INNERHEALTH

PROBIOTICS AND VITAMIN D FOR SKIN HEALTH IN CHILDREN

Eczema, also known as atopic dermatitis, affects many infants and children. 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]. Disruption of the skin barrier, as well as irregular immune system responses that favour an allergic response, have both been implemented in the pathogenesis of eczema[7].

This document will investigate & explain:

1) Eczema and the Gut
   a. The Immune System Response
   b. Gut and Skin Integrity
   c. Vitamin D and the Microbiome
2) The Benefits of Eczema Shield Kids for Eczema in Children
   a. Modulating the Immune System to Reduce Atopic Response
   b. Supporting Gut Integrity
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Probiotic Strains and Nutrients That May Assist

Lactobacillus rhamnosus (LGG®)

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

Cholecalciferol

(Microencapsulated* Vitamin D)

Clinical Applications

- Modulating the immune system to reduce atopic response
- Reduce mild eczema symptoms
- Support the microbiome

*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)

1) Eczema and the Gut

The link between the gut and the skin has long been established,[8] even if it is not yet completely understood.[9] Dysbiosis of the gut is implicated as a large contributing factor to disorders of the skin, particular inflammatory conditions.[10] The main basis of this relationship is the way the microbiota interacts with the immune system to modulate inflammation, as well as barrier integrity in both the skin and the gut.[11]

a. The Immune System Response

Given that over 70% of the body's immune system is in the gut,[12] 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 and maturation.[13] The composition of the gut microbiota modulates T helper cell activity by influencing two key mediators, dendritic cells (DCs)

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and T regulatory cells (Tregs).[14] 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.[15] 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.[16]

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.[17,18] 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 removal via peristalsis.[19] Importantly, sIgA also regulates immune tolerance to benign antigens, such as food antigens and commensal flora,[20] 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.[21]

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.[22] These factors result in irregular immune system activity that skews towards a Th2/IgE response, and a tendency to be overly sensitive to allergens.[23] It is this imbalance that supplementation with probiotics aims to correct.

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.[24] 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),[25] thus increasing the likelihood of a systemic cycle of immune activation and inflammation,[26] as antigens, food, and microbes cross the mucosal barrier and cause an allergic response, aggravating the conditions associated with this response, such as eczema.[27] The production of short-chain-

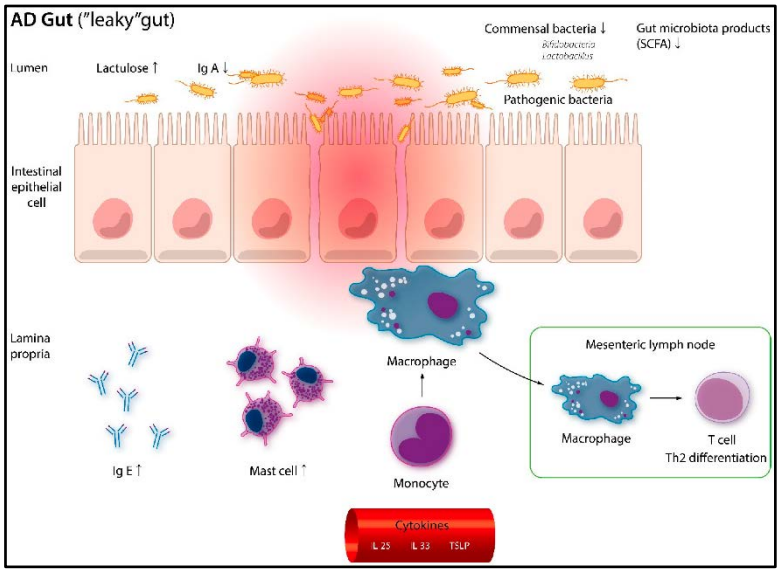

Figure 1: Disruption to TJs due to dysbiosis and consequent lack of SCFAs. Monocytes migrate and differentiate into macrophages due to a response to inflammatory cytokines. T cells mature into Th2 cells due to an increased exposure to luminal antigens. Cytokines also stimulate an increase in expression of IgE and a decrease in IgA.

fatty-acids (SCFA) by commensal flora helps to strengthen these TJs,[28] making a healthy gut microbiome essential for barrier integrity.

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.[29] 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,[30] and therefore a compromised skin barrier. Given that poor integrity of the skin barrier is one of the proposed mechanisms for eczema flares,[31] it is important to protect gut barrier integrity so as not to further exacerbate disease pathogenesis.

It is also important to note that the skin of eczema sufferers have increased colonisation of certain bacteria,[32] 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.[33] This can result in a local immune/inflammatory response that, like that initiated in the gut, can have systemic implications.[34]

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.[35] Given that data reveals that >50% of newborns in Australia and New Zealand have inadequate levels of **vitamin D**,[36,37,38,39] and the evinced link between **vitamin D** and the gut microbiome health, supplementing with **vitamin D** makes sense to support microbiome health and further, the health of the immune system.

2) The Benefits of LGG®, BB-12® in Eczema in Children (Figure2)

a. Modulating the Immune System to Reduce Atopic Response

The microbiome is essential for the development and ongoing modulation of immune responses,[40] signalling TLRs in the intestinal epithelium, as well as in the skin itself,[41] and balancing between Th1 and Th2 responses, and in this way, the composition of the gut microbiota can impact atopic conditions, such as eczema.

A growing body of evidence indicates that some probiotic strains can modulate the immune system at both the systemic and the mucosal levels.[42] Specific strains of probiotics may be used to support the induction of Tregs, in turn supporting the balancing of the Th1 and Th2 pathways,[43] as well as provide additional anti-inflammatory support via the stimulation of the production of immunoglobulin A (IgA),[44] and suppression of IgE.[45] Specifically, **LGG®**[46] and **BB-12®**[47] possess considerable

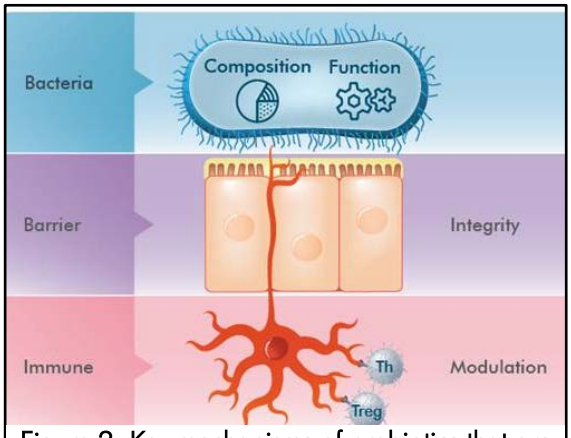

Figure 2: Key mechanisms of probiotics that are of benefit in eczema sufferers

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.[48] Specifically, the range of LGG® immune-regulating mechanisms is extensive; LGG® increases IL-10,[49] and TGF-β2,[50] cytokines and down-regulates TNF-α, IL-6, and IFN-γ, thus promoting Th1/Th2 balance.[51] LGG® has also been shown to increase IgA levels,[52] as well as decrease circulating levels of IgE.[53]

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.[54]

It is also of note that LGG® and BB-12®, both separately and in combination, have been shown to modulate the immune response in children specifically. Studies supporting are summarised further below.

b. Supporting Gut Integrity

There is evidence to suggest that there is dysbiosis in both the gut and the skin microbiome in eczema.[55] 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.[56]

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[57,58] and an *in vitro* study investigating the effects of BB-12® on cell junctions found that supplementation significantly enhanced the integrity of transepithelial junctions.[59] This is because LGG® and BB-12® can increase the formation of SCFAs such as acetate, propionate and butyrate.[60] 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.[61]

c. Supporting a Healthy Microbiome

i. With Probiotics

The gut microbiota in non-allergic individuals has been shown to differ from allergic individuals.[62,63] Studies have shown that numbers of *Clostridia* are higher, whereas numbers of *bifidobacteria* and *lactobacilli* groups are lower in allergy sufferers,[64,65] suggesting that these latter species in particular offer benefits to the host that may lower allergy incidence.

Also, as previously mentioned, the production of SCFAs by commensal flora is believed to exert strong immunomodulatory effects[66] and strengthen enterocyte health.[67]

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*[68] and *lactobacillus/enterococcus*[69,70] therefore contributing to increased microbial diversity to support SCFA production, mucosal barrier function[71] and thus a lower incidence of allergy. BB-12® supplementation in infants has also been shown to increase faecal levels of *bifidobacteria*,[72] which is particularly significant as *bifidobacteria* cross-feed

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other important commensal species within the gut microbiota.[73] 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*.[74] 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.[75]

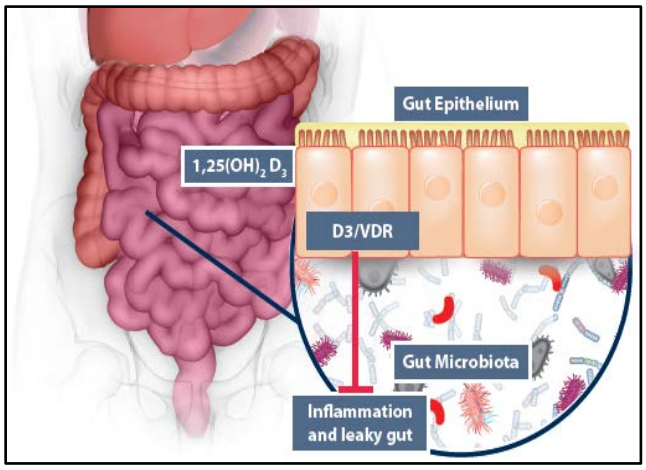

Figure 3: Vitamin D, VDR and the microbiome in the intestine[1]

ii. With Vitamin D

As previously mentioned, **vitamin D** deficiency is one causative factor linked to the disruption of a healthy microbiome.[76] It has also been shown that children with allergic disease states, including eczema, are more likely to have insufficient levels of **vitamin D**[77,78,79] and VDR.[80] **Vitamin D** and VDRs regulate host-bacterial interactions and innate immune responses of the gut microbiota, including the production of antimicrobial peptides,[81] as well as maintain gut tolerance and barrier function,[82] to help to control microbial dysbiosis,[83] and inhibit inflammation[84](Figure 3). Further, probiotics have been shown to increase **vitamin D** and VDR in the gut.[85]

3) Clinical Evidence to Support the Use of Probiotics and Vitamin D for Eczema in Children

Summary of Key Evidence to Support Probiotic Use in Children with Eczema					
Study	**Population studied**	**Ingredient**	**Supplement duration**	**Equivalent daily dose**	**Outcome**
Sofrankova et al 2015[86]	Pilot study of 39 children (22 allergic, 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 indicates increased intestinal permeability.	**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.
Kirjavainen PV, Salminen SJ, Isolauri E. 2003[87]	Double-blind placebo-controlled trial of 35 infants with atopic eczema allergic to cow's milk – mean age 5.5 months. Groups received either extensively hydrolised 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. ($P=0.02$)
Majamaa H, Isolauri MD. 1997[88]	Randomised double-blind study with 27 children given extensively hydrolysed whey formula (EHWF) with ($n=13$) or without ($n=14$) **LGG®**. Severity of eczema was assessed with concentrations of faecal a_1-antitrypsin, tumour necrosis factor-a, and eosinophil cationic protein.	**LGG®**	1 month	Formula contained **LGG®** concentration equivalent to $5x10^8$ CFU/g. Dose varied with amount consumed by child.	In the **LGG®** group, concentration of a_1-antitrypsin ($P=0.03$), and tumour necrosis factor-a ($P=0.003$) decreased significantly. Eosinophil cationic protein concentrations remained unchanged.
Schmidt et al 2019[89]	Randomised, placebo-controlled trial of 290 (144 probiotic group vs 146 placebo) children	**LGG® and BB-12®**	6 months	1 billion live bacteria of each **LGG®** and **BB-12®**	Receiving probiotic intervention significantly lowered eczema incidence ($P= 0.036$)

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	aged 8-14 months, to observe incidence of developing eczema.				
Isolauri E, et al. 2000[90]	27 exclusively breastfed infants (mean age 4.6 months) with early onset atopic disease, were weaned to EHWF, or 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)
Summary of Key Evidence to Support Probiotic Use in Children to Lower Allergic Response					
Pohjavuori et al. 2004[91]	Randomised, double-blind, Placebo-controlled trial of 119 infants (aged 1.4-11.5 months) with suspected cow's milk allergy (CMA). Participants were given **LGG®** (n=42), a mix of 4 strains of probiotic(n=41), or placebo (n=36). Levels of inflammatory markers produced by monocytes and lymphocytes were measured pre- and post-intervention to ascertain whether levels were associated with CMA and whether intervention improved these levels.	**LGG®**	4-week treatment with follow up 4 weeks later	10 billion live bacteria	IFN-γ was significantly lower in infants with CMA (n=65) (P=0.016) and IgE-associated CMA (n=42) (P=0.003) com[pared to infants without CMA (n=54), at baseline. Post intervention, IFN-γ levels were significantly increased in those in the **LGG®** group with CMA (n=33) (P=0.006), and in those with IgE-associated dermatitis (P=0.017), when compared to placebo group, suggesting IFN-γ deficiency is related to CMA. Those receiving the probiotic mix did not have significantly increased IFN-γ levels.
Berni Canani R et al. 2012[92]	Double-blind, placebo-controlled food challenge (DBPCFC) of infants aged 1-12 months with CMA. Group 1: extensively hydrolysed casein formula (EHCF) (Nutramigen) n=22 Group 2: EHCF containing **LGG®** (at least 14 million CFU/100 ml) (Nutramigen **LGG®**) n=28	**LGG®**	Follow-ups at 6 and 12 months	9.8 billion live bacteria	Supplementation of EHCF with **LGG®** accelerated the development of tolerance in infants to cow's milk protein. (P=0.03)
Tan-Lim CSC, Esteban-Ipac NAR 2018[93]	Systematic review and meta-analysis of studies with children aged 1-12 months at baseline.	**LGG®**	Follow-ups performed at 12, 24, and 36 months	1.4 x 10^7 CFU **LGG®** / 100 mL in EHCF daily. Maximum likely daily dose = 140 million live bacteria	Moderate certainty that the use of probiotics can relieve symptoms of children with cow's milk allergy. **LGG®** administration likely results in inducing tolerance among infants with suspected cow's milk allergy.
Berni Canani R et al. 2017[94]	Randomised control trial of 220 children with IgE mediated cow's milk allergy (CMA) (110 in EHCF + **LGG®** group, and 110 in EHCF group) Median age was 5 months (interquartile range 3-8 months). Outcome assessed was oral tolerance of cow's milk, and development of other allergic manifestation (AM).	**LGG®**	3 year follow up	9.8 billion live bacteria	EHCF+**LGG®** reduced the incidence of other AM and hastens the development of oral tolerance in children with IgE-mediated CMA, more so than EHCF alone. (P<0.001)
Summary of Key Evidence to Support Vitamin D Use in Children to Lower Allergic Response					
Camargo et al. 2014[95]	Randomised, double-blind, placebo-controlled, trial of 107 children aged 2-17 years with atopic eczema that worsens in winter.	**Vitamin D** drops	1 month	1000IU	Eczema Area and Severity Index (EASI) score for children receiving vitamin D was significantly more decreased than scores of those receiving placebo (P=0.01)
Di Filippo et al 2015[96]	59 children (39 with eczema, 20 nonallergic) in a controlled intervention, measuring inflammatory markers and SCROAD indicis	**Vitamin D**	3 months	1000IU	SCORAD indicis were significantly reduced in the eczema group following intervention (P,0.001)

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4) Dosage 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.[97]

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.[98]

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.[99] 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.[100,101,102]

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.[103,104,105,106]

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.[107] For doses under 2000 IU, use caution and only under medical supervision.[108,109]

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.[110,111]

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.[112]

Sarcoidosis or other granulomatous disease: The synthesis of vitamin D is altered by granulomatous inflammation, resulting in increased production of 1, 25-dihydroxyvitamin D.[113] 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.[114,115]

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.[116,117]

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.[118,119]

Cautions – Low level

Immunosuppressants: Theoretically, Lactobacillus could cause infection in patients taking medications that suppress the immune system. These include cyclosporine (Neoral, Sandimmune), tarolimus (Prograf), azathioprine (Imuran), and cancer chemotherapeutic agents like cycophosphamide (Cytoxan) and cisplatin (Platinol-AQ), and others.[120,121] 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.[122,123] Based on these occurrences, a theoretical concern of bacteraemia and sepsis extends to bifidobacteria probiotics.[124,125] 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.[126,127]

Pregnancy

Likely safe. While there is evidence to support the use of these ingredients during pregnancy,[128,129,130,131,132,133] and a review did not identify concerns for use, Practitioner discretion is advised.

Breastfeeding

Appropriate for use.[134,135,136,137,138]

Children

Appropriate for use.[139,140,141 142,143]

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;[144] 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[145,146]; 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.[147]

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.[148,149,150]

6) References

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