AVS INGREDIENTS

ARTEMISININ

Artemisinin in the quantity of 125 mg on the first day and 62.5 mg for the next 6 days, with piperaquine in the quantity of 750 mg for the first day and 375 mg for the next 6 days almost halved the time to reach undetectable SARS-CoV-2 level vs. the control group, according to the clinical study disclosed in Guoming Li et al., “Safety and efficacy of artemisinin-piperaquine for treatment of COVID-19: an open-label, non-randomised and controlled trial,” *International Journal of Antimicrobial Agents*, January 2021, 57(1), 106216, https://doi.org/10.1016/j.ijantimicag.2020.106216, JIF 15.441 (top 3% journals in Pharmacology & Pharmacy).

Artemisinin family drugs are potent anti-malarial agents with high efficacy and low toxicity. Besides the outstanding antimalarial activity, artemisinin and its derivatives are also able to regulate various aspects of immune responses, such as macrophage activation, T cell activation and proliferation, T cell subsets differentiation (Th1, Th17, Treg). Furthermore, the recent finding that artesunate can regulate GC B cells highlights artesunate's role in humoral immune response, according to Lifei Hou et al., “Immune suppressive properties of artemisinin family drugs,” *Pharmacology and Therapeutics*, 166 (2016), pp. 123-127, https://doi.org/10.1016/j.pharmthera.2016.07.002, JIF (top 4% journals in Pharmacology & Pharmacy / top 3% journals in Pharmacology & Pharmacy in 2016).

This article reviews the data-based immunomodulatory effects of artemisinins on different immune cells including neutrophils, macrophages, splenocytes, T and B cells in conjunction with their therapeutic prospective with regard to inflammation, autoimmunity and delayed-type hypersensitivity, according to Lubna Shakir et al., “Artemisinins and immune system,” *European Journal of Pharmacology*, 668 (2011), pp. 6-14, https://doi.org/10.1016/j.ejphar.2011.06.044, JIF (top 26% journals in Pharmacology & Pharmacy / top 40% journals in Pharmacology & Pharmacy in 2011).

Artemisinin and its analogs, such as dihydroartemisinin, artemether, artesunate, artemiside, artemisone, and arteether, possess not only potent antimalarial activity but also anti-viral, antifungal, anticancer, and anti-inflammatory properties. Artemisinins have an immunomodulatory effect on diverse components of the immune system through affecting various immune cells responses. They suppress the secretion of cytokines and related signaling pathway, induce decrease in neutrophils, reduce macrophage functional responses, and inhibit lymphocyte proliferation and maintenance. Also, artemisinins affect signaling pathway cascades, including those for TLR, PLCγ, PKC, Akt, MAPK, Wnt, STATs, NF-κB, and Nrf2/ARE, according to Wenbo Yao et al. “Immunomodulation of artemisinin and its derivatives,” *Science Bulletin*, 61 (2016), pp. 1399-1406, https://doi.org/10.1007/s11434-016-1105-z, JIF (top 7% journals in multidisciplinary sciences / top 18% journals in multidisciplinary sciences in 2016).

As demonstrated in recent years, the class of artemisinin-type compounds has activity against malaria, cancer cells, and schistosomiasis. Interestingly, the bioactivity of artemisinin and its semisynthetic derivative artesunate is even broader and includes the inhibition of certain viruses, such as human cytomegalovirus and other members of the Herpesviridae family (e.g., herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus, and bovine viral diarrhea virus, according to Thomas Efferth et al., “The antiviral activities of artemisinin and artesunate,” *Clinical Infectious Diseases*, 47 (2008), pp. 804-811, https://doi.org/10.1086/591195, JIF (top 5% journals in Immunology / top 10% journals in Immunology in 2008, top 7% journals in Infectious Diseases / top 4% journals in Infectious Diseases in 2008, and top 5% journals in Microbiology / top 7% journals in Microbiology in 2008).

NIGELLA SATIVA

Nigella sativa in the form of ThymoQuinone Formula (TQF) with 1.7% thymoquinone and the quantity of 3,000 mg per day (3 capsules with 500 mg twice a day) for 14 days completely eliminated hospitalizations from COVID-19 to 0.0% vs. 4.3% in the control group, according to the clinical study disclosed in Hassan Bencheqroun et al., "A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of ThymoQuinone formula (TQF) for treating outpatient SARS-CoV-2," *Pathogens*, 7 May 2022, 11(5), 551, https://doi.org/10.3390/pathogens11050551, JIF 4.531 (top 42% journals in Microbiology).

Nigella sativa oil in the quantity of 1,000 mg per day (a capsule with 500 mg twice a day) for 10 days eliminated 75% of hospitalizations from COVID-19 compared to the control group according to the clinical study disclosed in Abdulrahman E. Koshak et al., "Nigella sativa for the treatment of COVID-19: An open-label randomized controlled clinical trial," *Complementary Therapies in Medicine*, September 2021, 61, 102769, https://doi.org/10.1016/j.ctim.2021.102769, JIF 3.335 (top 40% journals in Integrative & Complementary Medicine).

Nigella sativa in the quantity of 40 mg/kg (3,000 mg for 75 kg person weight) per day for 14 days completely eliminated deaths from COVID-19 to 0.0% vs. 5.4% in the control group, according to the clinical study disclosed in Kadhim Ali Abbas Al-Haidari et al., "Clinical trial of black seeds against COVID – 19 in Kirkuk City/Iraq," *Indian Journal of Forensic Medicine & Toxicology*, July-September 2021, 15(3), 3393-3399, https://doi.org/10.37506/ijfmt.v15i3.15825, JIF N/A.

The seeds of Nigella sativa L. (NS), a plant of the *Runanculaceae* family, are used in traditional medicine in North Africa and the Middle East for the treatment of diabetes. This study evaluated the effects of NS seed crude ethanol extract on insulin secretion in INS832/13 and β TC-tet lines of pancreatic β-cells and on glucose disposal by C2C12 skeletal muscle cells and 3T3-L1 adipocytes. An 18-h treatment with NS amplified glucose-stimulated insulin secretion by more than 35% without affecting sensitivity to glucose. NS treatment also accelerated β-cell proliferation. An 18-h treatment with NS increased basal glucose uptake by 55% (equivalent to approximately two-fold the effect of 100 nM insulin) in muscle cells and approximately by 400% (equal to the effect of 100 nM insulin) in adipocytes; this effect was perfectly additive to that of insulin in adipocytes. Finally, NS treatment of pre-adipocytes undergoing differentiation accelerated triglyceride accumulation comparably with treatment with 10 μM rosiglitazone. It is concluded that the well-documented in vivo antihyperglycemic effects of NS seed extract are attributable to a combination of therapeutically relevant insulinotropic and insulin-like properties, according to Ali Benhaddou-Andaloussi et al., "Antidiabetic Activity of Nigella sativa. Seed Extract in Cultured Pancreatic β-cells, Skeletal Muscle Cells, and Adipocytes," *Pharmaceutical Biology*, 46:1-2, 96-104, https://doi.org/10.1080/13880200701734810, JIF 3.889 (top 24% journals in Plant Sciences).

Nigella sativa seeds have wide therapeutic effects and have been reported to have significant effects against many ailments such as **skin diseases, jaundice, gastrointestinal problems, anorexia, conjunctivitis, dyspepsia, rheumatism, diabetes, hypertension, intrinsic hemorrhage, paralysis, amenorrhea, anorexia, asthma, cough, bronchitis, headache, fever, influenza and eczema.** Thymoquinone (TQ) is one of the most active constituent and has different beneficial properties. Focus on antimicrobial effects, different extracts of Nigella sativa as well as TQ, have a broad antimicrobial spectrum including Gram-negative, Gram-positive bacteria, viruses, parasites, schistosoma and fungi. The effectiveness of Nigella sativa seeds and TQ is variable and depends on species of target microorganisms, according to Fatemeh Forouzanfar et al., "Black cumin (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects," *Iranian Journal of Basic Medical Sciences*, 2014; 17:929-938, https://doi.org/10.22038/ijbms.2015.3849, JIF 2.532 (top 73% journals in Pharmacology & Pharmacy).

Nigella sativa (Family *Ranunculaceae*) is widely used medicinal plant throughout the world. Nigella sativa is referred in the Middle East as a part of an overall holistic approach to health. Pharmacological properties of Nigella sativa including immune stimulant, hypotensive, anti-inflammatory, anti-cancer, antioxidant, hypoglycemic, spasmolytic and bronchodilator have been shown. Reactive oxygen species (ROS) and oxidative stress are known as the major causes of many diseases such as liver injury and many substances and drugs can induce oxidative damage by generation of ROS in the body. Many pharmacological properties of Nigella sativa are known to be attributed to the presence of thymoquinone and its antioxidant effects. Thymoquinone protects liver from injury via different mechanisms including inhibition of iron-dependent lipid peroxidation, elevation in total thiol content and glutathione level, radical scavengering, increasing the activity of quinone reductase, catalase, superoxide dismutase and glutathione transferase, inhibition of NF-κB activity and inhibition of both cyclooxygenase and lipoxygenase. Therefore, this review aimed to highlight the roles of ROS in liver diseases and the mechanisms of Nigella sativa in prevention of liver injury, according to Hamid Mollazadeh et al., "The protective effect of Nigella sativa against liver injury: a review," *Iranian Journal of Basic Medical Sciences* 2014; 17:958-966, https://doi.org/10.22038/ijbms.2015.3852, JIF 2.532 (top 73% journals in Pharmacology & Pharmacy).

Nigella sativa seeds have a lot of nutritional and medicinal benefits and contain many bioactive compounds like thymoquinone, α-hederin, alkaloids, flavonoids, antioxidants, fatty acids and many other compounds that have positive effects on curing of different diseases. **Several medicinal properties of Nigella sativa like its anti-cancer, anti-inflammatory, anti-diabetic, antioxidant activities and many others are well acknowledged. However, this article focuses on activity of Nigella sativa against cardiovascular diseases and cancer.** For gathering required data the authors went through vast number of articles using search engines like Science direct, ELSEVIER, Pub Med, Willey on Line Library and Google scholar and the findings were classified on the basis of relevance of the topic and were reviewed in the article. Nigella sativa has found effective in controlling number of cardiovascular diseases and various cancers both in vivo and in vitro studies, according to Hammad Shafiq et al., "Cardio-protective and anti-cancer therapeutic potential of Nigella sativa," *Iranian Journal of Basic Medical Sciences*, December 2014; 17(12):967-979, https://doi.org/10.22038/ijbms.2015.3853, JIF 2.532 (top 73% journals in Pharmacology & Pharmacy).

Nigella sativa has anti-cancer, anti-inflammatory, anti-diabetic, antioxidant activities and many other medicinal properties, and can be used against cardiovascular diseases, according to F. Shakeri et al., “Cardiovascular effects of Nigella Sativa L. and its Constituents,” *Indian Journal of Pharmaceutical Sciences*, November-December 2018, 80(6), 971-983, https://doi.org/10.4172/pharmaceutical-sciences.1000447, JIF 0.664 (top 97% journals in Pharmacology & Pharmacy).

QUERCETIN

Quercetin in the quantity of 400 mg (2 tablets with 200 mg each) per day during 3 months, provided 4 times less COVID-19 infection rate vs. the control group, according to the clinical study diclosed in Mariangela Rondanelli et al., "Promising effects of 3-month period of Quercetin Phytosome® supplementation in the prevention of symptomatic COVID-19 disease in healthcare workers: A pilot study," *Life* 2022, 4 January 2022, 12(1), 66, https://doi.org/10.3390/life12010066, JIF 3.253 (top 42% journals in Biology).

Quercetin in the quantity of 600 mg (3 tablets with 200 mg each) per day in the first week and 400 mg (2 tablets of 200 mg) per day in the second week completely eliminated deaths from COVID-19 to 0.0% vs. 4.8% in the control group; completely eliminated the progression to intensive care units (ICU) to 0.0% vs. 4.8% in the control group; and completely eliminated hospitalizations to 0.0% vs. 4.8% in the control group, according to the clinical study disclosed in Francesco Di Pierro et al., "Potential clinical benefits of quercetin in the early stage of COVID-19: Results of a second, pilot, randomized, controlled and open-label clinical trial," *International Journal of General Medicine*, 24 June 2021, 14, 2807-2816, https://doi.org/10.2147/IJGM.S318949, JIF 2.145 (top 66% journals in Medicine, General & Internal).

Quercetin in the quantity of 400 mg (2 tablets with 200 mg each) per day during 30 days completely eliminated deaths from COVID-19 to 0.0% vs. 3.9% deaths in the control group, and completely eliminated the progression to intensive care units (ICU) to 0.0% vs. 10.5% in the control group, according to the clinical study disclosed in Francesco Di Pierro et al., "Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: A prospective, randomized, controlled, and open-label study," *International Journal of General Medicine*, 8 June 2021, 14, 2359-2366, https://doi.org/10.2147/ijgm.s318720, JIF 2.145 (top 66% journals in Medicine, General & Internal).

Flavonoids have been proven to be active against hypertension, inflammation, diabetes and vascular diseases. Quercetin protects against atherosclerosis, oxidative stress, cardiotoxicity, endothelial cell dysfunction, heart failure etc., according to Rahul V. Patel et al., "Therapeutic potential of quercetin as a cardiovascular agent," *European Journal of Medicinal Chemistry*, 15 July 2018, 155, 889-904, https://doi.org/10.1016/j.ejmech.2018.06.053, JIF 7.088 (top 8% journals in Chemistry, Medicinal).

Quercetin is a naturally-occurring flavonol (a member of the flavonoid family of compounds) that has a long history of consumption as part of the normal human diet. Because a number of biological properties of quercetin may be beneficial to human health, interest in the addition of this flavonol to various traditional food products has been increasing. Prior to the use of quercetin in food applications that would increase intake beyond that from naturally-occurring levels of the flavonol in the typical Western diet, its safety needs to be established or confirmed. This review provides a critical

examination of the scientific literature associated with the safety of quercetin. Results of numerous genotoxicity and mutagenicity, short- and long-term animal, and human studies are reviewed in the context of quercetin exposure in vivo. To reconcile results of in vitro studies, which consistently demonstrated quercetin-related mutagenicity to the absence of carcinogenicity in vivo, the mechanisms that lead to the apparent in vitro mutagenicity, and those that ensure absence of quercetin toxicity in vivo are discussed. The weight of the available evidence supports the safety of quercetin for addition to food, according to M. Harwood et al., "A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties," *Food and Chemical Toxicology* 2007;45(11):2179–205, https://doi.org/10.1016/j.fct.2007.05.015, JIF 5.572 (top 16% journals in Toxicology, top 24% journals in Food Science & Technology).

High levels of cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6, are associated with chronic diseases like rheumatoid arthritis, asthma, atherosclerosis, Alzheimer's disease and cancer; therefore cytokine inhibition might be an important target for the treatment of these diseases. Most drugs used to alleviate some inflammation-related symptoms act by inhibiting cyclooxygenases activity or by blocking cytokine receptors. Nevertheless, these drugs have secondary effects when used on a long-term basis. It has been mentioned that flavonoids, namely **quercetin, apigenin and luteolin, reduce cytokine expression and secretion**. **In this regard, flavonoids may have therapeutical potential in the treatment of inflammation-related diseases as cytokine modulators**. This review is focused on current research about the effect of flavonoids on cytokine modulation and the description of the way these compounds exert their effect, according to Nayely Leyva-Lopez et al. "Flavonoids as cytokine modulators: a possible therapy for inflammation-related diseases," *International Journal of Molecular Sciences* 2016;17(6):921. https://doi.org/10.3390/ijms17060921, JIF 6.208 (top 24% journals in Biochemistry & Molecular Biology and top 28% journals in Chemistry, Multidisciplinary).

Quercetin as a member of flavonoids, has emerged as a potential **therapeutic agent in cardiovascular diseases (CVDs) in recent decades**. Experimental studies including both in vitro methods and in vivo animal models mainly outline the following effects of quercetin: (1) antihypertensive, (2) hypolipidemic, (3) hypoglycemic, (4) anti-atherosclerotic, and (5) cardioprotective (suppressed cardiotoxicity), according to Paraskevi Papakyriakopoulou et al., "Potential pharmaceutical applications of quercetin in cardiovascular diseases," *Pharmaceuticals*, 2022, 15, 1019, https://doi.org/10.3390/ph15081019, JIF 5.125 (top 25% journals in Pharmacology & Pharmacy).

Research in animals and humans has indicated that polyphenols can delay the age-related decline in learning, memory and neurodegenerative diseases. Among the polyphenols, berry phenolics have extensive beneficial effects because of their antioxidant and anti-inflammatory properties. Long-term consumption of grapes results in accumulation of polyphenols in the brain, which modulates cell-signalling pathways and neutralises the redox imbalance in the aging brain. Here we review the in vivo and in vitro evidence for considering grape-derived polyphenolics, the flavonoids- catechins, epicatechin, anthocyanidin, and quercetin, and non-flavonoids-gallic acid and resveratrol, as effective dietary sources to facilitate cognition in adults and lessen the decline in the old

and pathogenic states, Alzheimer's and Parkinson's disease. Furthermore, a combined intervention of polyphenols along with regular physical exercise provides cognitive benefits for the aging brain and holds promising venues for preclinical and clinical studies in formulating neuro-nutraceuticals as functional foods for a healthy brain, according to S. Asha Devi et al., “Polyphenols as an effective therapeutic intervention against cognitive decline during normal and pathological brain aging,” *Advances in Experimental Medicine and Biology* 2020;1260:159–74, https://doi.org/10.1007/978-3-030-42667-5_7, JIF 3.650 (top 35% journals in Biology and top 60% journals in Medicine, Research & Experimental).

Flavonoids are present in almost all terrestrial plants, where they provide UV-protection and colour. Flavonoids have a fused ring system consisting of an aromatic ring and a benzopyran ring with a phenyl substituent. The flavonoids can be divided into several classes depending on their structure. Flavonoids are present in food and medicinal plants and are thus consumed by humans. They are found in plants as glycosides. Before oral absorption, flavonoids undergo deglycosylation either by lactase phloridzin hydrolase or cytosolic β-glucosidase. The absorbed aglycone is then conjugated by methylation, sulphatation or glucuronidation. Both the aglycones and the conjugates can pass the blood-brain barrier. In the CNS several flavones bind to the benzodiazepine site on the GABA(A)-receptor resulting in sedation, anxiolytic or anti-convulsive effects. Flavonoids of several classes are inhibitors of monoamine oxidase A or B, thereby working as anti-depressants or to improve the conditions of Parkinson's patients. Flavanols, flavanones and anthocyanidins have protective effects preventing inflammatory processes leading to nerve injury. Flavonoids seem capable of influencing health and mood, according to Anna K. Jager AK, “Flavonoids and the CNS,” *Molecules* 2011;16(2):1471–85, https://doi.org/10.3390/molecules16021471, JIF 4.927 (top 37% journals in Chemistry, Multidisciplinary and top 39% journals in Biochemistry & Molecular biology).

Quercetin is the major flavonoid involved in vegetables and fruits. Quercetin is ingested from the daily diet, but in 1970s it was reported as mutagenic. Quercetin possesses a variety of pharmacological activities, and in order for further clinical application, it is important to evaluate its safety. In Ames test, quercetin is regarded as mutagenic. However, recent in vitro studies indicate that quercetin is protective against genotoxicants, and regarded as antimutagenic. Some in vivo studies including National Toxicology Program reported carcinogenic effect of quercetin in F344 rats. However, the method used in the study was unusual and the result was not reproduced. Most of the results of in vivo studies indicate that quercetin is not carcinogenic. Since 1969, the International Agency for Research on Cancer (IARC) has undertaken a program to evaluate the carcinogenic risk of chemicals. In 1999, IARC concluded that quercetin is not classified carcinogenic to humans. In the U.S. and Europe, supplements of quercetin is commercially available, and beneficial effects of quercetin supplements were reported in clinical trials. Overall, quercetin is genotoxic to salmonella, but its safety upon human application is approved, according to Toshihiro Okamoto et al., “Safety of quercetin for clinical application (review),” *International Journal of Molecular Medicine* 2005;16(2):275–8, https://doi.org/10.3892/ijmm.16.2.275, JIF 5.314 (top 38% journals in Medicine, Research & Experimental).

The inflammatory process in the human body is a physiological response involving many cellular types and mediators. It results in scar formation to separate the damaged area from the surrounding

healthy tissue. Because of increased blood-brain barrier permeability following inflammation, leukocytes infiltrate the central nervous system (CNS) and are also supplemented by proinflammatory mediators. However, an acute inflammatory process after cerebral trauma or stroke may also result in a prolonged lesion formation, leading to a severe neuronal loss. The prolonged inflammatory process in the CNS may cause serious damage to the neuronal system. It may lead to CNS damage in such a way that endangers functional integration and proinflammatory system balance. Effects of different flavonoid species on ischemia-reperfusion injury and cognition and function have also been shown in experimental studies. Flavonoids are presented broadly in plants and diets. They are believed to have various bioactive effects including anti-viral, anti-inflammatory, cardioprotective, anti-diabetic, anti-cancer, anti-aging, etc. Quercetine is the predominant dietary flavonoid. Main sources are tea, onion, and apple. It is demonstrated that the frequently consumed food like soybean, peanut, mustard, rice, sesame, olive, potatoes, onion, and oats contain flavonoids, according to Zehra Calis et al., “The roles of flavonoles/flavonoids in neurodegeneration and neuroinflammation,” *Mini-Reviews in Medicinal Chemistry* 2020;20(15):1475–88, http://doi.org/10.2174/1389557519666190617150051, JIF 3.737 (top 50% journals in Chemistry, Medicinal).

CURCUMIN

Curcumin in the quantity of 160 mg (2 soft gels with 40 mg twice a day) per day for 21 days completely eliminated deaths from COVID-19 to 0.0% vs. 5.0% in the control group, according to the clinical study disclosed in Safa Tahmasebi et al., "Nanocurcumin improves Treg cell responses in patients with mild and severe SARS-CoV2," *Life Sciences*, 28 March 2021, 276, 119437, https://doi.org/10.1016/j.lfs.2021.119437, JIF 6.780 (top 13% journals in Pharmacology & Pharmacy).

Curcumin in the quantity of 160 mg (2 soft gell with 40 mg twice a day) per day for 2 weeks completely eliminated progression to intensive care units (ICU) from COVID-19 to 0.0% vs. 40% in the control group, according to the clinical study disclosed in Niloofar Saber-Moghaddam et al., "Oral nano-curcumin formulation efficacy in management of mild to moderate hospitalized coronavirus disease-19 patients: An open label nonrandomized clinical trial," *Phytotherapy Research*, 03 January 2021, 35(5), 2616-2623, https://doi.org/10.1002/ptr.7004, JIF 6.388 (top 13% journals in Chemistry, Medicinal and top 16% journals in Pharmacology & Pharmacy).

Curcumin in the quantity of 1,050 mg (a tablet with 525 mg twice a day) per day and piperine in the quantity of 5 mg (tablet with 2.5 mg twice a day) per day for 14 days completely eliminated deaths from COVID-19 to 0.0% vs. 20.0% in the control group, according to the clinical study disclosed in Kirti S. Pawar et al., "Oral curcumin with piperine as adjuvant therapy for the treatment of COVID-19: A randomized clinical trial," *Frontiers in Pharmacology*, 28 May 2021, 12, 669362, https://doi.org/10.3389/fphar.2021.669362, JIF 5.988 (top 18% journals in Pharmacology & Pharmacy).

Curcumin in the quantity of 160 mg (2 soft gels with 40 mg twice a day) per day for 2 weeks completely eliminated hospitalizations from COVID-19 to 0.0% vs. 10.0% in the control group, according to the clinical study disclosed in Reze Ahmadi et al., "Oral nano-curcumin formulation efficacy in the management of mild to moderate outpatient COVID-19: A randomized triple-blind placebo-controlled clinical trial," *Food Science and Nutrition*, 16 June 2021, 9(8), 4068-4075, https://doi.org/10.1002/fsn3.2226, JIF 3.553 (top 43% journals in Food Science & Technology).

The preclinical studies of curcumin in cardiovascular diseases, such as cardiac hypertrophy, heart failure, drug-induced cardiotoxicity, myocardial infarction, atherosclerosis, abdominal aortic aneurysm, stroke and diabetic cardiovascular complications are analyzed in Hong Li et al., "Curcumin, the golden spice in treating cardiovascular diseases," *Biotechnology Advances*, January-February 2020, 38, 107343, https://doi.org/10.1016/j.biotechadv.2019.01.010, JIF 17.681 (top 3% journals in Biotechnology & Applied Microbiology).

Curcumin is a yellow pigment in the Indian spice Turmeric (Curcuma longa). **At the molecular level, this multitargeted agent has been shown to exhibit anti-inflammatory activity through the**

suppression of numerous cell signaling pathways including NF-κB, STAT3, Nrf2, ROS and COX-2. Numerous studies have indicated that curcumin is a highly potent antimicrobial agent and has been shown to be active against various chronic diseases including various types of cancers, diabetes, obesity, cardiovascular, pulmonary, neurological and autoimmune diseases. Furthermore, this compound has also been shown to be synergistic with other nutraceuticals such as resveratrol, piperine, catechins, quercetin and genistein. To date, over 100 different clinical trials have been completed with curcumin, which clearly show its safety, tolerability and its effectiveness against various chronic diseases in humans, according to Ajaikumar B. Kunnumakkara et al., "Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases," *British Journal of Pharmacology* (2017), 174, 1325–1348, https://doi.org/10.1111/bph.13621, JIF 9.473 (top 7% journals in Pharmacology & Pharmacy).

Numerous studies have shown that curcumin possesses a wide spectrum of biological and pharmacological properties, acting, for example, as anti-inflammatory, anti-angiogenic and anti-neoplastic, while no toxicity is associated with the compound. Recently, curcumin's antiviral and antibacterial activity was investigated, and it was shown to act against various important human pathogens like the influenza virus, hepatitis C virus, HIV and strains of Staphylococcus, Streptococcus, and Pseudomonas, according to Dimas Praditya et al., "Anti-infective Properties of the Golden Spice Curcumin," *Frontiers in Microbiology*, 2019, 10:912, https://doi.org/10.3389/fmicb.2019.00912, JIF 6.064 (top 25% journals in Microbiology).

Pro-inflammatory cytokines are associated with inflammation and angiogenesis, although there is a discrete variability in the doses of the mediators investigated among the different vitreous samples. Curcumin, homotaurine, and vitamin D3 individually have a slightly appreciable anti-inflammatory effect. However, when used in combination, these substances are able to modify the average levels of the soluble mediators of inflammation and retinal damage, according to Mariaelena Filippelli et al., "Anti-inflammatory effect of curcumin, homotaurine, and vitamin D3 on human vitreous in patients with diabetic retinopathy," *Frontiers in Neurology*, 2021, 11, 592274, https://doi.org/10.3389/fneur.2020.592274, JIF 4.086 (top 42% journals in Clinical neurology and top 45% journals in Neurosciences).

The studies on the antioxidant, anti-inflammatory, antiviral, and antifungal properties of curcuminoids are included. Studies on the toxicity and anti-inflammatory properties of curcumin have included in vitro, animal, and human studies, according to Nita Chainani-Wu, "Safety and anti-inflammatory activity of curcumin: A component of tumeric (*curcuma longa*)," *The Journal of Alternative and Complementary Medicine*, 9 (1), 2003, 161-168, https://doi.org/10.1089/107555303321223035, JIF 2.381 (top 67% journals in Integrative & Complementary Medicine).

N-ACETYL CYSTEIN

N-acetylcysteine in the quantity of 1200-1800 mg intravenously per day, 3 times decreased risk of death vs. the control group, 4 times decreased risk of mechanical ventilation vs. the control group and 4 times decreased risk of ICU admission vs. the control group, according to the clinical study disclosed in Sergey N. Avdeev et al., "N-acetylcysteine for the treatment of COVID-19 among hospitalized patients," *Journal of Infection*, 09 July 2021, 84(1), 94-118, https://doi.org/10.1016/j.jinf.2021.07.003, JIF 38.637 (top 4% journals in Infectious Diseases).

N-acetylcysteine in the quantity of 600 mg per day for 14 days, 6 times decreased death from COVID-19 vs. the control group, according to the clinical study disclosed in Stelios F. Assimakopoulos et al., "N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study," *Infectious Diseases*, 29 June 2021, 53(11), 847-854, https://doi.org/10.1080/23744235.2021.1945675, JIF 5.838 (top 33% journals in Infectious Diseases).

NAC in the quantity of 2-30 mg/kg/day, given after the establishment of diabetes, may offer protection against the risk for stroke by altering both systemic and vascular prothrombotic responses, according to Bin Wang et al. "N-acetylcysteine attenuates systemic platelet activation and cerebral vessel thrombosis in diabetes," *Redox Biology*, 14 (2018), 218-228, http://doi.org/10.1016/j.redox.2017.09.005, JIF 10.787 (top 9% journals in Biochemistry & Molecular Biology).

NAC is an effective and safe alternative to currently available antithrombotic agents to restore vessel patency after arterial occlusion, according to Sara Martinez de Lizarrondo et al. "Potent thrombolytic effect of N-Acetylcysteine on arterial thrombi," *Circulation*, 2017, 136, 646-660, https://doi.org/10.1161/CIRCULATIONAHA.117.027290, JIF 39.922 (top 1.4% journals in Cardiac & Cardiovascular Systems and top 1.5% journals in Peripheral Vascular Disease).

Multiple Sclerosis (MS) is a neurological disorder associated with white and gray matter injury significantly due to autoimmune mediated inflammation processes. NAC positively affects cerebral glucose metabolism in MS patients, which is associated with qualitative, patient reported improvements in cognition and attention, according to Daniel A. Monti et al., "N-acetyl Cysteine Administration Is Associated With Increased Cerebral Glucose Metabolism in Patients With Multiple Sclerosis: An Exploratory Study," *Frontiers in Neurology*, 14 February 2020, Volume 11, https://doi.org/10.3389/fneur.2020.00088, JIF 4.086 (top 35% journals in Clinical Neurology and top 43% journals in Neurosciences).

BROMELAIN

Bromelain inhibits SARS-CoV-2 infection, and its profound fibrinolytic activity suggests that bromelain or bromelain-rich pineapple could be used as an antiviral against SARS-CoV-2 and future outbreaks of other coronaviruses, according to Satish Sagar et al., “Bromelain inhibits SARS-CoV-2 infection via targeting ACE-2, TMPRSS2, and spike protein,” *Clinical and Translational Medicine*, 2021 Feb, 11(2), e281, https://doi.org/10.1002/ctm2.281, JIF 8.554 (top 17% journals in Oncology and top 17% journals in Medicine, Research & Experimental).

Bromelain is a major sulfhydryl proteolytic enzyme found in pineapple plants, having multiple activities in many areas of medicine. Due to its low toxicity, high efficiency, high availability, and relative simplicity of acquisition, it is the object of inexhaustible interest of scientists. This review summarizes scientific reports concerning the possible application of bromelain in treating cardiovascular diseases, blood coagulation and fibrinolysis disorders, infectious diseases, inflammation-associated diseases, and many types of cancer. However, for the proper application of such multi-action activities of bromelain, further exploration of the mechanism of its action is needed. It is supposed that the anti-viral, anti-inflammatory, cardioprotective and anti-coagulatory activity of bromelain may become a complementary therapy for COVID-19 and post-COVID-19 patients, according to Pawel Hikisz et al., “Beneficial Properties of Bromelain,” *Nutrients* 2021, 13, 4313, https://doi.org/10.3390/nu13124313, JIF 6.706 (top 17% journals in Nutrition & Dietetics).

Bromelain exhibits various fibrinolytic, antiedematous, antithrombotic, and anti-inflammatory activities. Bromelain is considerably absorbable in the body without losing its proteolytic activity and without producing any major side effects. Bromelain accounts for many therapeutic benefits like the treatment of angina pectoris, bronchitis, sinusitis, surgical trauma, and thrombophlebitis, debridement of wounds, and enhanced absorption of drugs, particularly antibiotics. It also relieves osteoarthritis, diarrhea, and various cardiovascular disorders. Bromelain also possesses some anticancerous activities and promotes apoptotic cell death, according to Rajendra Pavan et al., “Properties and theraupetic application of bromelain: A review,” *Biotechnology Research International*, 10 December 2012, 976203, https://doi.org/10.1155/2012/976203, JIF N/A.

COVID-19 pathophysiology involves the activation of three main pathways: the inflammatory, the coagulation and the bradykinin cascades. Bromelain (a cysteine protease isolated from the pineapple stem) and curcumin (a natural phenol found in turmeric) exert important immunomodulatory actions interfering in the crucial steps of COVID-19 pathophysiology. Their anti-inflammatory properties include inhibition of transcription factors and subsequent downregulation of proinflammatory mediators. They also present fibrinolytic and anticoagulant properties. Additionally, bromelain inhibits cyclooxygenase and modulates prostaglandins and thromboxane, affecting both inflammation and coagulation, and also hydrolyzes bradykinin. Panagiotis Kritis et al., “The combination of bromelain and curcumin as an immune-boosting nutraceutical in the prevention of severe COVID-19,” *Metabolism Open* (2020), Volume 8, 100066, https://doi.org/10.1016/j.metop.2020.100066, JIF N/A.

PIPERINE

There was a significant improvement in health status, including dry cough, sputum cough, ague, sore throat, weakness, muscular pain, headache, and dyspnea at week 2, in curcumin-piperine group more than in placebo group, according to Gholamreza Askari et al., “The efficacy of curcumin-piperine co-supplementation on clinical symptoms, duration, severity, and inflammatory factors in COVID-19 outpatients: a randomized double-blind, placebo-controlled trial,” *Trials* (2022) 23:472, https://doi.org/10.1186/s13063-022-06375-w, JIF 2.728 (top 76% journals in Medicine, Research & Experimental).

The medicinal properties of curcumin obtained from Curcuma longa L. cannot be utilised because of poor bioavailability due to its rapid metabolism in the liver and intestinal wall. In this study, the effect of combining piperine, a known inhibitor of hepatic and intestinal glucuronidation, was evaluated on the bioavailability of curcumin in rats and healthy human volunteers. In humans after a dose of 2 g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine 20 mg produced much higher concentrations from 0.25 to 1 h post drug, the increase in bioavailability was 2000%. The study shows that in the dosages used, piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in humans with no adverse effects, according to G. Shoba et al., “Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers,” *Planta Medica*, 1998 May;64(4):353-6, https://doi.org/10.1055/s-2006-957450, JIF 3.007 (top 36% journals in Plant Sciences and top 47% journals in Integrative & Complementary Medicine).

Curcumin acts as an antioxidant, anti-inflammatory, anticarcinoma, antimicrobial, antiviral, hypoglycemic and wound healer. It has shown therapeutic efficacy in numerous chronic diseases and in some kinds of cancer *in vitro* and *in vivo*. Despite much evidence of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent due to its low bioavailability, instability at physiological pH, insolubility in water, slow uptake by cells and rapid metabolism inside cells. Piperine (20mg) 20 times enhances the bioavailability of Curcumin (2g), according to Angelo Siviero et al., “Curcumin, a golden spice with a low bioavailability,” *Journal of Herbal Medicine*, Volume 5, Issue 2, June 2015, Pages 57-70, https://doi.org/10.1016/j.hermed.2015.03.001, JIF 2.542 (top 35% journals in Integrative & complementary Medicine).

ZINC

Zinc in the quantity of 50 mg of elemental zinc (from 220 mg capsules with zinc sulfate) per day for 5 days 5 times reduced mortality from COVID-19 vs. the control group, according to the clinical study disclosed in Roland Derwand et al., "COVID-19 outpatients – early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: A retrospective case series study," *International Journal of Antimicrobial Agents*, December 2020, 56(6), 106214, https://doi.org/10.1016/j.ijantimicag.2020.106214, JIF 15.441 (top 3% journals in Pharmacology & Pharmacy).

Zinc 20 mg, vitamin D3 2000 IU, and selenium 100 µg taken by Hashimoto's thyroiditis outpatients, completely eliminated risk of mechanical ventilation from COVID-19 to 0.0% vs. 10.5% in the control group, completely eliminated risk of hospitalization from COVID-19 to 0.0% vs. 27.9% in the control group, completely eliminated risk of severe case from COVID-19 to 0.0% vs. 59.3% in the control group, according to the clinical study disclosed in Zelija Velija Asimi et al., "Selenium, zinc, and vitamin D supplementation affect the clinical course of COVID-19 infection in Hashimoto's thyroiditis," *Endocrine Abstracts*, *European Congress of Endocrinology 2021*, 22 May 2021 – 26 May 2021, 73, https://doi.org/10.1530/endoabs.73.PEP14.2, JIF N/A.

https://www.researchgate.net/publication/351652823_Selenium_zinc_and_vitamin_D_supplementation_affect_the_clinical_course_of_COVID-19_infection_in_Hashimotos_thyroiditis/link/60aaa24592851ca9dcdda5ae/download

This study data clearly show that a significant number of COVID-19 patients were zinc deficient. These zinc deficient patients developed more complications, and the deficiency was associated with a prolonged hospital stay and increased mortality, according to Dinesh Jothimani et al., "COVID-19: Poor outcomes in patients with zinc deficiency," *International Journal of Infectious Diseases*, 100 (2020) 343-349, https://doi.org/10.1016/j.ijid.2020.09.014, JIF 12.073 (top 14% journals in Infectious Diseases).

The importance of zinc (Zn) for cardiovascular health continuously gains recognition. As shown earlier, compromised Zn homeostasis and prolonged inflammation are common features in various cardiovascular diseases (CVDs). Similarly, Zn biochemistry alters several vascular processes, and Zn status is an important feature of cardiovascular health. Zn deficiency contributes to the development of CVDs; thus, Zn manipulations, including Zn supplementation, are beneficial for preventing and treating numerous cardiovascular (CV) disorders. Compromised Zinc homeostasis and prolonged inflammation are common features in various cardiovascular diseases, according to Marija Knez et al., "Zinc as a Biomarker of Cardiovascular Health," *Frontiers in Nutrition*, July 2021, Volume 8, Article 686078, https://doi.org/10.3389/fnut.2021.686078, JIF 6.590 (top 18% journals in Nutrition & Dietetics).

Zinc has protective effects in coronary artery disease and cardiomyopathy according to Peter J. Little et al., “Zinc and cardiovascular disease,” *Nutrition*, November-December 2010, 26(11-12), 1050-1057, https://doi.org/10.1016/j.nut.2010.03.007, JIF 4.893 (top 37% journals in Nutrition & Dietetics).

Zinc, an essential micronutrient, affects the heart by modulating cardiomyocyte oxidative stress and maintaining myocardial structure, among other mechanisms. In cross-sectional studies, patients with heart failure have often had zinc deficiencies, suggesting effects on the ongoing pathogenesis of heart failure. Low plasma and myocardial zinc levels may cause reversible cardiomyopathy in patients who have nutritional deficiencies. We present the case of a 24-year-old woman with anorexia nervosa and new-onset heart failure whose depressed left ventricular systolic function improved after zinc supplementation. To our knowledge, this is the first report of low plasma zinc levels as the chief cause of cardiomyopathy that resolved after zinc supplementation, according to Hannah Rosenblum et al., “Zinc Deficiency as a Reversible Cause of Heart Failure,” *Texas Heart Institute Journal*, April 2020, Vol. 47, No. 2, https://doi.org/10.14503/THIJ-17-6586, JIF 1.103 (top 97% journals in Cardiac & Cardiovascular Systems).

VITAMIN A

Vitamins in the quantities of 25,000 IU vitamin A daily, 600,000 IU vitamin D once, 300 IU of vitamin E twice a day, 500 mg vitamin C four times a day, and one ampule daily of B complex vitamins [thiamine nitrate 3.1 mg, sodium riboflavin phosphate 4.9 mg (corresponding to vitamin B2 3.6 mg), nicotinamide 40 mg, pyridoxine hydrochloride 4.9 mg (corresponding to vitamin B6 4.0 mg), sodium pantothenate 16.5 mg (corresponding to pantothenic acid 15 mg), sodium ascorbate 113 mg (corresponding to vitamin C 100 mg), biotin 60 µg, folic acid 400 µg, and cyanocobalamin 5 µg] completely eliminated deaths from COVID-19 to 0.0% vs. 13.3% deaths in the control group, according to the clinical study disclosed in Mohammad Taghi Beigmohammadi et al., "The effect of supplementation with vitamins A, B, C, D, and E on disease severity and inflammatory responses in patients with COVID-19: a randomized clinical trial," *Trials*, 14 November 2021, 22, 802, https://doi.org/10.1186/s13063-021-05795-4, JIF 2.728 (top 76% journals in Medicine, Research & Experimental).

Vitamin A in the quantity of 200,000 IU per day for 2 days 3 times reduced progression to severe COVID-19 disease vs. the control group, according to the clinical study disclosed in Mahmood M. Al-Sumiadai et al., "Therapeutic effect of vitamin A on COVID-19 patients and its prophylactic effect on contacts," *Systematic Reviews in Pharmacy*, January 2021, 12(1), 207-210, https://www.researchgate.net/profile/Rafi-Al-Ani/publication/351637178_THERAPEUTIC_EFFECT_OF_VITAMIN_A_ON_COVID-19_PATIENTS_AND_ITS_PROPHYLACTIC_EFFECT_ON_CONTACTS/links/60a3a278299bf1d21d6f0b9d/THERAPEUTIC-EFFECT-OF-VITAMIN-A-ON-COVID-19-PATIENTS-AND-ITS-PROPHYLACTIC-EFFECT-ON-CONTACTS.pdf, JIF N/A.

Vitamin A in the quantity of 200,000 IU per day for 2 days 7 times reduced deaths from COVID-19 vs. the control group according to the clinical study disclosed in Mahmood M. Al-Sumiadai et al., "Therapeutic effect of Vitamin A on severe COVID-19 patients," *EurAsian Journal of Biosciences*, 31 December 2020, 14(2), 7347-7350, https://www.researchgate.net/publication/352006870_Therapeutic_effect_of_Vitamin_A_on_severe_COVID-19_patients, JIF N/A.

Nutraceuticals, including vitamin D, vitamin A, zinc, lactoferrin, polyphenols coenzyme Q, magnesium, and selenium, are implicated in the modulation of the complex molecular pathways involved in the immune response against viral pathogens. A common element of the activity of nutraceuticals is their ability to enhance the innate immune response against pathogens by acting on the major cellular subsets and inducing the release of pro-inflammatory cytokines and antimicrobial peptides. Furthermore, nutraceuticals act through complex molecular mechanisms to minimize the damage caused by the activation of the immune system against pathogens, reducing the oxidative damage, influencing the antigen presentation, enhancing the differentiation and proliferation of regulatory T cells, driving the differentiation of lymphocyte subsets, and modulating the production of pro-inflammatory cytokines, according to Giorgio Costagliola et al., "Nutraceuticals in Viral Infections:

An Overview of the Immunomodulating Properties," *Nutrients* 2021, 13, 2410, https://doi.org/10.3390/nu13072410, JIF 6.706 (top 17% journals in Nutrition & Dietetics).

VITAMIN D3

Vitamin D in the quantity of 50,000 IU / weak for 2 weeks followed by 5,000 IU / day for 2.5 months completely eliminated symptomatic case from COVID-19 to 0.0% vs. 22.5% in the control group, according to the clinical study disclosed in Tatiana L. Karonova et al., "Vitamin D intake may reduce SARS-CoV-2 infection morbidity in health care workers," *Nutrients*, 24 January 2022, 14, 505, https://doi.org/10.3390/nu14030505, JIF 6.707 (top 17% journals in Nutrition & Dietetics).

Vitamin D in the quantity of 266 µg on day 3 and 7, and then weekly until discharge or ICU admission completely eliminated deaths from COVID-19 to 0.0% vs. 7.7% in the control group, according to the clinical study disclosed in Marta Entrenas Castillo et al., "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study," *Journal of Steroid Biochemistry and Molecular Biology*, 29 August 2020, 203, https://doi.org/10.1016/j.jsbmb.2020.105751, JIF 5.011 (top 33% journals in Endocrinology & Metabolism and top 37% journals in Biochemistry & Molecular Biology).

Vitamin D in the quantity of 0.5 µg per day for 14 days or hospital discharge completely eliminated deaths from COVID-19 to 0.0% vs. 12.0% in the control group, and completely eliminated risk of mechanical ventilation from COVID-19 to 0.0% vs. 8.0% in the control group, according to the clinical study disclosed in Yasmine M. Elamir et al., "A randomized pilot study using calcitriol in hospitalized patients," *Bone*, 8 September 2021, 154, 116175, https://doi.org/10.1016/j.bone.2021.116175, JIF 4.626 (top 41% journals in Endocrinology & Metabolism).

Vitamin D in the quantity of 200,000 IU once completely eliminated symptomatic cases from COVID-19 to 0.0% vs. 20.0% in the control group in the following 2 months, according to the clinical study disclosed in Sidra Jabeen et al., "Protective effect of vitamin-D supplementation in patients of acute coronary syndrome during COVID-19 pandemic," *Pakistan Journal of Medical and Health Sciences*, 11 May 2022, 16(03), https://doi.org/10.53350/pjmhs221631053, JIF N/A.

Vitamin D has long been recognized as essential to the skeletal system. Newer evidence suggests that it also plays a major role regulating the immune system, perhaps including immune responses to viral infection. Interventional and observational epidemiological studies provide evidence that vitamin D deficiency may confer increased risk of influenza and respiratory tract infection. Vitamin D deficiency is also prevalent among patients with HIV infection. Cell culture experiments support the thesis that vitamin D has direct anti-viral effects particularly against enveloped viruses. Though vitamin D's anti-viral mechanism has not been fully established, it may be linked to vitamin D's ability to up-regulate the anti-microbial peptides LL-37 and human beta defensin 2, according to Jeremy A. Beard et al., "Vitamin D and the anti-viral state," *Journal of Clinical Virology* 2011 Mar, 50(3):194-200, https://doi.org/10.1016/j.jcv.2010.12.006, JIF 14.481 (top 8% journals in Virology).

Vitamin D3 improves circulation and may prove to be beneficial in the treatment of hypertension and other cardiovascular diseases, including heart failure, myocardial infarction, vasculopathy, stroke and diabetes, according to Alamzeb Khan et al., "Nanomedical studies of the restoration of nitric oxide/peroxynitrite balance in dysfunctional endothelium by 1,25-dihydroxy vitamin D3 – clinical implications for cardiovascular diseases," *International Journal of Nanomedicine*, 19 January 2018, 13, 455-466, https://doi.org/10.2147/IJN.S152822, JIF 7.033 (top 12% journals in Pharmacology & Pharmacy).

Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines, according to William B. Grant et al., "Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths," *Nutrients*, 2020, 12, 988; https://doi.org/10.3390/nu12040988, JIF 6.706 (top 17% journals in Nutrition & Dietetics).

Non-classical actions of vitamin D were first suggested over 30 years ago when receptors for the active form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), were detected in various tissues and cells that are not associated with the regulation of calcium homeostasis, including activated human inflammatory cells. The question that remained was the biological significance of the presence of vitamin D receptors in the different tissues and cells and, with regard to the immune system, whether or not vitamin D plays a role in the normal immune response and in modifying immune mediated diseases. In this article findings indicating that vitamin D is a key factor regulating both innate and adaptive immunity are reviewed with a focus on the molecular mechanisms involved. In addition, the physiological significance of vitamin D action, as suggested by in vivo studies in mouse models is discussed. Together, the findings indicate the importance of 1,25(OH)2D3 as a regulator of key components of the immune system, according to Ran Wei et al., "Mechanisms Underlying the Regulation of Innate and Adaptive Immunity by Vitamin D," *Nutrients* 2015, 7(10), 8251–8260, https://doi.org/10.3390/nu7105392, JIF 6.706 (top 17% journals in Nutrition & Dietetics).

Vitamin D insufficiency and deficiency affect approximately half of the US population, with increased rates in people with darker skin, reduced sun exposure, people living in higher latitudes in the winter, nursing home residents, and healthcare workers. Populations with low levels of Vitamin D have also experienced higher rates of COVID-19, according to Jason B. Gibbons et al., "Association between vitamin D supplementation and COVID-19 infection and mortality," *Scientific Reports* (2022) 12:19397, https://doi.org/10.1038/s41598-022-24053-4, JIF 4.997 (top 26% journals in Multidisciplinary Sciences).

Pro-inflammatory cytokines are associated with inflammation and angiogenesis, although there is a discrete variability in the doses of the mediators investigated among the different vitreous samples. Curcumin, homotaurine, and vitamin D3 individually have a slightly appreciable anti-inflammatory effect. However, when used in combination, these substances are able to modify the

average levels of the soluble mediators of inflammation and retinal damage, according to Mariaelena Filippelli et al., “Anti-inflammatory effect of curcumin, homotaurine, and vitamin D3 on human vitreous in patients with diabetic retinopathy,” *Frontiers in Neurology*, 2021, 11, 592274, https://doi.org/10.3389/fneur.2020.592274, JIF 4.086 (top 42% journals in Clinical neurology and top 45% journals in Neurosciences).

In the last 5 years, there has been a remarkable change in our understanding of the health benefits of vitamin D. The classical actions of vitamin D as a determinant of mineral metabolism and rachitic bone disease have been expanded to include a broader role in skeletal homoeostasis and prevalent bone disorders such as osteoporosis. However, it is the nonskeletal function of vitamin D that has attracted most attention. Although pluripotent responses to vitamin D have been recognized for many years, our new perspective on nonclassical vitamin D function stems from two more recent concepts. The first is that impaired, vitamin D status is common to many populations across the globe. This has prompted studies to explore the health impact of suboptimal circulating levels of vitamin D, with association studies linking vitamin D 'insufficiency' to several chronic health problems including autoimmune and cardiovascular disease, hypertension and common cancers. In support of a broader role for vitamin D in human health, studies in vitro and using animal models have highlighted immunomodulatory and anticancer effects of vitamin D that appear to depend on localized activation of vitamin D. The conclusion from these reports is that many nonclassical actions of vitamin D are independent of conventional vitamin D endocrinology and are therefore more sensitive to variations in vitamin D status. The current review summarizes these developments, with specific reference to the newly identified effects of vitamin D on the immune system, but also highlights the challenges in translating these observations to clinical practice, according to Martin Hewison, “An update on vitamin D and human immunity,” *Clinical Endocrinology* 2012, 76, 315–325, https://doi.org/10.1111/j.1365-2265.2011.04261.x, JIF 3.523 (top 64% journals in Endocrinology & Metabolism).

VITAMIN K2

Vitamin D3 deficiency 5 times increases risk of having severe COVID-19. Vitamin K2 and Magnesium should be supplemented together with Vitamin D3, in order to prevent long-term health-risk and improve immunoregulatory effects based on a causal loop diagram, disclosed in Simon Goddek, “Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate,” *International Journal of Infectious Diseases*, 99 (2020) 286-290, https://doi.org/10.1016/j.ijid.2020.07.080, JIF 12.073 (top 14% journals in Infectious Diseases).

Menatetrenone, a vitamin K2 analogue, plays an important role in the production of blood coagulation factors. Menatetrenone has also be shown to have antineoplastic effects against several cancer cell lines including hepatocellular carcinoma (HCC) cells. Vitamin K2 inhibits the growth of HCC cells via suppression of cyclin D1 expression through the IKK/InB/NF-nB pathway, according to Iwata Ozaki et al., “Menatetrenone, a Vitamin K2 Analogue, Inhibits Hepatocellular Carcinoma Cell Growth by Suppressing Cyclin D1 Expression through Inhibition of Nuclear Factor KB Activation,” *Clinical Cancer Research* 2007;13(7) April 1, 2007, https://doi.org/10.1158/1078-0432.CCR-06-2308, JIF 13.801 (top 7% journals in Oncology / top 12% journals in Oncology in 2007).

Animal and human studies suggest that optimal concentrations of both vitamin D and vitamin K are beneficial for bone and cardiovascular health as supported by genetic, molecular, cellular, and human studies, according to Adriana J. van Ballegooijen et al., “The Synergistic Interplay between Vitamins D and K for Bone and Cardiovascular Health: A Narrative Review,” *International Journal of Endocrinology*, Volume 2017, Article ID 7454376, 12 pages, https://doi.org/10.1155/2017/7454376, JIF 2.803 (top 77% journals in Endocrinology & Metabolism).

MAGNESIUM

Vitamin D3 deficiency 5 times increases risk of having severe COVID-19. Vitamin K2 and Magnesium should be supplemented together with Vitamin D3, in order to prevent long-term health-risk and improve immunoregulatory effects based on a causal loop diagram, disclosed in Simon Goddek, "Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate," *International Journal of Infectious Diseases*, 99 (2020) 286-290, https://doi.org/10.1016/j.ijid.2020.07.080, JIF 12.073 (top 14% journals in Infectious Diseases).

In SARS-CoV-2, magnesium (Mg) activates protein kinases, stimulates T-cell receptors and production by generating ATP, controls cell membrane inflammation, and has vasodilatory and antithrombotic effects. Is a modulator of the release of acetylcholine and histamine in the inflammatory cascade in viral infections, according to Theo A.T.G van Kempen et al., "SARS-CoV-2: Influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19," *American Journal of Physiology Endocrinology and Metabolism*, **2021**, 320, E2–E6, https://doi.org/10.1152/ajpendo.00474.2020, JIF 5.900 (top 16% journals in Physiology and top 25% journals in Endocrinology & Metabolism).

We found reduced maternal TNF-a and IL-6 production following in vivo MgSO4 treatment. In summary, MgSO4 reduced cytokine production in intrapartum women, term and preterm neonates, demonstrating effectiveness in those at risk for inflammation-associated adverse perinatal outcomes. By probing the mechanism of decreased cytokine production, we found that the immunomodulatory effect was mediated by magnesium and not the sulfate moiety, and it was reversible. Cellular magnesium content increased rapidly upon MgSO4 exposure, and reduced cytokine production occurred following stimulation with different TLR ligands as well as when magnesium was added after TLR stimulation, strongly suggesting that magnesium acts intracellularly. Magnesium increased basal IκBa levels, and upon TLR stimulation was associated with reduced NF-kB activation and nuclear localization. These findings establish a new paradigm for innate immunoregulation, whereby magnesium plays a critical regulatory role in NF-kB activation, cytokine production, and disease pathogenesis, according to Jun Sugimoto et al., "Magnesium Decreases Inflammatory Cytokine Production: A Novel Innate Immunomodulatory Mechanism," *The Journal of Immunology*, 2012 Jun 15;188(12):6338-46, https://doi.org/10.4049/jimmunol.1101765, JIF 5.430 (top 39% journals in Immunology / top 18% journals in Immunology in 2012).

Magnesium and vitamin D each have the possibility of affecting the immune system and consequently the cytokine storm and coagulation cascade in COVID-19 infections, according to James J. DiNicolantonio et al., "Magnesium and vitamin D deficiency as a potential cause of immune dysfunction, cytokine storm and disseminated intravascular coagulation in COVID-19 patients," *Missouri Medicine,* 118(1), 68–73 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7861592/pdf/ms118_p0068.pdf, JIF N/A.

Magnesium is an essential element required as a cofactor for over 300 enzymatic reactions and is thus necessary for the biochemical functioning of numerous metabolic pathways. Emerging evidence confirms that nearly two thirds of the population in the western world is not achieving the recommended daily allowance for magnesium, a deficiency problem contributing to various health conditions. Level I evidence supports the use of magnesium in the prevention and treatment of many common health conditions including migraine headache, metabolic syndrome, diabetes, hyperlipidemia, asthma, premenstrual syndrome, preeclampsia, and various cardiac arrhythmias. Magnesium may also be considered for prevention of renal calculi and cataract formation, as an adjunct or treatment for depression, and as a therapeutic intervention for many other health-related disorders, according to Gerry K. Schwalfenberg et al., "The Importance of Magnesium in Clinical Healthcare," *Scientifica*, Volume 2017, Article ID 4179326, 14 pages, https://doi.org/10.1155/2017/4179326, JIF N/A.