Repairing a Disrupted Blood-Brain Barrier (BBB)

The blood brain barrier (BBB) describes the highly selective, semi-permeable interface that separates the brain and brain interstitial fluid from the peripheral circulatory system and the compounds within it.[1,2] The BBB serves to modulate the influx of immune cells, inflammatory cytokines, hormones, neurotransmitters, pathogens, toxins and drugs from the peripheral circulation into the brain.[1-3]

The BBB therefore plays an indispensable role in maintaining brain homeostasis, as well as in creating an optimal environment for neuronal survival and brain function.[1-4] This precise control of CNS homeostasis is critical for proper neuronal function and also serves to protect the brain and neural tissue from various toxins, drugs, pathogens, inflammation and injury.[1,2,5]

Various factors may however cause detrimental changes to the physical and biochemical properties of the blood-brain barrier, leading to compromised BBB integrity, BBB dysfunction and increased permeability.[1,2] This, in turn, may result in a failure to regulate entry of unwanted compounds into the brain and CNS.[1,2] The loss of BBB integrity and subsequent increased barrier permeability may result in neuronal dysfunction, neuroinflammation, altered brain homeostasis as well as compromised brain function, cognitive function, mood and nervous system health.[1,3-6]

Inflammation, neuroinflammation, oxidative stress and impaired gut barrier integrity have all been identified as key risk factors for the development of BBB disruption and increased BBB permeability.[1,3,5,6] Addressing these modifiable causative factors may facilitate repair of the BBB and help reduce the risk of ongoing triggers that may damage BBB integrity, providing both short-term and importantly long-term benefits.[1,3] In addition, several ingredients have been identified as having a more direct role in supporting BBB repair or reducing BBB disruption.[7]

Ingredient	Mechanisms to Reduce Disruption and Support Repair of the Blood-Brain Barrier
Magnesium	Magnesium has been shown to directly influence BBB properties, with evidence suggesting that magnesium can play a pivotal role in protecting the BBB, preventing disruption, reducing BBB hyperpermeability and in supporting BBB repair.[8-13] With BBB impairment, magnesium passes into the extracellular compartment in the brain in significantly higher concentrations. Raised free magnesium concentration in the brain capillary endothelial cells stimulates endothelial cell proliferation, restores the cell's ability to generate and utilise ATP for cellular repair mechanisms, supports vascular injury repair and improves disrupted BBB integrity.[8] Magnesium supplementation has been shown to attenuate BBB permeability, limit transient osmotic openings of the BBB and brain oedema and help protect blood brain barrier integrity, according to animal research.[8-13] Magnesium may also be protective to brain tissue by upregulating antioxidant enzyme activity.[10]
Acetyl-L-carnitine	Acetyl-L-carnitine has several neuro-modulatory and neuroprotective actions in humans.[14,15] Acetyl-L-carnitine is essential for normal mitochondrial function, acting as a transporter of acetyl CoA and long-chain fatty acids into the mitochondria for energy production and beta-oxidation.[16] Chronically elevated oxidative and nitrosative stress can lead to mitochondrial dysfunction and can damage BBB integrity.[1,3] Research has however shown that acetyl-L-carnitine may help to repair the BBB by reversing mitochondrial decay caused by oxidative damage.[17,18] In addition, acetyl-L-carnitine stimulates membrane phospholipids synthesis, which leads to stabilisation of cell membranes.[16]
Inositol	Inositol is an essential component of cell membrane phospholipids, with its primary function relating to cell membrane structure and integrity.[16] Inositol has been shown to decrease BBB permeability in animal research and it appears to exert a restorative effect on the Na+/K+ ATPase activity of the cerebral endothelial cells.[19]

Vitamin D3	Vitamin D is recognised as a neuro-steroid and is essential for brain health.[20,21] The neuro-steroid actions of vitamin D include anti-inflammatory, antioxidant and neuroprotective actions.[21,22] Circulating 25(OH) vitamin D (calcifediol) crosses the BBB and enters glial cells and neuronal cells to be converted into the active calcitriol form.[20,22] Vitamin D mediates its effects by binding to the vitamin D receptor (VDR), which are found to be widespread in brain tissue.[23-25] Preliminary research suggests that Vitamin D may protect endothelial cells and ameliorate disruption of the blood-brain barrier, mainly by reducing inflammation.[23,26,27]
Vitamin B1	Vitamin B1 (thiamine) is necessary for normal neurological function and supports nervous system and cognitive health.[28] Thiamine also plays a neuro-modulatory role in the acetylcholine neurotransmitter system and contributes to the structure and function of cellular membranes, including neurons and neuroglia.[29] Vitamin B1 deficiency has also been shown to damage the integrity of the BBB, with oxidative stress and inflammation being identified as contributing factors.[30-32] Vitamin B1 supplementation has been shown to help restore BBB integrity in patients with severe thiamine deficiency.[31]
Combination Vitamin B6, B12, Folic Acid	Vitamin B12, vitamin B9 (folate) and vitamin B6 all play a role in homocysteine regulation and deficiency of these nutrients may lead to hyperhomocysteinaemia.[33-37] Elevated homocysteine levels have been shown to increase permeability of the BBB, with several mechanism having been identified.[38] In addition, raised homocysteine levels have been linked to the development of cognitive impairment and some neurodegenerative disorders.[33-37] Research has shown that supplemental intake of vitamins B12, folate and B6 can restore the integrity of the BBB in adults that have elevated homocysteine levels and mild cognitive impairment.[33]
Cocoa	Cocoa supports brain and cognitive health and may reduce BBB dysfunction via a number of mechanisms.[39-42] The neurobiological effects of cocoa constituents appear to be mediated by a range of actions involving the ability to stimulate regeneration, protect vulnerable neurons, promote neuronal survival and enhance neuronal function, according to preliminary data.[39] The flavanols are believed to directly influence cellular cascades that result in expression of neuroprotective and neuro-modulatory proteins that promote neurogenesis, neuronal function and brain connectivity.[40] Clinical research in humans has shown that consumption of cocoa can improve brain blood flow, induce cerebral vasodilation and cerebral blood oxygenation and increase nitric oxide bioavailability, a key regulator of vascular function.[39-42] Adequate cerebral blood flow (CBF) is important for oxygenation, waste metabolite excretion and glucose distribution to neurons and may increase neurocognitive functions.[41]
Curcumin	Curcumin has been shown to have neuroprotective and cognitive-enhancing properties that may help delay or prevent neurodegenerative diseases, especially where inflammation or oxidative damage play a major role.[43-46] In animal studies, curcumin has been shown to reduce BBB disruption and hyperpermeability, reverse BBB dysfunction and improve overall integrity of the BBB.[47-49]
Feverfew (parthenolide)	The feverfew constituent, parthenolide, has been shown to ameliorate BBB permeability through upregulation of claudin-5 in animal research.[50] Parthenolide may also exert neuroprotective effects, reduce neuroinflammation, reduce oxidative stress, suppress the activation of A1 neurotoxic reactive astrocytes and may support neurological repair mechanisms, according to animal research.[51]
Holy basil (ursolic acid)	Holy basil is rich in phytoconstituents, including ursolic acid, which may protect brain cells from oxidative damage and neuronal loss.[52,53] Animal research also suggests ursolic acid may attenuate BBB disruption.[54] Ursolic acid has been shown to have neuroprotective mechanisms on neuronal glial cells in laboratory and animal studies.[52] It suppresses the generation of reactive oxygen species, advanced glycation end products and lipid peroxidation products as well as increasing antioxidant defences through upregulation of the Nrf2 pathway. Ursolic acid also inhibits key inflammatory cytokines via the NF-κB signalling pathway. By acting on multiple targets and reducing both oxidative stress and inflammation, ursolic acid may promote neuronal regeneration.[52] Holy basil has been shown to protect brain cells from the damaging effects and irreversible neuronal loss caused by electromagnetic field (EMF) exposure in animal research.[53] Exposure to EMF, even at low frequencies (900-1800 Hz), has been associated with increased permeability of the blood-brain barrier, disturbed neuronal function, oxidant and antioxidant imbalance, disturbed regional cerebral blood flow, neurotransmitter imbalance and alterations in genomic responses.[53]

**References available on request.*