic dermatitis in children. Dermatol. 2019; 235:196-204.
[119] Luthold RV, Fernandes GR, Franco-de-Moraes AC, Folchetti LG, Ferreira SR. Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals. Metabolism. 2017 Apr; 69:76-86.
[120] Mukherjee K, Kavalukas SL, Barbul A. Nutritional aspects of gastrointestinal wound healing. Adv Wound Care. 2015;5(11):507-15.
[121] Shang M, Sun J. Vitamin D/VDR, probiotics, and gastrointestinal diseases. Curr Med Chem. 2017;24(9):876-887.
[122] Sun J. Dietary vitamin D, vitamin D receptor, and microbiome. Curr Opin Clin Nutr Metab Care. 2018;21(6):471-4.
[123] Jones ML, Martoni CJ, Prakash S. Oral supplementation with probiotic *L. reuteri* NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: a post hoc analysis of a randomized controlled trial. J Clin Endocrinol Metab. 2013;98(7):2944-51.
[124] Miyazawa K, Harata G, Yoda K, Yamazaki K, He F, Hiramatsu M. Effects of intake of Lactobacillus rhamnosus GG on intestinal environment and skin condition in healthy adults: a randomized, double-blind, placebo-controlled study. Int J Probiotic Prebiotic. 2018;13(1):11-8.
[125] Kirjavainen PV, Salminen SJ, Isolauri E, Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. J. Pediatr. Gastroenterol. Nutr. 2003:36:223-27.
[126] Matsumoto M, Ebata T, Hirooka J, Hosoya R, Inoue N, Itami S, et al. Antipruritic effects of the probiotic strain LKM512 in adults with atopic dermatitis. Ann Allergy Asthma Immunol. 2014;1-8.
[127] Sofrankova, L Jakusova L, Kohutova M, Marusiakova L, Petrovicova O, Simekova M, et al. Intestinal permeability and SCORAD of children with atopic dermatitis after six weeks supplementation of *Lactobacillus rhamnosus* GG (the pilot study). Čes-slov Pediat. 2015;70(5):273-80.
[128] Schmidt RM, Laursen RP, Bruun S, Larnkjaer A, Mølgaard C, Michaelsen KF, et al. Probiotics in late infancy reduce the incidence of eczema: A randomised controlled trial. Pediatr Allergy Immunol. 2019;1-6.
[129] Fabbrocini G, Bertona M, Picazo O, Pareja-Galeano H, Monfrecola G, Emanuele E. Supplementation with Lactobacillus SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. Beneficial Microbes. 2016;7(5):625-30.
[130] Amon U, Baier L, Yaguboglu R, Ennis M, Holick MF, Amon J. Serum 25-hydroxyvitamin D levels in patients with skin diseases including psoriasis, infections, and atopic dermatitis. Dermato-endocrinology. 2018;10(1): e1442159.
[131] Navarro-Trivino FJ, Arias-Santiago S, Gilaberte-Calzada Y. Vitamin D and the skin: a review for dermatologists. Actas Dermosifiliogr. 2019 May;110(4):262-72
[132] Camargo CA, Ganmaa D, Sidbury R, Erdenedelger K, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J Allergy. Clin. Immunol. 2014: 134(4);831-837.
[133] Van der Schaft J. Serum vitamin D status in adult patients with atopic dermatitis: recommendations for daily practice. J Am Acad Dermatol. 2016 Dec; 75(6):1257-9.
[134] Di Filippo P, Scaparrotta A, Rapino D, Cingolani A, Attanasi M, Petrosino MI et al. Vitamin D supplementation modulates the immune system and improves atopic dermatitis in children. Int Arch Allergy Immunol 2015; 166:91–96.
[135] Yildizgoren MT, Togral AK. Preliminary evidence for vitamin D deficiency in nodulocystic acne. Dermato-Endocrinol. 2014;6(1): e983687-1.
[136] Lim S-K, Ha J-M, Lee Y-H, Lee Y, Seo Y-J, Kim C-D, et al. Comparison of vitamin D levels in patients with and without acne: a case-control study combined with a randomized controlled trial. PLoS ONE. 2016;11(8): e0161162.
[137] El-Hamd MA, El Taieb MA, Ibrahim HM, Aly SS. Vitamin D levels in acne vulgaris patients treated with oral isotretinoin. J Cosmet Dermatol. 2019; 18:16-20.
[138] Kemeritz F, Tuncer SC, Acar EM, Ayanoglu BT. Evaluation of 25-hydroxy Vitamin D levels and Disease Severity in Patients with Acne Vulgaris. Dermatol Ther. 2020 Apr 8; e13393. doi: 10.1111/dth.13393. Online ahead of print.
[139] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[140] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[141] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[142] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.

[143] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 1125-49.
[144] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[145] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[146] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney: Elsevier/Churchill Livingstone. 2015. p. 1125-1146.
[147] Vitamin D. In: IM Gateway [database on the internet]. Unity Health Proprietary Limited; 2001-2018 [cited 2018 September 28]. Available from: http://www.imgateway.net/page.jsp?p_name=InteractionsDatabase subscription required to view.
[148] Ulbricht CE. Vitamin D. In: Natural Standard. Herb & Supplement Guide. An evidence-based reference. Maryland heights (MIS): Mosby Elsevier. 2010. p. 741-5.
[149] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[150] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[151] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[152] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[153] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[154] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[155] Burke RR, Rybicki BA, Rao DS. Calcium and vitamin D in sarcoidosis: how to assess and manage. In: Seminars in respiratory and critical care medicine. Thieme Medical Publishers. 2010;31(4):474-484.

[156] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[157] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[158] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[159] Ulbricht CE. Vitamin D. In: Natural Standard. Herb & Supplement Guide. An evidence-based reference. Maryland heights (MIS): Mosby Elsevier. 2010. p. 741-5.
[160] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[161] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[162] Lactobacillus. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2018 [updated 2018 Mar 13; cited 2018 Mar 15]. Available from: https://naturalmedicines.therapeuticresearch.com/. Subscription required to view.

[163] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 771-96.
[164] Lactobacillus. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2018 [updated 2018 Mar 13; cited 2018 Mar 15]. Available from: https://naturalmedicines.therapeuticresearch.com/. Subscription required to view.
[165] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 771-96.
[166] Natural Medicines. Bifidobacteria. [Online]. 2015. Available from: https://naturalmedicines.therapeuticresearch.com/. [Cited 30/03/2017].
[167] Braun L, Cohen M. Probiotics In: Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney: Elsevier/Churchill Livingstone. 2015:771-96.
[168] Lactobacillus. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2018 [updated 2018 Mar 13; cited 2018 Mar 15]. Available from: https://naturalmedicines.therapeuticresearch.com/. Subscription required to view.
[169] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 771-96.
[170] Elias J, Bozzo P, Einarson A. Are probiotics safe for use during pregnancy and lactation? Can Fam Physician. 2011 Mar;57(3):299-301.
[171] Laitinen K, Poussa T, Isolauri E; Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr. 2009 Jun;101(11):1679-87.
[172] Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr. 2010 Jun;103(12):1792-9.
[173] Hajifaraji M, Jahanjou F, Abbasalizadeh F, Aghamohammadzadeh N, Abbasi MM, Dolatkhah N. Effect of probiotic supplements in women with gestational diabetes mellitus on inflammation and oxidative stress biomarkers: a randomized clinical trial. Asia Pac J Clin Nutr. 2018;27(3):581–91.
[174] Dotterud CK, Avershina E, Sekelja M, et al. Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child? J Pediatr Gastroenterol Nutr. 2015;61(2):200–207.
[175] National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Vitamin D [Internet]. Canberra (ACT): Australian Government. 2014 Sept 4. [cited 2020 Jul 30]. Available from: https://www.nrv.gov.au/nutrients/vitamin-d.
[176] Elias J, Bozzo P, Einarson A. Are probiotics safe for use during pregnancy and lactation? Can Fam Physician. 2011 Mar;57(3):299-301.
[177] Fernández L, Langa S, Martín V, Jiménez E, Martín R, Rodríguez JM. The microbiota of human milk in healthy women. Cell Mol Biol (Noisy-le-grand). 2013 Nov 3;59(1):31-42.
[178] Laitinen K, Poussa T, Isolauri E; Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr. 2009 Jun;101(11):1679-87.
[179] Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr. 2010 Jun;103(12):1792-9.
[180] National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Vitamin D [Internet]. Canberra (ACT): Australian Government. 2014 Sept 4. [cited 2020 Jul 30]. Available from: https://www.nrv.gov.au/nutrients/vitamin-d.
[181] Elias J, Bozzo P, Einarson A. Are probiotics safe for use during pregnancy and lactation? Can Fam Physician. 2011 Mar;57(3):299-301.
[182] Laitinen K, Poussa T, Isolauri E; Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr. 2009 Jun;101(11):1679-87.
[183] Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr. 2010 Jun;103(12):1792-9.
[184] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 776-777-96.
[185] Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet. 2003 May 31;361(9372):1869-71.
[186] National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Vitamin D [Internet]. Canberra (ACT): Australian Government. 2014 Sept 4. [cited 2020 Jul 30]. Available from: https://www.nrv.gov.au/nutrients/vitamin-d.
[187] Vitamin D. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2008 [cited 2018 September 28]. Available from: http://www.naturaldatabase.com. subscription required to view.
[188] Baghurst K. Vitamin D. In: Nutrient References Values for Australia and New Zealand. Australian Government: Department of Health and Ageing, National Health and Medical Research Council, Canberra. 2005. p. 127-38.
[189] Stargrove MB, Treasure J, McKee DL. Herb, nutrient, and drug interactions. St Louis (MO): Mosby Elsevier; 2010. p. 399-421.
[190] Lactobacillus. In: Natural Medicines Comprehensive Database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2018 [updated 2018 Mar 13; cited 2018 Mar 15]. Available from: https://naturalmedicines.therapeuticresearch.com/. Subscription required to view.
[191] Natural Medicines. Bifidobacteria. [Online]. 2015. Available from: https://naturalmedicines.therapeuticresearch.com/. [Cited 30/03/2017]
[192] Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 4th ed. Vol 2. Sydney (AU): Elsevier/Churchill Livingstone; 2015. p. 771-96.