Comprehensive immune support for chronic conditions

KEY LEARNINGS

Oncology support

- A number of natural compounds such as green tea, curcumin, reishi, shiitake and coriolus have been found to inhibit the molecular events and signalling pathways associated with various stages of cancer development.
- These herbs may offer protection from and prevent recurrence of various cancer types, including breast, prostate, ovarian, endometrial, and gastrointestinal cancers.
- Various vitamins and minerals, such as vitamins A, D, E, and zinc and selenium have shown to protect tissues from the pro-inflammatory stressors that promote cancer and may directly target cancer cells by inducing differentiation, inhibiting cell growth and promoting apoptosis.

Autoimmune diseases

- By reducing pro-inflammatory cytokines and enhancing T-regulatory cells, curcumin, green tea, reishi and shiitake may attenuate the progression of autoimmune diseases (AIDs).
- Given oxidative stress is a major contributor to a dysregulated immune system, selenium, zinc and, vitamins A and E may play a protective role in AID development.
- Vitamins A, D, E and zinc and selenium also exhibit immunomodulatory effects by modulating specific functional aspects of the immune response.

Immune insufficiency and infections

- Reishi, shiitake, coriolus, curcumin and green tea modulate the innate and adaptive immune system and have been shown to restore immune parameters, such as natural killer (NK) cell activity, T helper cells and lymphocytes.
- Since every stage of the immune response relies on the presence of micronutrients, vitamins A, D, E, and zinc and selenium may reduce the risk of infection and support faster recovery.

Fibromyalgia

- Both chronic and acute infections, such as Epstein-Barr virus (EBV) often trigger autoimmunity and may precede the onset of fibromyalgia (FM).
- Studies suggest green tea and reishi may inhibit EBV replication, while curcumin positively affects inflammatory pathways associated with pain.
- Vitamins A and E may reduce oxidative damage and hypoxia, which is often a debilitating feature in FM. Vitamin D modulates several inflammatory and pain pathways.

Chronic fatigue syndrome

- Increased oxidative stress as a result of viral or bacterial infections may be associated with the pathogenesis of chronic fatigue syndrome (CFS).
- Consequently, various natural compounds including green tea, zinc and vitamin E may play a pivotal role in scavenging free radicals and attenuating the disabling mechanisms of CFS.

Liver disease

- Evidence supports the role of inflammation and oxidative stress in promoting the progression of liver diseases.
- Known for their antioxidant, anti-inflammatory and hepatoprotective effects, green tea, curcumin and mushrooms may benefit liver disease progression.
- Vitamins D, E and zinc have exhibited protective effects against liver dysfunction and may influence the inflammatory response associated with chronic liver injury.

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Oncology support

Characterised by uncontrolled cell growth, cancer is reported to be the leading cause of death in Australia, accounting for approximately three in every ten deaths.[1] In Western populations, cancer in both males and females is gradually increasing. Living with a cancer diagnosis is usually an ongoing and difficult experience that affects patient's physical health, mental wellbeing and relationships with loved ones. As a result of their potential mortality, patients often turn to alternative solutions, with results revealing an average of 51% of cancer patients utilise complementary and alternative medicines (CAM).[2]

Role of immune system in cancer

A dysregulated immune system allows cancer cells to spread and it has been postulated that a lowered immune system may increase the chance of cancer development.[3] Additionally, immune cells play a central role in smouldering inflammation in tumour cell proliferation, survival and metastasis.[3] Tumours may originate at sites of chronic inflammation and their growth is influenced and affected by immune cells from their early initiation stages to progression and dissemination.[4] The immune system protects the host from tumours by eliminating viral infections, preventing inflammation conducive to tumorigenesis and aids in identifying and eliminating tumour cells. By manipulating the immune system and the major immune cell types, such as macrophages, neutrophils, NK cells, and T and B cells, tumour growth can be restrained.[3]

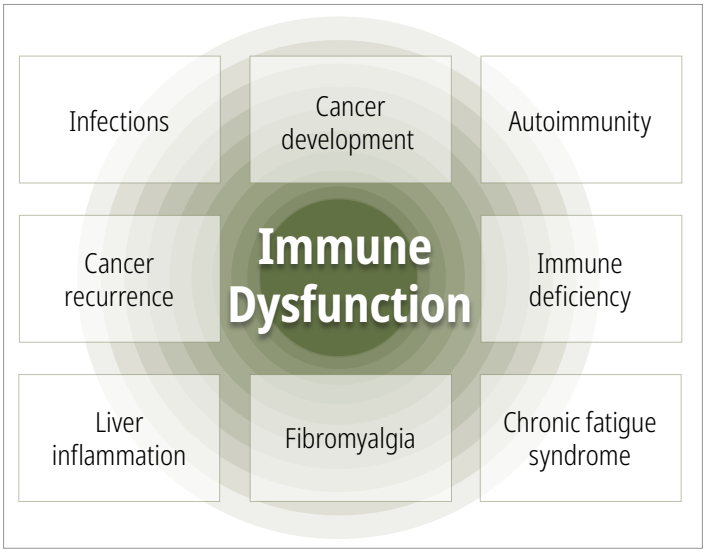
Cancer support and prevention

There is increasing evidence that CAM practitioners have a crucial role in supporting cancer patients and preventing the development and recurrence of cancer. A plethora of *in vitro* and animal studies exists, recognising the potential of various herbal and nutritional supplements that effectively modify anti-cancer mechanisms of the immune system. While human clinical trials are still in its infancy, a select group of complementary medicines have proved effective in patients undergoing cancer treatment. Moreover, by utilising dietary and lifestyle changes alongside herbal and nutritional medicine, CAM practitioners can enhance the effectiveness of medical treatments, reduce the side effects and potential pharmaceutical load on patients, and improve their overall quality of life.

Herbal medicine for cancer management

A number of natural compounds have been found to inhibit the molecular events and signalling pathways associated with various stages of cancer development and, therefore, show promise as strategies for cancer treatment and prevention.

Figure 1: Consequences of immune dysfunction



Green tea

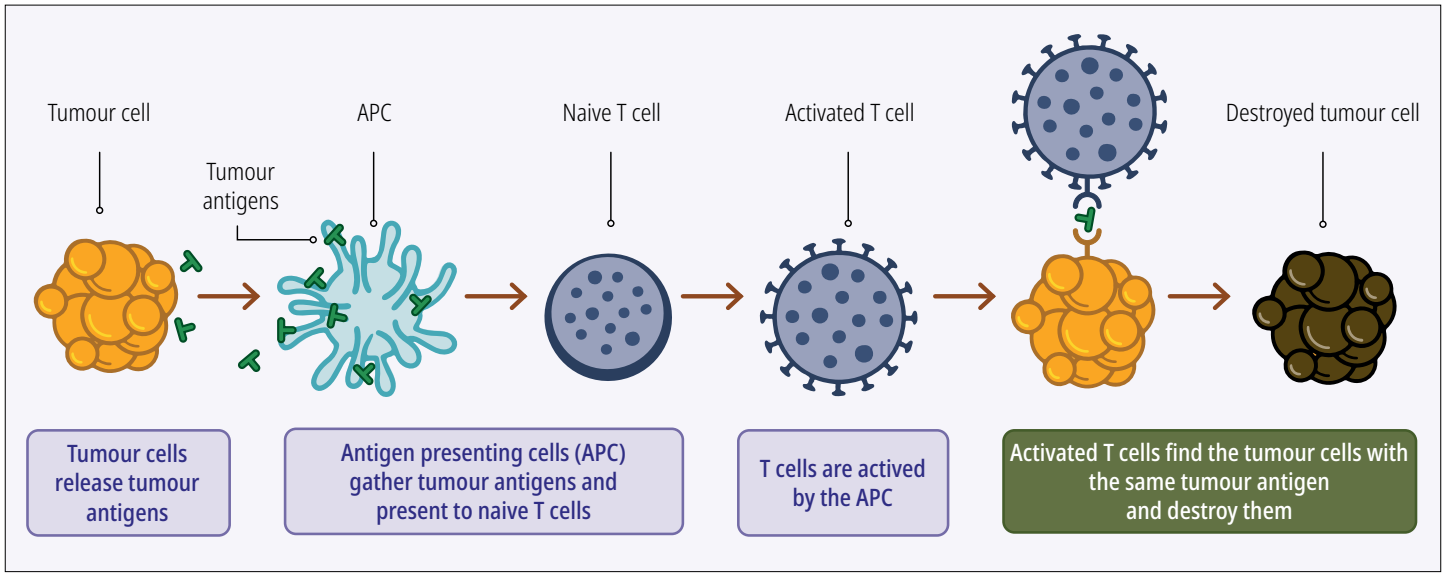
Green tea is one of the most popular beverages consumed worldwide,[5] with the health benefits mainly attributed to its antioxidant properties.[6] Epigallocatechin-3-gallate (EGCG) is the principal polyphenol in green tea and is thought to be responsible for its cancer-protective effects. Evidence suggests that green tea polyphenols can modulate multiple signalling pathways, regulating growth, survival and metastasis of cancer cells at multiple levels.[7] It is also well understood that inflammation plays a significant role in cancer progression. One of the mechanisms by which green tea exerts its anti-cancer activities is via the ability of catechins to inhibit the production of inflammatory mediators such as leukotrienes and lipoxygenase and by inhibiting NF-κB, resulting in nitric oxide synthase prevention.[6] Furthermore, green tea has been shown to prevent tumour metastasis and invasion by inhibiting matrix metalloproteinases (MMPs) and vascular endothelial growth factor, which are implicated in tumour cell behaviour and progression.[7]

In animal models, the preventative effects of green tea against tumorigenesis have been demonstrated in various cancers, including breast, prostate, lung and skin.[6] While the results of a Cochrane Review assessing the effect of green tea for the prevention of cancer in human trials was inconsistent, positive associations were found in prostate, lung, pancreatic and colorectal cancers.[8] From this review, authors concluded the desirable green tea intake is 3–5 cups per day, providing a minimum of 250mg of catechins daily.[8] Other systematic reviews and meta-analyses have suggested a trend towards protection and preventing recurrence in breast,[9] and prostate cancers,[10] improved survival rates in epithelial ovarian cancer,[11] and reduced risk of upper gastrointestinal tract cancers,[12] liver cancer[13] and endometrial cancer.[14]

Curcumin

In epidemiological studies, the incidence of cancer has shown to be less in people who consume curcumin, the major component of the Indian spice turmeric.[15] Clinical studies have

Figure 2: How the immune system attacks cancer[3]



revealed the therapeutic potential of curcumin as an antioxidant, immunomodulatory, hepatoprotective and antiangiogenic agent.[16] Curcumin appears to have an action on numerous signalling pathways involved in the induction of inflammation, cell cycle apoptosis, proliferation, survival, invasion, angiogenesis and metastasis and has been shown to prevent multiple cancers in animal studies.[15] NF-κB is a transcription factor involved in regulating inflammation, proliferation, transformation and tumorigenesis, and has shown particular responsiveness to curcumin. Suppression of NF-κB by curcumin subsequently down-regulates cyclooxygenase-2 (COX-2) and therefore mediates pro-inflammatory prostaglandins and inflammatory cytokines involved in the growth of cancer cell lines, including interleukin (IL)-6, IL-8 and TNF-α.[17] Curcumin also modulates MMPs, which regulate endothelial cell attachment and migration.[18] Additionally, evidence indicates curcumin exerts its therapeutic effects via regulating microRNA expression, which play a key role in inducing a sequence of molecular pathways involved in cancer development.[19]

The ability of curcumin to affect multiple targets is proved through its efficacy at providing symptomatic relief from cancer treatment and improving tumour markers associated with a variety of cancers, including skin cancer, multiple myeloma, head and neck tumours, brain, lung, breast, prostate, colon and prostate cancers.[20] Furthermore, overexpression of P-glycoprotein (P-gp) is one of the proposed mechanisms by which cancer cells develop resistance to anti-tumour drugs, a phenomenon known as multidrug resistance (MDR).[21] Curcumin has been described as an inhibitor of P-gp in several *in vitro* and *in vivo* models and consequently may enhance the efficacy of certain cancer therapies by increasing intracellular drug levels.[22]

Numerous human randomised clinical trials using Curcumin C3 Complex® have found it to be a safe and effective therapeutic in cancer patients. Studies have found that Curcumin C3 Complex® down-regulates NF-κB, COX-2 and pSTAT3 production (implicated in tumorigenesis and chemoresistance) in patients with advanced pancreatic cancer[23] and reduced chemotherapy-related symptoms, including fatigue, pain and constipation.[24] In colorectal cancer patients, curcumin decreased TNF-α levels, increased cancer cell apoptosis, upregulated p53 molecules,[25] inhibited prostaglandin E2 (PGE2)[26] and reduced the formation of precancerous lesions.[27] Curcumin was determined safe and tolerable combined with FOLFOX (folinic acid/5-fluorouracil/oxaliplatin) therapy and may benefit patients with colorectal liver metastases.[28,29] Additionally, this curcumin extract conferred radioprotective effects by reducing the severity of urinary symptoms in prostate cancer[30] and dermatitis in patients with breast cancer.[31] Curcumin has been administered safely at doses of up to 12g daily in clinical studies.[32]

Mushrooms

Ganoderma lucidum (reishi), *Lentinula edodes* (shiitake) and *Trametes versicolor* (coriolus) are mushrooms that have been used in Traditional Chinese Medicine to support both the innate and adaptive immune systems. Regarded as biological response modifiers (BRMs), these mushrooms contain polysaccharides, namely β-glucans with a 1,3/1,6 glycosidic linkage pattern, which are responsible for the immune modulating effects by activating macrophages, T cells, NK cells and cytokines that inhibit the proliferation of cancer cells and promote apoptosis.[33] Mushroom derived beta 1,3/1,6 glucans are recognised by receptors on host immune cells as a pathogen-associated molecular pattern (PAMPs). Immune cells such as macrophages detect PAMPs through various Pattern Recognition Receptors (PRR's) such as toll-like receptor-2, dectin-1, complement receptor-3 and lactosylceramide.[34] Subsequently, identifying β-glucans as non-self-molecules by mammalian cells induces beneficial innate and adaptive immune responses, modulating inflammatory, antimicrobial, and anti-tumour activities.[34] Research has demonstrated that shiitake mushroom exerts a beneficial effect on interferon and interleukin immune parameters associated with cancer progression, along with preventing white blood cell depression and increasing NK

cell activity during treatment with chemotherapy.[35-37] Shiitake also has the potential to improve the quality of life in a broad range of cancer treatments, including breast cancer,[35,36] gastrointestinal cancer,[37] colorectal and gastric cancers,[38] possibly mediated by the immune-active principles found in the polysaccharides.[39] Results of a Cochrane Review revealed cancer patients who were given reishi alongside conventional treatment were more likely to respond positively and were found to have a better quality of life after treatment than those in the control group.[40] Authors concluded these effects were attributed to reishi's ability to stimulate the host immune system by considerably increasing CD3+, CD4+ and CD8+ lymphocyte percentages and moderately elevating NK cells.

Vitamins & minerals for cancer management

Vitamin D

Vitamin D is well known for its role in bone and mineral metabolism; however, recent literature also validates its anti-proliferative and pro-apoptotic effects.[41] 1,25-dihydroxyvitamin D is the biologically active form that regulates gene transcription via the vitamin D receptor (VDR) and exhibits anti-cancer mechanisms by enhancing DNA repair and preventing oxidative damage.[42] By modulating a number of immune cells, vitamin D protects tissues from the pro-inflammatory stressors that promote cancer by altering dendritic cell differentiation, suppressing NF-κB signalling needed for T cell activation, and increasing regulatory T cell activity.[43] A vast body of evidence implies lower serum levels are also associated with poorer prognoses in patients diagnosed with various malignancies,[42] and low vitamin D status is related to a greater risk of certain cancers, including breast, prostate, colorectal and haematological.[44]

Vitamin A

Retinoids are derivatives of vitamin A and have shown to be crucial in the development of the immune system. Regarding cancer, retinoids directly target neoplastic cells by inducing differentiation, inhibiting cell growth and promoting apoptosis.[45] The proposed mechanism of action involves increasing inhibitory levels of specific signalling pathways in cancer cells and inhibiting protein kinase C (PKC) activity (promotes cancer progression), and reducing the expression of oncogenes.[46] Vitamin A has shown to inhibit the growth and the development of skin, breast, oral cavity, liver, lung, bladder and prostatic cancers,[47] and has displayed promising results when used concurrently with standard cancer medications in cell cultures.[48]

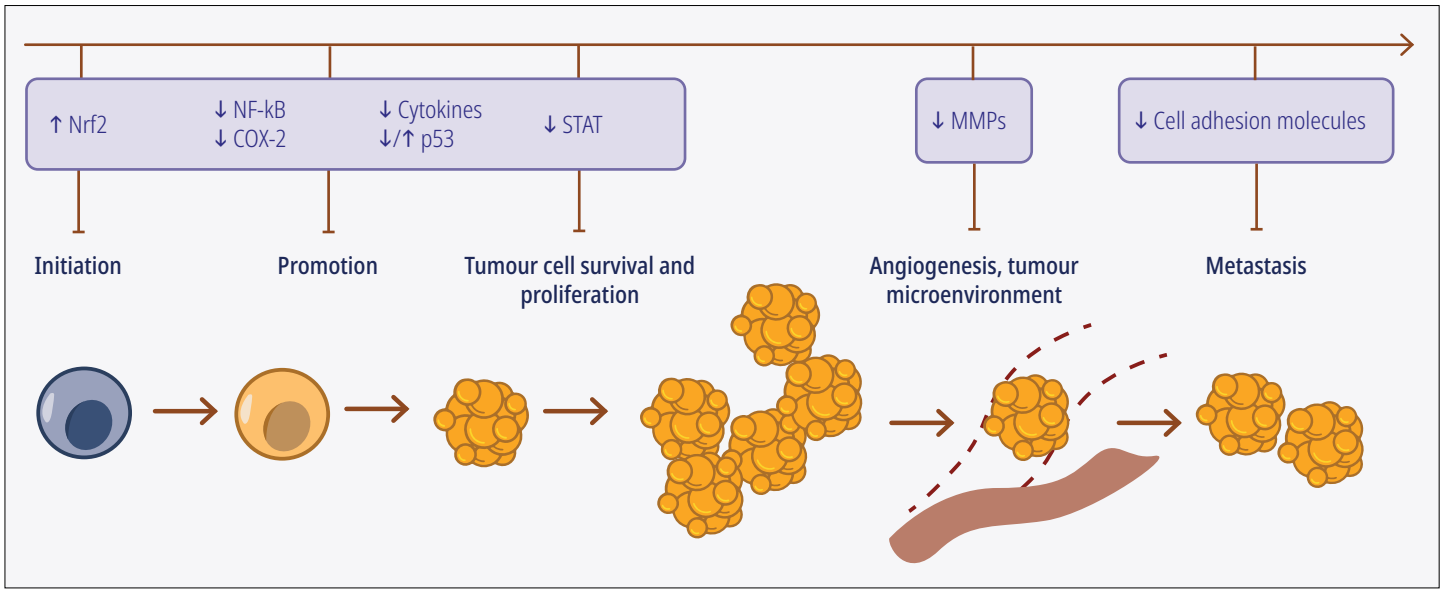
Vitamin E

As previously stated, PKC is an important signalling molecule involved in the proliferation and differentiation of cancer cells. Due to its antioxidant effects, vitamin E (α-tocopherol) has shown to inhibit PKC activity and tumour promotion.[49] It was found to inhibit growth and induce apoptosis in oestrogen receptor-negative breast cancer cells *in vivo*,[50] and in combination with omega-3 fatty acids, prolonged the life of patients with generalised malignancy.[51] Additionally, vitamin E may enhance chemotherapy outcomes by increasing the release of transforming growth factor-β, thereby inhibiting growth signals in malignant cells.[46] Combining vitamin E with standard therapies has shown to reduce neurotoxicity[52] and radiation-induced side effects;[53] however, further studies are required to confirm these positive outcomes.

Selenium

Selenium is a crucial cofactor in the endogenous antioxidant system and has a potential role in cancer prevention, improving cancer prognosis and reducing side effects of conventional therapies.[54] A proposed mechanism by which selenium possesses cancer preventative activity is via inhibiting proliferation, survival, and matrix degradation of endothelial cells critical for angiogenesis.[55] The mineral acts as a mutagenic agent by producing superoxide radicals that selectively induce apoptosis of cancer cells without damaging normal functioning cells.[56] Due to its antioxidative functions against reactive oxygen species (ROS) caused by

Figure 3: Stages in tumour progression inhibited by curcumin[18]



radiation, selenium supplementation has shown to reduce side effects without affecting treatment efficacy.[57] The results of a recent review have also demonstrated cancer patients often have lower selenium levels compared to healthy controls, indicating a need to assess selenium status before, during and after radiotherapy.[57]

Zinc

The role of zinc in cellular and humoral immune responses is of particular importance regarding its anti-cancer activity.[58] While the anti-tumour effect of zinc is not fully understood, increasing evidence implies a zinc deficiency upregulates inflammatory cytokines and oxidative stress, induces apoptosis, triggers endothelial and epithelial cell dysfunction, disrupts DNA interaction and depresses T cell-mediated immune responses.[59] Given that low levels of serum zinc are associated with a variety of cancers, namely lung, breast, head and neck,[58] supplementation may be useful in the prevention and treatment of such malignancies. Furthermore, zinc supplementation in conjunction with radiotherapy and/or chemotherapy has been shown to decrease the development of side effects, specifically severe mucositis and dermatitis.[60]

Immune system support

Autoimmune diseases

More than 80 systemic and organ-specific autoimmune diseases (AIDs) have been identified, with women affected disproportionately greater than men and prevalence increasing in first-degree relatives.[61] Generally characterised by chronic inflammation with a loss of tolerance to self-antigens, the aetiology of AIDs is considered to be multifactorial with a combination of genetic, environmental, hormonal and immune factors.[62] While various hypotheses have been raised regarding the pathogenesis, the most dominant theory suggests AIDs are triggered by exposure to an environmental agent in a genetically predisposed individual, resulting in organ and systemic damage.[63] Ultimately, there is an abnormal responsiveness in the immune system, involving cell migration, antigen presentation, T-cell co-stimulation, activation and proliferation, cytokine release and antibody production.[64]

Herbal medicine for autoimmune management

Curcumin

It is well recognised that an abnormal and poorly regulated inflammatory response is at the forefront of most chronic diseases. A plethora of both animal and human studies has shown that curcumin regulates pro-inflammatory cytokines that contribute to the manifestation of various AIDs, including multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease (IBD).[65] TNF-α is a potent pro-inflammatory cytokine produced by macrophages, mast cells, NK cells and activated T cells, and when stimulated, produces cytokines, chemokines, inducible nitric oxide synthase (iNOS) and COX-2.[65] Studies have demonstrated curcumin to be an inhibitor of NF-κB signalling pathways in immune cells, leading to a downstream regulation and inhibition of these pro-inflammatory genes and cytokines.[66] *In vitro* and *in vivo* studies have also demonstrated the ability of curcumin to selectively enhance T-regulatory cells and suppress macrophage and dendritic cell-mediated differentiation of Th1 and Th17, indicating its positive role in attenuating the progression of AIDs.[67]

Green tea

Another critical pathogenic factor in the development of AIDs is a dysregulated immune system, in particular, T cell function.[68] While earlier studies attribute the anti-inflammatory properties of green tea in managing AIDs, more recent evidence suggests EGCG has desirable effects during the initiation and development of autoimmunity.[69] Green tea and EGCG are known to affect various types of immune cells in both the adaptive and innate immune systems, particularly T cell activation, proliferation and differentiation.[68] While the working mechanisms underlying EGCG's protective role in autoimmunity is not completely understood, animal models have demonstrated dietary EGCG suppresses the proliferation of autoreactive T cells, decreases Th1 and Th17 populations, increases T-regulatory populations and reduces pro-inflammatory cytokines, including IFN-γ, IL-6 and TNF-α.[69] These results imply that green tea may have a preventive and therapeutic potential in dealing with T cell-mediated autoimmune diseases, such as RA, IBD, systemic lupus erythematosus (SLE), Sjogren's syndrome, and type 1 diabetes.[69]

Mushrooms

Employed as anti-inflammatory and immunomodulatory compounds, mushroom metabolites, in particular β-D-glucans, triterpenes, lipids and phenols, have demonstrated the ability to downregulate the gene expression of different types of inflammatory mediators.[70] Recent studies show that many immune disorders are attributable to the collapse of the system controlling the proportion of Th1 to Th2 cells. Mushroom extracts modulate the differentiation capacity of CD4+ T cells to mature into either Th1 and Th2 subsets, thus having profound effects in chronic immune conditions, such as autoimmunity.[70] In addition, terpenoids found in reishi have shown to exert anti-inflammatory and anti-proliferative effects mediated by inhibition of NF-κB in liposaccharide stimulated macrophages.[71] These terpenoids also inhibited the secretion of TNF-α and IL-6, along with downregulating the inflammatory mediator's nitric oxide and PGE2.[72] Likewise, shiitake consumption exhibited a reduction in TNF-α levels and attenuated bone erosion associated with RA in mice models.[73] By reducing inflammatory cytokines and upregulating anti-inflammatory mediators, shiitake influences the immune system and may play a protective role in AID management.[74]

Vitamins & minerals for autoimmune management

Vitamin D

As a prohormone, vitamin D exerts an action on the immune system via generating anti-inflammatory and immunoregulatory actions.[75] By attaching to VDR's, vitamin D regulates numerous functions and elicits a wide range of biological responses that influence cellular growth, proliferation, apoptosis and immune modulation.[76] Vitamin D has exhibited immunosuppressive effects via inhibition of T cell stimulatory functions of dendritic cells, which have emerged as a central player in the progression of autoimmunity.[77] Physiopathology studies confirm low vitamin D levels additionally impair self-tolerance by compromising the regulation of dendritic cells, T-lymphocytes and Th1 cells.[75] Low vitamin D levels have been associated with the manifestation of multiple AIDs, such as SLE, RA, MS, autoimmune thyroid disease, Crohn's disease and alopecia areata,[76] and supplementation in humans should be considered as a preventative measure in predisposed individuals.[78]

Vitamin A and vitamin E

Oxidative stress is a major contributor to a dysregulated immune system and leads to the development of chronic conditions. Consequently, antioxidants such as vitamins A and E may play a protective role in their pathogenesis and should be considered adjuvant therapy in managing AIDs. Adequate vitamin A levels is an essential factor for maintaining T cell function and the prevention of inflammatory reactions.[79] Vitamin A metabolites also modulate specific functional aspects of the immune response, such as the Th1/Th2 balance and the differentiation of T-regulatory and Th17 cells.[80] While the evidence is limited, Vitamin E supplementation in animal models has been shown to reduce inflammatory cytokines, namely IL-6, TNF-α and PGE2, which indirectly regulates pro-inflammatory processes and, consequently, the immune response.[81]

Zinc

Zinc homeostasis is essential in inflammatory diseases, needed to regulate different aspects of the immune system, including cell cycle progression, cell maturation and differentiation.[82] As a result, zinc deficiency has been associated with a disturbed ratio between Th1 and Th2 cells[83] and between pro-inflammatory and regulatory cells.[84] Additionally, zinc has been shown to inhibit Th17 lymphocytes, which may contribute to the development and progression of autoimmunity due to their strong inflammatory properties.[85]

Selenium

Selenium is an essential element that plays a pivotal role in the antioxidant defence system and is crucially involved in regulating immune responses and dampening chronic inflammatory conditions. Selenium has been shown to inhibit the activation of NF-κB signalling pathways, which is correlated with the release of inflammatory cytokines, such as TNF-α and IL-6.[86] By decreasing the production of ROS and suppressing NF-κB, selenium leads to the downregulation of the leukotriene pathway and attenuates inflammatory processes associated with autoimmunity.[86] In autoimmune thyroid disease, the benefits of selenium supplementation are thought to be due to modification of immune and inflammatory responses. By enhancing glutathione peroxidase and thioredoxin reductase activity, selenium has been shown to reduce oxidative stress and toxic concentrations of hydrogen peroxide and lipid hydroperoxides that are produced from thyroid hormone synthesis.[87]

It has been observed in recent systematic and meta-analyses that both zinc and selenium deficiencies are correlated with various autoimmune diseases.[84, 88] It can be assumed that sufficient quantities of these minerals may contribute to managing such inflammatory conditions and improving the quality of life in patients with AIDs.

Immune insufficiency and infections

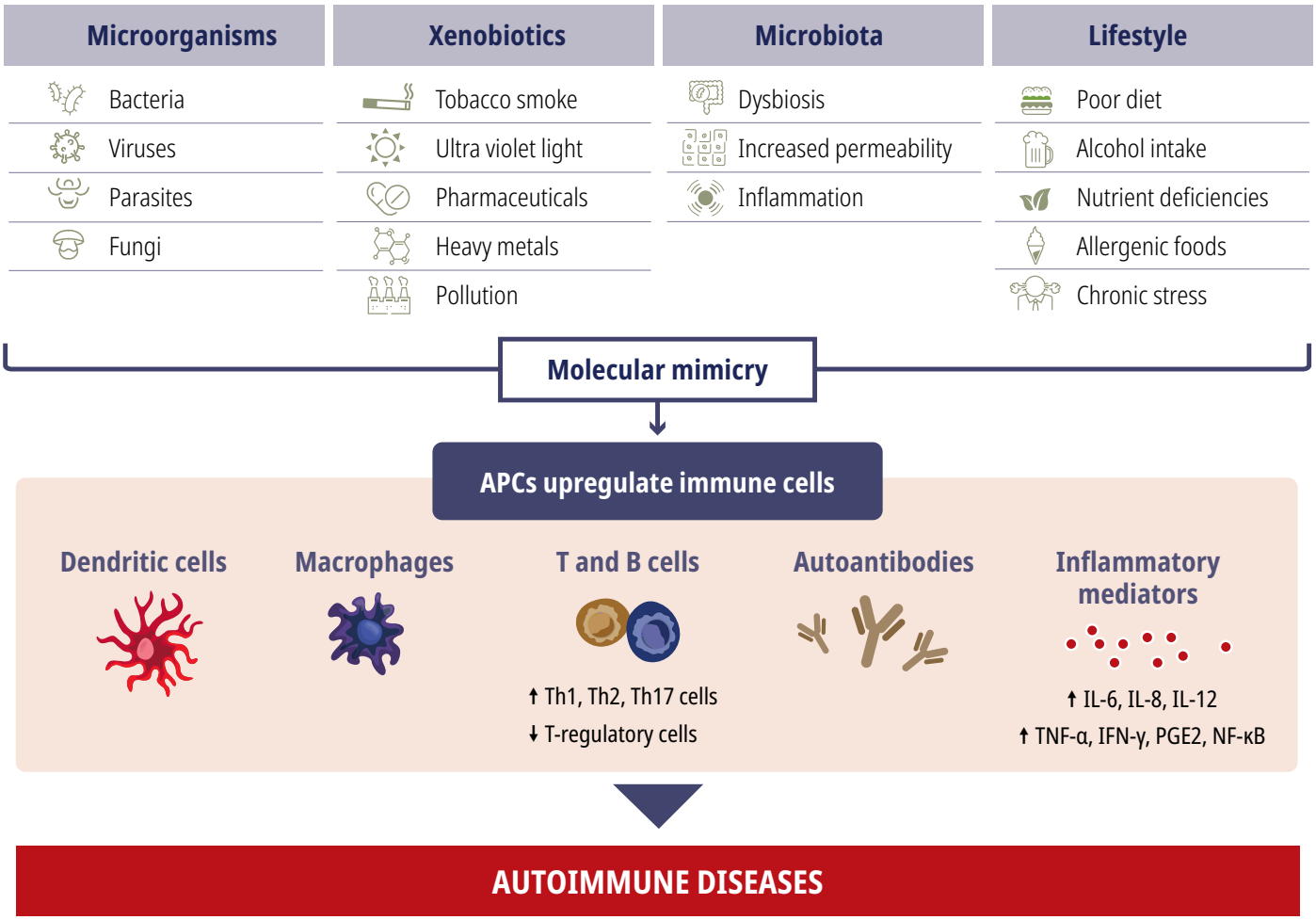
Many factors deplete the immune system and may predispose a person to develop recurring infections, particularly those with immune insufficiencies, such as the elderly or immunocompromised. Causes of lowered innate and adaptive immune resistance are multifactorial and include genetic predisposition, chronic stress, malnutrition, environmental toxins, age, prior infection and the consequence of inflammatory states.[89] Responsible for the immunosurveillance of pathogens, the innate immune system is dominant in the early stages of infection to prevent the initial entry of pathogens;[90] therefore, restoring immune responses is advantageous to improve immune resilience and prevent the risk of infections.

Herbal medicine for immune insufficiency and infections

Mushrooms

Mushrooms are valuable agents that are capable of modifying the hosts defence response and consequently are utilised in the treatment and prevention of diseases that stem from immunodeficient states.[70] Growing evidence from animal studies indicates that oral β-glucans stimulate the innate immune defences and increases resistance to a wide variety of infections.[91] These β-glucans, specifically the β-(1,6) and (1,3) side chains found in reishi, shiitake and coriolus are responsible for enhancing immune-modulatory pathways by stimulating the activity of both innate and adaptive immune systems and affecting the production of NK cells, macrophages, T cells and cytokines.[92] By enhancing the function and maturation of antigen-presenting cells and promoting phagocytosis, these BRMs also function as immune stimulants against infectious diseases, including viruses, bacteria and protozoa.[93]

Figure 4: Contributing factors to autoimmune development[61]



In human trials, regular shiitake consumption was associated with improved immunity, as seen by increased γδ-T cell proliferation, secretory IgA and activation responses.[74] The authors concluded the mechanism of action was associated with shiitake's ability to prime innate lymphocytes, making them more able to respond appropriately when challenged. Shiitake could also offer a novel treatment adjunct in improving the immune system in immunocompromised cancer patients, as research has shown it prevents white blood cell depression and increases NK cell activity.[35-37] Moreover, extracts found in both reishi and shiitake have been shown to improve immune function by increasing the number of CD3+, CD4+, and CD8+ T cells and plasma levels of IL-2, IL-6, and IFN-γ in immunosuppressed patients.[38,94] Based on clinical data, coriolus is highly efficient at restoring blood levels of immune parameters, such as NK cell activity, leukocyte cytotoxicity, T helper cells and lymphocytes, suggesting its positive role in improving immune function.[95]

In animal models, reishi enhanced the recovery of leukocytes and CD4+/CD8+ T cell subsets after γ-irradiation[96] and strengthened the activity of immunological effector cells and haematopoiesis in immunosuppressed mice,[97] indicating its role in improving cellular immunocompetence and accelerating recovery.[96] Enhanced B cell and phagocytic activity of macrophages was demonstrated by a polysaccharide extract of coriolus.[98] Additional studies verified a protein-bound polysaccharide derived from the mushroom reversed NK cell activity as well as lymphocyte proliferation and white blood cell production caused by cyclophosphamide-induced immune suppression.[99] Coriolus has also demonstrated a broad spectrum of antibacterial and antifungal activity against certain pathogens, including *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae* and *Listeria monocytogenes*,[95] and a number of constituents found in reishi and shiitake have also been identified to possess anti-viral activity, particularly against HIV infection.[100,101]

Curcumin

Curcumin was found to significantly increase white blood cells, macrophage phagocytic activity and circulating antibodies in mice models.[102] The authors concluded these results were due to curcumin's ability to regulate the proliferation of cells, indicating its potential use in enhancing humoral immunity. As a potent inhibitor of NF-κB and TNF-α, curcumin has also been shown to protect against *Klebsiella pneumoniae* induced liver injury,[103] enhance systemic humoral immunity against parasitic infections[104] and inhibit viral replication[105] in animal models. Collectively, these results highlight that curcumin plays a vital role in modulating certain pathways involved in the inflammatory response following pathogenic infections.

Green tea

Green tea has been shown to be effective in modulating both the innate and adaptive immune system. In human trials, green tea intake has been associated with the prevention of influenza in children[106] and adults[107,108] owing to its capability to enhance systemic immunity and increase the activity of γδ T-cells (first-line defenders). According to *in vitro* studies, green tea has moderate inhibitory effects on the growth of many types of bacteria, including *Staphylococcus spp.*, *Streptococcus spp.*, *Escherichia coli* and *Salmonella spp.*,[109] and viral families, including Retroviridae (HIV), Flaviviridae (HCV), Herpesviridae (HSV, EBV), Hepadnaviridae (HBV), Adenoviridae (Adenovirus), and Orthomyxoviridae (Influenza).[110] Green tea catechins inhibit viral activity and proliferation *in vivo* by binding to the hemagglutinin molecule of the virus, thereby blocking its adsorption to the host cell.[106]

Vitamins and minerals for immune insufficiency and infections

Micronutrient status is known to have a significant impact on the immune response and risk of infection. It is well known that overt and clinical deficiencies adversely affect the immune system and predispose individuals to infections in developing and industrialised countries. The severity of the impact to the immune system is primarily determined by the extent and duration of micronutrient deficiencies.[111]

In order to combat pathogenic insults from microorganisms, the immune system has evolved multiple protective measures, which includes physical and biochemical barriers, specialised immune cells and antibodies that defend against specific pathogens.[111] Every stage of the immune response relies on the presence of micronutrients, and there is growing evidence suggesting that supplementation is beneficial to reduce the risk of infection and support faster recovery.[111] Key micronutrients include, but are not limited to, vitamins A, D, and E, and the minerals zinc and selenium.

Vitamin A

Low levels of vitamin A diminishes the development of protective immune cells, including neutrophils, macrophages and NK cells, and causes a wide variety of immunological defects.[112] Vitamin A deficiency also degrades mucosal epithelial barrier function and decreases the resistance of tissues to pathogens; thus, reducing the innate immune system and promoting a number of infectious

Table 1: Impact of micronutrients on the innate and adaptive immune system.[111]

Micronutrient	Innate Immunity	Adaptive Immunity
Vitamin A	» Supports structural and functional integrity of mucosal cells e.g., skin, respiratory tract, gastrointestinal tract » Required for the functioning of immune cells e.g., NK cells, macrophages, neutrophils	» Essential for T and B lymphocyte function and consequently generation of antibody responses to antigens » Involved in development and differentiation of Th1 and Th2 cells; supports Th2 anti-inflammatory response
Vitamin D	» VDR expressed in innate immune cells e.g., monocytes, dendritic cells, macrophages » Increases differentiation of monocytes to macrophages » Stimulates proliferation and cytokine production to protect against infections » Regulates antimicrobial proteins cathelicidin and defensin, which kill bacteria	» Regulates production of dendritic cells, T-lymphocytes, Th1 cells and T-regulatory cell activity
Vitamin E	» Fat-soluble antioxidant that protects cell membranes against free radical damage » Enhances IL-2 production and NK cell cytotoxic activity	» Enhances T cell function and lymphocyte proliferation » Optimises Th1 and suppresses Th2 response
Selenium	» Required for selenoproteins that act as redox regulators and cellular antioxidants » Important for antioxidant host defence system affecting leukocytes and NK cell function	» Involved in T lymphocyte proliferation » Plays a role in immunoglobulin production
Zinc	» Antioxidant that protects against ROS and RNS » Modulates cytokine release and induces proliferation of CD8+ T cells » Maintains skin and mucosal membrane integrity	» Role in cellular growth and differentiation of immune cells » Required for T lymphocyte development and activation » Supports Th1 response

diseases,[113] including respiratory tract infections, diarrhoea, HIV and measles.[114] Furthermore, provitamin A carotenoids have been shown to be suppressed during inflammation, suggesting a greater demand of vitamin A during acute infections.[115]

Vitamin D

Evidence has accumulated on the regulatory role of vitamin D on the immune system due to its numerous functions in both innate and adaptive immunity. Vitamin D increases antimicrobial activity by enhancing cathelicidin antimicrobial peptide and defensin β-2 while also upregulating the phagocytic activity of immune cells to aid in the clearance of pathogens.[116] Vitamin D also enhances chemotaxis and phagocytosis, regulates antibody production in B cells, inhibits interleukins (IL-2, IL-9, IL-22), interferon-γ and TNF-α, and increases IL-3, IL-4, IL-5, and IL-10 production.[117] It has also been suggested that adequate vitamin D concentration protects the respiratory epithelium from pathogens,[118] and a significant linear relationship between serum vitamin D concentration and lower risk of acute respiratory tract infection has been demonstrated.[119]

Vitamin E

The proposed mechanism of the immunomodulatory effects of vitamin E is displayed through its ability to enhance T cell-mediated function by promoting membrane integrity and positively modulating T cell signalling in immune synapses.[120] In addition to being an effective free radical scavenger, vitamin E contributes to the function of the immune system by enhancing humoral and cell immune responses, as well as phagocytic functions.[121] Vitamin E has been shown to confer protection against several infectious diseases in animal and human models, possibly by directly enhancing T cell activation and suppressing PGE2.[122]

Zinc

Zinc deficiency is known to impair or completely suppress phagocyte and lymphocyte activity, resulting in diminished cytokine and antibody responses and increased risk of infection.[115] Zinc may benefit respiratory infections by exerting a direct anti-viral effect, reducing inflammation, improving mucociliary clearance, modulating anti-viral immunity and preventing ventilator-induced lung injury.[123] It can also interfere directly with viral replication and protein synthesis, providing beneficial and therapeutic effects against viral infections.[118] Furthermore, correcting a zinc deficiency through supplementation has been shown to improve the immune system response and reduce mortality from infectious diseases.[120]

Selenium

Selenium plays essential roles in regulating the migration, proliferation, differentiation, activation, and optimal function of immune cells, thus influencing innate immunity, B cell-dependent antibody production, and T cell immunity.[124] Due to its role in redox regulation, selenium is protective against oxidative stress generated by the microbicidal effects of macrophages and during inflammatory reactions.[125] As low levels of selenium allow viruses to undergo mutations to more virulent forms, selenium deficiency has been linked to a decrease in immune function and an increased susceptibility to viral infections.[124]

Mounting evidence suggests that increased intake of some micronutrients above the RDA may help optimise or maximise immune function and consequently improve resistance to infection. Thus, a gap exists between recommended dietary intakes and levels for optimal immune function, providing a rationale to supplement the diet with micronutrients to help support the immune system and reduce the risk of infection.

Fibromyalgia

Fibromyalgia (FM) is characterised by widespread pain and increased pain sensitivity in the absence of a known aetiology, alongside multiple somatic symptoms such as fatigue, sleep disturbances, headaches, irritable bowel syndrome and impaired mood.[126] While the development of FM is multifactorial and may be influenced by environmental and genetic traits, there is evidence to suggest several features point towards an autoimmune origin.[127] A higher prevalence of autoimmune diseases, including RA, SLE, Sjorgren's syndrome, Hashimoto's thyroiditis, and IBD were found in patients with FM. This hypothesis is founded on the evidence that both chronic and acute infections often trigger autoimmunity and are among the most common events preceding the onset of FM.[127]

Herbal medicine for fibromyalgia management

In line with this notion, certain features of fibromyalgia (FM), such as chronic pain, tenderness and fatigue, are typical with chronic viral infections.[128] Epstein-Barr virus (EBV) has been associated with the pathogenesis of FM as patients with FM have exhibited higher EBV IgG concentrations, which correlate with pain intensity.[129] *In vitro* studies have demonstrated the ability of EGCG to inhibit EBV replication via suppressing certain signalling pathways, and curcumin has been shown to block EBV induced B cell immortalisation by enhancing apoptosis.[130] Furthermore, terpenoids from reishi exhibited antibacterial and anti-viral effects against EBV in cell lines.[131] While future human clinical trials are necessary to support these findings, the ability of certain herbs to inhibit EBV reactivation may pose a potential treatment in the management of associated diseases such as FM.

As the main clinical feature of FM is chronic musculoskeletal pain, one of the most essential objectives for practitioners is to improve patient's quality of life by adequately reducing inflammation. Released from immunocompetent cells, high levels of pro-inflammatory cytokines have been found in patients with FM.[132] Curcumin possesses analgesic, anti-inflammatory, antirheumatic and antiarthritic properties and has shown to downregulate inflammatory cytokines and COX pathways.[133] These pathways are required to convert arachidonic acid to prostaglandins, which are mediators in the exaggerated sensation of pain.[134] In animal models, curcumin plays an important role in pain regulation at central and

peripheral levels via its ability to positively affect COX enzymes; thus, curcumin should be considered an effective treatment in disorders of inflammation and chronic pain.[134]

Vitamins and minerals for fibromyalgia management

An imbalance between antioxidant and oxidative stress pathways has been suggested to play a part in the development of FM. In clinical studies, patients with FM exhibited significantly lower total antioxidant status than control groups.[135,136] Given the protective effects of vitamins A and E against ROS, supplementation may be warranted to reduce oxidative damage and hypoxia, which is often a debilitating feature in FM.[136]

A number of patients with FM have also shown to be vitamin D deficient.[137] Due to its role in modulating several inflammatory and pain pathways, including reducing PGE2 and modulating pro-inflammatory Th1 and Th17 cells, this vitamin has potential in alleviating symptoms associated with FM, particularly muscular pain.[137] Certain studies have also shown that patients with FM have a greater risk of developing osteoporosis.[138,139] Given the role of vitamin D in bone health, supplementing may benefit patients with FM.

Considering the pathogenesis of FM is far from elucidated, the treatment approach must be multifactorial. Utilising natural compounds to reduce inflammation, improve the immune capacity and reduce oxidative damage may prove essential in increasing patients' quality of life.

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is characterised by persistent and relapsing fatigue in the absence of an explained medical condition[140] and is often associated with a variety of additional symptoms, including post-exertional malaise, cognitive impairment, musculoskeletal pain, sleep disturbances, sore throat, lymphadenopathy, orthostatic intolerance and gastrointestinal issues.[141]

It has been speculated that increased production of ROS as a result of certain viral or bacterial infections are associated with the pathogenesis of CFS.[142] The generation of ROS causes a reduction in the endogenous antioxidant pool, leading to cytotoxic mechanisms such as lipid peroxidation, mitochondrial dysfunction and cellular injury and death.[143] Consequently, various natural compounds play a pivotal role in scavenging these free radicals and attenuating the disabling mechanisms of CFS.[142]

The antioxidant profile of green tea polyphenols may be a novel therapeutic agent for neurological disorders such as CFS.[140] Catechins found in green tea have been shown to decrease levels of lipid peroxidase and increase glutathione levels in the brains of fatigued mice, which are often reduced in CFS patients.[140] A trend has been observed between the severity of CFS and serum zinc levels, and supplementation may be of use in patients to protect against oxidative damage.[144] Additionally, lower vitamin E levels have been observed in patients with CFS compared to healthy controls, suggesting oxidative stress is higher in these individuals.[145]

While the aetiology is still misunderstood, observations suggest CFS is associated with low grade, chronic infection and inflammation and is considered part of a spectrum of diseases, including certain AIDs and FM.[146] Viral overload has been considered a triggering factor in the onset of CFS, and hypotheses suggest reactivation of latent viruses could damage the immune system and contribute to the morbidity of CFS.[141] Additionally, it has been observed that patients with CFS commonly have immune dysfunction, increasing their susceptibility to acute viral infections. While clinical trials involving CFS and viral infections are limited, supporting the immune system using specific vitamins and minerals along with herbal interventions, may play a major role in preventing CFS and reducing disease severity.

Additional therapeutic indications

Liver support

Emerging evidence supports the role of inflammation and oxidative stress in promoting the progression of liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), and viral infections.[147, 148]

Known for its antioxidant and anti-inflammatory properties, green tea consumption increases the level of adiponectin, which has been shown to attenuate the progression of NAFLD by increasing apoptosis and decreasing the proliferation of hepatic cells.[149] Moreover, polyphenols found in green tea prevent free radical damage and impede lipopolysaccharide-induced liver injury through the inhibition of nitric oxide synthase and TNF-α expression.[150] Results of a recent systematic review revealed green tea intake reduced liver enzymes in participants with impaired lipid profiles and patients with NAFLD.[147] Earlier reviews also concur with these findings, indicating green tea intake was associated with a reduced risk of liver disease.[150]

Curcumin has also shown favourable effects on liver function and NAFLD via its ability to reduce ROS and pro-inflammatory cytokines. A recent systematic review concluded curcumin in higher doses ameliorated hepatic steatosis and blocked fatty liver disease progression by inhibiting fatty acid synthesis, facilitating β-oxidation and decreasing lipogenesis.[151]

Metabolites found in mushrooms such as phenolics, steroids and terpenes have demonstrated hepatoprotective effects against liver dysfunction in animal models.[92] Due to its ability to reduce lipid accumulation during the development of fatty liver and alleviating inflammation, an extract of coriolus has also shown to ameliorate

ethanol-induced hepatic steatosis and injury in mice, supporting its potential role in the management of ALD.[152] An additional study demonstrated an extract of reishi possessed significant antioxidant activity and was protective against lipid peroxidation in animal liver.[153]

Certain vitamins and minerals have also exhibited protective effects against liver dysfunction, including vitamin D, vitamin E and zinc. Owing to its anti-fibrotic, anti-inflammatory, and insulin-sensitising properties, vitamin D deficiency has been associated with liver inflammation and the occurrence and development of insulin resistance-related diseases, such as type 2 diabetes, metabolic syndrome, and NAFLD.[154] Furthermore, vitamin D may influence the inflammatory response to chronic liver injury seen in both NASH and chronic hepatitis C by means of specific vitamin D receptors.[155]

Current literature also confirms the promising role of vitamin E in the management of NAFLD and NASH. A 2015 meta-analysis concluded supplementation significantly reduced liver enzymes (aspartate transaminase and alkaline phosphate) and improved histological changes in patients with these liver diseases.[156] Considering oxidative stress and inflammation mediates all events involved in the progression of liver fibrosis,[157] antioxidant compounds such as vitamin E may positively impact the extent of liver damage by scavenging ROS and suppressing lipid accumulation, lipid peroxidation and inflammation.[158]

Previous studies have demonstrated the relationship between zinc deficiency and liver disorders, including chronic hepatitis C, cirrhosis and hepatic fibrosis in NAFLD.[159] The mechanism of action is explained through the minerals ability to decrease pro-inflammatory cytokine production and oxidative stress, and attenuate apoptotic hepatocyte death.[160] Supplementation has also shown to reverse the many manifestations of zinc deficiency observed in ALD, such as impaired night vision, skin lesions and immune dysfunction.[160]

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