Addressing systemic chronic inflammation with herbal and nutritional solutions

KEY LEARNINGS

Inflammation in disease development

- One of the most important medical discoveries has been that the immune system and inflammatory processes are involved in a wide range of modern-day health problems.
- While acute inflammation is a physiological response required to restore homeostasis, sustained inflammation leads to tissue dysfunction and the development of various chronic diseases.
- Chronic inflammation exerts cellular effects, mainly through the excessive production of free radicals.

Consequences of oxidation

- Free radicals are an obligatory response to metabolic processes as they act as signalling molecules involved in a variety of physiological processes.
- Under normal conditions, free radicals are maintained at low levels by various antioxidant systems; however, during times of oxidative stress, higher levels of free radicals result in systemic cellular damage.

Key biological pathways of inflammation

- The inflammatory pathway consists of four phases: the inducers, the sensors, the mediators, and the target tissues that are affected.
- The primary mediators in chronic inflammation include reactive oxygen species, cytokines, chemokines, inflammatory enzymes, bioactive lipids, and transcription factors.
- Therapeutic strategies aimed at blocking or reducing these mediators represent an attractive approach to chronic disease management.

Addressing inflammatory conditions with herbal and nutritional solutions

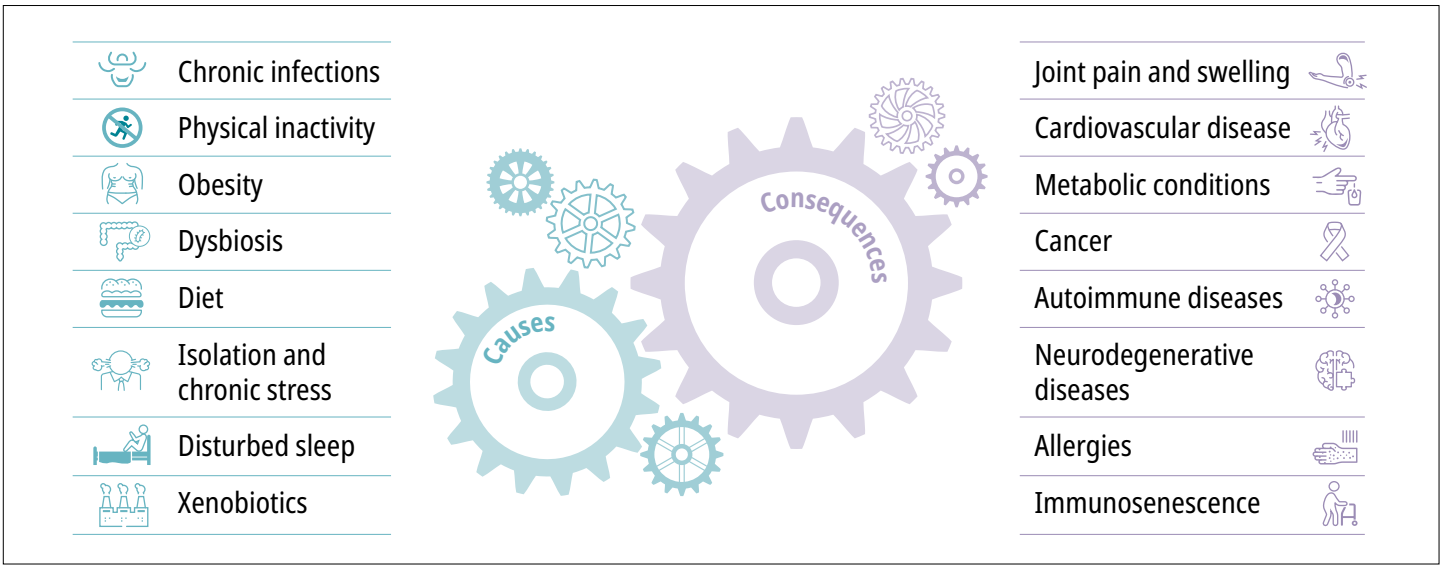
- It is well established that chronic and unresolved inflammatory manifestations appear to be the critical causative agent triggering the onset of many diseases, including osteoporosis, joint pain, cardiovascular disease, metabolic conditions, autoimmune disease, cancer, reproductive concerns, allergies, and neurodegenerative diseases.
- Various herbal and nutritional solutions have been shown to target inflammatory pathways and reduce oxidation and should be considered in the management and prevention of chronic inflammatory diseases.

The role of inflammation in disease

Over the past two decades, one of the most important medical discoveries has been that the immune system and inflammatory processes are involved in not just a few select conditions but a wide range of health problems that dominate present-day morbidity and mortality.[1,2] Inflammation is a physiological response of the innate immune system, which attempts to maintain internal homeostasis to changing environmental pressures.[3] Triggers can originate from various causes, including mechanical, physical, chemical, infectious, immunological, traumatic injury or metabolic dysfunction. The inflammatory response aims to reduce the agent that causes tissue injury and minimise these effects while facilitating wound healing and tissue repair to restore homeostasis.[3] If the immune response eliminates the infectious agent or repairs the initial tissue injury,

This technical sheet (V.09/22) is intended for the further education of practitioners. Any statements made do not intend to claim a cure for any condition mentioned.

Figure 1: Causes and consequences of systemic chronic inflammation[4]



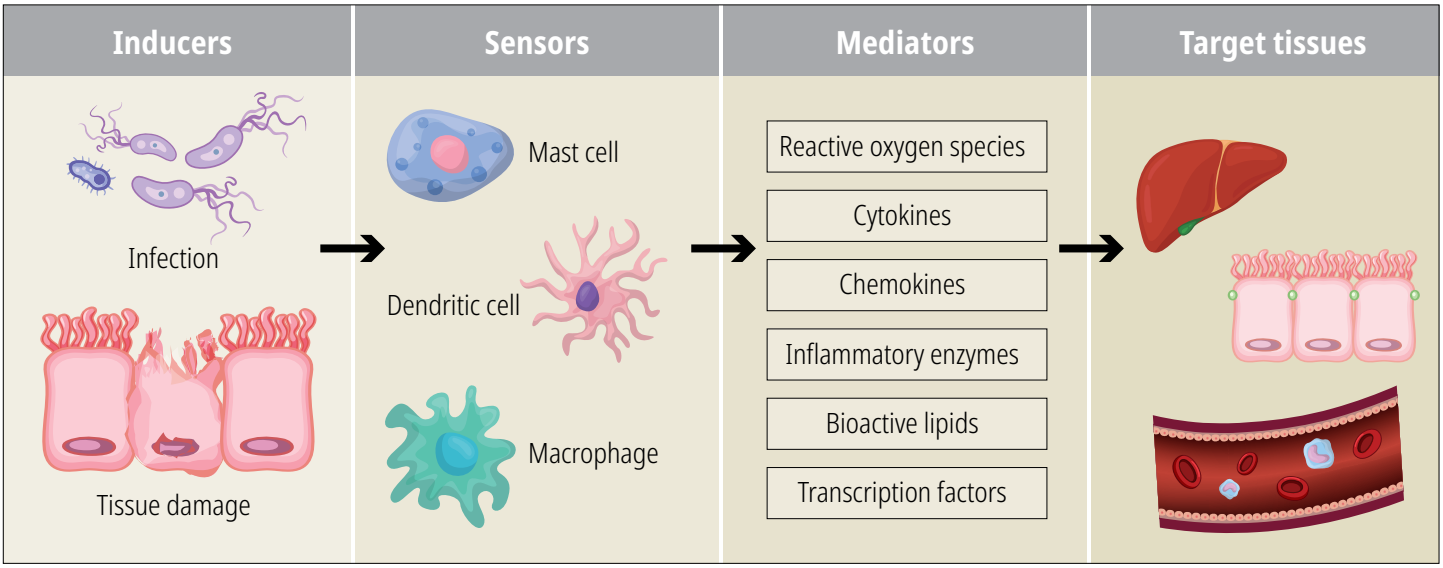
the inflammatory process will be terminated and only affects tissue function transiently. In cases where the inflammation fails to resolve due to the persistence of the triggering agent or unsuccessful repair of the initial tissue injury, a sustained inflammatory process develops, leading to further tissue dysfunction and the development of chronic disease.

It is now well established that chronic and unresolved inflammatory manifestations appear to be the critical causative agent, at the molecular and cellular level, triggering the onset and development of chronic diseases such as atherosclerosis and subsequent cardiovascular disease (CVD), metabolic syndrome (MetS), cancer, diabetes, neurodegenerative disorders, osteoporosis, autoimmune diseases (AIDs) and immunosenescence (see Figure 1).[4] Moreover, chronic inflammation exerts cellular effects mainly through the excessive production of free radicals and the depletion of antioxidants.[5]

Consequences of oxidation

Free radicals and other oxidants have gained importance in the field of biology due to their central role in various physiological conditions as well as their implication in a diverse range of diseases. The production of free radicals, including both reactive oxygen species (ROS) and reactive nitrogen species (RNS), is an obligatory response to metabolic processes in all aerobically respiring organisms. Free radicals are signalling molecules involved in a variety of physiological processes such as cell growth, differentiation, preconditioning and cell death.[6] Under normal conditions, the physiologically critical intracellular levels of free radicals are maintained at low levels by various antioxidant systems.[7] However, during times of oxidative stress, higher levels of free radicals, either due to excess production or decreased removal rate, can result in cellular damage. This damage can increase the risk of developing chronic diseases such as AIDs, cancer, CVDs, neurological and metabolic disorders.[8]

Figure 2: Components of inflammatory pathways[9]



Targeting key biological pathways in inflammation

The inflammatory pathway consists of four phases: the inducers, the sensors that detect them, the induction of mediators and the target tissues that are affected (see Figure 2). Each component of this pathway comes in multiple forms and the type of pathway induced under given conditions depends on the nature of the inflammatory trigger.[9]

The primary mediators in chronic inflammation include ROS, cytokines, chemokines, inflammatory enzymes, bioactive lipids and transcription factors.[10,11] Almost all mediators of inflammation have been shown to be regulated by the transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), which regulates the expression of many gene products involved in immune and inflammatory responses, including tumour necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), interleukins (IL), adhesion molecules and C-reactive protein (CRP).[12] The activation of NF-κB is often elevated in several chronic inflammatory diseases,[13] and as such, therapeutic strategies aimed at blocking or reducing its activity and the associated regulated gene products represent an attractive approach to chronic disease management (see the resource Effective solutions to modulate key inflammatory pathways).

Attenuating inflammation: Clinical applications

Arthritis and joint pain/swelling

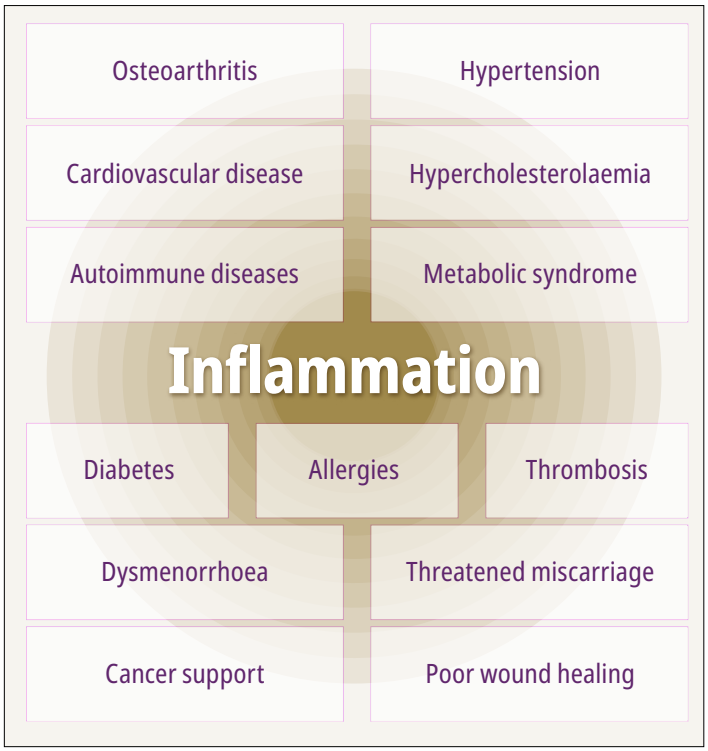
The process of inflammation plays a central role in many disorders of the musculoskeletal system, and when inflammation is present, the breakdown of cells and tissues creates a burden of oxidation.[14] Osteoarthritis (OA) is the leading cause of disability in the Western world and affects approximately 250 million people worldwide.[15] In OA, unresolved inflammation in joints leads to the development of symptoms, including pain and stiffness, and the progressive destruction of articular cartilage and remodelling of joint tissues. Tissue injury stimulates the release of inflammatory signalling molecules, such as bradykinin, and the release of inflammatory cytokines, chemokines, and adhesion molecules.[12] Likewise, arachidonic acid (AA) is released from cell membranes and converted by either COX-2 or 5-LOX, to series 2 inflammatory prostaglandins (PGE2) and thromboxane's, or series 4 leukotrienes (LTB4) respectively (see Figure 4). These powerful modulators of inflammation are responsible for pain, vasodilation, erythema, oedema, platelet aggregation, and free radical production often observed in arthritides.[16] Consequently, the overproduction of ROS and inflammatory mediators in the synovial fluid induces matrix metalloproteinases (MMPs) and other hydrolytic enzymes resulting in cartilage breakdown secondary to proteoglycan and collagen destruction.[17,18]

Curcumin

The effects of curcumin on OA may be attributed to its ability to prevent apoptosis and suppress the release and expression of NF-κB, proteoglycans and MMPs in chondrocytes.[19] By interacting with multiple receptors and signalling pathways, curcumin inhibits the production of inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, and IL-12.[20,21] Curcumin is also a dual inhibitor of the arachidonic cascade. It exerts anti-inflammatory effects by downregulating multiple enzymes in this cascade, including COX, 5-LOX, and inducible nitric oxide synthase (iNOS), which are involved in cartilage erosion and swelling (see Figure 5).[22-24] Recent evidence has also suggested that curcumin may benefit arthritic conditions by activating the vagus nerve and affecting the cholinergic pathway via modulation of the gut microbiota.[25,26]

Several human clinical trials have demonstrated curcumin's efficacy in reducing symptoms associated with arthritic conditions. A recent review of 16 randomised controlled trials (RCTs) suggested that curcumin at doses between 500mg to 1,500mg leads to decreased pain and improved stiffness, physical function and standardised scores in patients with OA.[15] Moreover, studies comparing turmeric with ibuprofen and diclofenac (Voltaren) have shown similar efficacy without the adverse effects associated with these standard non-steroidal anti-inflammatory drugs.[27-30] An earlier meta-analysis of seven clinical trials (n=797) using between 180mg to 2g of curcumin daily also demonstrated that curcumin supplementation significantly reduced knee pain and improved quality of life in patients with knee OA.[31]

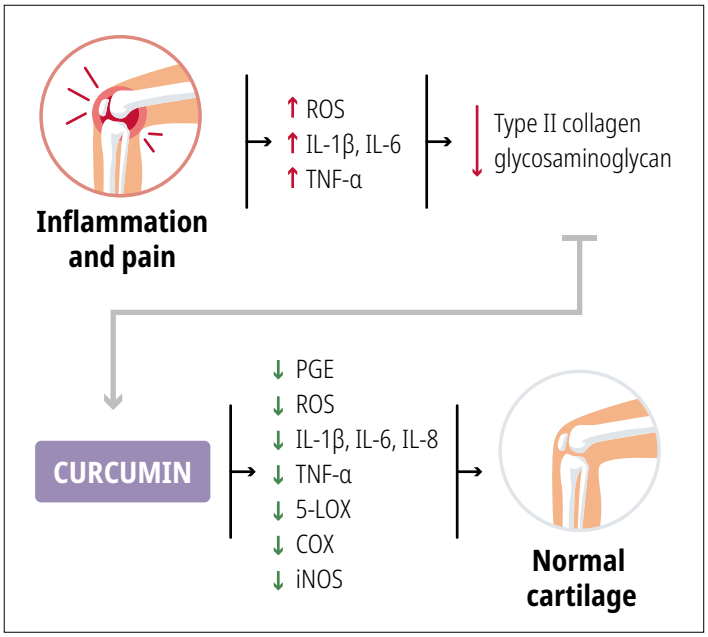
Figure 3: Inflammation plays a central role in many health problems



Bromelain, rutin and papain

Bromelain is the collective term for several proteolytic and non-proteolytic enzymes, which are responsible for protein catabolism and are involved in many physiological reactions, including highly regulated cascades in inflammation. Bromelain has been recognised as a safe therapy that exhibits clinical applications, including anti-oedematous, fibrinolytic and anti-inflammatory effects, making it an attractive phytochemical for joint pain and swelling conditions.[32] Experimental evidence proposes that bromelain exerts broad anti-inflammatory effects via various mechanisms. Firstly, bromelain increases fibrinolysis via stimulating plasminogen to plasmin, thus reducing plasma fibrinogen levels.[33] Secondly, bromelain decreases bradykinin levels by inhibiting the conversion of kininogen to kinin, which results in reduced vascular permeability and consequently lowers oedema and pain.[34] Thirdly, bromelain mediates prostaglandin synthesis by inhibiting the enzyme thromboxane synthase, thereby reducing pro-inflammatory mediators PGE2 and thromboxane A2.[35]

Figure 5: Pathophysiological aspects of osteoarthritis and the effects of curcumin[15]



Recent studies have demonstrated that bromelain alone or with other nutraceuticals, such as rutin, trypsin, turmeric, boswellia or devil's claw, results in significantly enhanced efficacy in the treatment of painful degenerative joint diseases, particularly joint pain, stiffness and soft tissue swelling.[36-40] A number of researchers have speculated that the mechanisms involved may be an indirect effect of the anti-inflammatory actions of bromelain, including the reduction of oedema and its influence on bradykinin.

Supplementation with proteolytic enzymes may additionally reduce swelling and pain from surgery, injury, or muscle damage.[41] Bromelain, alongside rutoside and trypsin, has been shown to have comparable effects to diclofenac therapy in providing analgesic relief and resolving oedema in dental surgery patients.[42-44] Furthermore, human studies suggest bromelain and papain improve muscle function after eccentric exercise and may attenuate muscle losses after exercise by regulating leukocyte activity and inflammation and allowing for faster muscle regeneration.[45,46]

Quercetin

Since the overproduction of nitric oxide (NO) and other ROS is associated with osteoarthritic cartilage[47] and the extent of damage,[48] the potent antioxidant and anti-inflammatory activity of quercetin may be efficacious for OA and joint-related conditions. Human and animal studies suggest that quercetin may delay the occurrence and development of OA[49-51] and alleviate the pain associated with joint disorders.[49] In animal studies, quercetin upregulates the production of superoxide dismutase (SOD), maintains joint cartilage integrity, inhibits apoptosis of chondrocytes, reduces cartilage degradation,

Figure 4: Certain herbs and nutrients reduce inflammatory markers of the AA pathway

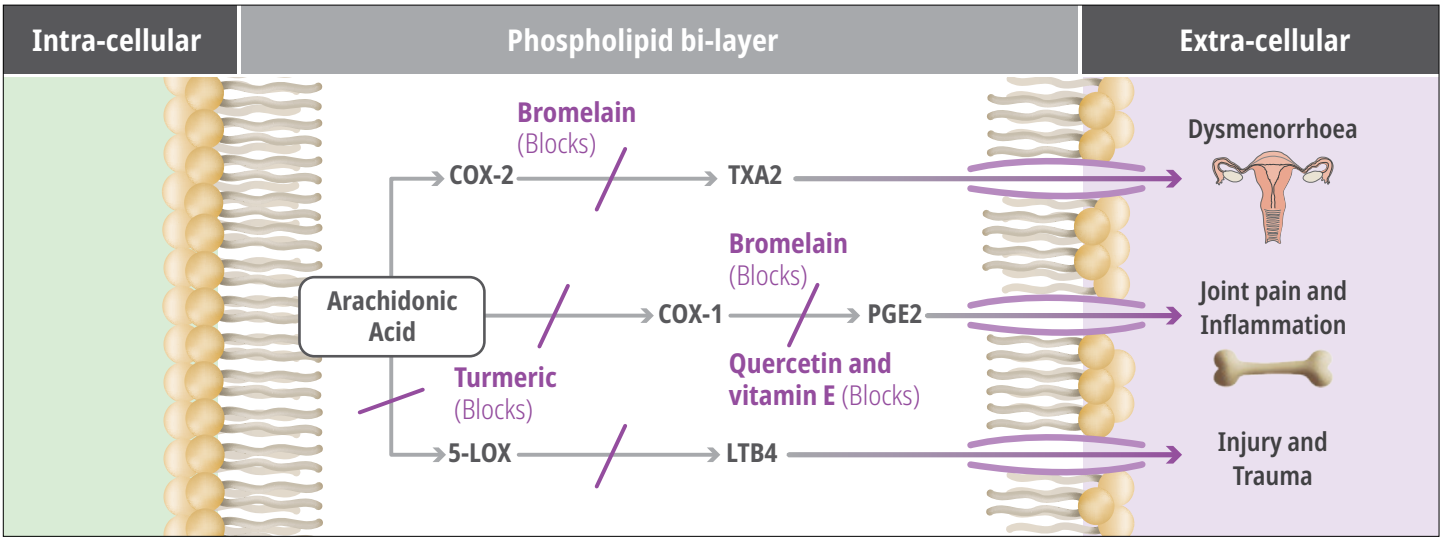
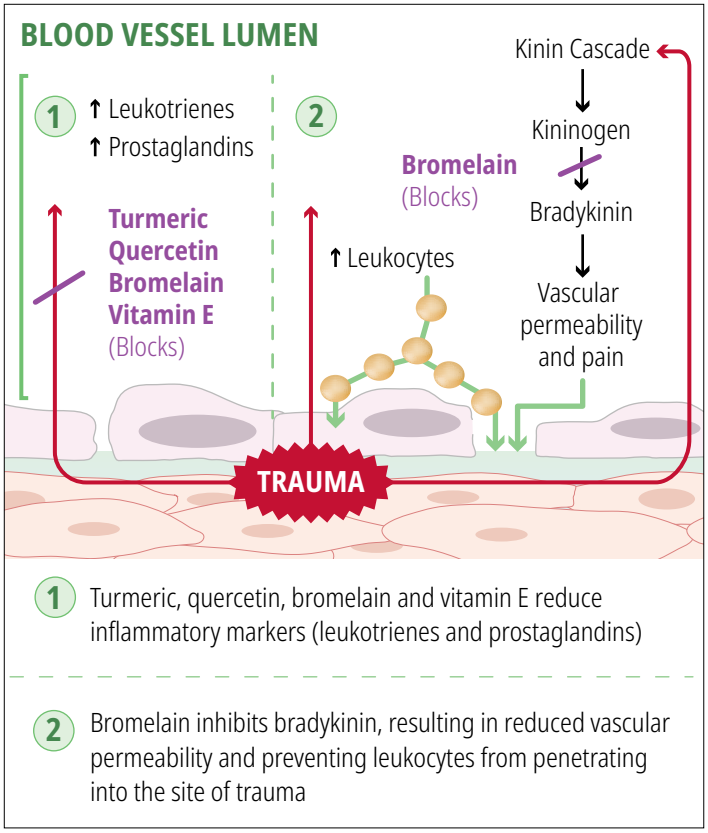


Figure 6: Curcumin, quercetin, bromelain and vitamin E relieve joint swelling and inflammation



and promotes cartilage synthesis.[51-53] These results suggest this flavonoid may serve as a potential therapeutic option for degenerative joint disorders.

Vitamin C and vitamin E

Cartilage degeneration often occurs due to the formation and accumulation of free radical damage. As such, antioxidants such as vitamin C and vitamin E could serve a protective function in preventing oxidative stress-induced chondrocyte dysfunction from occurring. Vitamin C is essential for the production of connective tissue and is required for collagen biosynthesis and other connective tissue substances, including elastin, proteoglycans, and fibronectin.[54,55] Vitamin C is a co-factor for the prolysyl and lysyl hydroxylases, which are responsible for the hydroxylation of proline and lysine residues of procollagen, promoting the stabilisation and cross-linking of collagen molecules.[56] Vitamin C is needed by the body to produce both bone protein and the cells that generate bone; thus, adequate levels are required in order to maintain bone density. Vitamin E has been suggested to exert analgesic, anti-inflammatory, and immunological activity in OA, with several small studies advocating 600-900IU daily to reduce pain and symptoms associated with OA.[57-59]

Copper

Copper is essential for normal bone growth and development and promotes articular cartilage and subchondral bone regeneration.[60] Copper inhibits the inflammatory response, reduces cartilage tissue damage and promotes chondrocytes' proliferation and maturation.[61] Copper functions as a co-factor of certain enzymes in cartilage, such as SOD and lysyl oxidase. In particular, lysyl oxidase plays a critical role in collagen and elastin synthesis; thus, copper is essential for cartilage formation, wound healing and maintaining connective tissue integrity.[61,62]

Low copper levels have been linked with bone malformation during development and may contribute to the risk of developing osteoporosis later in life.[62] Dietary copper supplementation has been reported to reduce the severity of osteochondrosis and other developmental cartilage lesions *in vitro*, possibly due to improved collagen cross-linking and enhanced synthesis of type II collagen.[63]

Manganese

Manganese is an essential trace element required for the function of several human enzymes, including those involved in bone and cartilage formation. Manganese is the preferred co-factor for enzymes called glycosyltransferases, which are required for the synthesis of proteoglycans that are necessary for the formation of healthy cartilage and bone.[64] A component of the mitochondrial antioxidant enzyme, manganese-superoxide dismutase (SOD2) acts to remove damaging superoxide free radicals and is therefore crucial for the protection of joints from damage. Studies have confirmed a significant decrease of SOD2 in the cartilage of OA patients; therefore, manganese may be useful in its management due to its essential role in the synthesis of SOD2.[65] Lastly, the combination of manganese with glucosamine and chondroitin was found to regulate the metabolism of the articular cartilage matrix, relieve symptoms, and improve imaging indicators in 72 patients with mild to moderate OA of the knee.[66]

Zinc

Zinc plays a role in cartilage growth and maturation and promotes the differentiation of mesenchymal stem cells into chondrocytes.[67] Articular cartilage depends on zinc intake, which aids connective tissue maintenance and functions as an antioxidant and anti-inflammatory mediator.[68] *In vitro* and *in vivo* studies suggest zinc supplementation may prevent the progression of OA by upregulating the gene expression of antioxidants, inhibiting pro-inflammatory cytokines and decreasing protein levels of MMPs.[69] In a small placebo-controlled study involving patients with OA (knee or hip), a nutraceutical formula containing zinc showed a remarkable improvement in symptoms compared to placebo and reduced the need for analgesics and non-steroidal anti-inflammatories.[70]

Cardiovascular disease

Numerous reports have highlighted the major role that inflammation and oxidation play in most CVDs.[71] Atherosclerosis, the common pathological substrate underlying many CVDs, is characterised by oxidative damage, affecting lipoproteins, blood vessel walls, and subcellular membranes.[72] During disease progression, a fibrous plaque is built upon the arterial wall leading to the narrowing of the vessel lumen. One of the key events in the initiation of atherosclerosis, besides cholesterol deposition and chronic inflammatory reactions, is endothelial dysfunction, which occurs in areas of arteries prone to plaque development.[72] Consequently, atherosclerosis affects various circulation regions and will present with unique clinical symptoms depending on the vascular bed affected. For example, in coronary arteries, it causes myocardial infarction and angina, in peripheral circulation, it can result in intermittent claudication, while stroke and ischaemia can occur when present in the arteries of the nervous system.[73,74]

NF-κB regulates the expression of genes involved in atherosclerotic pathogenesis and has been implicated in pathological processes, including foam cell formation, vascular inflammation, the proliferation of vascular smooth muscle cells, arterial calcification and plaque formation.[75] In vascular endothelial cells, NF-κB mediates the induction of pro-inflammatory cytokines and adhesion molecules, thereby promoting monocyte recruitment and contributing to disease progression.[76,77] Inflammatory markers such as CRP, IL-6 and fibrinogen, which are also regulated by NF-κB, have been associated with CVDs and the risk of fatal vascular events.[78] The cornerstone of cardiovascular therapy is, therefore, attenuating oxidative stress and inflammation while restoring circulatory equilibrium, particularly in atherosclerosis and the resultant consequences.

Curcumin

An increasing number of clinical trials have demonstrated that curcumin exerts cardioprotective effects due to its antioxidant, anti-inflammatory, hypolipidemic and anti-atherosclerotic activities.[79] In preclinical studies, curcumin prevented lipid peroxidation and stimulated the conversion of cholesterol into bile acids, increasing cholesterol excretion and consequently attenuating atherosclerosis progression.[80-82] The effects of curcumin on CVDs may furthermore be exerted through the modulation of cellular and molecular targets.[79] Curcumin has been shown to inhibit NF-κB and consequently lower TNF-α-induced monocyte adhesion to endothelial cells, thereby improving endothelial functions.[83,84] By downregulating this pathway, curcumin treatment has been shown to reduce inflammation and oxidised low-density lipoprotein (LDL) in human microvascular endothelial cells, suggesting a potential use in the prevention of vascular processes.[85]

A meta-analysis and systematic review of seven randomised clinical trials found that turmeric and curcumin had beneficial effects on serum triglycerides and LDL cholesterol levels in patients with MetS and type 2 diabetes (T2D) at risk of CVDs.[86] Doses of 15mg, 30mg, or 60mg daily of curcumin were also a useful adjunct therapy for inpatients suffering from acute coronary syndrome, owing to its effect on total cholesterol and LDL cholesterol.[87] Furthermore, curcumin supplementation enhanced artery endothelial function via increasing vascular NO in healthy middle-aged and older adults,[88] and improved flow-mediated dilation and decreased systolic blood pressure in postmenopausal women, potentially improving the age-related decline in endothelial function and reducing the risk of CVD.[89]

Bromelain

Several *in vitro* and *in vivo* studies indicate that bromelain may reduce or minimise symptoms associated with several CVDs, including thrombophlebitis, angina, transient ischemic attack, atherosclerosis, and coronary artery disease.[41,90] Bromelain has been described as a potential treatment for CVDs as it inhibits blood platelet aggregation, thus minimising the risk of arterial thrombosis and embolism.[91] Bromelain was also shown to possess cardioprotective activity against ischemia-reperfusion injury in animal models by inhibiting the degree of cardiomyocyte apoptosis via the Akt signalling pathway.[92] Early human studies suggest bromelain may reduce angina attacks[93] and symptoms of inflammation, oedema and pain in patients with acute thrombophlebitis;[94] however, further quality clinical trials are essential to solidify these findings.

Quercetin and rutin

Numerous biological actions of quercetin have been described *in vitro* and *in vivo*, including antioxidant, anti-inflammatory, anti-thrombotic and vasodilatory activity, suggesting there may be clinically relevant effects regarding CVD risk factors.[95] Quercetin decreased malondialdehyde levels, increased SOD and catalase activity, and regulated anti-inflammatory and anti-apoptosis processes to protect against myocardium damage.[96,97] Research has additionally established that quercetin exhibits significant cardiac benefits by activating and attenuating various signalling pathways involved in CVD development.[98] Other potential mechanisms include its ability to inhibit LDL oxidation and alleviate atherosclerotic lesions,[99,100] reduce adhesion molecules and other inflammatory mediators in aortic cells,[101] protect against mitochondrial dysfunction,[102] and decrease platelet aggregation.[95]

Growing evidence from human clinical data indicates that quercetin may positively influence the metabolism of lipids and may effectively lower blood pressure.[103] Two recent meta-analyses have revealed that quercetin leads to a significant reduction in total and LDL cholesterol in patients with MetS,[104]

and overweight and obese subjects.[105] A meta-analysis of seven clinical trials showed significant reductions in systolic and diastolic blood pressure following quercetin supplementation.[106] The authors hypothesised that the mechanisms responsible for these effects were quercetin's ability to increase endothelial NO synthase activity, downregulate angiotensin II receptor expression in the kidney and improve the balance between NO and endothelin-1 (an endothelial vasoconstrictor). These results suggest quercetin may represent a promising compound against endothelial dysfunction and its associated risk factors.

The initiation of thrombosis is believed to involve platelet adherence and aggregation, which may play a crucial role in the atherothrombotic process.[107] Rutin has been shown to inhibit platelet aggregation in both *in vitro* and *in vivo* studies; however, the direct inhibitory mechanisms remain ambiguous. It has been proposed that rutin impedes protein kinase C activation and thromboxane A2 formation, thereby inhibiting intracellular calcium mobilisation and platelet aggregation.[108] Consequently, these findings suggest rutin may be an effective nutrient in treating thromboembolic-related disorders.

Alpha-lipoic acid

Over the last few decades, investigations in human and animal models have provided evidence that oxidative stress plays a significant role in CVDs, and antioxidants may improve the course of specific diseases, including atherosclerosis, hypertension, ischaemia-reperfusion and heart failure.[109] Alpha-lipoic acid (ALA) is a specific antioxidant that may strengthen the antioxidant network and improve endothelial function by regenerating other antioxidants, such as coenzyme Q10, glutathione, vitamin E and vitamin C.[109] There is convergent evidence from clinical trials, animal models, and *in vitro* studies that ALA enhances endothelium-dependent vasodilation, primarily by increasing NO and preventing a loss in endothelial NO synthase phosphorylation.[110] ALA reduces NF-κB-mediated inflammatory responses by regulating pro-inflammatory gene expression and reducing adhesion molecules.[111] In animals fed high-fat, high-cholesterol diets, ALA supplementation was shown to reduce plaque formation, T-cell content in plaque, and vascular smooth muscle proliferation and improve lipid profiles,[112-114] which have been implicated in atherosclerosis development.

ALA may have a beneficial effect in preventing the development of hypertension by inhibiting pathological changes and normalising changes in blood pressure. In addition to improving endothelial NO synthase, ALA is thought to reduce sulfhydryl group denaturation of calcium channels in vascular smooth muscles through the regeneration of reduced glutathione and by inhibiting renal and vascular overproduction of endothelin-1.[115] A recent meta-analysis of 10 clinical trials observed a statistically significant reduction in diastolic blood pressure and systolic blood pressure after supplementation in hypertensive subjects, suggesting ALA could be considered a hypotensive agent.[116]

Vitamin E

Vitamin E is best known for its positive effects on the cardiovascular system as it has been shown to inhibit platelet aggregation and adhesion, improve endothelial function and decrease lipid peroxidation.[117] Its ability to reduce oxidative stress is particularly important regarding CVDs as oxidation of LDL is a crucial process in atherogenesis.[118] Moreover, vitamin E modulates the expression of genes involved in atherosclerosis, including scavenger receptors, integrins, selectins, cytokines and cyclins.[119] Although clinical studies have shown inconsistent effects, many *in vitro*, animal, and epidemiological studies support the use of vitamin E in the prevention of CVDs.[120-122] Moreover, supplementation has been shown to decrease blood pressure in hypertensive patients[123,124] and reduce the incidence of angina in patients with coronary heart disease.[125,126] Doses as low as 25IU have been shown to offer protection; however, doses over 400IU are likely required to produce clinically significant effects.[127-129]

Vitamin C

Vitamin C is inversely related to several risk factors and indicators of atherosclerotic CVD, such as hypertension, dyslipidaemia, acute-phase proteins, and haemostatic factors.[130] Specifically, vitamin C inhibits the oxidation of LDL cholesterol via free radical scavenging and increases glutathione and vitamin E concentrations within cell membranes.[131] Low levels of vitamin C have additionally been observed in patients with heart failure, potentially by scavenging free radicals, improving myocardial efficiency[132] and improving endothelial function and cardiomyocyte apoptosis.[133] While the majority of studies have administered vitamin C intravenously, oral supplementation >2g appears to be beneficial.[134]

B vitamins

Elevated blood total homocysteine (Hcy) is a recognised modifiable risk factor for more than 100 diseases or syndromes, including cerebral and CVD.[135] In particular, hypertension, accompanied by elevated Hcy can synergistically increase the risk of stroke, which is the second leading cause of death globally.[136] Given elevated Hcy levels have been attributed to insufficient folate intake, dietary deficiency of vitamin B6 and absorptive deficiency of B12, supplementation may be warranted (see Figure 7).[137]

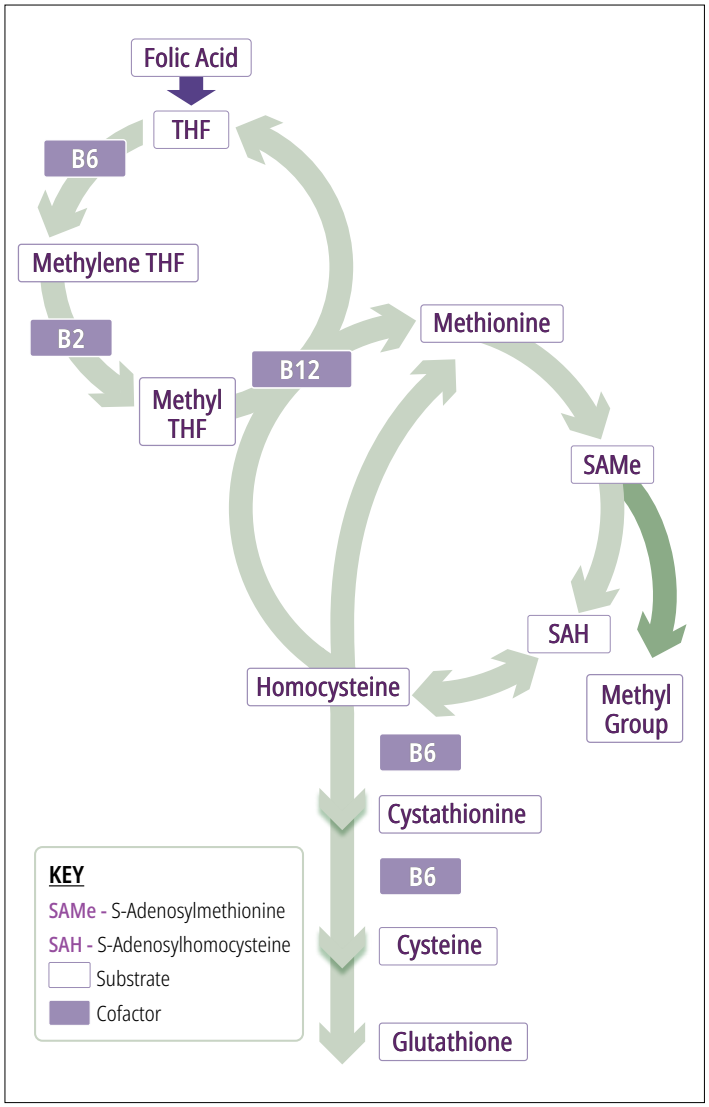
Copper

The heart is one of the main organs affected by copper deficiency, causing reduced metabolism and energy supply to the heart.[138] In humans and animals, copper deficiency results in glucose intolerance, hypercholesterolaemia, and hypertension,

all of which are risk factors for the development of CVD.[139] Copper deficiency increases the susceptibility of both LDL and very-low-density lipoprotein (VLDL) to oxidation,[140] which is thought to play a significant role in atherosclerosis development.[141] Copper functions as a co-factor in the enzyme SOD, which is known to regulate various factors in cardiovascular function.[142,143] Dietary copper deficiency may also result in changes to myocardial gene expression, which has been shown to alter cardiac function and lead to cardiac hypertrophy and heart failure.[144-145]

In patients with hypercholesterolaemia, supplementation of copper at 5mg daily for 45 days decreased total cholesterol, LDL and triglycerides and increased high-density lipoprotein (HDL) cholesterol.[146] Furthermore, copper supplementation for eight weeks reduced oxidative stress markers in women[147] and raised the activities of SOD and plasma ceruloplasmin in adults with moderately high cholesterol.[148] It has been proposed that copper intake may reduce the risk of CVD and atherosclerosis by decreasing concentrations of plasminogen activator inhibitor type 1 (PAI-1), thus improving fibrinolytic capacity.[149]

Figure 7: Nutrients required to reduce oxidative damage and support healthy methylation



Zinc

Growing evidence from experimental models provides biological plausibility for the role of zinc in CVD prevention. Findings in cell and animal studies support the protective role of zinc against certain risk factors, particularly the development of atherosclerosis.[150] The modulating effects of zinc on atherosclerotic plaque formation are primarily attributed to its role in supporting the integrity of endothelial cells and attenuating lipid peroxidation through zinc-regulated redox signalling pathways.[151] Moreover, zinc has been shown to regulate the activity of iNOS, thereby reversing the detrimental effects of inflammation on the endothelium.[152]

Zinc regulates angiotensin-converting enzyme and MMPs, which are involved in the myocardial wall structure.[153] Zinc deficiency has been shown to increase autophagy and hypertrophy of the myocardium, causing degeneration and fibrosis of cardiomyocytes and upregulating pro-inflammatory cytokines.[153] Intracellular zinc additionally plays a critical role in the redox signalling pathway, whereby certain triggers such as ischemia and infarction lead to the release of zinc and cause myocardial damage. Replenishing with zinc has been shown to improve cardiac function and prevent further damage in such states.[154]

Observational studies have observed serum zinc concentrations to be associated with a reduction in CVD death,[155] and higher dietary zinc intakes have been correlated with the reduced prevalence of coronary artery disease and T2D.[150] Given that impaired zinc homeostasis and increased levels of oxidative stress feature prominently in a number of CVD-related disorders, including atherosclerosis, hypertension, and dyslipidaemia,[151] supplementation may be warranted in at-risk populations.

Metabolic conditions

MetS is a broad term used to describe several abnormalities, including hypertension, central obesity, insulin resistance, and dyslipidaemia, triggered by dietary, lifestyle and genetic influences. These metabolic conditions are known to increase the risk of developing T2D, fatty liver disease and CVDs,[156] which contribute to mortality and morbidity rates.[157] Evidence suggests that a bidirectional link between the immune system and metabolism exists, in which inflammation plays an essential role in promoting metabolic abnormalities, and metabolic factors regulate immune cell functions.[156]

Adipose tissue appears to play a central role in the induction of inflammation as over-nutrition leads to changes in cellular composition, resulting in the local production of pro-inflammatory cytokines and chemokines.[158] The progression

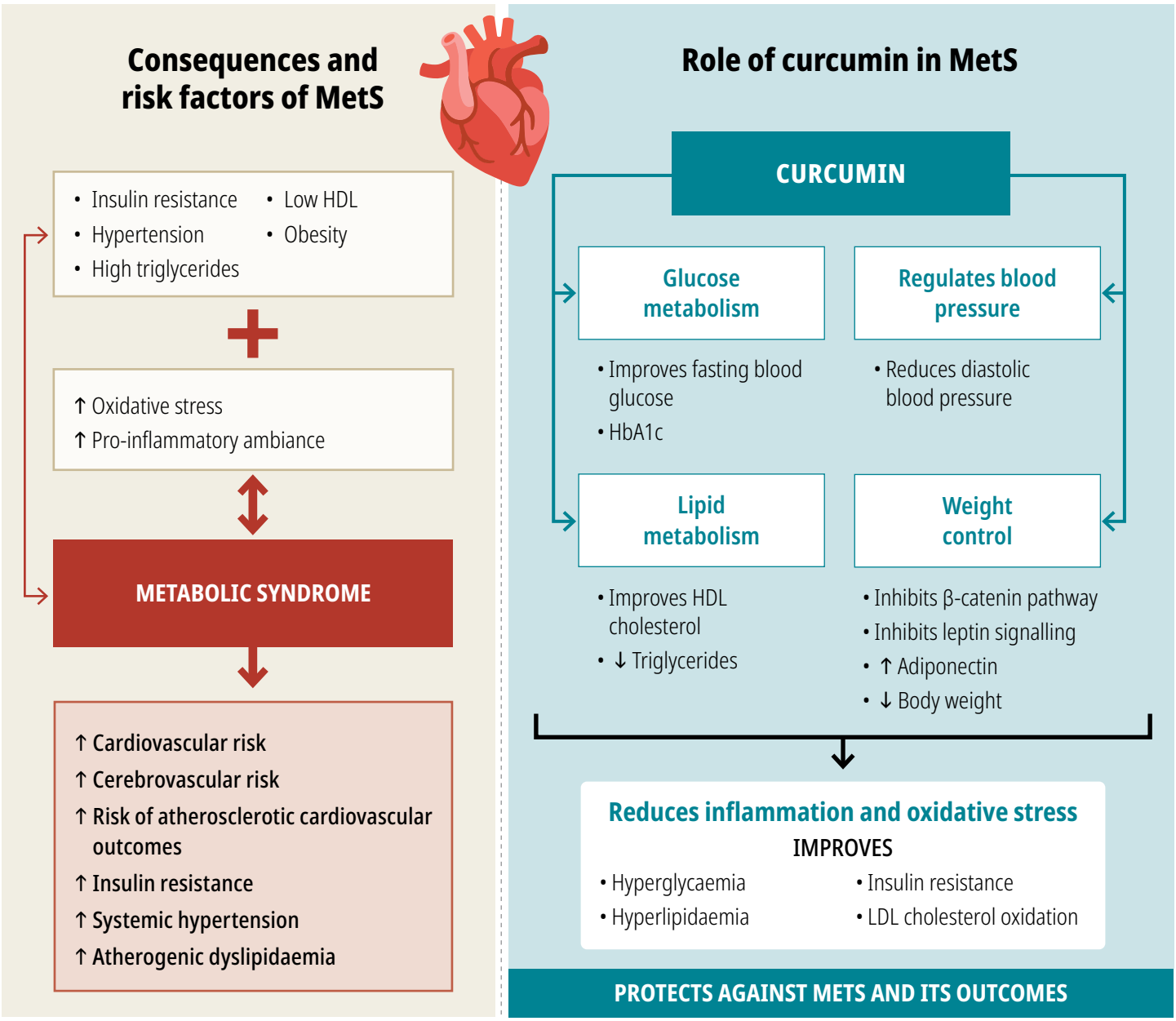
from insulin resistance to T2DM remains poorly understood but implicates a failure of pancreatic β-cells to compensate for insulin resistance leading to chronic hyperglycaemia.[159] Hyperglycaemia promotes mitochondrial dysfunction and induces ROS formation, thus causing oxidative stress in several tissues, including blood vessels and pancreatic beta cells.[160] Consequently, chronic low-grade inflammation, elevated intracellular levels of ROS and subsequent oxidative stress play an essential role in the development of diabetes and vascular complications.

Curcumin

In addition to curcumin's antioxidant and anti-inflammatory activity, its lipid-lowering and anti-glycaemic effects make it a promising therapeutic for preventing and supporting metabolic disorders and their related vascular complications. Its action is thought to be mediated via downregulating numerous inflammatory pathways, protecting against pancreatic β-cell dysfunction and enhancing the insulin signalling cascade.[15,161] Moreover, curcumin can induce peroxisome proliferator-activated receptor-gamma (PPAR-γ), which regulates genes involved in glucose and lipid metabolism, thus improving insulin secretion and sensitivity, and fat metabolism.[162-164]

Curcumin has been shown to attenuate several aspects of metabolic conditions by suppressing adipogenesis,[165] improving insulin sensitivity,[166,167] and reducing elevated blood pressure,[168] inflammation,[169] and oxidative stress[170] (see Figure 8). Various meta-analyses have conclusively found curcumin to be a safe and beneficial therapeutic option for metabolic conditions, including obesity, non-alcoholic fatty liver disease (NAFLD), MetS and T2D.[161,171,172] Researchers have postulated that curcumin benefits these patients by significantly improving various biomarkers associated with metabolic disease, including fasting blood

Figure 8: Risk factors of MetS, its consequences, and the role of curcumin[173]



glucose, triglycerides, HDL cholesterol, diastolic blood pressure, body weight index, waist circumference, leptin levels and HbA1c.

Alpha-lipoc acid

A number of clinical studies have demonstrated that ALA improves endothelial function, enhances glucose disposal and utilisation, decreases cholesterol biosynthesis and increases NO synthase, thereby restoring vasodilation and protecting against the development of diabetes.[174,175] ALA also activates the electron transport chain in mitochondria and induces heme oxygenase-1, reducing ROS release.[176] While mechanisms are yet to be fully elucidated, it is thought to be acting through PI3K/Akt signalling pathways.[175] Various systematic reviews and meta-analyses have observed improvements in symptoms of MetS and diabetic complications after ALA supplementation. In one review, ALA was found to significantly decrease fasting glucose, insulin, HbA1c, triglycerides and total cholesterol,[177] while another review involving 18 clinical trials concluded that ALA significantly decreased CRP, IL-6 and TNF-α levels in patients with Mets and related disorders.[178] Many complications associated with diabetes are due to the overabundance of ROS produced by the mitochondrial transport chain as a result of a sustained hyperglycaemic state. Consequently, clinical trials examining ALA supplementation on diabetic neuropathy, nephropathy, cardiomyopathy and retinopathy have yielded positive results.[179]

Quercetin

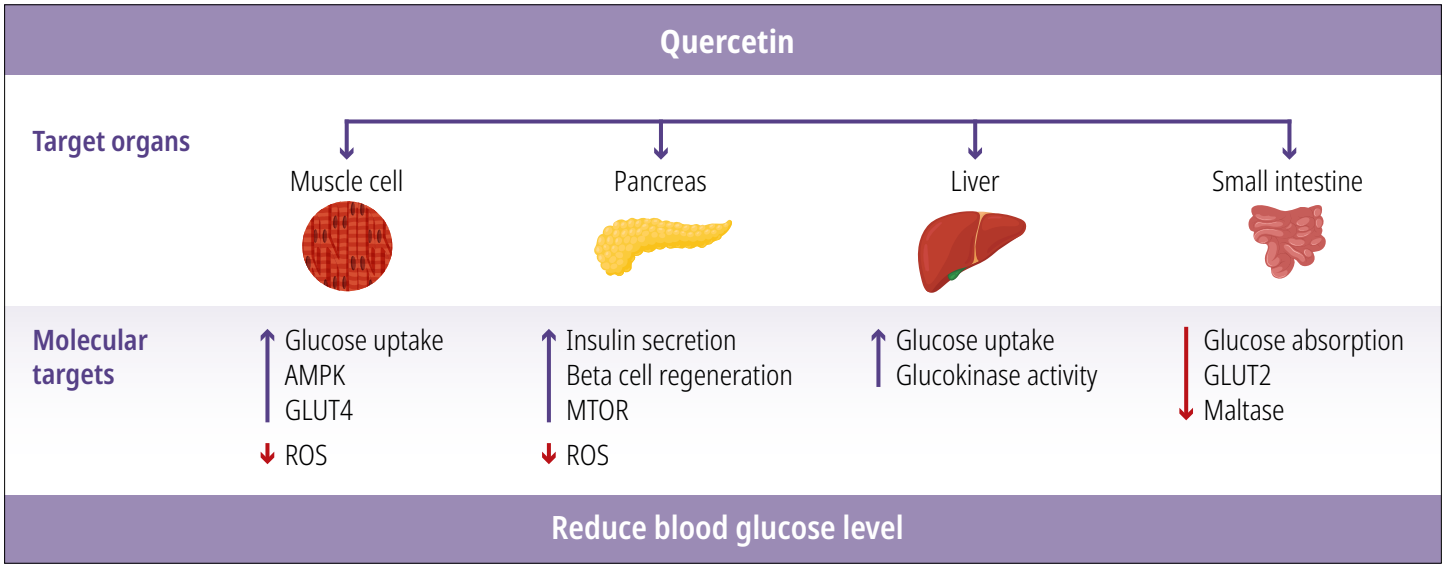
Over the last few decades, the anti-diabetic activity of quercetin has been reported, with studies suggesting the compound acts on multiple targets of diabetes pathogenesis and regulates signalling pathways (see Figure 9).[180] Specifically, quercetin activates adenosine monophosphate kinase (AMKP), which stimulates AKT and GLUT4 receptors, hence regulating glucose levels.[181] Additionally, quercetin has been shown to indirectly activate the mitochondrial target of rapamycin (mTOR) pathway, which induces mitogenesis and stimulates insulin secretion.[180]

By virtue of its antioxidant, anti-inflammatory and hypoglycaemic activity, a theoretical basis exists for quercetin in the prevention of long-term diabetic complications, particularly nephropathy, retinopathy and neuropathy.[131,180] While there are limited clinical trials observing the effects of quercetin in metabolic conditions, supplementation has been shown to inhibit α-glucosidase activity and decrease postprandial hyperglycaemia,[182] reduce inflammatory cytokines (TNF-α and IL-6)[183] and improve antioxidant status in diabetic patients.[184] In addition, quercetin may have potential therapeutic value in managing NAFLD due to its ability to ameliorate liver lipid accumulation and reduce inflammation and oxidative stress.[185] Few trials have observed beneficial effects of quercetin on biomarkers associated with NAFLD, including liver enzymes (ALT, AST, GGT), triglycerides, cholesterol and TNF-α.[186]

Copper

Copper deficiency has been associated with a variety of metabolic changes such as increased blood pressure, elevated cholesterol, insulin resistance and glucose intolerance, which are all implicated in the pathogenesis of diabetes, MetS and NAFLD.[143,187] The development of hepatic steatosis and insulin resistance in response to dietary copper restriction suggests that copper availability may be involved in the development of metabolic conditions.[188] Furthermore, epidemiological and animal studies have shown that copper deficiency is linked to atherogenic dyslipidaemia,[139] induces hypertriglyceridemia and hypercholesterolaemia, and modifies LDL and VLDL composition.[189-191] High fructose intake has additionally been linked to impaired copper status, and altered fructose-copper metabolism leads to exacerbated experimental MetS and NAFLD.[187]

Figure 9: Molecular targets of quercetin in diabetes management[180]



Vitamin B6

Animal models demonstrate that a vitamin B6 deficiency reduces circulating insulin levels, most likely due to the degenerative changes that occur in pancreatic β-cells. Vitamin B6 requirements are also increased in the diabetic state due to increased B6-dependent enzymatic reactions.[192,193] Vitamin B6 deficiency is proposed to contribute to diabetes onset through various mechanisms, including enhanced tryptophan catabolism through the kynurenine pathway, reduced rate of adipogenesis, impaired lipid metabolism, and reduced capability to counteract advanced glycation end-products.[194] Epidemiological and experimental studies have additionally indicated an inverse association between vitamin B6 levels and diabetes and a protective effect of vitamin B6 on diabetic complications, including retinopathy, nephropathy and dyslipidaemia.[192,194]

Vitamin C and vitamin E

Vitamin C has several actions that provide a basis for its use in metabolic conditions. Owing to its antioxidant activity, vitamin C reduces insulin resistance by improving endothelial function, reducing blood pressure, and lowering oxidative stress, which has been consistently observed in patients with diabetes.[195,196] Vitamin C is also involved in releasing insulin in response to glucose, enhancing endothelial NO synthase activity and NO bioavailability.[174] Emerging evidence suggests low serum vitamin C levels are significantly linked to diabetes onset and may play a role in preventing complications associated with disease progression.

Similarly, the antioxidant activity of vitamin E may help to preserve the integrity of the β-cells, which are susceptible to oxidative stress.[174] Vitamin E supplementation has been shown to reduce LDL cholesterol oxidation[197] and adhesion factors in diabetic patients, thereby decreasing the vascular complications associated with insulin resistance.[198]

Manganese

Manganese is an essential trace mineral involved in the synthesis and secretion of insulin and normal carbohydrate metabolism.[199] Experimentally induced manganese deficiency impairs glucose tolerance, and low red blood cell manganese levels are associated with diabetes and renal dysfunction.[200] Manganese is a potent antioxidant and co-factor of the enzyme SOD2 (otherwise known as Mn-SOD), and may therefore protect against diabetic complications related to glucose-induced oxidative stress, namely, microvascular diseases.[201] Preclinical trials demonstrate that manganese supplementation prevents diet-induced diabetes by increasing insulin secretion and protecting pancreatic islet cells against lipid peroxidation.[202]

Zinc

Zinc is an important inducer of insulin secretion, a sensitiser of insulin action and an anti-inflammatory agent, making it an attractive therapeutic option in managing T2D.[203] The benefits of zinc are not merely limited to diabetes but also the associated complications such as diabetic retinopathy, where zinc may exert a beneficial effect via its antioxidant activity. Diabetic patients commonly exhibit a disruption in metabolising zinc, evidenced by low zinc status.[204] As such, diabetics are more likely to have poorer glucose control and exhibit a higher degree of microvascular complications.[205] A systematic review and meta-analysis of human clinical trials demonstrated that zinc supplementation significantly reduces fasting blood glucose and insulin and improves HOMA-IR values in obese individuals.[206] The meta-analysis of 14 studies demonstrated that zinc improves glucose control in both healthy and insulin-resistant individuals; however, subgroup analyses revealed that the effect was more significant in individuals with metabolic diseases.

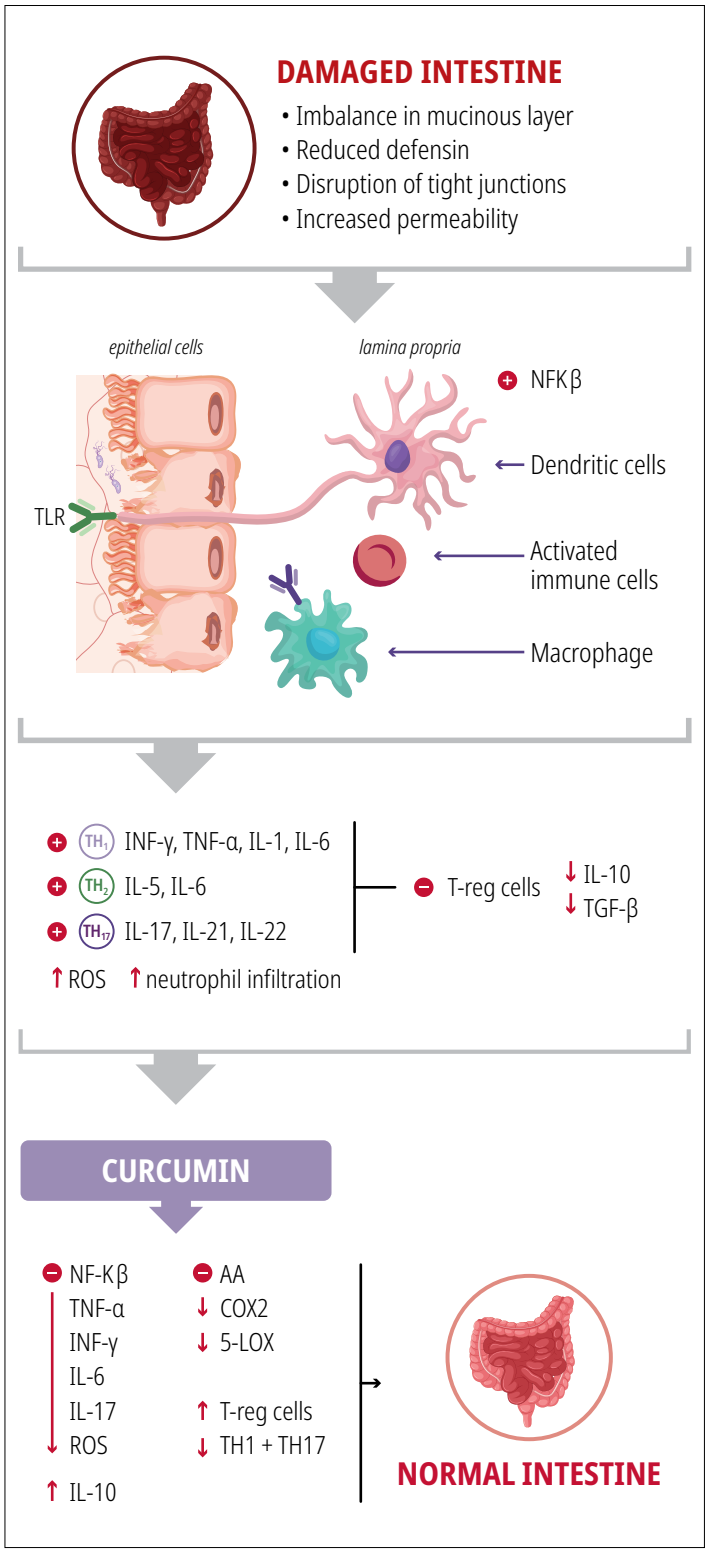
Autoimmune diseases

Autoimmune diseases (AIDs) are chronic inflammatory conditions characterised by deregulated immune function and a loss of tolerance to self-(auto) antigens. Pro-inflammatory cytokines and other inflammatory mediators are now recognised to drive tissue damage in AIDs. Likewise, emerging research has unravelled the role of ROS in the induction of AIDs by exacerbating the inflammatory process, inducing apoptotic death, modifying autoantigens and breaking down immunological tolerance.[207,208] Consequently, it can be speculated that anti-inflammatory and antioxidant substances may be used to treat autoimmunity based on the evidence that ROS eradication plays a role in immune regulation.[209]

Curcumin

Researchers have studied curcumin in a wide variety of inflammatory autoimmune conditions,[12,15] and it has been shown to exert therapeutic benefits by attenuating oxidative stress and regulating inflammatory cytokines and pro-inflammatory signalling pathways in immune cells. TNF-α is a potent pro-inflammatory cytokine produced by macrophages, mast cells, natural killer (NK) cells and activated T cells, and when stimulated, produces cytokines, chemokines, iNOS, and COX-2.[211] Studies have demonstrated curcumin to be an inhibitor of NF-kB signalling pathways in immune cells, leading to a downstream regulation and inhibition of these pro-inflammatory genes and cytokines.[212] Curcumin additionally affects the AA pathway by blocking the phosphorylation of cytosolic PLA2, decreasing the expression of COX2 and inhibiting the catalytic activities of 5-LOX.[213] *In vitro* and *in vivo* studies have also demonstrated

Figure 10: Pathophysiological aspects of IBD and the effects of curcumin[15]
⊕ increases the release; ⊖ decreases the release



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.[214] A plethora of both animal and human studies have also shown curcumin to regulate pro-inflammatory cytokines that contribute to the manifestation of multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, oral lichen planus, and inflammatory bowel disease (IBD).[12,15,215]

Bromelain and papain

Bromelain has been recommended as an adjuvant therapeutic option in treating chronic inflammation. It has been shown to modulate surface adhesion molecules on T cells, macrophages, and NK cells and induce the secretion of IL-1β, IL-6, and TNF-α *in vitro*.[216] Moreover, there is evidence that oral bromelain therapy produces certain analgesic and anti-inflammatory effects and may reduce soft tissue swelling and pain in patients with RA.[217,218] Likewise, papain combined with other proteolytic enzymes significantly reduced TGF-β1 levels in human serum, a growth factor that contributes to persistent inflammation associated with RA.[219]

Alpha-lipoic acid

In addition to its role in biological mitochondrial reactions, ALA protects cell membranes and has been shown to have beneficial effects in several clinical conditions characterised by inflammation, specifically MS.[220] ALA is hypothesised to affect neuronal injury via its various biological functions, including free radical scavenging, downregulating inflammatory cytokines, and preventing T-cell infiltration into the central nervous system. Experimental autoimmune encephalitis studies and human clinical trials involving MS patients have demonstrated reduced disease severity with ALA supplementation.[221] A pilot study suggested that ALA may decrease immunologic markers of MS activity, namely serum MMP-9 and sICAM-1, which are indirectly associated with T-cell migration.[222] Additional studies involving patients with relapsing-remitting MS demonstrated reductions in interferon-gamma (IFN-γ), ICAM-1, TGF-β and IL-6 and increases in total antioxidant capacity after ALA supplementation compared to placebo.[223,224] Moreover, a two-year trial of ALA in secondary-progressive MS demonstrated a significant reduction of whole-brain atrophy[225] and a trend toward improved walking speed.[226]

Quercetin and rutin

Quercetin has a variety of biological activities and possesses neuroprotective, antioxidant, anti-inflammatory, and immunomodulatory actions, making it an attractive option for AID management.[227] *In vitro* studies suggest the anti-inflammatory activity of quercetin is mediated through NF-κB regulation, COX and LOX expression reduction, immune cell inhibition, and suppression of inflammatory cytokines including TNF-α, IL-1β and IL-6.[227] Additionally, quercetin exerts its antioxidant activity via upregulating antioxidant enzymes and modulating signal transduction pathways involved in ROS production.[228] Various *in vitro* and animal studies have reported positive effects of quercetin in specific AIDs, including RA,[229-232] IBD,[233-236] MS,[237] SLE,[238] and Grave's disease.[239] In human clinical

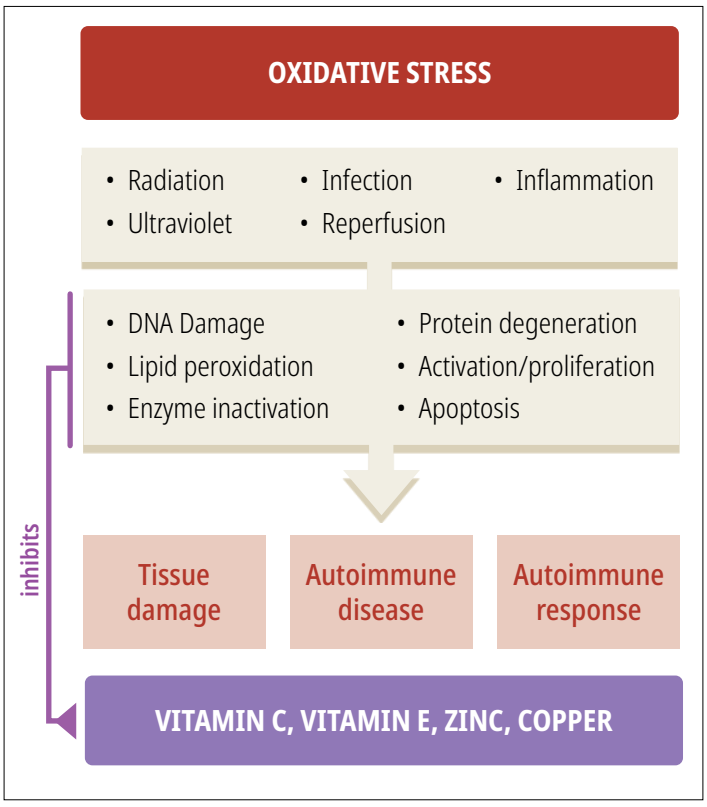
trials, quercetin supplementation significantly reduced pain, early morning stiffness, inflammatory markers (TNF-α) and active disease in women with RA compared to placebo[240] and reduced markers of oxidative stress and inflammation in patients with sarcoidosis.[241]

While quercetin is one of the most abundant flavonoids, the glycoside compound rutin releases quercetin into the gut microbiota and may be an effective therapy for IBD.[227] Dietary rutin, even at low doses, has been shown to be effective at attenuating the production of inflammatory mediators and iNOS, thereby ameliorating drug-induced colitis.[242-244] While further human clinical trials are warranted, patients with AIDs may benefit from quercetin and rutin supplementation to reduce disease severity and prevent further systemic damage.

Vitamin E, vitamin C and zinc

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.[245] Moreover, deficiencies in vitamin E and vitamin C have been associated with AIDs, including RA, SLE and MS.[246] Zinc homeostasis is essential in inflammatory diseases, and a deficiency has been associated with a disturbed ratio between Th1 and Th2 cells[247] and between pro-inflammatory and regulatory cells.[248] Results of a recent meta-analysis also showed zinc concentration in the serum of patients with type 1 diabetes, juvenile idiopathic arthritis, RA, alopecia areata, Hashimoto's thyroiditis, MS, SLE and Sjogren's syndrome (SS) were significantly lower compared to healthy controls.[248] Given the importance of zinc in regulating immune system function, it is logical to associate an imbalance in the homeostasis of this element with the state of autoimmunity.

Figure 11: Oxidative stress and autoimmune reaction[249]



Cancer support

Most cancer cells have high levels of oxidative stress and are more likely to be vulnerable to further damage by ROS insults. ROS play a role in signal transduction in many physiological processes, including inflammatory and immune regulatory processes. Numerous clinical and epidemiological studies demonstrate a clear association between inflammation and cancer development.[250] Consequently, modulating the inflammatory cascade to positively affect initiation, promotion, progression, and metastasis may be a pivotal approach to cancer support. By way of their antioxidant and anti-inflammatory activity, various phytochemicals in food or via supplementation are particularly effective at preventing or controlling various types of cancers.[251-257]

Curcumin

Curcumin represents a promising candidate as an effective anti-cancer nutraceutical to be used alone or in combination with other medications as it affects different signalling pathways and molecular targets involved in the development of several cancers. Curcumin suppresses transformation and proliferation, inhibits tumour metastasis, and induces apoptosis by regulating various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes.[258] The chemoprotective and anti-tumour activities of curcumin have been extensively studied *in vitro* and in animal models since 1985.[258] There have been several clinical studies carried out in human subjects to evaluate the efficacy and safety of treatment with curcumin in different types of cancer either alone or in combination with other chemotherapy agents, including pancreatic,[259] colorectal,[260,261] metastatic breast cancer,[262] and disease precursors to multiple myeloma.[263,264]

Bromelain

The existing clinical data provides little information regarding the anti-tumour activity of bromelain. However, it has been suggested that the ability of bromelain to inhibit tumour cell proliferation and induce tumour cell death may be due to its proteolytic and immunomodulatory properties.[41] *In vitro* and *in vivo* studies have shown that bromelain inhibits the proliferation of cancer cells primarily by modulating the expression of genes

crucial for cell differentiation and proliferation, including mitogen-activated protein kinase (MAPK) and Akt signalling pathways, COX-2 and NF-κB. Furthermore, bromelain induces cell death by apoptosis/autophagy and blocks the cell cycle by inhibiting the necessary cyclins for this process.[41]

Bromelains' therapeutic potential in activating programmed cell death and modulating the expression of apoptosis-associated proteins has been investigated in many *in vivo* and *in vitro* cancer models, including breast cancer,[265-267] melanoma,[268] prostate cancer,[266] colorectal cancer,[270-273] oral cancer,[274] and leukemia.[275,276] Furthermore, the positive effects of bromelain in combination with conventional chemotherapies have been demonstrated in pancreatic, hepatic, breast, and prostate cancer cell lines.[276-280] It should be noted that the synergistic anti-cancer effect of bromelain and commercial chemotherapeutic agents may depend on the dose of the drug used and the type of cancer.

Alpha-lipoic acid

In cancer research, ALA substantially potentiates and synergises the cytotoxic effect of antineoplastic agents while protecting normal tissue against damage. ALA produces cell cycle arrest in G0/G1 phases in tumour cell lines[281] and exhibits anti-tumour activities in cancer models by impacting several hallmarks on signalling pathways implicated in proliferation, invasion, migration, and apoptosis.[282] Furthermore, ALA decreases cell viability and proliferation in breast, ovarian, colorectal, thyroid, and lung cancer cells.[282-290]

Several studies have shown that ALA sensitises cancer cells to chemotherapeutic agents, particularly paclitaxel in breast and lung cancer cells[289,291] and 5-fluorouracil (5-FU) and doxorubicin in colorectal cancer.[287,292] Moreover, ALA has demonstrated protective activity from chemotherapy-induced side effects, including paclitaxel, cisplatin, frataxin, and methotrexate in human cell models and animal studies.[293-296]

Various published case reports have suggested that ALA supplementation with other agents may possess anti-cancer activity among patients with advanced disease. Intravenous ALA (300-600mg, twice per week) alongside naltrexone was reported to improve survival outcomes in patients with pancreatic cancer.[297] The combination of subcutaneous IL-2, medroxyprogesterone acetate and antioxidants (ALA and N-acetyl-cysteine) administered for one year improved clinical outcomes, laboratory parameters and quality of life in patients with advanced solid tumours.[298] Likewise, a case series of 10 patients with a life expectancy of two to six months reported that the combination of ALA with hydroxy-citrate and low-dose naltrexone had limited toxicity, with seven of the patients experiencing a response.[299] Though randomised, controlled clinical trials are needed, preliminary studies suggest ALA may be a safe adjuvant alongside standard oncology.

Quercetin

Quercetin is a lipophilic compound that crosses cellular membranes and induces apoptosis by initiating multiple intracellular signalling pathways implicated in chemoprevention. At the molecular level, quercetin has been shown to inhibit the PI3K-Akt and MAPK pathways,[300,301] stabilise p53,[302] and suppress NF-κB signalling[303] in various cancer cell lines. One of the unique abilities of quercetin in cancer support may be due to its dual function as a pro-oxidant and antioxidant. At high concentrations, quercetin increases oxidative stress and cytotoxicity by elevating damage and inducing apoptotic pathways in tumour cells.[304,305] Based on the available evidence, quercetin has been shown to inhibit breast,[306] lung,[307] nasopharyngeal,[308] colorectal,[309] prostate,[310] pancreatic,[311] and ovarian cancers.[312] Quercetin has additionally been reported to have synergistic effects when combined alongside certain chemotherapies and irradiation.[313-315]

B vitamins

B vitamins are required for nucleotide synthesis and the methylation of proteins and DNA and they also directly affect the immune response.[316] Vitamin B2 plays an important role as a regulator of oxidative stress and activates phagocytosis and the proliferation of macrophages and neutrophils.[317] Vitamin B2 deficiency may be a risk factor for various cancers, including breast,[318] oesophageal,[319] lung,[320] and colorectal cancers.[321]

Vitamin B6 and its metabolites act as co-factors for more than 140 enzymatic reactions in the human genome, and a deficiency may be associated with mutation and DNA strand breaks.[316] Preclinical research has demonstrated the bioactivity of vitamin B6 in cancer models as inhibitors of cell proliferation, enhancement of chemotherapy cytotoxicity and alterations to gene expression. Growth inhibition was observed in melanoma,[322] and hepatoma cell lines,[323] and reduced dietary intake has been documented as a risk factor for developing lung,[324] colorectal,[325] pancreatic,[326] and breast cancer.[327]

The role of folate in regulating the immune system is less understood; however, a deficiency has been found to negatively influence the immune system.[316] A lack of folate in lymphocytes reduced cell proliferation, increased DNA strand breaks, apoptosis and cell cycle arrest, and reduced T-helper and T-regulatory cell populations.[316]

Vitamin B12 also plays an important immune regulatory role for specific immune cell types, including NK cells, via upregulation of their expression.[328] Animal studies have demonstrated that B12 deficiency was associated with reduced NK cell activity and a reduction in B lymphocytes.[329]

Vitamin E, vitamin C and zinc

Vitamin E and zinc play an essential role in controlling cell cycle progression and inducing apoptosis in cancer cells by regulating various signalling pathways.[330-332] Vitamin E reduces the mutant p53 gene while stimulating wild-type p53, a tumour suppressor gene.[333-336] Vitamin E and vitamin C possess anti-angiogenesis activity by decreasing the expression of vascular endothelial growth factor (VEGF), a protein required in tumour growth. Vitamin C has been shown to reduce the secretion of inflammatory molecules, such as COX-2 and iNOS, which are associated with proliferation, metastasis, angiogenesis and apoptosis.[337] Moreover, the anti-cancer activity of vitamin C may also be attributed to the ROS-dependant downregulation of specificity protein (Sp) transcription factors and Sp-regulated genes involved in cancer proliferation and angiogenesis.[338]

The combination of vitamin C and E reduced the adverse effects of various chemotherapeutic agents on normal cells,[339] inhibited tamoxifen-induced hyperlipidaemia in breast cancer patients,[340] and reduced DNA damage associated with 5-FU, doxorubicin and cyclophosphamide.[341] Combining vitamin E with standard therapies has been shown to reduce neurotoxicity[342-343] and radiation-induced side effects[344] without reducing its effectiveness, along with increased survival time in terminal cancer patients.[345]

Zinc supplementation in conjunction with radiotherapy and/or chemotherapy decreased the development of mucositis in leukemia,[346] fatigue in colorectal cancer,[347] and dermatitis in head and neck cancer.[348]

Dysmenorrhoea

While the leading cause of primary dysmenorrhoea is not well understood, an elevation in prostaglandins and leukotrienes has been observed during menstruation, resulting in amplified uterine muscle contraction, hypoxia and pain.[349] In primary dysmenorrhea, this increase may be caused by the drop in progesterone levels at the onset of menstruation. As recurrent menstrual pain is associated with central sensitisation and may predispose women to develop other painful conditions, appropriate disease management is vital.[349]

Curcumin

Curcumin's mechanism of action for period pain relief may be explained by its ability to inhibit prostaglandins, a similar action shared by NSAIDs.[350] Curcumin reduced the force and frequency of contractions induced by oxytocin,[351] suggesting inhibition of oxytocin or oxytocin receptors may play a beneficial role in lowering uterine pain. In a recent study, the combination of turmeric (500mg) and mefenamic acid (250mg) significantly reduced primary dysmenorrhoea pain compared to placebo ($P = 0.031$), while turmeric alone was slightly more effective than mefenamic acid alone ($P = 0.043$ and $P = 0.044$ respectively).[350]

Bromelain and papain

Bromelain, either alone or in combination with papain, has been shown to reduce primary dysmenorrhoea pain, potentially by inhibiting phospholipase A2 activity and consequently reducing prostaglandin production.[352-354]

Vitamin E and zinc

A recent systematic review and meta-analysis suggested vitamin E and zinc may reduce pain severity in patients with primary dysmenorrhoea by inhibiting AA release and thereby reducing the production of prostaglandins.[355] Moreover, zinc inactivates free radicals by increasing CuZn-SOD levels, which are present in the endometrium.[356]

Other indications

Threatened miscarriage

Threatened miscarriage is a common problem in pregnancy, often affected by complications due to genetic abnormalities, inflammatory processes, and immunologic disorders. ALA may play a protective role in preventing miscarriages by reducing pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, and INFγ, and inducing anti-inflammatory IL-10 release.[357] ALA also induces VEGF to stimulate tissue epithelialisation, collagen deposition, and smooth muscle actin fibrogenesis to resolve subchorionic haematoma associated with threatened miscarriage.[358]

It has been suggested that disturbances in maternal and foetal homocysteine metabolism may result in miscarriage, and hyperhomocysteinaemia is considered a risk factor for recurrent spontaneous early pregnancy losses.[359,360] While there is insufficient evidence regarding optimum dosages required to prevent repeated pregnancy loss, vitamin B6, folate and vitamin B12 are necessary for healthy methylation and should be considered in predisposed individuals. Women with threatened miscarriages have also been shown to have lower folate, vitamin B6,[361] vitamin C,[362] vitamin E,[363] zinc,[364] copper,[365,366] and manganese[364] levels compared to healthy pregnant women, suggesting optimal levels may reduce the occurrence of spontaneous abortions.

Allergies

Allergies are among the fastest-growing chronic conditions in Australia, with 4.1 million Australians suffering from at least

one allergic condition.[366] Common to allergies is the complex signalling cascade triggered in response to allergen exposure in sensitised individuals — the resulting hypersensitivity reaction results in mast cell degranulation, histamine release, and other inflammatory molecules. The primary cause of histamine intolerance is compromised enzymatic function of diamine oxidase (DAO) or histamine-N-methyltransferase (HNMT) caused by genetic or acquired impairment.[367] Given that vitamin C, vitamin B6, zinc, and copper are essential for DAO activity, sufficient levels may benefit patients with histamine intolerance.[368] *In vitro* studies have demonstrated that quercetin impedes histamine release by acting as a mast cell stabiliser and impeding mast cell and basophil degranulation. It has been shown to inhibit platelet aggregation and enzymes involved in releasing inflammatory mediators, including phospholipase A and lipoxygenase.[369,370] Whilst human intervention studies are currently lacking, animal studies provide evidence that quercetin may deliver the therapeutic potential for allergic diseases.[371]

Immune system dysregulation

As previously discussed, inflammation is a critical physiological process mediated by the innate immune system in response to foreign pathogens. However, in a compromised immune system, excess inflammation occurs from overproduction and prolonged exposure to inflammatory mediators, which are produced by the immune response and include cytokines, prostaglandins, ROS, and RNS.[372] Inadequate intake of B vitamins has been associated with impaired quantity and quality of lymphocytes, cytokines, and NK cells.[316] Vitamin C plays a vital role in many immune mechanisms by stimulating the activity of white blood cells and antibody responses. It has been demonstrated to increase phagocyte function, particularly neutrophils and monocytes, and it has positive effects on the proliferation of lymphocytes and the synthesis of immunoglobulin antibodies.[373] Adequate vitamin E intake also demonstrates immune-enhancing effects by increasing T-lymphocyte response, antibody production, cell-mediated immunity, and NK cell activity.[131] Vitamin E also decreases PGE2 production and therefore reduces its immunosuppressive effects.[131] Zinc contributes to immune system function via its critical role in cell-mediated and humoral immunity aspects. A mild zinc deficiency has been shown to adversely affect T-cell functions.[373,374] Lastly, copper has been shown to play a role in the development and maintenance of immune system function, with studies demonstrating copper status affects several aspects of neutrophil, monocyte, and T-cell function.[375]

Cognitive function

Oxidative stress and neuroinflammation are two major factors involved in the development and progression of various neurodegenerative diseases.[376] ROS and RNS damage proteins, lipids, carbohydrates, and nucleic acids in brain tissue, resulting in cell death and neuronal loss.[377] Activation of microglial cells promotes the release of pro-inflammatory cytokines, such as TNF-α and IFNγ, which infiltrate immune cells and lead to the phagocytosis of synapses and neuronal dysfunction.[377] Consequently, it has been suggested that antioxidant supplementation, such as vitamin E, vitamin C, zinc and curcumin could potentiate the efficacy of current treatment options, even in the early stages of neurodegenerative diseases.[378] Moreover, oxidative stress is a consequence of copper deficiency, and although controversial, low plasma copper has been linked to an earlier decline in cognitive ability in Alzheimer's disease.[379-381]

Impaired methylation reactions have also been proposed to reduce neurocognitive function, and numerous studies have observed an association between hyperhomocysteinaemia, brain atrophy and cognitive decline.[382,383] Therefore, lowering excess homocysteine with nutrient co-factors, such as vitamin B6, vitamin B12 and folate, could be an appropriate therapeutic target for improving neurocognitive function and preventing neurodegenerative diseases.

Wound healing

The contribution of poor nutritional status to wound healing has been well established in the literature. Vitamin C plays a comprehensive role in all phases of wound healing regarding cellular apoptosis and clearance, antioxidant processes and collagen synthesis.[384] Vitamin B2, vitamin B6 and vitamin B12 deficiencies indirectly affect the wound healing process by impairing antibody production and white blood cell function, consequently increasing the risk of infectious complications.[385] Copper is a required co-factor for the enzyme lysyl oxidase, which is essential in developing connective tissue. Zinc deficiency impairs DNA and protein synthesis and cellular proliferation, all processes that play a pivotal role in wound healing.[385] Curcumin may accelerate the healing process by facilitating collagen synthesis, fibroblast migration and differentiation and inducing apoptosis of inflammatory cells.[386,387]

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