G.I. InnerCalm™
Scientific Validation of Ingredients

Author: Joseph Katzinger, ND

Ingredients: Glycine, Ginger powder (*Zingiber officinale*, standardized to 10% gingerols), Organic Chamomile flower (*Matricaria recutita*), Organic Lemon Balm leaf (*Melissa officinalis*), DGL (as GutGard, std. to >3.5% glabrindin & >10% total flavonoids), Quercetin (fruit powder, std. 95% dihydrate), Aloe vera Gel (certified Plus Aloe vera gel SD 200x), Zinc carnosine

Overview

G.I. InnerCalm™ provides a unique combination of botanicals and key nutrients with well-established roles and proven safety and efficacy for the promotion of digestive tract health, and in supporting an intact and functional intestinal epithelium. Each component of G.I. InnerCalm™ has a distinct influence on epithelial health, ranging from the antioxidant protection of mucosal cells to the upregulation of tight junction proteins that restore the intestinal barrier and mitigate intestinal hyperpermeability.

Multiple anti-inflammatory ingredients in G.I. InnerCalm™ have been shown to reduce inflammatory processes, including downregulation of the NF-κB pathway and inhibition of inflammatory mediators such as C-reactive protein and TNF-α. Increasing the synthesis of glutathione and upregulation of heat shock proteins and antioxidant enzymes, such as superoxide dismutase and catalase, also underlie the protection provided to gastric and small intestinal mucosa from a number of toxic agents, including NSAIDs and lipopolysaccharide (LPS). Components of G.I. InnerCalm™ have also been shown in clinical trials to enhance the eradication of *H. pylori* and improve symptoms of functional dyspepsia, while still supporting a healthy microbiome. Additionally, while G.I. InnerCalm™ contains well-researched ingredients that support intestinal epithelial health, it contains no glutamine, avoiding possible adverse effects of this amino acid, including heightened ammonia synthesis and dysfunctional glutamatergic neurotransmission.[1,2,3,4] Rather than isolated nutrients, the combination of ingredients provided in G.I. InnerCalm™ target diverse mechanisms which both protect and restore intestinal epithelial health, supporting optimal digestive function.

---

[1] Holecek M. Side effects of long-term glutamine supplementation. JPEN J Parenter Enteral Nutr. 2013 Sep;37(5):607-16.
[2] Montanari M, Martella G, Bonsi P, et al. Autism Spectrum Disorder: Focus on Glutamatergic Neurotransmission. Int J Mol Sci. 2022 Mar 31;23(7):3861.
[3] Nisar S, Bhat AA, Masoodi T, et al. Genetics of glutamate and its receptors in autism spectrum disorder. Mol Psychiatry. 2022 May;27(5):2380-2392.
[4] Rojas DC. The role of glutamate and its receptors in autism and the use of glutamate receptor antagonists in treatment. J Neural Transm (Vienna). 2014 Aug;121(8):891-905.

Glycine

Scientific Evidence:

The smallest of amino acids, glycine represents 11.5% of the total amino acids and 20% of amino acid nitrogen in body proteins. It is a major constituent in structural proteins, such as collagen and elastin, as well as the major amino acid for the conjugation of bile acids, important for the digestion and absorption of lipids and lipid-soluble vitamins. Additionally, glycine has both anti-inflammatory, cytoprotective, and immunomodulatory effects, and is needed for the synthesis of many crucial proteins, including hemoproteins such as hemoglobin and myoglobin, as well as glutathione, creatine, porphyrins, and purines.[5]

Glycine is now recognized to be a conditionally essential amino acid; endogenous synthesis is not always adequate to meet metabolic needs, and low plasma levels have been consistently reported for several metabolic conditions, including obesity, diabetes, and non-alcoholic fatty liver disease, with some evidence for decreased *de novo* synthesis in these conditions.[6,7,8,9,10] Additionally, plasma levels of glycine have been inversely associated with the risk of myocardial infarction among people at higher cardiovascular risk in a study with over 4,000 participants, most likely related to the activity of the enzyme glycine-N-methyltransferase (GNMT), though C-reactive protein levels were nearly double in the lowest plasma glycine quartile compared to the highest, so inflammation may also play a role.[11] Animal models suggest both that glycine supplementation may mitigate atherosclerosis and also that glycine deficiency may exacerbate this process, an effect mediated at least in part by enhanced glutathione synthesis following supplementation.[12] In humans, glycine is also a rate-limiting factor in glutathione synthesis, and supplementation, often with cysteine, has been shown to increase serum glutathione levels in several patient populations.[13,14] In study participants with metabolic syndrome, supplementation of glycine alone was associated with reduced oxidative stress as well as a reduction in

---

[5] Wang W, Wu Z, Dai Z, et al. Glycine metabolism in animals and humans: implications for nutrition and health. Amino Acids. 2013 Sep;45(3):463-77.

[6] Meléndez-Hevia E, De Paz-Lugo P, Cornish-Bowden A, et al. A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. J Biosci. 2009 Dec;34(6):853-72.

[7] Alves A, Bassot A, Bulteau AL, et al. Glycine Metabolism and Its Alterations in Obesity and Metabolic Diseases. Nutrients. 2019 Jun 16;11(6):1356.

[8] Guasch-Ferré M, Hruby A, Toledo E, et al. Metabolomics in Prediabetes and Diabetes: A Systematic Review and Meta-analysis. Diabetes Care. 2016 May;39(5):833-46.

[9] Tan HC, Hsu JW, Tai ES, et al. De Novo Glycine Synthesis Is Reduced in Adults With Morbid Obesity and Increases Following Bariatric Surgery. Front Endocrinol (Lausanne). 2022 Jun 9;13:900343.

[10] Imenshahidi M, Hossenzadeh H. Effects of glycine on metabolic syndrome components: a review. J Endocrinol Invest. 2022 May;45(5):927-939.

[11] Ding Y, Svingen GF, Pedersen ER, et al. Plasma Glycine and Risk of Acute Myocardial Infarction in Patients With Suspected Stable Angina Pectoris. J Am Heart Assoc. 2015 Dec 31;5(1):e002621.

[12] Rom O, Liu Y, Finney AC, et al. Induction of glutathione biosynthesis by glycine-based treatment mitigates atherosclerosis. Redox Biol. 2022 Jun;52:102313.

[13] McCarty MF, O'Keefe JH, DiNicolantonio JJ. Dietary Glycine Is Rate-Limiting for Glutathione Synthesis and May Have Broad Potential for Health Protection. Ochsner J. 2018 Spring;18(1):81-87.

[14] Sekhar RV, Patel SG, Guthikonda AP, et al. Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. Am J Clin Nutr. 2011 Sep;94(3):847-53.

systolic blood pressure.[15] Supplementation with cysteine (as N-acetylcysteine) has been shown to increase glutathione levels and improve a number of related factors, ranging from insulin sensitivity and blood pressure to mitochondrial function, in several human clinical trials.[16,17,18]

Glycine also plays important roles both in protecting intestinal epithelial cells from damage, and in restoring intestinal barrier dysfunction partly via the above mechanisms. In animals, glycine has been shown to provide protection from ischemia-reperfusion injury in both hepatocytes and intestinal cells.[19,20,21] *In vitro* analysis suggests that in intestinal epithelial cells, glycine is transported into cells by a specific transporter (GLYT1), and glycine provides protection largely via enhanced glutathione synthesis in these cells.[22] Protection for intestinal epithelial cells has been observed in human studies as well; in a non-interventional trial, glycine supplementation was associated with a nearly 2-fold reduction in GI complaints attributed to long-term antiplatelet (aspirin) therapy.[23]

Additionally, *in vitro* studies indicate that glycine also protects against intestinal barrier dysfunction at least in part by inactivating the IRE1α-JNK signaling pathway, preventing apoptosis in intestinal epithelial cells. Glycine was also shown to mitigate the downregulation of tight junction proteins induced by brefeldin A (an endoplasmic reticulum (ER) stress inducer), including occludin, claudin-1, and zonula occludens (ZO-1 and ZO-2).[24] ER stress and associated inflammation have recently

---

[15] Díaz-Flores M, Cruz M, Duran-Reyes G, et al. Oral supplementation with glycine reduces oxidative stress in patients with metabolic syndrome, improving their systolic blood pressure. Can J Physiol Pharmacol. 2013 Oct;91(10):855-60.

[16] Kumar P, Liu C, Hsu JW, et al. Glycine and N-acetylcysteine (GlyNAC) supplementation in older adults improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscle strength, and cognition: Results of a pilot clinical trial. Clin Transl Med. 2021 Mar;11(3):e372.

[17] Kumar P, Liu C, Suliburk J, et al. Supplementing Glycine and N-Acetylcysteine (GlyNAC) in Older Adults Improves Glutathione Deficiency, Oxidative Stress, Mitochondrial Dysfunction, Inflammation, Physical Function, and Aging Hallmarks: A Randomized Clinical Trial. J Gerontol A Biol Sci Med Sci. 2022 Aug 17:glac135.

[18] Sekhar RV. GlyNAC (Glycine and N-Acetylcysteine) Supplementation Improves Impaired Mitochondrial Fuel Oxidation and Lowers Insulin Resistance in Patients with Type 2 Diabetes: Results of a Pilot Study. Antioxidants (Basel). 2022 Jan 13;11(1):154. doi: 10.3390/antiox11010154.

[19] Schaefer N, Tahara K, Schuchtrup S, et al. Perioperative glycine treatment attenuates ischemia/reperfusion injury and ameliorates smooth muscle dysfunction in intestinal transplantation. Transplantation. 2008 May 15;85(9):1300-10.

[20] Kallakuri S, Ascher E, Pagala M, et al. Protective effect of glycine in mesenteric ischemia and reperfusion injury in a rat model. J Vasc Surg. 2003 Nov;38(5):1113-20.

[21] Yamanouchi K, Eguchi S, Kamohara Y, et al. Glycine reduces hepatic warm ischaemia-reperfusion injury by suppressing inflammatory reactions in rats. Liver Int. 2007 Nov;27(9):1249-54.

[22] Howard A, Tahir I, Javed S, et al. Glycine transporter GLYT1 is essential for glycine-mediated protection of human intestinal epithelial cells against oxidative damage. J Physiol. 2010 Mar 15;588(Pt 6):995-1009.

[23] Kusche W, Paxinos R, Haselmann J, et al. Acetylsalicylic acid tablets with glycine improve long-term tolerability in antiplatelet drug therapy: results of a noninterventional trial. Adv Ther. 2003 Sep-Oct;20(5):237-45.

[24] Yang Y, Fan X, Ji Y, et al. Glycine represses endoplasmic reticulum stress-related apoptosis and improves intestinal barrier by activating mammalian target of rapamycin complex 1 signaling. Anim Nutr. 2022 Mar;8(1):1-9.

been shown to disrupt intestinal epithelial integrity, and glycine may directly mitigate this damage.[25,26] In an animal model, obesity-associated ER stress was linked to a decrease in the abundance of tight junction proteins, and glycine supplementation both improved the intestinal barrier as well as insulin resistance.[27] Indeed, low glycine levels appear to be a consequence of insulin resistance, as suggested by a meta-analysis of genome-wide association studies involving over 80,000 participants. This meta-analysis also suggests that lower glycine levels are associated with coronary heart disease, and that a causal relationship is plausible.[28]

Ginger (*Zingiber officinale*)

Scientific Evidence:

Ginger has many active constituents, including volatile oil, gingerol analogs, diarylheptanoids, phenylalkanoids, and sulfonates. Over 70 compounds have been identified in the volatile oil alone, including sesquiterpenoids and monoterpenes, primarily α-zingiberene and smaller amounts of β-sesquiphellandrene, β-bisabolene, β-phellandrene, and geraniol. The pungent and warm sensation of ginger is largely attributed to the gingerol analogs, including gingerols (predominantly 6-gingerol), shogaols, paradols, and zingerone.[29] Over 40 diarylheptanoids compounds have been discovered in ginger, many with antioxidant, anti-inflammatory, and hepatoprotective properties. Protective effects on the gastrointestinal, nervous, and cardiovascular systems, as well as the liver and kidney, have been shown for various components of ginger.[29]

Many of ginger's constituents have been shown to have anti-inflammatory effects; *in vitro* and animal studies have outlined several mechanisms of action for 6-gingerol, for example, including prevention of reactive oxygen species formation, upregulation of the Nrf2 pathway, inhibition of p38 MAPK activation, down-regulation of the NF-κB pathway, and protection against LPS-induced inflammation, all of which have been associated with protection of the intestinal mucosa and

[25] Chotikatum S, Naim HY, El-Najjar N. Inflammation induced ER stress affects absorptive intestinal epithelial cells function and integrity. Int Immunopharmacol. 2018 Feb;55:336-344.
[26] Chen J, Yang Y, Yang Y, et al. Dietary Supplementation with Glycine Enhances Intestinal Mucosal Integrity and Ameliorates Inflammation in C57BL/6J Mice with High-Fat Diet-Induced Obesity. J Nutr. 2021 Jul 1;151(7):1769-1778.
[27] Chen J, Yang Y, Yang Y, et al. Dietary Supplementation with Glycine Enhances Intestinal Mucosal Integrity and Ameliorates Inflammation in C57BL/6J Mice with High-Fat Diet-Induced Obesity. J Nutr. 2021 Jul 1;151(7):1769-1778.
[28] Wittemans LBL, Lotta LA, Oliver-Williams C, et al. Assessing the causal association of glycine with risk of cardio-metabolic diseases. Nat Commun. 2019 Mar 5;10(1):1060.
[29] Zhang M, Zhao R, Wang D, et al. Ginger (Zingiber officinale Rosc.) and its bioactive components are potential resources for health beneficial agents. Phytother Res. 2021 Feb;35(2):711-742.

maintenance of an intact barrier.[30,31,32,33] In an animal model of neuropathic pain, a gingerol-enriched ginger supplement was shown to improve intestinal permeability, demonstrated by an increase in the lactulose/mannitol ratio, most likely by reducing neuroinflammation in both the colon and amygdala.[34]

In vitro studies also suggest that ginger has favorable effects on the gut microbiome, promoting the growth of beneficial bacterial populations, such as *Bifidobacterium* and *Enterococcus*, as well as enhancing the production of short-chain fatty acids.[35] Animal models also indicate reductions at the genus level in *Escherichia, Shigella,* and *Bacteroides,* despite overall increases in bacterial diversity, as well as restoration of the tight junction protein zonula occludens-1 (ZO-1).[36] *In vivo*, ginger was shown to have anti-parasitic effects, demonstrating a significant reduction of the shedding of the cysts of *Blastocystis spp.* in an animal model, with a corresponding reduction in nitric oxide and malondialdehyde (comparable to nitazoxanide).[37] Several constituents of ginger, particularly [10]-gingerol, were previously shown to have larvicidal effects against the parasite *Angiostrongylus cantonensis*.[38] Additionally, ethanol extracts of ginger have been shown to inhibit the embryogenesis, infectivity, and viability of *Toxocara canis* eggs in animal studies, the parasitic roundworm spread by both dogs and cats for which 5% of the U.S. population has detectable antibodies against.[39,40]

Ginger also has anti-emetic effects likely to be mediated through several mechanisms, though 5-HT_3 receptor antagonism is perhaps the strongest candidate.[41] Interestingly, these receptors have recently been linked with inflammatory and metabolic disorders, providing another pathway for ginger's

---

[30] Li Y, Xu B, Xu M, et al. 6-Gingerol protects intestinal barrier from ischemia/reperfusion-induced damage via inhibition of p38 MAPK to NF-κB signalling. Pharmacol Res. 2017 May;119:137-148.
[31] Saha P, Katarkar A, Das B, et al. 6-Gingerol inhibits Vibrio cholerae-induced proinflammatory cytokines in intestinal epithelial cells via modulation of NF-κB. Pharm Biol. 2016 Sep;54(9):1606-15.
[32] Guo XX, Zhang YD, Wang TC, et al. Ginger and 6-gingerol prevent lipopolysaccharide-induced intestinal barrier damage and liver injury in mice. J Sci Food Agric. 2022 Feb;102(3):1066-1075.
[33] Hong MK, Hu LL, Zhang YX, et al. 6-Gingerol ameliorates sepsis-induced liver injury through the Nrf2 pathway. Int Immunopharmacol. 2020 Mar;80:106196.
[34] Shen CL, Wang R, Yakhnitsa V, et al. Gingerol-Enriched Ginger Supplementation Mitigates Neuropathic Pain via Mitigating Intestinal Permeability and Neuroinflammation: Gut-Brain Connection. Front Pharmacol. 2022 Jul 8;13:912609.
[35] Wang J, Chen Y, Hu X, et al. Assessing the Effects of Ginger Extract on Polyphenol Profiles and the Subsequent Impact on the Fecal Microbiota by Simulating Digestion and Fermentation In Vitro. Nutrients. 2020 Oct 19;12(10):3194.
[36] Ma ZJ , Wang HJ , Ma XJ , et al. Modulation of gut microbiota and intestinal barrier function during alleviation of antibiotic-associated diarrhea with Rhizoma Zingiber officinale (Ginger) extract. Food Funct. 2020 Dec 1;11(12):10839-10851.
[37] Abdel-Hafeez EH, Ahmad AK, Kamal AM, et al. In vivo antiprotozoan effects of garlic (Allium sativum) and ginger (Zingiber officinale) extracts on experimentally infected mice with Blastocystis spp. Parasitol Res. 2015 Sep;114(9):3439-44.
[38] Lin RJ, Chen CY, Chung LY, et al. Larvicidal activities of ginger (Zingiber officinale) against Angiostrongylus cantonensis. Acta Trop. 2010 Jul-Aug;115(1-2):69-76.
[39] El-Sayed NM. Efficacy of Zingiber officinale ethanol extract on the viability, embryogenesis and infectivity of Toxocara canis eggs. J Parasit Dis. 2017 Dec;41(4):1020-1027.
[40] https://www.cdc.gov/parasites/toxocariasis/gen_info/faqs.html. Accessed 4-5-2022.
[41] Walstab J, Krüger D, Stark T, et al. Ginger and its pungent constituents non-competitively inhibit activation of human recombinant and native 5-HT3 receptors of enteric neurons. Neurogastroenterol Motil. 2013 May;25(5):439-47, e302.

broad effects.[42] The antiemetic and antinausea activities of ginger have been demonstrated in numerous clinical trials, and assessed in several systematic reviews and meta-analyses, demonstrating efficacy during pregnancy, post-operatively, as well as for nausea/vomiting associated with chemotherapy.[43,44,45,46] Ginger has also been shown to enhance gastric emptying in healthy patients as well as those with functional dyspepsia.[47,48]

Ginger's anti-inflammatory actions may also underlie its benefit for other body systems. Among people with migraine, a meta-analysis of 3 randomized clinical trials found that in addition to a reduction in nausea and vomiting, ginger was also associated with a significant decrease in pain.[49] A systematic review of 16 randomized and controlled trials found a significant reduction in several biomarkers of inflammation, including CRP, hs-CRP, and TNF-α with ginger supplementation.[50] In addition to a hypotensive effect, an increase in nitric oxide synthesis expression, and an inhibition of platelet aggregation, this anti-inflammatory effect provides a plausible explanation for enhanced cardiovascular health attributed to ginger consumption.[51,52] Ginger has also been associated with hypoglycemic effects, and an improvement in the metabolic profile of people with diabetes. In a systematic review of randomized and controlled trials, ginger supplementation was associated with reductions in fasting blood glucose levels as well as HbA1c, along with both systolic and diastolic blood pressure.[53]

Chamomile (*Matricaria recutita*)

Scientific Evidence:

---

[42] Irving H, Turek I, Kettle C, et al. Tapping into 5-HT3 Receptors to Modify Metabolic and Immune Responses. Int J Mol Sci. 2021 Nov 2;22(21):11910.

[43] Viljoen E, Visser J, Koen N, et al. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J. 2014 Mar 19;13:20.

[44] Thomson M, Corbin R, Leung L. Effects of ginger for nausea and vomiting in early pregnancy: a meta-analysis. J Am Board Fam Med. 2014 Jan-Feb;27(1):115-22.

[45] Zhu W, Dai Y, Huang M, et al. Efficacy of Ginger in Preventing Postoperative Nausea and Vomiting: A Systematic Review and Meta-Analysis. J Nurs Scholarsh. 2021 Nov;53(6):671-679.

[46] Chang WP, Peng YX. Does the Oral Administration of Ginger Reduce Chemotherapy-Induced Nausea and Vomiting?: A Meta-analysis of 10 Randomized Controlled Trials. Cancer Nurs. 2019 Nov/Dec;42(6):E14-E23.

[47] Wu KL, Rayner CK, Chuah SK, et al. Effects of ginger on gastric emptying and motility in healthy humans. Eur J Gastroenterol Hepatol. 2008 May;20(5):436-40.

[48] Hu ML, Rayner CK, Wu KL, et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. World J Gastroenterol. 2011 Jan 7;17(1):105-10.

[49] Chen L, Cai Z. The efficacy of ginger for the treatment of migraine: A meta-analysis of randomized controlled studies. Am J Emerg Med. 2021 Aug;46:567-571.

[50] Morvaridzadeh M, Fazelian S, Agah S, et al. Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Cytokine. 2020 Nov;135:155224.

[51] Li C, Li J, Jiang F, et al. Vasculoprotective effects of ginger (Zingiber officinale Roscoe) and underlying molecular mechanisms. Food Funct. 2021 Mar 15;12(5):1897-1913.

[52] Fakhri S, Patra JK, Das SK, et al. Ginger and Heart Health: From Mechanisms to Therapeutics. Curr Mol Pharmacol. 2021;14(6):943-959.

[53] Ebrahimzadeh A, Ebrahimzadeh A, Mirghazanfari SM, et al. The effect of ginger supplementation on metabolic profiles in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2022 Jan 11:102802.

Chamomile (*Matricaria recutita*) is a popular herbal remedy that has been in use for centuries, primarily for its antimicrobial, antioxidant, anti-diarrheal, hepatoprotective, spasmolytic, and anti-inflammatory properties.[54] It contains a high content of organic acids, flavanols, flavones, terpenoids, and other phenolic compounds, including quercetin, luteolin, chlorogenic acid, rutin, naringenin, and apigenin.[55,56,57]

Many of the benefits of Chamomile have been attributed to the antioxidant effect of its phenolic compounds. Chamomile extracts have been found to protect against alcohol-induced oxidative damage, providing hepatoprotection as well as inhibiting reactive oxygen species generation in animal studies.[58,59] Protection of the gastric mucosa from ethanol toxicity as well as prevention of damage to the small intestine following aspirin exposure have both been documented in animal studies, most likely via upregulation of antioxidant enzyme activity.[60,61] Chamomile has also demonstrated anthelmintic activity both *in vitro* and *in vivo* in animal models.[62] Additionally, its anti-diarrheal activity appears to be mediated both by antioxidant activity and activation of potassium channels.[63,64]

Animal studies have also demonstrated a protective effect against a high-fat diet, including the mitigation of neuroinflammation and other neurobehavioral changes.[65] High-fat diets have also been used to induce obesity and lipotoxicity in animal studies, both conditions which were substantially reduced with the use of chamomile extracts, as well as the prevention of renal and hepatic oxidative

---

[54] Hajaji S, Jabri MA, Alimi D, et al. Chamomile Methanolic Extract Mitigates Small Bowel Inflammation and ROS Overload Related to the Intestinal Nematodes Infection in Mice. Acta Parasitol. 2019 Mar;64(1):152-161.

[55] Guimarães R, Barros L, Dueñas M, et al. Infusion and decoction of wild German chamomile: bioactivity and characterization of organic acids and phenolic compounds. Food Chem. 2013 Jan 15;136(2):947-54.

[56] Nováková L, Vildová A, Mateus JP, et al. Development and application of UHPLC-MS/MS method for the determination of phenolic compounds in Chamomile flowers and Chamomile tea extracts. Talanta. 2010 Sep 15;82(4):1271-80.

[57] Qureshi MN, Stecher G, Bonn GK. Determination of total polyphenolic compounds and flavonoids in Matricaria chamomella flowers. Pak J Pharm Sci. 2019 Sep;32(5):2163-2165.

[58] Jabri MA, Sani M, Rtibi K, et al. Chamomile decoction extract inhibits human neutrophils ROS production and attenuates alcohol-induced haematological parameters changes and erythrocytes oxidative stress in rat. Lipids Health Dis. 2016 Mar 31;15:65.

[59] Sebai H, Jabri MA, Souli A, et al. Chemical composition, antioxidant properties and hepatoprotective effects of chamomile (Matricaria recutita L.) decoction extract against alcohol-induced oxidative stress in rat. Gen Physiol Biophys. 2015 Jul;34(3):263-75.

[60] Jabri MA, Aissani N, Tounsi H, et al. Protective effect of chamomile (Matricaria recutita L.) decoction extract against alcohol-induced injury in rat gastric mucosa. Pathophysiology. 2017 Mar;24(1):1-8.

[61] Jabri MA, Hajji, N, Wannes, D, et al. HPLC/PDA/ESI-MS/MS analysis of chamomile decoction and mechanism of its protective effects on aspirin-induced small bowel injuries. RSC Adv., 2017,7: 53472-53480

[62] Hajaji S, Jabri MA, Alimi D, et al. Chamomile Methanolic Extract Mitigates Small Bowel Inflammation and ROS Overload Related to the Intestinal Nematodes Infection in Mice. Acta Parasitol. 2019 Mar;64(1):152-161.

[63] Sebai H, Jabri MA, Souli Aet al. Antidiarrheal and antioxidant activities of chamomile (Matricaria recutita L.) decoction extract in rats. J Ethnopharmacol. 2014 Mar 14;152(2):327-32.

[64] Mehmood MH, Munir S, Khalid UA, et al. Antidiarrhoeal, antisecretory and antispasmodic activities of Matricaria chamomilla are mediated predominantly through K(+)-channels activation. BMC Complement Altern Med. 2015 Mar 24;15:75.

[65] Jabri MA, Rtibi K, Sebai H. Chamomile decoction mitigates high fat diet-induced anxiety-like behavior, neuroinflammation and cerebral ROS overload. Nutr Neurosci. 2022 Jul;25(7):1350-1361.

stress, along with depletion of glutathione and other antioxidant enzymes.[66] In a single-blind clinical trial in humans with type 2 diabetes, an increase in several antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and catalase) was observed following chamomile tea consumption, as well as improvements associated with glycemic control, compared to placebo.[67] Apigenin alone has been shown to improve lipid metabolism *in vitro*, and both apigenin and a chamomile extract were found to blunt the intestinal absorption of glucose.[68,69] Additionally, chamomile extract has also been found to activate peroxisome proliferator-activated receptor gamma (PPARγ) *in vitro*, which could potentially improve glycemic control, an effect observed in multiple animal and *in vitro* studies, as well as small clinical trials in participants with type 2 diabetes.[70,71,72,73]

Lemon balm (*Melissa officinalis*)

Scientific Evidence:

Lemon balm (*Melissa officinalis*) has been extensively used in traditional medicine for at least two thousand years, largely as a sedative and anxiolytic, but is also recognized to have hepatoprotective, anti-inflammatory, antioxidant, and antispasmodic properties.[74,75] It has a wide range of active chemical constituents present in both the leaves and essential oil, including terpenes and polyphenolic compounds. The leaves specifically contain monoterpenes, sesquiterpenes, triterpenes (ursolic and

[66] Jabri MA, Sakly M, Marzouki L, et al. Chamomile (Matricaria recutita L.) decoction extract inhibits in vitro intestinal glucose absorption and attenuates high fat diet-induced lipotoxicity and oxidative stress. Biomed Pharmacother. 2017 Mar;87:153-159.
[67] Zemestani M, Rafraf M, Asghari-Jafarabadi M. Chamomile tea improves glycemic indices and antioxidants status in patients with type 2 diabetes mellitus. Nutrition. 2016 Jan;32(1):66-72.
[68] Lu J, Meng Z, Cheng B, et al. Apigenin reduces the excessive accumulation of lipids induced by palmitic acid via the AMPK signaling pathway in HepG2 cells. Exp Ther Med. 2019 Oct;18(4):2965-2971.
[69] Villa-Rodriguez JA , Kerimi A , Tumova S , et al. Inhibition of intestinal glucose transport by polyphenols: a mechanism for indirect attenuation of cholesterol absorption? Food Funct. 2019 Jun 19;10(6):3127-3134.
[70] Weidner C, Wowro SJ, Rousseau M, et al. Antidiabetic effects of chamomile flowers extract in obese mice through transcriptional stimulation of nutrient sensors of the peroxisome proliferator-activated receptor (PPAR) family. PLoS One. 2013 Nov 12;8(11):e80335.
[71] Bayliak MM, Dmytriv TR, Melnychuk AV, et al. Chamomile as a potential remedy for obesity and metabolic syndrome. EXCLI J. 2021 Jul 26;20:1261-1286.
[72] Villa-Rodriguez JA, Kerimi A, Abranko L, et al. Acute metabolic actions of the major polyphenols in chamomile: an in vitro mechanistic study on their potential to attenuate postprandial hyperglycaemia. Sci Rep. 2018 Apr 3;8(1):5471.
[73] Rafraf M, Zemestani M, Asghari-Jafarabadi M. Effectiveness of chamomile tea on glycemic control and serum lipid profile in patients with type 2 diabetes. J Endocrinol Invest. 2015 Feb;38(2):163-70.
[74] Moacă EA, Farcaş C, Ghiţu A, et al. A Comparative Study of Melissa officinalis Leaves and Stems Ethanolic Extracts in terms of Antioxidant, Cytotoxic, and Antiproliferative Potential. Evid Based Complement Alternat Med. 2018 May 16;2018:7860456.
[75] Miraj S., Azizi N., Kiani S. A review of chemical components and pharmacological effects of Melissa officinalis L. 2016;8(6):229–237.

oleanolic acids), and phenolic compounds such as rosmarinic acid, caffeic acid, protocatechuic acid, flavonoids (quercetin, rhamnocitrin, apigenin, and luteolin) as well as tannins.[76,77]

Lemon balm extracts have been shown to scavenge a wide range of free radicals both *in vitro* and *in vivo*, reduce lipid peroxidation and increase levels of reduced glutathione in animal models.[78] The antioxidant effects of Lemon balm have also been shown to have a gastroprotective effect in an animal model. An extract of Lemon balm was found to prevent the formation of gastric ulcers in response to several irritants, including indomethacin, with increases in superoxide dismutase and glutathione peroxidase activity underlying this protective effect. Lemon balm has been used traditionally for relief from mild gastrointestinal (GI) symptoms, such as flatulence, bloating, and minor GI spasms. A spasmolytic effect in the jejunum and ileum has been shown in an *ex vivo* animal model, attributed primarily to rosmarinic acid, which may explain the benefits observed with traditional use.[79] An anti-nociceptive effect has previously been shown for an extract from the leaves of Lemon balm, also attributed to rosmarinic acid.[80]

Additionally, animal models indicate rosmarinic acid may favorably modify the microbiome, as it has been shown to increase the proportion of diabetes-resistant bacteria, and that it has anti-inflammatory activity both *in vitro* and *in vivo*.[81,82] *In vitro* data suggests that Lemon balm extracts have both antimicrobial and anti-fungal activity, inhibiting the growth of *Aspergillus carbonarius* and several Gram-positive bacteria, including *Staphylococcus aureus*.[83] Both rosmarinic acid and Lemon balm extract have demonstrated antiviral activity against HSV-1 *in vitro*, with greater activity for the extract than rosmarinic acid alone, suggesting other constituents contribute to this effect.[84] Lemon balm has also been shown to have favorable cardiometabolic effects, reducing both systolic and diastolic blood pressure as well as triglyceride levels in several human clinical trials, with rosmarinic acid and several

---

[76] Draginic N, Jakovljevic V, Andjic M, et al. Melissa officinalis L. as a Nutritional Strategy for Cardioprotection. Front Physiol. 2021 Apr 22;12:661778.

[77] Ibragic S., Salihovic M., Tahirovic I., et al. Quantification of some phenolic acids in the leaves of Melissa officinalis L. from Turkey and Bosnia. Bull. Chem. Tech. 2014. Bosnia Herzegovina 42 47–50.

[78] Draginic N, Andjic M, Jeremic J, et al. Anti-inflammatory and Antioxidant Effects of Melissa officinalis Extracts: A Comparative Study. Iran J Pharm Res. 2022 May 5;21(1):e126561.

[79] Aubert P, Guinobert I, Blondeau C, et al. Basal and Spasmolytic Effects of a Hydroethanolic Leaf Extract of Melissa officinalis L. on Intestinal Motility: An Ex Vivo Study. J Med Food. 2019 Jul;22(7):653-662.

[80] Guginski G, Luiz AP, Silva MD, et al. Mechanisms involved in the antinociception caused by ethanolic extract obtained from the leaves of Melissa officinalis (lemon balm) in mice. Pharmacol Biochem Behav. 2009 Jul;93(1):10-6.

[81] Ou J , Huang J , Zhao D , et al. Protective effect of rosmarinic acid and carnosic acid against streptozotocin-induced oxidation, glycation, inflammation and microbiota imbalance in diabetic rats. Food Funct. 2018 Feb 21;9(2):851-860.

[82] Luo C, Zou L, Sun H, et al. A Review of the Anti-Inflammatory Effects of Rosmarinic Acid on Inflammatory Diseases. Front Pharmacol. 2020 Feb 28;11:153.

[83] Abdellatif F, Begaa S, Messaoudi M, et al. HPLC-DAD Analysis, Antimicrobial and Antioxidant Properties of Aromatic Herb Melissa officinalis L., Aerial Parts Extracts. Food Anal Methods. 2022 Aug 23:1-10.

[84] Astani A, Reichling J, Schnitzler P. Melissa officinalis extract inhibits attachment of herpes simplex virus in vitro. Chemotherapy. 2012;58(1):70-7.

other compounds in Lemon balm shown to have cardioprotective properties, mediated in part through anti-inflammatory and antioxidant activity as well as an increase in nitric oxide production.[76,85,86,87]

DGL (as GutGard®)

Scientific Evidence:

Deglycyrrhizinated licorice (DGL) is derived from the roots of licorice (*Glycyrrhiza glabra*), a medicinal plant with a long history of use for its expectorant, diuretic, laxative, sedative, antipyretic, antimicrobial and anxiolytic properties. DGL (GutGard®) contains very little of the triterpenoid glycyrrhizin (<0.5% by weight (w/w)) which normally comprises up to 25% of licorice by weight. Because a metabolite of glycyrrhizin, glycyrrhetinic acid, may inhibit the activity of the enzyme 11-ß-HSD2 and effectively increase cortisol levels, regular high-dose consumption of licorice has the potential to induce mineralocorticoid overload.[88] To avoid this effect, DGL (GutGard®) contains very little glycyrrhizin, yet it is a rich source of other compounds with anti-inflammatory and gastroprotective properties, providing glabridin (≥3.5% w/w), glabrol (≥0.5% w/w), eicosanyl caffeate (≥0.1% w/w), docosyl caffeate (≥0.1% w/w), standardized to at least 10% total flavonoids by weight.

Most notable is the anti-ulcer effect of both licorice and DGL, which appears to be mediated via several mechanisms. In an animal model, DGL (GutGard®) was shown to protect against ulcer formation from several causative agents, including indomethacin. In this model, DGL (GutGard®) was shown to have potent antioxidant activity and to reduce gastric acidity in a dose-dependent fashion.[89] DGL has also been shown to protect against gastric mucosal damage by aspirin.[90] In humans, DGL (GutGard®) has also been shown to exhibit antimicrobial activity against *H. pylori*, the leading cause of peptic ulcers. In a randomized double-blind and placebo-controlled trial, after two months of treatment, 56% of participants receiving DGL (GutGard®) had a negative test for *H. pylori* vs. 4% in the placebo group.[91]

Multiple flavonoids have been shown to have anti-*H. pylori* activity via several mechanisms, including inhibiting urease activity, inhibiting the synthesis of the proinflammatory cytokine interleukin-8

---

[85] Nayebi N, Esteghamati A, Meysamie A, et al. The effects of a Melissa officinalis L. based product on metabolic parameters in patients with type 2 diabetes mellitus: A randomized double-blinded controlled clinical trial. J Complement Integr Med. 2019 Jan 25;16(3):/j/jcim.2019.16.issue-3/jcim-2018-0088/jcim-2018-0088.xml.

[86] Shekarriz Z, Shorofi SA, Nabati M, et al. Effect of Melissa officinalis on systolic and diastolic blood pressures in essential hypertension: A double-blind crossover clinical trial. Phytother Res. 2021 Dec;35(12):6883-6892.

[87] Karthik D, Viswanathan P, Anuradha CV. Administration of rosmarinic acid reduces cardiopathology and blood pressure through inhibition of p22phox NADPH oxidase in fructose-fed hypertensive rats. J Cardiovasc Pharmacol. 2011 Nov;58(5):514-21.

[88] Yoshino T, Shimada S, Homma M, et al. Clinical Risk Factors of Licorice-Induced Pseudoaldosteronism Based on Glycyrrhizin-Metabolite Concentrations: A Narrative Review. Front Nutr. 2021 Sep 17;8:719197.

[89] Mukherjee M, Bhaskaran N, Srinath Ret al. Anti-ulcer and antioxidant activity of GutGard. Indian J Exp Biol. 2010 Mar;48(3):269-74.

[90] Rees WD, Rhodes J, Wright JE, et al. Effect of deglycyrrhizinated liquorice on gastric mucosal damage by aspirin. Scand J Gastroenterol. 1979;14(5):605-7.

[91] Puram S, Suh HC, Kim SU, et al. Effect of GutGard in the Management of Helicobacter pylori: A Randomized Double Blind Placebo Controlled Study. Evid Based Complement Alternat Med. 2013;2013:263805.

(IL-8), and inhibiting DNA gyrase and ATPase enzymes.[92] DGL (GutGard®) specifically has been shown *in vitro* to inhibit protein synthesis, and the enzymes DNA gyrase and dihydrofolate reductase (DHFR), needed for bacterial DNA synthesis. Glabridin (the most abundant flavonoid in GutGard®) was found to have a potent antimicrobial effect against *H. pylori in vitro*, with little effect observed with glycyrrhizin.[93] Similarly, *in vitro* glycyrrhizin was found to have no effect on lipopolysaccharide (LPS) induced pro-inflammatory mediators, while glabridin and isoliquiritigenin inhibited several of these mediators, including IL-1 and nitric oxide.[94] In a previous trial, glabridin and isoliquiritigenin exhibited anti-inflammatory action 99on several LPS mediators, including thromboxanes and prostaglandins, while again, glycyrrhizin had no effect, suggesting the anti-inflammatory and anti-*H.pylori* effects of DGL are not related to the activity of glycyrrhizin.[95]

DGL (GutGard®) has also been evaluated for use in people with functional dyspepsia (per Rome III criteria), also referred to as non-ulcer dyspepsia, with symptoms including upper abdominal fullness, epigastric pain, belching, bloating, early satiety, nausea, vomiting, regurgitation, heartburn, and loss of appetite. In a randomized double-blind and placebo-controlled trial, a significant decrease in total symptom scores was observed with DGL (GutGard®) vs. placebo. For example, 56% of those receiving DGL had a marked improvement in symptoms, while no patients receiving a placebo reported similar improvements.[96] *In vitro*, DGL (GutGard®) has been shown to be compatible with probiotic organisms, lacking antimicrobial activity against several species, including *L. casei*, *L. fermentum*, *L. plantarum*, and S*. thermophilus.* Similarly, the same *in vitro* analysis found no inhibitory effect on most digestive enzymes, with the exception of lipase for which it had a mild effect. In comparison, orlistat had a 52-fold greater inhibition of lipase, suggesting DGL is unlikely to have appreciable effects on lipase activity.[97]

Quercetin

Scientific Evidence:

Quercetin is a flavanol that belongs to a group of polyphenolic substances known as flavonoids or bioflavonoids. It can be found in a wide variety of fruits and vegetables such as apples, berries, beans,

---

[92] Ivyna de Araújo Rêgo R, Guedes Silvestre GF, Ferreira de Melo D, et al. Flavonoids-Rich Plant Extracts Against Helicobacter pylori Infection as Prevention to Gastric Cancer. Front Pharmacol. 2022 Aug 31;13:951125.
[93] Asha MK, Debraj D, Prashanth D, et al. In vitro anti-Helicobacter pylori activity of a flavonoid rich extract of Glycyrrhiza glabra and its probable mechanisms of action. J Ethnopharmacol. 2013 Jan 30;145(2):581-6.
[94] Thiyagarajan P, Chandrasekaran CV, Deepak HB, et al. Modulation of lipopolysaccharide-induced pro-inflammatory mediators by an extract of Glycyrrhiza glabra and its phytoconstituents. Inflammopharmacology. 2011 Aug;19(4):235-41.
[95] Chandrasekaran CV, Deepak HB, Thiyagarajan P, et al. Dual inhibitory effect of Glycyrrhiza glabra (GutGard™) on COX and LOX products. Phytomedicine. 2011 Feb 15;18(4):278-84.
[96] Raveendra KR, Jayachandra, Srinivasa V, et al. An Extract of Glycyrrhiza glabra (GutGard) Alleviates Symptoms of Functional Dyspepsia: A Randomized, Double-Blind, Placebo-Controlled Study. Evid Based Complement Alternat Med. 2012;2012:216970.
[97] Asha MK, Debraj D, Dethe S, et al. Effect of Flavonoid-Rich Extract of Glycyrrhiza glabra on Gut-Friendly Microorganisms, Commercial Probiotic Preparations, and Digestive Enzymes. J Diet Suppl. 2017 May 4;14(3):323-333.

broccoli and grapes, onions and tomatoes. Quercetin is also naturally present in black tea, green tea, and red wine as well as in many seeds and nuts, flowers, bark, and leaves.[98]

Quercetin has several gastrointestinal-related beneficial actions, including antioxidant, anti-inflammatory, anticarcinogenic, antiviral, hepatoprotective, and gastroprotective activities.[99,100] Based on *in vivo* and *in vitro* research, quercetin has the ability to prevent oxidant injury and cell death by scavenging oxygen radicals, protecting against lipid peroxidation, and chelating metal ions.[101] The anti-inflammatory activity of quercetin is attributable to its antioxidant activity, including enhancing the expression of antioxidant enzymes (i.e. catalase, superoxide dismutase, and glutathione peroxidase), as well as its inhibitory effects on proinflammatory enzymes (specifically cyclooxygenase and lipoxygenase).[102] It is also involved in the inhibition of inflammatory mediators (leukotrienes and prostaglandins) and helps block histamine release by mast cells and basophils, possibly by binding to the TRPV1 channel.[103,104] Quercetin also has demonstrated antimicrobial effects via multiple mechanisms, including the destruction of the bacterial cell envelope, prevention of bacterial adhesion, inhibition of bacterial nucleic acid synthesis, and inhibition of biofilm formation.[105]

In vitro research has shown quercetin to enhance barrier function in human intestinal Caco-2 cells. The underlying mechanism is thought to be related to the ability of quercetin to promote the assembly of several tight junction proteins such as claudin-1, occludin and zonula occludens-2, and the expression of claudin-4 via the inhibition of protein kinase isoform.[106] Additionally, quercetin is thought to be highly metabolized by gut microbiota, with many active metabolites influencing gastrointestinal and hepatic function. For example, dihydroxyphenylacetic acid, a metabolite of quercetin, has been shown to upregulate transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), preventing acetaminophen-associated liver injury in an animal model.[107] Quercetin itself has also been shown to protect against indomethacin-induced oxidative stress and inflammation of gastric and ileal mucosa *in*

---

[98] Anand David AV, Arulmoli R, Parasuraman S. Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid. Pharmacogn Rev. 2016 Jul-Dec;10(20):84-89.

[99] Batiha GE, Beshbishy AM, Ikram M, et al. The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin. Foods. 2020 Mar 23;9(3):374.

[100] Ulusoy HG, Sanlier N. A minireview of quercetin: from its metabolism to possible mechanisms of its biological activities. Crit Rev Food Sci Nutr. 2020;60(19):3290-3303.

[101] Xu D, Hu MJ, Wang YQ, et al. Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. Molecules. 2019 Mar 21;24(6):1123.

[102] Chen B.H., Park J.H., Ahn J.H., et al. Pretreated quercetin protects gerbil hippocampal CA1 pyramidal neurons from transient cerebral ischemic injury by increasing the expression of antioxidant enzymes. Neural Regen. Res. 2017;12:220–227.

[103] Weng Z, Zhang B, Asadi S, et al. Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. PLoS One. 2012;7(3):e33805.

[104] Yang CC, Hung YL, Li HJ, et al. Quercetin inhibits histamine-induced calcium influx in human keratinocyte via histamine H4 receptors. Int Immunopharmacol. 2021 Jul;96:107620.

[105] Wang Y, Tao B, Wan Y, et al. Drug delivery based pharmacological enhancement and current insights of quercetin with therapeutic potential against oral diseases. Biomed Pharmacother. 2020 Aug;128:110372

[106] Suzuki T, Hara H. Quercetin enhances intestinal barrier function through the assembly of zonula [corrected] occludens-2, occludin, and claudin-1 and the expression of claudin-4 in Caco-2 cells. J Nutr. 2009 May;139(5):965-74.

[107] Xue H, Xie W, Jiang Z, et al. 3,4-Dihydroxyphenylacetic acid, a microbiota-derived metabolite of quercetin, attenuates acetaminophen (APAP)-induced liver injury through activation of Nrf-2. Xenobiotica. 2016 Oct;46(10):931-9.

vitro, mediated via upregulation of Nrf2 and inhibition of NF-kB activation (without interfering with the inhibition of prostaglandin synthesis by indomethacin).[108] Animal models also indicate that quercetin improves the diversity of the microbiota following antibiotic treatment, and helps to restore intestinal barrier function, marked by greater mucosal thickness and intestinal villi length.[109]

Research has shown that up to 100 µmol/L luminal quercetin concentration is associated with enhanced intestinal barrier function, which can be achieved by a daily oral intake of as little as 100 mg of quercetin.[106] Supplementation with 50, 100, or 150 mg per day of quercetin has also been found to increase plasma quercetin concentrations by 178% (median change: 92.2 nmol/L), 359% (median change: 171.8 nmol/L), and 570% (median change: 316.2 nmol/L) respectively.[110]

Aloe Vera Gel (*Aloe barbadensis*)

Scientific Evidence:

Aloe vera has traditionally been used internally as a general tonic, recognized to have many properties related to gastrointestinal health, including anti-inflammatory, antioxidant, carminative, laxative, antiulcer, and antimicrobial actions.[111] The key phytochemical compounds of aloe gel include anthraquinones (aloin and emodin), enzymes (catalase, amylase), fatty acids (lupeol and campesterol), polysaccharides (glucomannans) and glycoproteins.[112] Aloe resin, the solid residue obtained from the latex, consists of mainly hydroxyanthracene derivatives.[113] The aloe inner parenchyma, known as the fillet or leaf, also contains 4 tocopherol isoforms (primarily a, but also d, b, and g), as well as mannans, and a diverse variety of polyphenols, antioxidants, and antimicrobial compounds.[114]

Aloe vera has been reported to improve parameters of gastrointestinal function including colonic bacterial activity, gastrointestinal pH, stool specific gravity, and gastrointestinal motility.[115] Animal models have shown that aloe polysaccharides improve intestinal permeability, as assessed by the lactulose/mannitol ratio, via an upregulation of the tight junction protein zonula occludens (ZO)-1.[116] Animal studies also suggest that glucomannan from aloe vera increases intestinal epithelial cell

---

[108] Carrasco-Pozo C, Castillo RL, Beltrán C, et al. Molecular mechanisms of gastrointestinal protection by quercetin against indomethacin-induced damage: role of NF-κB and Nrf2. J Nutr Biochem. 2016 Jan;27:289-98.
[109] Shi T, Bian X, Yao Z, et al. Quercetin improves gut dysbiosis in antibiotic-treated mice. Food Funct. 2020 Sep 23;11(9):8003-8013.
[110] Egert S, Wolffram S, Bosy-Westphal A, et al. Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J Nutr. 2008 Sep;138(9):1615-21.
[111] Kumar R, Singh AK, Gupta A, et al. Therapeutic potential of Aloe vera-A miracle gift of nature. Phytomedicine. 2019 Jul;60:152996.
[112] Sánchez M, González-Burgos E, Iglesias I, et al. Pharmacological Update Properties of Aloe Vera and its Major Active Constituents. Molecules. 2020 Mar 13;25(6):1324.
[113] Fisher C. Materia Medica of Western Herbs. Nelson, New Zealand: Vitex Medica; 2009.
[114] Añibarro-Ortega M, Pinela J, Barros L, et al. Compositional Features and Bioactive Properties of Aloe vera Leaf (Fillet, Mucilage, and Rind) and Flower. Antioxidants (Basel). 2019 Oct 1;8(10):444.
[115] Braun L, Cohen M. Herbs and Natural Supplements an Evidenced Based Guide. Vol 2. 4th ed. Chatswood, NSW: Elsevier Australia; 2015
[116] Le Phan TH, Park SY, Jung HJ, et al. The Role of Processed Aloe vera Gel in Intestinal Tight Junction: An In Vivo and In Vitro Study. Int J Mol Sci. 2021 Jun 17;22(12):6515.

regeneration via upregulation of the Wnt/β-catenin signaling pathway.[117] Additionally, barbaloin (one of two isomers that comprise aloin, sometimes referred to as aloin A) has been shown to prevent ulcerative colitis in several animal models through multiple mechanisms; it was found to up-regulate the expression of tight junction proteins and inhibit the Notch signaling pathway, thereby promoting the secretion of *Muc2*, decreasing colonic permeability, and increasing mucus production.[118] Barbaloin was also shown to activate the AMPK signaling pathway, promoting intestinal barrier function and the production of anti-inflammatory factors in a model of ulcerative colitis.[119]

Several clinical trials have reported the beneficial effects of aloe vera administration. Aloe gel has been shown to reduce histological disease activity in patients with ulcerative colitis.[120,121] Supplementation with *Aloe barbadensis* extract (AVH200®) has demonstrated improvement in pain severity, pain frequency and bloating in adult patients with irritable bowel syndrome (IBS).[122] Similarly, two randomized and double-blinded trials found that an aloe inner leaf extract improved symptoms of IBS-D specifically, with significant improvements in abdominal pain severity and frequency.[123] Analysis of multiple randomized trials also indicates that aloe may help to improve both glycemic and lipid control, particularly among participants with metabolic abnormalities.[124] Although the mechanisms are unclear, aloe inner leaf gel has been shown to significantly improve the bioavailability of both vitamin C and vitamin B_{12} in healthy human volunteers when given simultaneously.[125]

Oral administration of aloe vera gel has also been found to reduce the growth of *Candida albicans* in the spleen and kidney (animal research), with *in vitro* data suggesting similar efficacy to standard anti-fungal treatments.[126,127] *In vitro* experiments also show that aloe possesses antimicrobial

---

[117] Zhang D, Zhou X, Liu L, et al. Glucomannan from Aloe vera Gel Promotes Intestinal Stem Cell-Mediated Epithelial Regeneration via the Wnt/β-Catenin Pathway. J Agric Food Chem. 2021 Sep 15;69(36):10581-10591.
[118] Jiang H, Shi GF, Fang YX, et al. Aloin A prevents ulcerative colitis in mice by enhancing the intestinal barrier function via suppressing the Notch signaling pathway. Phytomedicine. 2022 Nov;106:154403
[119] Gai L, Chu L, Xia R, et al. Barbaloin Attenuates Mucosal Damage in Experimental Models of Rat Colitis by Regulating Inflammation and the AMPK Signaling Pathway. Med Sci Monit. 2019 Dec 27;25:10045-10056.
[120] Langmead L, Feakins RM, Goldthorpe S, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. Aliment Pharmacol Ther. 2004 Apr 1;19(7):739-47.
[121] Foster M, Hunter D, Samman S. Evaluation of the Nutritional and Metabolic Effects of Aloe vera. In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. Chapter 3.
[122] Størsrud S, Pontén I, Simrén M. A Pilot Study of the Effect of Aloe barbadensis Mill. Extract (AVH200®) in Patients with Irritable Bowel Syndrome: a Randomized, Double-Blind, Placebo-Controlled Study. J Gastrointestin Liver Dis. 2015 Sep;24(3):275-80.
[123] Ahluwalia B, Magnusson MK, Böhn L, et al. Aloe barbadensis Mill. extract improves symptoms in IBS patients with diarrhoea: post hoc analysis of two randomized double-blind controlled studies. Therap Adv Gastroenterol. 2021 Oct 8;14:17562848211048133.
[124] Zhang Y, Liu W, Liu D, et al. Efficacy of Aloe Vera Supplementation on Prediabetes and Early Non-Treated Diabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016 Jun 23;8(7):388.
[125] Yun JM, Singh S, Jialal R, et al. A randomized placebo-controlled crossover trial of aloe vera on bioavailability of vitamins C and B(12), blood glucose, and lipid profile in healthy human subjects. J Diet Suppl. 2010 Jun;7(2):145-53.
[126] Im SA, Lee YR, Lee YH, et al. In vivo evidence of the immunomodulatory activity of orally administered Aloe vera gel. Arch Pharm Res. 2010 Mar;33(3):451-6.
[127] Nabila VK, Putra IB. The effect of Aloe vera ethanol extract on the growth inhibition of Candida albicans. Med Glas (Zenica). 2020 Aug 1;17(2):485-489.

activity against a number of pathogens including *Helicobacter pylori*, *Pseudomonas aeruginosa, Streptococcus pyogenes, Staphylococcus aureus* (methicillin-resistant strains)*, Escherichia coli, Shigella flexneri, Enterobacter cloacae* and *Enterococcus bovis*, and to inhibit *Staphylococcus aureus* (methicillin-resistant) biofilm formation, with components of aloe blocking the initial adhesion and proliferation of biofilms.[128,129,130]

Zinc Carnosine

Scientific Evidence:

Zinc is an essential mineral needed for multiple biological processes, including DNA and protein synthesis, and is estimated to be needed by 10% of all human proteins, providing a structural, catalytic, and signaling component.[131] It is needed by many enzymes involved in cell repair, especially in epithelial and epidermal cells, including epithelial cells lining the intestine.[132] L-carnosine is a dipeptide composed of beta-alanine and L-histidine, found in skeletal and cardiac muscle as well as neurons, associated with potent antioxidant activity and wound healing effects.[133]

Zinc carnosine (ZnC) is a chelate of zinc and L-carnosine in a 1:1 complex, which has been widely used as a mucoprotective agent and to promote ulcer healing for at least 2 decades.[134,135] Although zinc and carnosine are thought to dissociate during intestinal absorption, carnosine enhances the absorption of zinc, and may also deliver zinc to tissues in an extended-release manner, amplifying the benefit of either component used alone.[132,136] ZnC has demonstrated consistent benefits in the prevention and treatment of ulcers in many animal models as well as human trials, with multiple established mechanisms of action.[135] In an animal model, it has been shown to increase the expression of heat shock proteins associated with protection from several insults to the gastric mucosa, including

---

[128] Saddiq AA, Al-Ghamdi H. Aloe vera extract: A novel antimicrobial and antibiofilm against methicillin resistant Staphylococcus aureus strains. Pak J Pharm Sci. 2018 Sep;31(5(Supplementary)):2123-2130.
[129] Xiang H, Cao F, Ming D, et al. Aloe-emodin inhibits Staphylococcus aureus biofilms and extracellular protein production at the initial adhesion stage of biofilm development. Appl Microbiol Biotechnol. 2017 Sep;101(17):6671-6681.
[130] Cataldi V, Di Bartolomeo S, Di Campli E, et al. In vitro activity of Aloe vera inner gel against microorganisms grown in planktonic and sessile phases. Int J Immunopathol Pharmacol. 2015 Dec;28(4):595-602.
[131] Andreini C, Banci L, Bertini I, et al. Counting the zinc-proteins encoded in the human genome. J Proteome Res. 2006 Jan;5(1):196-201.
[132] Hewlings S, Kalman D. A Review of Zinc-L-Carnosine and Its Positive Effects on Oral Mucositis, Taste Disorders, and Gastrointestinal Disorders. Nutrients. 2020 Feb 29;12(3):665.
[133] Boldyrev AA, Aldini G, Derave W. Physiology and pathophysiology of carnosine. Physiol Rev. 2013 Oct;93(4):1803-45.
[134] Li M, Sun Z, Zhang H, et al. Recent advances on polaprezinc for medical use (Review). Exp Ther Med. 2021 Dec;22(6):1445.
[135] Efthymakis K, Neri M. The role of Zinc L-Carnosine in the prevention and treatment of gastrointestinal mucosal disease in humans: a review. Clin Res Hepatol Gastroenterol. 2022 Aug-Sep;46(7):101954.
[136] Furuta S, Toyama S, Miwa M, et al. Residence time of polaprezinc (zinc L-carnosine complex) in the rat stomach and adhesiveness to ulcerous sites. Jpn J Pharmacol. 1995 Apr;67(4):271-8.

hydrochloric acid and acetylsalicylic acid, as well as acetaminophen toxicity in hepatocytes.[137,138,139] In an ethanol-induced model of gastric mucosal damage, ZnC was also shown to reduce the levels of inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNFα, and increase the expression of antioxidant enzymes such as superoxide dismutase and glutathione transferase.[140] *In vitro,* ZnC has been shown to suppress NF-κB activation in response to lipopolysaccharide (LPS), which may also underlie its ability to protect the intestinal epithelium from injury.[141]

ZnC has also protected the small intestine from injury from indomethacin in animals, and in humans receiving low-dose aspirin, ZnC was also shown to reduce the number of lesions and ulcers compared to placebo, examined by capsule endoscopy.[142,143] In a small clinical trial, a 3-fold increase in permeability (measured by lactulose/rhamnose) was observed following treatment with indomethacin, yet no increase was seen with the coadministration of ZnC.[144] In humans, ZnC was found to increase heat shock protein expression and improve tight junction formation and stabilization following intense exercise, suggesting it may limit the intestinal permeability associated with extreme exertion.[145]

Given the role of *H.pylori* in ulcer pathophysiology, a systematic review and meta-analysis was recently conducted to evaluate the safety and efficacy of ZnC for the eradication of H. pylori. In this analysis of 3 randomized and controlled trials, when ZnC was combined with triple therapy, it was found to increase the eradication rate (165% per protocol) compared to triple therapy alone.[146] ZnC has also been shown to improve the effectiveness of proton pump inhibitors in the treatment of gastric ulcer following endoscopic submucosal dissection; when added to lansoprazole, ZnC significantly improved the

---

[137] Mikami K, Otaka M, Watanabe D, et al. Zinc L-carnosine protects against mucosal injury in portal hypertensive gastropathy through induction of heat shock protein 72. J Gastroenterol Hepatol. 2006 Nov;21(11):1669-74.
[138] Qin Y, Naito Y, Handa O, et al. Heat shock protein 70-dependent protective effect of polaprezinc on acetylsalicylic acid-induced apoptosis of rat intestinal epithelial cells. J Clin Biochem Nutr. 2011 Nov;49(3):174-81.
[139] Nishida T, Ohata S, Kusumoto C, et al. Zinc Supplementation with Polaprezinc Protects Mouse Hepatocytes against Acetaminophen-Induced Toxicity via Induction of Heat Shock Protein 70. J Clin Biochem Nutr. 2010 Jan;46(1):43-51.
[140] Choi HS, Lim JY, Chun HJ, et al. The effect of polaprezinc on gastric mucosal protection in rats with ethanol-induced gastric mucosal damage: comparison study with rebamipide. Life Sci. 2013 Jul 30;93(2-3):69-77.
[141] Ooi TC, Chan KM, Sharif R. Zinc Carnosine Inhibits Lipopolysaccharide-Induced Inflammatory Mediators by Suppressing NF-κb Activation in Raw 264.7 Macrophages, Independent of the MAPKs Signaling Pathway. Biol Trace Elem Res. 2016 Aug;172(2):458-464.
[142] Omatsu T, Naito Y, Handa O, et al. Reactive oxygen species-quenching and anti-apoptotic effect of polaprezinc on indomethacin-induced small intestinal epithelial cell injury. J Gastroenterol. 2010 Jul;45(7):692-702.
[143] Watari I, Oka S, Tanaka S, et al. Effectiveness of polaprezinc for low-dose aspirin-induced small-bowel mucosal injuries as evaluated by capsule endoscopy: a pilot randomized controlled study. BMC Gastroenterol. 2013 Jul 4;13:108.
[144] Mahmood A, FitzGerald AJ, Marchbank T, et al. Zinc carnosine, a health food supplement that stabilises small bowel integrity and stimulates gut repair processes. Gut. 2007 Feb;56(2):168-75.
[145] Davison G, Marchbank T, March DS, et al. Zinc carnosine works with bovine colostrum in truncating heavy exercise-induced increase in gut permeability in healthy volunteers. Am J Clin Nutr. 2016 Aug;104(2):526-36.
[146] Mahmoud A, Abuelazm M, Ahmed AAS, et al. Efficacy and Safety of Polaprezinc-Based Therapy versus the Standard Triple Therapy for Helicobacter pylori Eradication: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2022 Oct 4;14(19):4126.

ulcer healing scores, with similar efficacy to rebamipide in human clinical trials.[147,148] It has also been shown to prevent oral mucositis following chemotherapy.[149]

G.I. InnerCalm™ Safety Summary:

Although most of the botanicals in G.I. InnerCalm™ have no known warnings, precautions or contraindications at the dose recommended, it is contraindicated in individuals allergic to any of the individual ingredients in G.I. InnerCalm™, as well as those with allergies to plants from the Compositae (aka Asteraceae) family or known hypersensitivities to aloe.[150,151] Additionally, sedative drugs such as opioid analgesics and alcohol may have an additive effect when taken with Chamomile and Lemon balm, and should be used with caution.[150,152]

Adverse effects to quercetin supplementation are rare but may include nausea, dyspnea, headache, and mild tingling of the extremities. Animal studies suggest impaired kidney function may be a contraindication to quercetin supplementation, but no human data has confirmed this finding, and it is considered safe and well-tolerated at the recommended dose.[153] A theoretical concern with zinc administration is the possible induction of copper deficiency, as high doses of zinc are known to inhibit copper absorption. However, the amount of zinc should not be a concern when taken at recommended doses.[132] Safety during pregnancy and lactation has not been well-established for all ingredients, and should be avoided during these times.[154,155]

---

[147] Jung DH, Park JC, Lee YC, et al. Comparison of the Efficacy of Polaprezinc Plus Proton Pump Inhibitor and Rebamipide Plus Proton Pump Inhibitor Treatments for Endoscopic Submucosal Dissection-induced Ulcers. J Clin Gastroenterol. 2021 Mar 1;55(3):233-238.

[148] Inaba T, Ishikawa S, Toyokawa T, et al. Basal protrusion of ulcers induced by endoscopic submucosal dissection (ESD) during treatment with proton pump inhibitors, and the suppressive effects of polaprezinc. Hepatogastroenterology. 2010 May-Jun;57(99-100):678-84.

[149] Kitagawa J, Kobayashi R, Nagata Y, et al. Polaprezinc for prevention of oral mucositis in patients receiving chemotherapy followed by hematopoietic stem cell transplantation: A multi-institutional randomized controlled trial. Int J Cancer. 2021 Mar 15;148(6):1462-1469.

[150] McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). Phytother Res. 2006 Jul;20(7):519-30.

[151] Ferreira M, Teixeira M, Silva E, et al. Allergic contact dermatitis to Aloe vera. Contact Dermatitis. 2007 Oct;57(4):278-9.

[152] Kenda M, Kočevar Glavač N, et al. Medicinal Plants Used for Anxiety, Depression, or Stress Treatment: An Update. Molecules. 2022 Sep 15;27(18):6021.

[153] Andres S, Pevny S, Ziegenhagen R, et al. Safety Aspects of the Use of Quercetin as a Dietary Supplement. Mol Nutr Food Res. 2018 Jan;62(1).

[154] Stanisiere J, Mousset PY, Lafay S. How Safe Is Ginger Rhizome for Decreasing Nausea and Vomiting in Women during Early Pregnancy? Foods. 2018 Apr 1;7(4):50.

[155] Trabace L, Tucci P, Ciuffreda L, et al. "Natural" relief of pregnancy-related symptoms and neonatal outcomes: above all do no harm. J Ethnopharmacol. 2015 Nov 4;174:396-402.