RESEARCH ARTICLE

Molecular Mechanisms of Curcumin in COVID-19 Treatment and Prevention: A Global Health Perspective

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Abstract

Turmeric (*Curcuma Longa)* has a near 4000-year history of extensive medical use in South Asia. Its main physiologically active phytochemical is curcumin (diferuloylmethane), derived from the rhizome of turmeric. Curcumin is a hydrophobic polyphenol with a diketone moiety connecting two phenoxy rings. It is widely available, and exerts systemic and pleiotropic effects via several key mechanisms. Most famously, it is known to inhibit pro-inflammatory pathways such as PI3k/akt/NF-κB activation. It is also a potent antioxidant and free radical scavenger via a sequential proton loss electron transfer mechanism in ionizing solvents due to its extended conjugating ability across the entire molecule, and its ability to induce NRF-2. It has been implicated in the treatment of diseases ranging from asthma to various cancers, and is also a broad spectrum anti-microbial. COVID-19 is a novel beta-coronavirus that was declared a pandemic by the WHO in March, 2020. It is primarily a respiratory disorder, but it can spread hematogenously and effect many other organs such as the heart, nervous system, and kidneys. There is a significant intersection between the clinical manifestations of COVID-19 and curcumin's therapeutic effects. In addition, curcumin has been shown to inhibit initial viral infectivity. Thus, there is potential for curcumin to safely both prevent and treat COVID-19 infection across the globe.

Keywords: COVID-19, Curcumin, Anti-viral, Anti-inflammatory, Anti-oxidant, Molecular mechanisms

Introduction:

Curcumin (diferuloylmethane) is the major physiologically active phytochemical derived from the rhizome of Turmeric (*Curcuma Longa),* and is what gives Turmeric its golden-yellow color.[1] Turmeric is a rhizomatous, herbaceous, perennial plant; part of the ginger family Zingiberacae which is native to tropical South Asia. Turmeric has a near 4000-year history of extensive medical use in South Asia. It has a history of use in China dating back to 700 AD, and Susrata's Ayurvedic *Compendium*, dating back to 250 BC, endorses a Turmeric ointment to relieve food poisoning.[2] In addition to its use in medicine, Turmeric is used as a spice in cooking, and in food and cosmetics as a coloring agent and preservative. To date, more than 100 components from Turmeric root have been isolated, consisting of two main constituents of curcuminoids and sesquiterpenes.[2,3]

Curcumin, the main curcuminoid of Turmeric extract, was first isolated in 1815, and its chemical structure was determined in 1910.[1] In serum, curcumin exists as a keto-enol tautomer; it is a hydrophobic polyphenol with a diverse set of physiologic actions.[4] It has been shown to be anti-inflammatory, anti-apoptotic, anti-viral, anti-bacterial, anti-fungal, anti-oxidant, anti-arthritic, anti-depressive, suppress carcinogenesis, promote wound healing, neuroprotective, hepatoprotective, cardioprotective, anti-atherosclerotic and hypertensive, and indicated for many dyspeptic conditions such as IBS.[1,3,5–8,9(p),10–15]

SARS-COV-2, also known as COVID-19, is a beta-coronavirus that was first detected in Wuhan, China in December 2019. On March 11, 2020 the WHO declared the outbreak a Pandemic. COVID-19 is primarily a respiratory disorder, but it can spread hematogenously and effect many other organs such as the heart, nervous system, and kidneys.[16] It shares a 79.5% genomic identity to the 2003 SARS-COV outbreak, and it is 96.5% identical to bat coronavirus RaTG13 meaning bats are the most likely natural host of origin.[17] It invades host cells through the ACE2 receptor and primarily causes the disease state via induction of severe inflammation. In severe cases, it induces cytokine storm which leads to sepsis and organ failure and eventual death.[18] Those with underlying chronic conditions such as DM, CV disease, COPD, and CKD seem to be at increased risk for a severe course. This is possibly associated with an increased expression of ACE2 in those chronic conditions, thus aiding viral invasion.

As an anti-viral, curcumin utilizes its pleiotropic effects as a transcription regulator, cell cycle regulator, anti-inflammatory, and anti-oxidant to block multiple steps in the viral replication cycle.[19] Previous studies have shown curcumin, added prior to or upon infection, blocked infectivity of several enveloped viruses in vitro (poxvirus, flavivirus, herpes virus, orthomyxovirus).[20] Once inside the cell, it has been shown to block viral replication in several different viral models. In the treatment of COVID-19, curcumin has shown binding affinity for the receptor binding domain of the S protein (RBDS), the protease domain of ACE2, and the SARS-COV-2 main protease (6LU7).[21,22] Thus, it may prevent adhesion to host cells and prevent cleavage of the initial viral polyprotein to create functional proteins for further viral replication. Furthermore, its effects on expression of pro-inflammatory cytokines may reduce inflammation, fibrosis, and edema in the pulmonary and cardiovascular systems.[23]

Currently, no definitive therapy has been identified for the treatment of COVID-19. Many scientists are looking to repurpose currently commercially available drugs to help fight this pandemic. One such drug is Remdesevir, an anti-viral nucleoside analog previously used in the treatment of Ebola. However, A RCT in Hubei did not show

statistically significant clinical benefits compared to placebo in those admitted to the hospital for severe COVID-19.[24] Moreover, these drugs often come with a host of unwanted side effects and many have already been shown to not improve clinical outcomes.[24–26] A vaccine is still many months away from public use, and the world has already seen shortages of medications that people with other diseases desperately need for their condition. Thus, looking to nature for "tried and true" compounds could prove extremely bountiful. Curcumins' long history of medicinal use and consumption has proven its lack of toxicity, and the current evidence supports a role for curcumin in the possible prevention and treatment of COVID-19 infection.[5,27(p1)] Additionally, much of the global population already consumes or has access to curcumin at little cost to the individual. Therefore, curcumin represents a cost effective and already globally mobilized potential medication for the treatment and prevention of COVID-19.

1.0 - COVID-19

COVID-19 is a novel Coronavirus genetically similar to the SARS-COV outbreak of 2003.[17] The Coronavirus family are enveloped, positive sense, SS RNA viruses with an unsegmented genome of approximately 30 kb and a 5' cap and 3' poly A tail structure within a helical capsid.[28] It is primarily transmitted via respiratory droplets, although there is evidence to suggest the possibility of fecal-oral transmission.[29] It codes for a set of Non-structural proteins (NSP's) as well as five structural proteins: Spike (S), Envelope (E), Membrane (M), Nucleocapsid (N), and hemagglutinin esterase (HE). The S, E, M, and HE proteins are all embedded in the viral envelope, whereas the N protein binds its RNA genome and helps tether it to the replicase-transcriptase-complex (RTC).[28,30,31] Initial translation generates a large polyprotein that must be cleaved by the SARS-COV-2 main protease to generate the RTC which can then go on to transcribe and replicate mRNA and viral RNA for packaging and release. Final translation and packaging for virion exocytosis occurs in the RER and the golgi apparatus, respectively.

1.1– Pathophysiology

SARS-COV-2 gains entry to host cells through RBDS binding the ACE2 receptor which is expressed on the surface epithelium of the lungs, heart, kidney, endothelial cells, small intestine enterocytes, and in several structures of the central nervous system.[32] Once bound to ACE2, the S protein is cleaved in two locations by a transmembrane protease, serine 2 (TMPRSS2) to create a fusion peptide which can then fuse with the cell and enter via an endosome. Expression of the ACE2 receptor seems to correlate with disease activity, and possibly explains the diverse set of symptoms patients experience.[33] Symptoms include fever, dry cough, dyspnea, fatigue, anosmia, dysgeusia, and in severe cases a pneumonia that leads to ARDS and septic shock.[34] In addition to direct effects of SARS-COV-2 on ACE2 expressing cells, a significant portion of the systemic symptoms arise due to a dysregulated immune response that leads to cytokine storm, DIC, and microangiopathy's.[18,35]

1.2 – Current Treatment and Prevention Strategies

Currently, a definitive treatment for SARS-COV-2 does not exist. The standard of care is supportive with IV fluids, supplemental O_2 therapy, and regular monitoring of imaging and labs. Many pharmaceutical companies are working on vaccines, but those are many months down the line and do not help the immediate situation our society finds itself in. Others are working on repurposing existing drugs in the short term and several trials are ongoing to assess the clinical benefits of different potential therapies. Early data

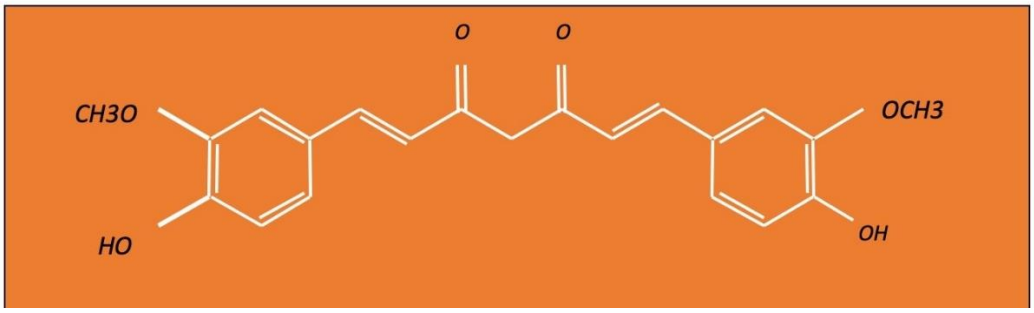
showed Remdesivir as a potential treatment option to shorten the duration of symptoms, but a RCT in Hubei did not show a statistically significant clinical benefit compared to placebo in those admitted for severe COVID-19.[24] Another RCT examined a combination therapy of Lopinavir and Ritonavir, two anti-retroviral protease inhibitors, in hospitalized patients with COVID-19 and found no observable benefit with treatment beyond standard of care.[25] Additionally, Hydroxychloroquine is now famous for being studied as a potential treatment for COVID-19. However, most studies have shown no and/or negative results associated with hydroxychloroquine.[36]

2.0 - Curcumin

Most of turmeric's therapeutic activity occurs through curcumin, although it is not the only physiologically active compound within turmeric extract. Turmeric extracts' main physiologically active constituents actually exist in near equal fractions consisting of curcuminoids and sesquiterpenes.[3] The main curcuminoids are curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). The major sesquiterpenes include ar-turmerone, α-turmerone, and β-turmerone. Interestingly, a study examining the hepatoprotective effects of various turmeric fractions found that both the sesquiterpene and curcuminoid fraction suppressed increases in LFT's in rats in a D-galactosamine induced liver injury model.[3] Because sesquiterpenes are expected to have little anti-oxidant activity, it was suggested that different hepatoprotective mechanisms are at play for sesquiterpenes than for the anti-oxidant curcuminoid fraction. The focus of this review, however, will be on the curcuminoid fraction of turmeric extract.

The structure of curcumin makes it highly lipid soluble and as such it is well known to position itself in cellular membranes where it exerts many of its beneficial effects.[37–39] Its central diketone moiety also makes it a Michael Acceptor electrophile capable of forming covalent bonds. Further, the central diketone and two phenoxy rings make it a very stable free radical intermediate and excellent free radical scavenger due to its extended conjugating ability between the two moieties (Figure1).

Figure 1: Structure of curcumin (Diferuloylmethane)



2.1- Mechanisms of Action

Curcumin has been shown to have extensive effects throughout nearly every organ system of the human body ranging from neuroprotective effects in diseases such as Alzheimer's, to promotion of healing and collagen deposition in wound models, to anti-microbial effects that have been demonstrated against a wide range of pathogens including COVID-19.[1,21,40,41] As mentioned previously, curcumin is able to achieve its wide range of effects through a few key mechanisms (Figure

2). Its lipophilic nature and strong anti-oxidant abilities give it a membranoprotective function in cells throughout the body and help alleviate symptoms in many inflammatory states.[7,37] Its Michael Acceptor capability allow it to covalently modify and inactivate key signaling proteins in the body such as ErbB2.[42] Its ability to modulate intracellular signaling cascades such as NF-κB, PI3k/akt, and MAPK pathways make it an excellent candidate to attenuate the immune response and halt aberrant cell cycle progression in a variety of conditions ranging from asthma to cancer.[6(p2),43,44] Curcumin also upregulates key transcription regulators, such as NRF2, which is a master control regulator gene involved in the anti-oxidant response via upregulation of expression of key anti-oxidant enzymes SOD, catalase, and glutathione peroxidase.[45] Additionally, and perhaps underappreciated, is its ability to cross the blood-brain-barrier and exert neuroprotective effects, a feature many modern synthetics drugs have a difficult time obtaining yet nature seems to have mastered.[15,46] Further detailed discussion of these mechanisms in specific organ systems and conditions will be presented in the following sections.

Figure 2: Possible curcumin effects against SARS-COV2 (COVID -19)

2.2 - Effects on Respiratory Disorders

Curcumin is well documented in Ayurveda to treat several respiratory conditions including asthma, allergies, bronchial hyperreactivity, and sinusitis among others.[2] For example, one home remedy calls for powdered turmeric taken with boiled milk to cure cough and other related respiratory ailments.[47] At the molecular level, much of curcumins ability to treat a disorder such as asthma relies on its ability to attenuate the inflammatory response through suppression of NF-κB signaling and its downstream gene products such as COX-2.[6] NF-κB is an inducible transcription factor heavily involved in regulating the immune and inflammatory response. It's downstream products include pro-inflammatory mediators such as TNF-α, COX-2, IL-1β, and IL-6.[48] Curcumin suppresses NF-κB activation and nuclear translocation through two distinct mechanisms. First, its anti-oxidant effects at the lipid bilayer inhibit initial membrane damage by decreasing the amount of reactive oxygen species present and subsequent activation of the PI3k/akt/NF-κB inflammatory pathway. Second, it was shown that it significantly inhibited IKBα kinase, leading to decreased degradation of IKBα which binds and inhibits NF-κB to prevent nuclear translocation.[49] It also downregulated expression of PI3k and akt proteins and downregulated expression of NF-κB at the mRNA level.[40] Another study in a viral-induced ARDS model found that curcumin decreased expression of key cytokines implicated in the development of ARDS: IL-6, IL-10, IFN-γ, and MCP-1. This was speculated to be due to a reduction in the phosphorylated form of NF-κB p65. It also significantly reduced expression of the TGF-β receptor II, effectively reducing TGF-β signaling, and key markers of myofibroblast activation such as α-smooth muscle actin and Tenascin-C. This data strongly supports a role of curcumin in reducing inflammation, fibrosis and edema associated with the development of a viral-induced ARDS.[23]

2.3 - Effects on Immune Disorders

In recent years, curcumin has been increasingly studied for its immunomodulatory effects. It has been shown to modulate activation and proliferation of T and B cells, macrophages, NK cells, dendritic cells, and neutrophils.[50] Its immunomodulating effects are also apparent due to its inhibition of the NF-κB pathway and its downstream pro-inflammatory cytokine and chemokine production. There is evidence to suggest curcumin inhibits IL-2 synthesis, along with the proliferation of CD4+ and CD8+ T cells, correlated with suppression of NF-κB in lymphocytes derived from human spleen.[51] Another study found a dose dependent effect of curcumin on the proliferation of splenic lymphocytes. At low doses there was upregulation of proliferation whereas at high doses there was suppression of proliferation of splenic lymphocytes, indicating an immunomodulatory rather than entirely suppressive effect on T cell proliferation.[52] Curcumin has also been shown to block EBV induced immortalization of human B cells, an effect thought to be associated with its ability to reduce oxidative stress associated with cyclosporine use, indicating a potential therapy to halt post-transplant lymphoproliferative disorder in patients receiving cyclosporine as an immunosuppressant.[53] In peritoneal macrophages, curcumin has been shown to enhance phagocytosis.[52] Further, it inhibits IL-17 induced iNOS expression at the mRNA level in activated macrophages.[54] Multiple reports suggest a beneficial role for curcumin in the treatment of many immune disorders such as Alzheimer's disease, Multiple Sclerosis, CV diseases, IBD, diabetes, allergies, asthma, rheumatoid arthritis, and scleroderma.[50]

Interestingly, curcumin seems to preferentially effect dysplastic and/or dysregulated cells over normal, healthy cells.[55] There are several hypotheses for why this might be the case. First, dysplastic cells often constitutively express and rely on NF-κB signaling for continued activation and proliferation. Second, cellular uptake of curcumin is higher in cancer cells than normal cells.[56] Third, curcumin seems to be a pro-oxidant at higher concentrations. At higher concentrations it provokes glutathione depletion, caspase-3 activation, and hepatotoxicity, whereas at lower concentrations hepatocytes are protected with less lipid peroxidation and cytochrome c release.[57] Thus, there is evidence that tumor cells are at increased susceptibility to Curcumin induced apoptosis while simultaneously inducing the classic redox modulating, cytoprotective effects of curcumin on normal cell lines.[58]

2.4 - Effects on Hypertension

Curcumin exerts anti-hypertensive effects primarily by downregulating AT1 receptor expression in vascular smooth muscle cells. It seems to do so by suppressing specificity protein-1 binding with the AT1 receptor promoter region, thereby decreasing AT1 receptor expression in vitro and in vivo.[59] There is potential for curcumin to have a synergistic effect with ACE inhibitors or ARBS, but there has yet to be a study examining such a synergism in the reduction of hypertension. Curcumins' pleiotropic effects are also at play in its role as an anti-hypertensive. Hypertension is a disease that works in a positive feedback loop where increased tension in the vascular endothelium induces oscillatory sheer stress that is associated with generation of ROS and subsequent inflammation that leads to vascular smooth muscle proliferation and further hypertension.[60] Not only does curcumin inhibit AT1 mediated vascular constriction, it also inserts itself in the middle of a major hypertensive pathway by reducing ROS, activating NRF-2 to increase anti-oxidant enzyme levels, and subsequently reducing ROS generated pro-inflammatory signaling.[45] Another study found administration of curcumin inhibited ATII-induced abdominal aortic aneurysms in Apo E-/E- mice through anti-oxidative, anti-inflammatory and downregulation of ERK signaling pathways.[61] There are other mechanisms curcumin uses to reduce blood pressure including its anti-hyperlipidemic and nephroprotective functions, however they will be discussed further in sections 2.5 and 2.8, respectively.

2.5 - Effects as a Cardio-protective Agent

As a cardioprotective agent, curcumin exhibits anti-oxidant, anti-inflammatory, anti-hypertensive, anti-atherosclerotic, anti-apoptotic, and anti-cardiac remodeling effects. In a rat model, curcumin was shown to significantly reduce MAP and improve cardiac fibrosis. It did so through upregulation of the AT2 type 2 receptor, downregulation of AT2 type 1 receptor, and increasing expression of ACE2 in the myocardium.[62] AT2 type 2 receptors are thought to counter-regulate AT2 type 1 receptor function and are associated with improved cardiac function in ischemic injury models.[63] Downregulating AT2 type 1 receptor is similar in mechanism to administering ARB's and can prevent AT2-induced cardiac remodeling. ACE2 is also cardioprotective. It is a functional receptor that acts as a counterbalance to ACE by cleaving angiotensin II into angiotensin (1-7), a vasodilator. Furthermore, the same study found that curcumin treatment significantly reduced macrophage populations and α-smooth muscle actin-expressing myofibroblasts. This was attributed to a reduced expression of TGF-β and phosphorylated SMAD-2 and 3, both part of a pro-fibrotic signaling cascade.[62] In an induced myocardial ischemia-reperfusion injury

model, turmeric at 100 mg/kg for 1 month provided significant cardio protection via reduction in apoptosis. It was found to significantly decrease TUNEL positivity and BAX expression while significantly increasing BCL-2 expression.[12]

Curcumin possesses noteworthy anti-hyperlipidemic effects as well. In a study of male Sprague-Dawley rats both turmeric root and turmeric extract enriched for curcumin repressed the expression of cholesterol biosynthesis genes. Upon Ingenuity Pathway Analysis it was found that curcumin activates expression of SREBF2, a gene controlling the transcription of the LDL receptor, cholesterol biosynthesis, and the fatty acid synthesis pathway, albeit the latter to a smaller extent.[64] Because statins cause feedback upregulation of cholesterol biosynthesis genes it was speculated that a synergism exists between curcumin and statins that would enable a lower therapeutic dosage and lessen the toxic side effects associated with statins such as myopathy.

2.6 – Effects as a Neuro-protective Agent

Curcumin is highly hydrophobic and is able to effectively penetrate the blood-brain-barrier to exert pleiotropic neuroprotective effects. It has shown positive actions in the treatment of Alzheimer's disease, tardive dyskinesia, depression, epilepsy, diabetic neuropathy, and others.[15] Its mechanisms of action include anti-oxidant and anti-inflammatory properties, inhibition of reactive astrocyte expression, and modulation of the central monoaminergic system. Multiple studies have shown turmeric extracts anti-depressive effects with its ability to modulate neurotransmitter levels as well as control inflammation.[11,65,66] In a forced swim test rat model, turmeric extract attenuated decreases in serotonin, 5-HIAA, noradrenaline, dopamine, and increases in serotonin turnover as well as corticotropin releasing factor and cortisol levels.[11] Another study found similar results of increased serotonin, noradrenaline, and dopamine in the brain, and also found curcumin inhibits monoamine oxidase activity in the mouse brain.[66] Another group showed pretreatment with curcumin for 7 days reversed LPS-induced alterations in the forced swim test, tail suspension test, and sucrose preference test.[65] They found that curcumin attenuated microglial cell activation and subsequent production of pro-inflammatory cytokines (IL-1β, TNF-α), iNOS, and COX-2 mRNA; most likely through attenuation of NF-κB activation. In Alzheimer's disease, it has been shown that β-amyloid oligomers induce c-jun N-terminal Kinase (JNK) activation leading to phosphorylation of Tau and Insulin receptor substrate-1 (IRS-1). IRS-1 is involved in insulin and neuroprotective signaling, and phosphorylation of IRS-1 leads to its degradation.[41] Curcumin has been shown to inhibit many protein kinases, including JNK, thus may be useful in the treatment and prevention of AD with a tau pathology.[5,41]

2.7 – Effects as a Hepato-protective Agent

As a hepatoprotective agent turmeric extract exerts anti-oxidant and anti-inflammatory effects among other mechanisms that have yet to be elucidated. In a rat model of D-galactosamine-induced liver injury, a turmeric extract supplemented diet suppressed increases in LDH, ALT, and AST levels. Interestingly, the same study showed that both the curcuminoid and sesquiterpene fractions of turmeric extract suppressed LFT increases suggesting there are other mechanisms, beyond anti-oxidative effects, unique to sesquiterpenes that need further study.[3] Furthermore, it is an excellent metal chelator, probably due to its multiple hydroxyl and methoxy groups, protecting the liver from toxic heavy metal exposure such as in hemochromatosis.[67] A group examined the hepatoprotective effects of curcumin on Lindane-induced oxidative stress in male

Wistar rats. They found that curcumin, given pre or post treatment with lindane, attenuated nearly all increases in lipid peroxidation and decreases in glutathione, SOD, catalase, glutathione-s-transferase, glutathione peroxidase, glutathione reductase, and NADPH quinine reductase activities.[68] Finally, a study extensively examined curcumin for the potential treatment of liver cirrhosis and found promising results. They found its anti-oxidant and anti-inflammatory functions were central to its anti-cirrhotic effects along with its ability to differentially induce apoptosis in damaged hepatocytes, reducing the subsequent inflammation, hepatic stellate cell activation, and fibrosis.[69,70] In a thioacetamide-induced hepatic fibrosis model, the same model used above, curcumin induced apoptosis by upregulating p53 and BAX mRNA expression while simultaneously downregulating BCL-2 mRNA expression, thus increasing susceptibility of damaged hepatocytes to thioacetamide-induced cytotoxicity and apoptosis, thereby decreasing further inflammation and fibrosis.[70]

2.8 – Effects as a Nephroprotective Agent

Much of curcumin's nephroprotective effects come from its abilities as an anti-inflammatory and to maintain renal perfusion and a favorable cellular redox state in the face of severe or long-term oxidative stress, inflammation, or nephrotoxicity. Curcumin's protective effects have been evaluated in diabetic nephropathy, nephrotoxicity, perfusion-reperfusion, and chronic renal failure models.[71] It's ability to induce NRF-2 and its downstream anti-oxidant products, preserve mitochondrial function, and its anti-inflammatory properties have been identified as key players in curcumins renoprotective effects.[45,71] Kuhad et al. showed pretreatment with curcumin reduced cisplatin-induced nephrotoxicity by restoring renal function and reducing lipid peroxidation and serum TNF-α levels; indicating a nephroprotective effect attributed to its anti-oxidant and anti-inflammatory capabilities.[72] Curcumin derivatives have also shown promising results. In streptozocin-induced type 2 diabetic rats, a curcumin analog known as B6 ((E, E)-1, 5-bis(2-bromophenyl)- 1,4-pentadiene-3-one) reduced blood urea nitrogen, creatinine, urine albumen/24 h, and angiotensin II levels while simultaneously increasing ACE2 expression.[73]

2.9 – Effects as an Anti-inflammatory Agent

In recent years, curcumin has become famous for its role as an anti-inflammatory. It is most well-known for its inhibition of the NF-κB pathway, a nuclear translocation factor that responds to a broad range of stimuli and promotes expression of many pro-inflammatory cytokines and chemokines including TNF-α and IL-1β. For example, Yuan et al. found curcumin attenuated airway inflammation and remodeling via inhibition of NF-κB and downstream COX-2 signaling in cigarette-smoke induced COPD mice.[6] The mechanism of action of NF-κB suppression seems to be due to curcumins ability to inhibit IKBα kinase, thus IKBα does not get phosphorylated or degraded and is free to continue to inhibit NF-κB's nuclear translocation and its pro-inflammatory downstream products.[49] Additionally, curcumin seems to work to reduce NF-κB activation via its anti-oxidant capacity and inhibition of reactive oxygen species generation. By eliminating ROS, further downregulation of the NF-κB pathway occurs. In a wound healing model on rats, Mohanty et al. found that the combination of curcumin's free radical scavenging ability along with its downregulation of the NF-κB pathway led to reduced inflammation and faster and stronger wound healing with early implementation of fibroblasts and collagen deposition on biochemical and histological analysis, compared to control. Biochemically, they saw a significant increase in expression of IKBα, downregulation of PI3k and pAKT proteins,

and downregulation of NF-κB at the mRNA level.[40]

Curcumin is also known to inhibit the arachidonic acid (AA) metabolism pathway at multiple points. First, it inhibits phosphorylation of cytosolic phospholipase A2 (cPLA2) thereby inhibiting the entire AA pathway before it begins.[74] They postulated cPLA2 inhibition probably occurs due to inhibition of a MEK related pathway, which is known to induce phosphorylation of cPLA2. It also inhibits the peroxidase activity of COX-1 and decreases the expression of COX-2, the latter most likely due to its inhibition of NF-κB activation, and inhibits the enzymatic activity of 5-LOX.[74] Another group found curcumin binds lipoxygenase in a non-competitive manner to inhibit its catalytic activities.[75] Thus, nearly the entire AA metabolism pathway is inhibited by curcuminoids and this is another mechanism through which curcumin is able to reduce inflammation and further tissue damage.

2.10 – Effects as an Anti-microbial Agent

Curcumin has exhibited broad spectrum antiviral, antifungal, and antibacterial effects.[1] It has shown antibacterial activity against gram positive and negative bacteria ranging from *S. Aureus* to *E. Coli*.[76] In fact, one study found curcumin to be bactericidal, and the most efficient plant extract at preventing adhesion to stomach sections and killing *H. pylori* within 15 minutes of incubation.[77] Thus, opening up the possibility to use curcumin as an alternative to antibiotics and prevent the associated antibacterial resistance that comes with prolonged use. Its mechanism of action as an antibacterial seems to involve suppressing FtsZ polymerization and assembly, leading to disruption of prokaryotic cell division.[78] Curcumin's antifungal effects have also been demonstrated against a wide range of pathogens. It has shown activity against *Cryptococcus Neoformans* and *Candida Albicans* among others, and it had the most activity against *F. solani* and *H. oryzae* with the lowest IC50 values recorded.[8]

As an anti-viral, curcumin seems to exert its effects through multiple mechanisms including modulating cell signaling pathways, cell growth and apoptosis, and reduction of oxidative stress and inflammation.[19] There is evidence to suggest it is an inhibitor of IMP dehydrogenase, an important rate limiting enzyme in the de novo synthesis of guanine nucleotides, in a both competitive and uncompetitive binding mechanism. In a dose-dependent manner it was found curcumin reduced the cellular GTP pool and cellular growth in HT-29 colonic carcinoma cells.[79] Additionally, Many viruses hijack signaling cascades such as PI3k/AKT and NF-κB to aid them in survival and efficient viral replication.[19] For example, *Influenza* virus redirects NF-κB's anti-viral activity toward a pro-viral function in which it induces apoptosis and increases the viral load via upregulation of Fas-L, TNF-related apoptosis inducing ligand, and others.[80] As discussed previously, curcumins ability to modulate these pathways represents a novel antiviral therapeutic approach. Furthermore, curcumin seems to modulate post-transcriptional and translational modifications including inducing dysfunction of the ubiquitin proteasome system (UPS).[81] In VSV infection, a rhabdoviridae, Dicer-1 activity was shown to be limited, whereas curcumin treatment increased Dicer-1 expression and limited VSV infection.[82] They found that curcumin alone had limited effect on Dicer-1 expression, thus concluded that curcumins' reduction of oxidative stress probably mediated its effects on VSV restriction. Finally, curcumins dysregulation of the UPS seems to be a communal mechanism in which it inhibits efficient viral replication. Among other viruses, curcumin treatment suppressed coxsackie virus B3 replication via reduction of 20s proteasome activity and cellular deubiquitinating activities. Si et al.

found an increased accumulation of ubiquitinated proteins and decreased levels of free ubiquitin leading to the postulation that UPS dysregulation plays a role in viral inhibition.[81]

Outside of intercellular signaling events, there is evidence that it directly inhibits both viral attachment and viral genome replication. Previous studies have shown curcumin, added prior to or upon infection, blocked infectivity of several enveloped viruses including Poxvirus, Flavivirus, Herpes virus, and Orthomyxovirus.[20] The mechanism has been alluded to throughout this review and is due to curcumins lipophilic structure. Because it positions itself in lipid bilayers, it disrupts the integrity of membranes through both thinning the bilayer as well as possibly weakening its elastic moduli, and therefore indirectly affects the properties of membrane bound proteins that aid in viral adhesion and entry.[38] Interestingly, curcumin seems to more greatly effect smaller liposomal membranes and does so at lower concentrations which helps to explain its differential effects on human cells versus enveloped viruses. For influenza virus (~100 nm diameter), the concentration of curcumin required to inhibit plaque formation was lower than for pseudorabies virus (~180 nm diameter) and the vaccinia virus (~335x200x200 nm).[20] Another group has shown curcumin to inhibit HIV-protease and integrase via direct intermolecular binding to their active sites; a function attributed to its keto-enol moiety as critical to its inhibitory action.[83] Finally, curcumin was shown to suppress TAT-dependent HIV transcription by ~55%, attributed to its Michael Acceptor electrophile capability.[84]

3.0 – Curcumin for COVID-19

As the COVID-19 pandemic continues to evolve, new research continues to be released on curcumin as a specific treatment and prevention option. First, a molecular docking study revealed curcumin and its two main derivatives (DMC, BDMC) to have binding affinity for the SARS-COV-2 RBDS, the protease domain of ACE2, and the SARS-COV-2 main protease.[21] The first two proteins are involved in cellular adhesion, fusion and entry, and the latter is involved in cleaving the initial viral polyprotein to create the RTC. The ΔG for curcumin was calculated to be -11.82 for the main protease, -8.39 for RBDS, and -9.04 for the protease domain of ACE2.[21] Furthermore, another group confirmed curcuminoids inhibitory nature of the main protease via hydrogen bonding to the active site pocket.[22] Binding energies were calculated for the compounds against the main protease, and curcumin and DMC had ΔG's of -7.05 and -7.99 respectively, effects comparable to the native ligand found to have a ΔG of -8.37. These binding energies were also compared to modern antiviral protease inhibitors Lopinavir and Nelfinavir who had binding energies of -9.41 and -10.72, respectively.[22] Thus, there are mixed results on curcumin's affinity for the SARS-COV-2 main protease relative to current viral protease inhibitors, but we do know that affinity is comparable to that of the native ligand for the enzyme. As discussed previously, curcumins ability to integrate into membranes to disrupt integrity and protein function of enveloped viruses also works to its advantage in preventing COVID-19 cellular adhesion, fusion and entry.

There is also evidence to suggest COVID-19 antagonizes STAT1 and disrupts cellular interferon signaling cascades leading to an inhibited anti-viral response by the body.[85] This may partially explain why the elderly have higher mortality rates and children have lower rates. The elderly have a higher response threshold to interferon stimulation and thus may not have an adequate response to COVID-19 infection. In PEDV infected cells as a coronavirus model, Ting et al. demonstrated that curcumin-cationic dots stimulated production of interferon stimulated

genes(ISG's) at the mRNA level; thus offering a possible treatment strategy to bypass innate interferon signaling cascades and activate the body's anti-viral response.[86] Previous studies on the original SARS-COV papain-like protease, a highly conserved and essential protein for coronavirus replication, showed it induces generation of ROS and activates the pro-fibrotic response via TGF-β1. As discussed in section 2.2, curcumin downregulates expression of the TGF-β receptor II and scavenges free radicals, and thus inhibits TGF-β mediated fibrosis.[23]

COVID-19 is also known to activate the coagulation cascade secondary to ARDS, hypoxia, and subsequent production of tissue factor inducing a hypercoagulable state sometimes leading to DIC.[87] In many use cases the main side effect of curcumin consumption is increased bleeding. However, in the treatment of COVID-19 this effect is a positive one. An *in vivo* study found curcumin and BDMC significantly increased aPTT and PT times, and inhibited the generation of thrombin and factor Xa.[88] It was concluded that daily consumption of turmeric or curcumin may help to maintain an anti-coagulant status, and thus represents another beneficial effect of curcumin in the treatment of COVID-19.

In summary, curcumin has been shown to inhibit enveloped viruses like COVID-19, to inhibit several key proteins involved in adhesion and replication, and to activate ISG's at the mRNA level to promote our innate immune system's anti-viral response. In addition, its potent anti-oxidant, anti-inflammatory, and anti-coagulation effects work to fight COVID-19 by inhibiting efficient viral replication, lowering the viral load, and reducing associated systemic inflammatory symptoms.

Discussion:

COVID-19 is largely a respiratory disease, but manifests in severe cases with systemic inflammatory symptoms leading to complications such as ARDS, AKI and myocardial injuries.[18] Curcumin's ability to systemically regulate transcription, inhibit pro-inflammatory pathways, scavenge free radicals, and inhibit viral adhesion and replication make it a candidate for use in the prevention and/or treatment of COVID-19 and other viruses. It is important to note the significant intersection of COVID-19 systemic manifestations and the benefits of curcumin administration noted herein, and by several others that have examined curcumin as a preventative or treatment option.[89–91] In every system where COVID-19 seems to manifest, including the CNS, curcumin has broad spectrum coverage of the associated inflammatory symptoms.

The most potent effects of curcumin in the treatment of COVID-19 are probably its roles as an anti-inflammatory and anti-oxidant. These two features synergistically act together to reduce cellular inflammation and manage the cellular redox state. Liu and Ying highlighted and summarized how curcumin has a growing pile of evidence in favor of its use in the treatment of pneumonia and ARDS, the major severe manifestation of COVID-19, by attenuating the pro-inflammatory response and resulting cytokine storm.[91]

Others have also pointed out the epidemiology of COVID-19 across the globe, and identified Southeast Asia as both a region that has had both persistently low death rates attributed to the virus and a distinctively high daily consumption rate of curcumin in their populations.[92] Obviously there could be many confounding variables in such a correlation, but given that most western healthcare systems historically provide excellent care we should analyze why more people may be dying in these wealthy countries, and consider the possibility that the significant overlap of curcumin and COVID-19 mechanisms are playing a role in this variation of death rate in Southeast Asia compared to many western countries.

Curcumin may be best used as a prophylactic measure across the globe as it inhibits viral entry and exerts its general anti-viral effects. In its use as a prophylactic, we may be able to reduce viral load, potentially leading to a suppressed clinical manifestation in a given patient. This is an extremely important point. This pandemic exposed healthcare systems around the globe as hospitals reached capacity, ventilators ran out, and medications became scarce. If supplementation with curcumin could reduce the number of people who experience a severe course, our healthcare systems would be better able to absorb the burden of the pandemic and we may see a reduced mortality rate. As a treatment option it must not be ignored as an adjuvant therapy in developed countries and in developing countries where medical supply chains are not as robust and access to modern medicines may be limited.

It is also important to note the lack of toxicity and side effects associated with curcumin. Since it has been used for so long and in so many industries, we know it is safe for consumption and does not exhibit any of the side effects that many if not all modern anti-viral drugs inherently come attached to. Furthermore, curcumin is immediately available around the globe, without a prescription, at a fair price to the consumer. There are very few, if any, treatment options available to people today with such ease of access.

Although curcumin alone may not be as strong as some anti-virals in directly treating COVID-19 infection, we must remember to "zoom out" and look at the whole body when fighting disease. Curcumin is not specific; it disseminates throughout the body and exerts pleiotropic effects to fight a wide range of conditions. Thus, in the case of COVID-19, we can fight nearly all manifestations with one molecule. Additionally, many patients at most risk for severe course have other underlying conditions such as CV disease, CKD, and COPD. As described above, curcumin plays a protective role in all of these conditions. Specifically with the respiratory manifestations of COVID-19, we know curcumin can help to fight viral-induced ARDS and should be used as an adjuvant to prevent lung fibrosis.[23]

Finally, it is worth mentioning curcumins Michael acceptor electrophile ability and its extended conjugation ability make it an excellent candidate for better drug designs moving forward. Furthermore, others have pointed out that it does not violate any of Lipinski's Rule of 5 and thus has a favorable structure for drug design.[93] Nature has many hidden gems yet to be discovered, yet we have today one of its most promising creations in curcumin. We should be taking cues from these ancient molecules like curcumin to design safer, more effective derivatives that exert specific and stronger effects.

Conclusion:

The current evidence on the pathophysiology of COVID-19 along with its enveloped structure supports a role for curcumin as a potentially viable prophylactic and therapeutic option. As an anti-viral, curcumin represents a non-toxic, cost-effective, prescription free, and immediately available preventative measure people across the globe can take advantage of today. This is especially important in developing countries where medical supply chains are severely limited, and modern treatment options largely inaccessible to the majority of the population. In developed countries its role as a prophylactic measure and possible adjuvant therapy in clinical treatment cannot be underestimated as an additional tool at our disposal. In addition, its overall anti-inflammatory effects offer something to gain for nearly everyone in supporting the longevity of the body. More work needs to be done regarding formulations to increase bioavailability as well as direct testing against

all coronaviruses, including COVID-19, so we are better prepared to handle the next inevitable outbreak.

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The authors have no conflicting interests to disclose.

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