Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter 18

Transforming curry extract-spice to liposome-based curcumin: lipocurc to restore and boost brain health in COVID-19 syndrome

Simon S. Chiu[1,2,8], Kristen Terpstra[3], Michel Woodbury-Farina[4], Vladimir Badmaev[5], Josh Varghese[6], Hana Raheb[1], Ed Lui[7], Zack Cernovsky[8], Yves Bureau[9], Mariwan Husni[10], John Copen[11], Mujeeb Shad[12], Autumn Carriere[13], Zahra Khazaeipool[14], Weam Sieffien[15], Marina Henein[16], Brendan Casola[17] and Siddhansh Shrivastava[18]

[1]Lawson Health Research Institute, London, ON, Canada; [2]Geriatric Mental Health Program, London Health Sciences Centre, London, ON, Canada; [3]Neurological Unit, St Michel's Hospital Affliliated with University Toronto, Toronto, ON, Canada; [4]Department of Psychiatry, School of Medicine, University of Puerto Rico, PR, United States; [5]Medical Holdings Inc, New York, NY, United States; [6]Marian University College of Osteopathic Medicine, Indianapolis, IN, United States; [7]Department of Pharmacology, Schulich School of Medicine, University Western Ontario, London, ON, Canada; [8]Department of Psychiatry, University of Western Ontario, London, ON, Canada; [9]Department of Psychology, University of Western Ontario London ON, Lawson Health Research Institute, London, ON, Canada; [10]Department of Psychiatry, Northern Ontario Medical School, Thunderbay, ON, Canada; [11]Department of Psychiatry, University of British Columbia, University of Victoria Medical Campus, Victoria, BC, Canada; [12]Department of Psychiatry, Oregon Health Sciences University, Portland, OR, United States; [13]Faculty Applied Sciences, Nipissing University, North Bay, ON, Canada; [14]University of Western Ontario, London, ON, Canada; [15]University of Toronto Faculty of Medicine, Toronto, ON, Canada; [16]National University of Ireland Galway, Research Institution in Galway, Galway, Ireland; [17]University of Guelph, Guelph, ON, Canada; [18]Avalon University School of Medicine, Sta. Rosaweg 122-124 WIllemstad, Curacao, Girard, OH, United States

Chapter outline

COVID-19 pandemic

Recently, the novel Coronovirus-2 (COVID-19) has reached pandemic scale in terms of both morbidity and mortality on the global level, let alone its devastating impact on disrupting the socioeconomic fabric worldwide. As of June 8, 2020, World Health Organization is reporting 6,931,000 confirmed cases of COVID-19, including 400,857 deaths [1]. The Central Disease Control (CDC), USA, reports confirmed COVID-19 cases to be around 2.3 million with 11% positive tests and overall mortality exceeding 100,000 in late May 2020 [2]. In Canada with one-tenth the population of USA, the mortality rate has reached 7800 of COVID-19 patients [3]. Mitigation measures and public health surveillance strategies: "stay at home," "social distancing," "Personal Protective Envelope," and ventilator in hospital settings have produced positive results in flattening the curve and stabilized the pandemic crisis, especially in the USA and in Canada. USA

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has the highest reported cases and mortality rate, followed closely by United Kingdom, Italy, and more recently, Brazil.

It is noteworthy that COVID-19 has only recently been reported to spread in South America, primarily Brazil, and to a certain extent to Russia and India. The elderly often carry high comorbid medical diagnosis: diabetes mellitus, cancer, hypertension, and cardiovascular disorders. While COVID-19 deaths are primarily related to acute respiratory stress syndrome (ARDS), pneumonia, and sepsis, [4], recent studies have drawn attention to the emergence of CNS involvement. In a recent study of 214 hospitalized patients in Wuhan, China, 36.4% showed neurologic symptoms (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), and even full-blown encephalitis syndrome [5]. There is a paucity of data from Europe and North America on extent of neurological impairment. Management of postacute care involves coordination in addressing functional impairment related to muscle weakness, physical deconditioning, cardiopulmonary fitness, gait balance.

The landscape of COVID-19 therapeutics is constantly evolving. Conflicting clinical trial findings are reported for the antiviral drug hydroxychloroquine. Hydrochloroquine (HCQ) the antimalaria drug has drawn widespread publicity both for prophylaxis and for the acute treatment of ARDS; however, the multinational registry questions the safety issue of HCQ regarding increased mortality and the occurrence of de-novo ventricular arrhythmias risk [6]. In the study using global big database: the Surgical Outcome Collaborative Registry, from 169 hospitals in Asia, Europe, and North America, to evaluate the relationship of cardiovascular disease and the mortality rate among hospitalized COVID-19 patients admitted between December 2019 and March 2020, the investigators conclude that antihypertensive drugs belonging to the class of angiotensin receptor blockade (ARB) and angiotensin converting enzyme inhibitors (ACEinhibitors), carried no increased risk of death [7]. The issue is whether ACE, angiotensin ACE-2, the coreceptor of the spike protein of COVID-19, regulates the attachment and replication of COVID-19 and sensitive toward ACE-inhibitors and ARB, and whether ACE-inhibitors and ARB therapy should be discontinued amid COVID-19 pandemic. The complexities of cardiovascular control through the renin-angiotensin-aldosterone pathways remain to be delineated better in translational models of gene knockout of ACE-2. The editorial decision of two highly prestigious peer-reviewed journals: *Lancet* and *New England Journal of Medicine* to retract both studies within 1 week based on the veracity of data source and clinical trial methodology adds to the overwhelming climate of fear and hypervigilance of the seriousness of the COVID pandemic. Further controlled studies are currently in progress to evaluate critically the role of HCQ in COVID-19 and to establish the safety profile of ACE-inhibitors and ARB in COVID-19 cohort worldwide.

Similar apparently discrepant findings from two studies in USA and China are reported with remdesvir (patented product of Gilead Inc. Calif. USA) shown in vitro to inhibit the viral polymerase and the proofreading exoribonuclease [8–10], In the Chinese study, remdesivir use was not associated with a statistically significant difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87-1·75]); however, remdesivir seemed to accelerate improvement rate to a nonstatistically significant degree [8]. On the other hand, the NIH funded USA study [9] found that patients who received remdesivir had a 31% faster recovery than those who received placebo ($P < .001$). Specifically, the median time to recovery was 11 days for remdesivir-treated patients treated with remdesivir compared with 15 days for those who received placebo. The survival benefit as shown in the mortality rate of 8.0% for remdesivir-group versus 11.6% for the placebo group ($P = .059$).

With regard the convalescent plasma transfusion (CPT), a recent review of five controlled studies [11] found evidence of efficacy of CPT therapy in reducing mortality in critically ill patients [9]. The beneficial effects are most likely related to the increase in neutralizing antibody titers. Disappearance of SARS-CoV-2 RNA was observed in post-CPT therapy.

In searching through the pipeline drugs with potential efficacy against COVID-19, we are not able to identify specific drug lead targeting epigenetic signaling in COVID-19 while counteracting the treacherous immunity hijacking move by the COVID-19; and furthermore, recruiting nanotechnology to enhance the efficacy and minimizing toxicity. In the concise synopsis, we attempt to characterize the multifaceted pharmacology of curcumin to combat COVID-19 and to describe the transformative roadmap from curry extract and spices extracted from *Curcuma longa* to US-FDA approved drug lead (Fig. 18.1) earmarked for oncology therapeutics in Phase I clinical trial. Liposome-based curcumin: Lipocurc has the distinct advantage over other anti-COVID drugs under investigation in that it readily penetrates through the BBB: blood-brain barrier, and is active in translational models of brain disorders including Parkinson disease (PD).

Curcumin pharmacology and COVID-19

In the postgenomic era, there has been escalating interest in epigenetics signaling involved in regulation of gene expression in the context of diverse medical conditions and disorders. In the aging process, epigenetics drift and

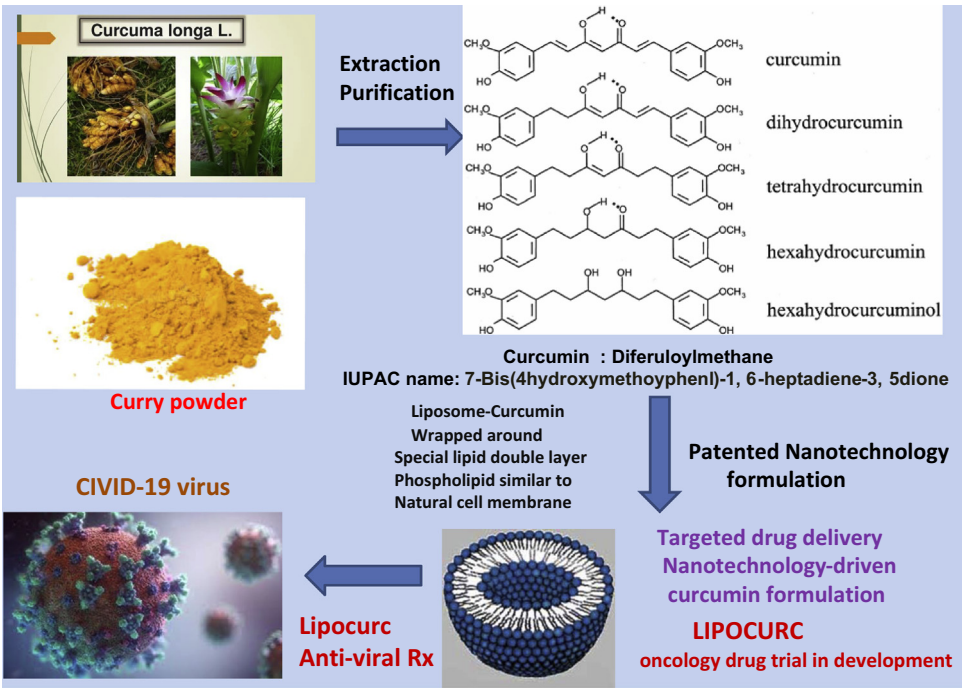

FIGURE 18.1 Transforming Curry as Lipocurc as novel drug candidate for COVID-19.

senescence explain the genome bias toward aging and carcinogenesis [12]. Since COVID-19 exhibits age-specific effect in triggering relentlessly a cascade of inflammation and tissue damage leading to cell death, as shown by the highest mortality rate in the elderly, the epigenetics mechanisms in neurodegenerative and neuropsychiatric disorders are directly relevant to our understanding of COVID-19. The phenotype of Alzheimer dementia (AD) is not only influenced by AD at-risk genes, but also buffered by AD protective genes. It soon becomes evident that epigenetics dysregulation underlies the pathophysiological mechanisms of brain disorders: AD, PD, schizophrenia, and mood disorders.

To reiterate, our overall objective of the drug development platform is to transform curry spice and extract liposome-curcumin (patented Lipocurc pipeline drug candidate SignPath Pharmac. Salt Lake City, Utah, USA) through fusing nanotechnology with epigenetics signaling and to develop an innovative milestone-driven drug development program in the landscape of central nervous system (CNS) and viral therapeutics development. Lipocurc has filed formal FDA patent for both cancer and CNS brain disorders.

Very few CNS drugs possess antiviral properties. Converging evidence suggests that curcumin functions as a pan antiviral agent. While curcumin is active against viral replication with reference to hepatitis C, HIV virus, influenza virus, dengue virus, *Herpes simplex*, prion virus, and SARS-related coronavirus, very little has been invested to further develop curcumin as a bona fide broad-spectrum antiviral agent exhibiting sustained drug effect against viral resistance [13,14]. With the spread of COVID-19 outside China to Korea, Japan, and Europe, we have data from the two PK studies to determine the maximum tolerated dosage. A pilot Asian study conducted in Taiwan found efficacy of curcumin in reducing replication of SARS-related coronavirus [15]. In the cell-based assay measuring severe acute respiratory syndrome—associated coronavirus (SARS-COV) based on the cytopathogenic effect on Vero E6 cells, curcumin was found to be a potent inhibitor at concentration of 3.3—10 microM. Curcumin inhibited the catalytic activity of SARS-COV 3CL protease at 40 microM in vitro. The recent identification of ACE-2—angiotensin as the coreceptor of S-protein of COVID-19 may lead to targeting ACE-2 for another therapeutic avenue [16]. The controversies regarding the benefits versus risks of maintenance antihypertensive therapy with angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockade (ARB) amid COVID-19 pandemic underscores the relevance of ACE-2 in pathophysiology of COVID-19. In angiotensin II—induced hypertension model, curcumin downregulates angiotensin receptor in A10 cells through blocking angiotensin-mediated vasoconstriction. Modulating the function of ACE-2 in COVID-2 represents another novel target of curcumin [17].

A more recent published study from Virology Central Laboratory in Wuhan province, the epicenter of COVID-19

in China, found evidence for efficacy of curcumin against enteric coronavirus [18]. In the porcine epidemic diarrhea virus (PEDV) model akin to coronavirus model, curcumin was reinforced with uniform and stable cationic carbon dots (CCM-curcumin) for investigating its antiviral properties. The formulated CCM-CDs were pharmacologically active through inhibiting viral entry, suppressing the synthesis of the negative strand RNA of virus, and virus budding. It appears to stimulate the inflammatory cascade involving the interferon stimulating genes (ISGs) and proinflammatory cytokines. It will be intriguing to compare the relative efficacies of CCM-CD and Lipocurc in the standard cytotoxicity, virus yield, and infection rate of COVID-19 virus in vitro. COVID-19 belongs to the same family of betacoronavirus as MERS-COV and SARS-COV.

Targeting epigenetics signaling may be the common pathway underling MERS-COV and Influenza A/Vietnam/123/2004 (H5N1-VN1203) influenza. Preliminary data showed that both groups of virus: MERS-COV and H5N1/VN1203 antagonize antigen presentation through epigenetic modulation involving DNA methylation [19]. Lipocurc may be the likely drug candidate to reverse virus-induced antagonism of antigen-presentation of DNA epigenetics pathway.

Blockade of viral entry at the epigenetics doorstep can be as efficacious as antagonizing viral polymerase. The ultrarapid rate of spread of COVID-19 remains an enigma. COVID-19 likely adopts the all too familiar "trick" to evade host viral defense through excessive activation of endoribonuclease [20]. Under normal circumstances, viral infection triggers the endogenous antiviral protective innate immune defense system mediated through RNase-L. In COVID-19 overactivation of RNase-L expression can lead to hyperinflammatory condition as the precursor to apoptosis and cell death. In this respect the finding that curcumin inhibited RNase-L-activity through its antiinflammatory and antioxidant properties may be interpreted that the polyphenol counteracts the hijacked immune responses and restores host viral defense. We are not aware of any COVID-19 investigational agents exhibiting the anti-endoribonuclease property.

There is growing evidence in support of the central role of interleukin-6 in the "cytokine release storm" in ARDS, the terminal event in COVID-19 [21]. Monoclonal antibody developed against interleukin-6 may hold promise in improving COVID-19 core symptoms and reducing mortality rate. Very few investigators are aware of the findings of studies showing curcumin inhibit interleukin-6 [22].

While many drug trials on COVID-19 are launched to combat COVID-19, few studies have adopted the repurposing paradigm to take advantage of the overlapping immunity , epigenetics and angiogenesis targets in both oncology drugs and anti-viral drugs. We propose to translate the multi-faceted pharmacology of Curry extract from the Tumeric longata to potential COVID-19 therapeutics through recruiting the novel nanotechnology.

More significantly, none of the pipeline antiviral drugs has been shown to cross the BBB and exert beneficial effects on brain health. This aspect of curcumin pharmacology is of prime importance with the increased attention being drawn toward the spectrum of neurological symptoms [23,24], complicating cardiovascular and pulmonary distress leading to death. During the postviral infection era, the neurological and neuro-sequelae of COVID-19 are only beginning to be recognized, let alone the guidelines for navigating through the recovery phase.

Our choice of curcumin as an antiviral agent, and the harnessing of nanotechnology to localize the site to the brain regions, with the wealth of CNS studies on the beneficial effects of curcumin in enhancing brain health [25,26] are unique and exceedingly positive as therapeutic potential to restore brain health.

Nanotechnology, epigenetics, and PK studies of liposome-curcumin

SignPath Pharma, PA owns the patent of the agent Lipocurc and has agreed to provide the pharmaceutical for our proposed clinical trial in PD. The curcumin component of Lipocurc is originally synthesized at Sami Labs, Bangalore, to 99.2% purity for the treatment of cancer. While SignPath has taken the lead in carrying out oncology trials with Lipocurc, our proposal will be the first in organizing Lipocurc trial in brain disorders. Despite numerous pharmacological studies with curcumin derived from *Curcuma longa*, L. extract the major drawback in translating the efficacy of curcumin from preclinical models to clinical arena of PD is the low systemic bioavailability of oral curcumin usually available as dietary supplements due to the high first-pass metabolism [27–29]. SignPath Inc. succeeded in utilizing an intravenous liposomal formulation to optimize penetration across the BBB. For the past few years, there has been almost explosive interest in searching for brain-specific drug delivery system for CNS disorders. Nanotechnology through encapsulating the active drug inside biocompatible materials—liposomes and polymers like hydrogel has taken a highly promising lead in drug development platform [25–29]. Nanotechnology has applications in oncology as well as neurodegenerative disorders [28]. SignPath Pharmac. (Salt Lake City Utah, USA) has succeeded in formulating a patented liposome-based curcumin shown to be bioactive in tumor models and brain disorder models.

Curcumin has been identified as a potent modifier of epigenetics signal pathways at multiple sites: HDAC (histone deacetylase) isoforms 1, 3, 8, HAT (histone acetyltransferase), noncoding RNA miRNA-22, miRNA186a, and miRNA-199a [25,26,29]. Curcumin suppresses DNA

methyltransferase (DNA MET) and induces global genomic hypomethylation of genes. In addition, curcumin inhibits Class I HDAC (histone deacetylase) isoforms 1, 3, 4, 5, 8; however, curcumin concomitantly activates Class III HDAC(Sirtuin1). Class III HDACs prefer NAD^+ as a reactant to deacetylate acetyl lysine residues of protein substrates forming nicotinamide, the deacetylated product, and the metabolite 2′-*O*-acetyl-ADP-ribose. In high throughput epigenetic screening assay using HeLa nuclear extract, curcumin was found to be more potent in inhibiting HDAC than valproic acid and sodium butyrate. The inhibition constant Ki of curcumin (539 nM) was comparable to Ki of trichostatin A (504 nM). Curcumin is more potent than valproic acid (Ki 564 nM) and sodium butyrate (Ki 365 nM). Cross-talks of HDAC with miRNA exert synergistic effects in orchestrating and coordinating multiple gene expression. HDAC inhibitors in controlling epigenetic programming involved in affective regulation, and behavior control, may alter the course of schizophrenia and bipolar spectrum disorders through remodeling chromatin, histone-related modifications, and even catalyze the access of gene promoters to transcription complex.

Pharmacokinetic studies have been completed in three species: rodents, dogs, and humans [30−34]. In the rodent species, rats were given intravenous bolus injections three times a week for 4 weeks (empty liposomes, and 10, 20, and 40 mg/kg Lipocurc) [30]. In our study, we compared the differential brain localization of three nanotechnology-driven curcumin formulations in rats. Our results found that following intravenous administration of liposomal curcumin, polymeric nanocurcumin and polylactic glycolic acid copolymer (PLGA)−curcumin in rats, these formulations were observed to cross the BBB using a sensitive HPLC assay. All three formulations are localized in specific sites in the brain without observable adverse events. One hour following intravenous injection of 5 mg/kg nanocurcumin or 20 mg/kg PLGA−curcumin or liposomal curcumin, up to 0.5% of the injected material is localized in the brain stem, the striatum, and the hippocampus with varied accumulation and clearance rates. On the other hand, we reported that dogs administered 1 h intravenous infusions at 10 mL/kg/h for 4 weeks (5% dextrose in water, empty liposomes, and 5 and 20 mg/kg Lipocurc) experienced no adverse events [31,32]. For both the canine and rodent species, there were no deaths on the study, and no changes in the clinical signs, body weight, food consumption, clinical chemistries, or organ weights, and no treatment-related adverse effects. In view of the wide safety margin, the NOAEL (no observed-adverse-effect-level: the highest dose at which there was not an observed toxic or adverse effect) for the rat was considered to be greater than 40 mg/kg dosage. For the beagle dogs [31,32] treated with 5 mg/kg Lipocurc, the analysis of all generated data—clinical observations, ophthalmology, ECGs, clinical pathology, gross necropsy and histopathology—concluded with no treatment-related toxicity.

The SignPath research group completed Phase I dose-escalating study of Lipocurc recruiting subjects from Europe (Study 1001) [33]. The protocol consisted of dose escalation study of single infusions of Lipocurc over 2 h in healthy volunteers allocated to five subjects/group (4 active drug and l placebo) over nine dosage groups.10, 20, 40, 80, 120, 180, 240, 320, and 400 mg/m^2. The results showed that Lipocurc exhibited favorable tolerability and toxicity profile in normal subjects. We have fully characterized the pharmacokinetic parameters of Lipocurc in humans. Blood was collected at baseline, during the infusion at 15, 30, 90 min, at the end of infusion: 0, 5, 10, 15, 30, 45 min and 1, 2, 4, 8, 24, and 48 h for determining the total curcumin and curcumin metabolite—tetrahydrocurcumin after the EOI dose escalation was performed until the highest planned dose (400 mg/m^2) was reached. Transient echinocyte formation with no long lasting adverse effects was observed. The infusion of Lipocurc resulted in rapid and dose-dependent development of plasma levels of curcumin with Tmax values ranging from 0.9 to 1.7 h. Cmax ranged between 42 $\pm$ 22 ng/mL and 2359 $\pm$ 412 ng/mL for 10 and 400 mg/m^2. Pharmacologically active metabolites have been reported in previous studies.

The findings of a Phase II PK study conducted in Europe reported similar safety and favorable tolerability in a cohort of subjects diagnosed with metastatic tumors [34]. In the Phase I PK, single-center, open-label study, liposomal curcumin was administered as a weekly intravenous infusion for 8 weeks. Dose escalation was started at 100 mg/m^2 over 8 h and the dose increased to 300 mg/m^2 over 6 h. Results: 32 patients were treated. No dose-limiting toxicity was observed in 26 patients at doses between 100 and 300 mg/m^2 over 8 h. Of six patients receiving 300 mg/m^2 over 6 h, one patient developed hemolysis, and three other patients experienced hemoglobin decreases $>$2 g/dL without signs of hemolysis. Pharmacokinetic analyses revealed stable curcumin plasma concentrations during infusion followed by rapid declines to undetectable levels after the infusion. Antitumor activity by RECIST V1.1 was not detected. Significant tumor marker responses and transient clinical benefit were observed in two patients. The study concluded that 300 mg/m^2 liposomal curcumin over 6 h was the maximum tolerated dose in the cohort of metastatic cancer patients who were pretreated with chemotherapy for their cancer, and 300 mg/m^2 is the recommended starting dose for future randomized anticancer trials.

The safety data can instruct and guide Phase II/Phase Ib studies to repurpose Lipocurc from oncology therapeutics development to CNS therapeutics landscape for neuropsychiatric disorders: schizophrenia, mood disorders, AD, and PD, and more recently, COVID-19 infection. Signpath

Pharmaco. Inc. PA, USA, has essentially overcome the limited systemic bioavailability of oral curcumin, hence creating a drug candidate for launching clinical trials in neurodegenerative disorders and cancer. Our innovative Drug Discovery Platform (DDP) is largely inspired by our earlier synopsis of nutraceuticals hitting overlapping epigenetics targets mediating the vast array of pharmacological activities in AD, PD, diabetes mellitus, anxiety, and depressive disorders [25,26,35]. We embark upon an ambitious plan to transform curry spice to liposome-based curcumin (Lipocurc) through innovative collaboration with SignPath Pharm. Co. (Salt Lake city, Utah, USA). The academic-industry team has for the first time succeeded in formulating liposome-encapsulated curcumin from curry extract and has progressed through vigorous FDA (US) regulatory approval process of securing an IND number. The positive results from PK studies in rodent and canine species and PK Phase I studies are sufficiently encouraging for the academia-industry team to explore therapeutic indications in neuropsychiatric and neurodegenerative disorders.

COVID-19 brain rehabilitation: role of epigenetics diet and exercise

We extend to acute lung injury resulting in acute respiratory distress syndrome (ARDS).driven by the cytokine release storm [23,24]. As discussed earlier, recent evidence highlights emerging CNS involvement, as shown in case series studies of COVID-infected patients. Very recently, COVID-19 infection has been found to increasingly involve the CNS. A wide array of neurological and neuropsychiatric symptoms have been described: anosmia, ataxia, epilepsy, altered level of consciousness and delirium, and myalgia [23,24]. Cognitive impairment and mood changes are anticipated to occur following the acute COVID-19 infection. Very few studies have focused on rehabilitation in domains of cognitive, affective, and behavioral domains.

Curcumin hits two arms of dysregulated immunity: innate and adaptive immunity, in COVID-19 and will be in a highly favored position to reset the homeostasis mechanisms for both the acute and subchronic phase. As a tumor-necrosis factor (TNF) and key regulator of family of cytokines, curcumin is strategically positioned to arrest and reverse the cytokine release storm. Curcumin participates in shifting the phenotype of the main players of inmate and adaptive immunity: macrophages, microglial cells (CNS), and T-cell populations and B-cell populations, toward the antiinflammatory and the antioxidant pathways, which in turn are regulated by the epigenetics signaling [25,26]. The frontier of epigenetics landscape has only recently been rediscovered as contributing toward the pathological hallmarks of COVID-19: virulence, transmission, and toxicity at the end-organs: the pulmonary system, cardiovascular and cerebrovascular system, and the CNS.

We have reviewed extensively the role of curcumin, especially the liposome-based curcumin ad drug lead in PD and AD [25,26]. The cognitive enhancing effects of curcumin in ameliorating the functional decline in both PD and AD are well delineated primary through the signal transduction pathways downstream from the epigenetics hits of Histone deacetylase (HDAC) and DNA methylation. Furthermore, in our study with supercurcumin we have shown that oral formulation of curcumin not only improved the negative symptoms but also the depressive symptoms of schizophrenia [35]. Our results are consistent with the findings of a systematic review of curcumin in depressive symptoms of unipolar depression [36]. A metaanalysis of curcumin in depressive disorder found that curcumin treatment significantly reduced depression symptoms [SMD = −0.34; 95% confidence interval (CI) = −0.56, −0.13; $P = .002$]. It is anticipated that the post-COVID-19 viral syndrome embraces behavioral, cognitive, and mood disturbances. Hence Lipocurc will be the ideal drug candidate for both COVID-19 in the acute phase and in the recovery phase.

Since curcumin is the bioactive ingredient of diet and menu in Asia with increased popularity in the Western world, our discussion calls into question whether curcumin-enriched diet has beneficial effect in counteracting the cognitive affective and behavioral domains of post-COVID syndrome. Growing evidence suggests that the epigenetics diet (Fig. 18.2) enriched with phenolic compounds extracted from curry overlaps with the Mediterranean diet and DASH diet and ketogenic diet in hitting similar epigenetics signatures modulating oxidative stress and inflammation [12,25,26,37−40] to achieve the three goals: to accelerate the recovery of COVID(+) exposed and symptomatic individuals via participating in wellness, physical (musculoskeletal), cardiovascular fitness, neurobehavioral programs, to boost their immunological defenses for preventing trapped in cytokine release storm COVID-19 and to enhance cognition and brain-behavioral health, especially in the elderly. We have reviewed evidence from PD studies relating diet and exercises and found that both diet-probiotics-prebiotics and therapeutic dance movements and physical activities can facilitate healthy and cognitive aging, enhance both cardiovascular and metabolic benefits, and prevent motor complications in PD [41,42]. The findings of the gut-microbiome-brain nexus, mediated by neuroimmunity landscape, can equally be applied to acute COVID-19 syndrome and the host of COVID-19-related neurological complications in severe COVID-19-infected

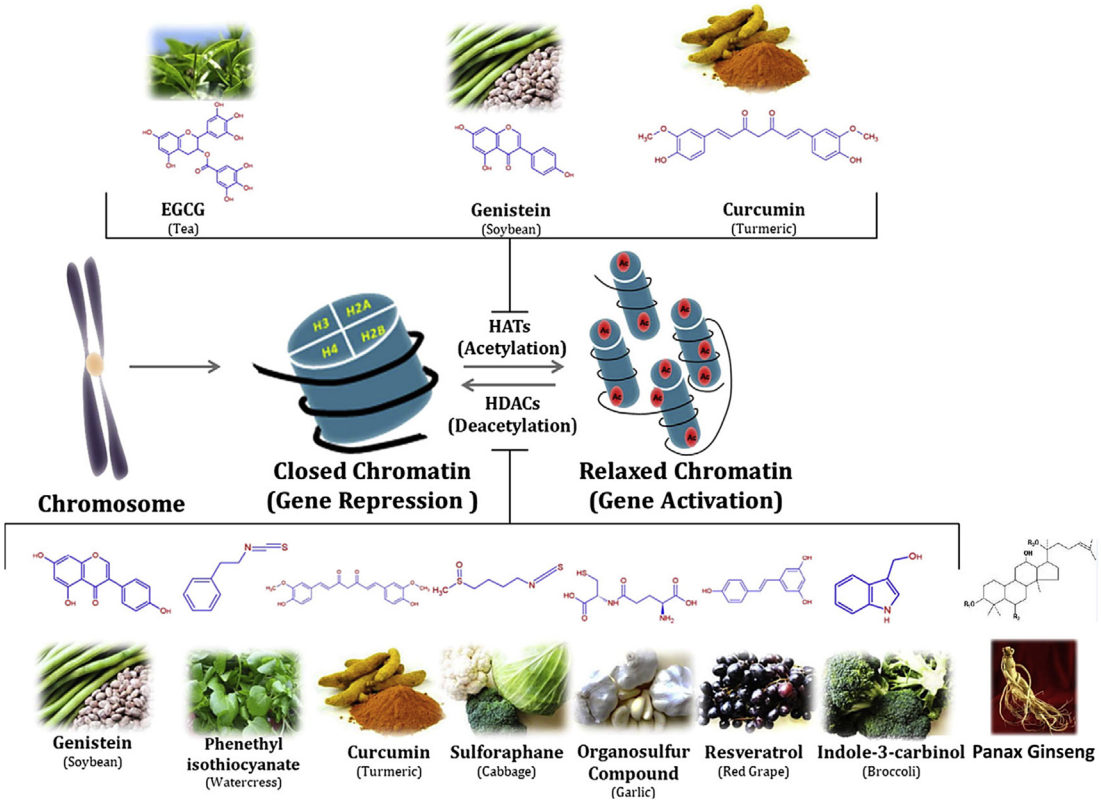

FIGURE 18.2 Latest newcomer: Epigenomics Diet for cognitive recovery in COVID19.

patients [42]. Taken together, growing evidence strongly suggests that the neurobehavioral sequlae may persist beyond the acute cytokine storm and ARDS. Epigenetics diet and exercise—physical activity—modules can be invaluable partners in COVID-19 rehabilitation phase. Curcumin's action in reducing culprits in AD: tau and amyloid may equally be applied to COVID-19 recovery phase in restoring synaptic plasticity and neurogenesis (Fig. 18.3).

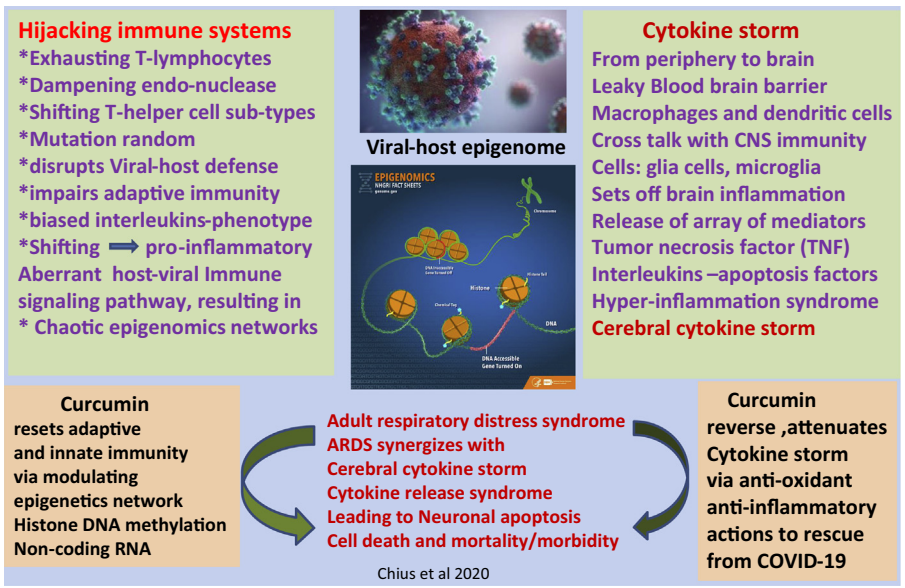

FIGURE 18.3 Model of dysregulation of COVID-19 Genomes/Epigenomics missing key to cerebral Cytokine Storm and Curcumin protection.

Summary

Our choice of curcumin as an antiviral agent, and the harnessing of nanotechnology to localize the site to the brain regions, coupled with the wealth of CNS studies on the beneficial effects of curcumin in enhancing brain health are unique and exceedingly positive as therapeutic potential to restore and enhance brain-behavior functions in the post-COVID-19 period.

References

[1] World Health Organization (WHO). Corona virus disease dashboard. June 8, 2020.

[2] Center for Disease Control and Prevention (CDC) USA. June 8, 2020.

[3] Public health Agency Canada (PHAC). June 8, 2020.

[4] Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on Coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res March 13, 2020;7(1):11. https://doi.org/10.1186/s40779-020-00240-0. PMID: 32169119 Free PMC article.

[5] Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. MedRxiv 2020. https://doi.org/10.1101/2020.02.22.20026500.

[6] Mehra MR, Desai SS, Frank R, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet June 2020.

[7] Rubin EJ, Expression of Concern, Mehra MR, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2007621. PMID: 32484612.

[8] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B. Wang Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet May 16, 2020;395(10236):1569–78. https://doi.org/10.1016/S0140-6736(20)31022-9. Epub 2020 Apr 29. PMID: 32423584 Free PMC article.

[9] Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, Case JB, Feng JY, Jordan R, Ray AS, Cihlar T, Siegel D, Mackman RL, Clarke MO, Baric RS, Denison MR. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. Am Soc Microbiol March 6, 2018;9(2). https://doi.org/10.1128/mBio.00221-18. e00221-18, PMID: 29511076.

[10] Remdesmir NIH-funded study results posted in Available from: www.gilead.com/remdesivir.

[11] Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran AJ. Convalescent plasma transfusion for the treatment of COVID-19: systematic review. Med Virol May 1, 2020. https://doi.org/10.1002/jmv.25961.

[12] Chiu S, Woodbury-Fariña MA, Shad MU, Husni M, Copen J, Bureau Y, Cernovsky Z, Hou JJ, Raheb H, Terpstra K, Sanchez V, Hategan A, Kaushal M, Campbell R. The role of nutrient-based epigenetic changes in buffering against stress, aging, and Alzheimer's disease.(invited book chapter). Psychiatr Clin North Am December 2014;37(4):591–623.

[13] Praditya D, Kirchhoff L, Brüning J, Rachmawati H, Steinmann J, Steinmann E. Anti-infective properties of the golden spice curcumin. Front Microbiol May 3, 2019;10:912. https://doi.org/10.3389/fmicb.2019.00912.

[14] Moghadamtousi SZ, Abdul Kadir H, Hassandarvish P, Hassan T, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. Biomed Res Int 2014. Article ID 186864.

[15] Wen C-C, Kuo Y-H, Jan J-T, Liang P-H, Wang S-Y, Liu Ching-Kuo Lee H-G, Chang XS-T, Kuo C-J, Lee S-S, Hou C-C, Hsiao P-W, Chien S-C, Shyur L-F, Yang N-S. Specific plant Terpenoids and Lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem 2007;**5**0:4087–95.

[16] Magrone T, Magrone M, Jirillo E. Focus on receptors for coronaviruses with special reference to angiotensin-converting enzyme 2 as a potential drug target - a perspective. Endocr Metab Immune Disord Drug Targets April 27, 2020. https://doi.org/10.2174/1871530320666200427112902.

[17] Yao Y, Wang W, Li M, Ren H, Chen C, Wang J, Wang WE, Yang J, Zeng C. Curcumin exerts its anti-hypertensive effect by down-regulating the AT1 receptor in vascular smooth muscle cells. Sci Rep May 5, 2016;6:25579. https://doi.org/10.1038/srep25579.

[18] Ting Du, Dong N, Fang L, Lu J, Bi J, Xiao S, Han H. Multisite inhibitors for enteric coronavirus: antiviral cationic carbon dots based on curcumin. ACS Appl Nano Mater 2018;1(10):5451–9. https://doi.org/10.1021/acsanm.8b00779. Publication Date:September 12, 2018.

[19] Menachery VD, Schäferb A, Burnum-Johnsonc KE, Mitchellc HD, Eisfeldd AJ, Waltersd KB, Nicorac CD, Purvinec SO, Caseyc CP, Monroec ME, Weitzc KK, Strattonc KG, Webb-Robertsonc B-JM, Gralinskib LE, Metzc TO, Smithc RD, Waters KM, Simsb AC, Kawaokad Y, Baricb RS. MERS-CoV and H5N1 influenza virus antagonize antigen presentation by altering the epigenetic landscape. Proc Natl Acad Sci January 16, 2018.

[20] Deng X, Baker SC. An "Old" protein with a new story: coronavirus endoribonuclease is important for evading host antiviral defenses. Virology April 2018;517:157–63. https://doi.org/10.1016/j.virol.2017.12.024. Epub 2018 Jan 4.

[21] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. S0163-4453(20)30165-1 J Infect April 10, 2020. https://doi.org/10.1016/j.jinf.2020.03.037 [Epub ahead of print].

[22] Ghandadi M, et al. Curcumin: an effective inhibitor of interleukin-6. Curr Pharm Des 2017.

[23] Jasti M, Nalleballe K, Dandu V, Onteddu S. A review of pathophysiology and neuropsychiatric manifestations of COVID-19. J Neurol June 3, 2020:1–6. https://doi.org/10.1007/s00415-020-09950-w [Epub ahead of print].

[24] Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol May 29, 2020. https://doi.org/10.1001/jamaneurol.2020.2065. Online ahead of print.

[25] Chiu SS, Terpstra K, Woodbury-Farina M, Mishra R, Badmaev V, Vaughese J, Raheb H, Lui E, Cernovsky Z, Bureau Y, Husni M, Copen J, Shad M, Hou J, Carriere A, Khazaeipool Z, Campbell R, Sieffien W. Transforming curry extract to liposomal curcumin (LipocurcTM) in Parkinson disease (PD) therapeutics landscape: emerging role of epigenetics signaling and nanotechnology. EC Neurol March 2020. Online Pub.

[26] Chiu S, Woodbury-Farina M, Terpstra K, Hou J, Bureau Y, Cernovsky Z, Mariwan Husni MUS, Copen J, Hategan A, Seeley Johnson A, Varghese J, Carrie A, Khazaeipool Z, Foskett A. Exploring the architecture of epigenetics in Alzheimer's Dementia: evidence and promises and challenges. Invited book chapter. USA: SMGroup Publisher; September 2016. www.smgebooks.com.

[27] Kunnumakkara AB, Harsha C, Banik K, Vikkurthi R, Sailo BL, Bordoloi D, Gupta SC, Aggarwal BB. Is curcumin bioavailability a problem in humans: lessons from clinical trials. Expert Opin Drug Metab Toxicol September 2019;15(9):705−33. https://doi.org/10.1080/17425255.2019.1650914. Epub 2019 Aug 29.

[28] Yavarpour-Bali H, Ghasemi-Kasman M, Pirzadeh M. Curcumin-loaded nanoparticles: a novel therapeutic strategy in treatment of central nervous system disorders. Int J Nanomed June 17, 2019;14:4449−60. https://doi.org/10.2147/IJN.S208332. eCollection 2019.

[29] Boyanapalli SS, Tony Kong AN. "Curcumin, the king of spices": epigenetic regulatory mechanisms in prevention of cancer, neurological, and inflammatory diseases. Curr Pharmacol Rep April 2015;1(2):129−39.

[30] Chiu S, Liu E, Majeed M, Vishwanatha JK, Ranjan A, Maitra A, Dipanker P, Smith JA, Helson L. Intravenous curcumin distribution in the rat brain. J Anticancer Res 2011;31(3):907−12.

[31] Helson L, Bolger G, Majeed M, Vcelar B, Pucaj K, Matabudul D. Infusion pharmacokinetics of Lipocurc (liposomal curcumin) and its metabolite tetrahydrocurcumin in Beagle dogs. Anticancer Res October 2012;32(10):4365−70.

[32] Matabudul D, Pucaj K, Bolger G, Vcelar B, Majeed M, Helson L. Tissue distribution of (Lipocurc™) liposomal curcumin and tetrahydrocurcumin following two- and eight-hour infusions in Beagle dogs. Anticancer Res October 2012;32(10):4359−64.

[33] Storka A, Vcelar B, Klickovic U, Gouya G, Weisshaar S, Stegan A, Gordon B, Lawrence H, Michael W. Safety, Tolerability and pharmacokinetics of liposomal curcumin (Lipocurc™) in healthy humans. Int J Clin Pharmacol Therapeut September 2014;23:1−12.

[34] Greil R, Greil-Ressler S, Weiss L, Schönlieb C, Magnes T, Radl B, Bolger GT, Vcelar B, Peter P. SordilloA phase 1 dose-escalation study on the safety, tolerability and activity of liposomal curcumin (Lipocurc) in patients with locally advanced or metastatic cancer. Published online 2018 Aug 3 Canc Chemother Pharmacol 2018;82(4):695−706. https://doi.org/10.1007/s00280-018-3654-0. PMCID: PMC6132848 PMID: 30074076.

[35] Chiu S, Woodbury-Farina M, Terpstra K, Badmaev V, Cernovsky Z, Bureau Y, Raheb H, Husni M, Copen J, Shad M, Jirui H, Campbell R, Khazaeipool Z, Carriere A. Exploratory study of curcumin isolated from turmeric *Curcuma longa*, the putative histone Deacetylase inhibitor, as added-on strategy to antipsychotics in treating negative symptoms and neuro-cognitive deficits in schizophrenia. ISSN: 2456-1045 Adv Res J Multidisc Discov 2019;40(1). I CHAPTER-2 PUBLISHER: INTERNATIONAL JOURNAL FOUNDATION (IJF).

[36] Dalia A-K, Mamoori DAA, Tayyar Y. The role of curcumin administration in patients with major depressive disorder: mini meta-analysis of clinical trials. Phytother Res February 2016;30(2):175−83. https://doi.org/10.1002/ptr.5524. Epub 2015 Nov 27.

[37] Chiu S., et al. SMART rehabilitation program blueprint.

[38] Caccialanza R, Laviano A, Lobascio F, et al. Early nutritional supplementation in noncritically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): rationale and feasibility of a shared pragmatic protocol. Nutrition April 3, 2020:110835. https://doi.org/10.1016/j.nut.2020.110835 [Epub ahead of print].

[39] Jiménez-Pavón D, Carbonell-Baeza A, Lavie CJ. Physical exercise as therapy to fight against the mental and physical consequences of COVID-19 quarantine: special focus in older people. Prog Cardiovasc Dis March 24, 2020. S0033-0620(20)30063-3.

[40] Zhao C, Zhao W. NLRP3 inflammasome-A key player in antiviral responses. Front Immunol February 18, 2020;11:211. https://doi.org/10.3389/fimmu.2020.00211. eCollection 2020. Review.

[41] Sieffien W, Siddu S, Chiu M, Woodbury F. "Exploring the new frontier of synergy and coupling of music with dance movement to modify the course of Parkinson Disease (PD): synthesis of evidence" XXIV world congress on Parkinson's disease and related disorders, Montreal, Canada on June 16−19. 2019. Proceedings published in ABSTRACT book.

[42] Autumn Carriere, Chiu S, Husni M, Copen J, Shad M, Woodbury-Farina M. Exploring emerging role of epigenetics landscape intercepting with mediterranean diet and ketogenic diet and nutraceuticals at gut-microbiota-brain axis in enhancing outcome in Parkinson disease." to the XXIV world congress on Parkinson's disease and related disorders montreal, Canada on June 16−19,. 2019. Published in ABSTRACT book.