Chapter 21
Antiviral Mechanisms of Curcumin and Its Derivatives in Prevention and Treatment of COVID-19: A Review

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Abstract The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now plagued the world for almost 3 years. Although vaccines are now available, the severity of the pandemic and the current dearth of approved effective medications have prompted the need for novel treatment approaches. Curcumin, as a food nutraceutical with anti-inflammatory and antioxidant effects, is now under consideration for the prevention and treatment of

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COVID-19. Curcumin has been demonstrated to retard the entrance of SARS-CoV-2 into cells, interfere with its proliferation inside cells, and curb the hyperinflammatory state caused by the virus by modulating immune system regulators, minimizing the cytokine storm effect, and modulating the renin-angiotensin system. This chapter discusses the role of curcumin and its derivatives in the prevention and treatment of COVID-19 infection, considering the molecular mechanisms involved. It will also focus on the molecular and cellular profiling techniques as essential tools in this research, as these can be used in the identification and development of new biomarkers, drug targets, and therapeutic approaches for improved patient care.

Keywords Nutraceutical · Phytochemical · Curcumin · COVID-19

1 Introduction

Coronaviruses are single-stranded ribonucleic acid (RNA) viruses belonging to the family of Coronaviridae. They were first recognized as enzootic infection factors and also as human-contaminating agents [1]. Coronavirus disease 2019 (COVID-19) is a newly emerged disease with a rapid rise in mortality cases after its first detection in December 2019 [2]. The international virus classification committee proposed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the name of the virus which causes COVID-19 disease [3]. The symptoms of COVID-19 infection can resemble those of the common cold and acute respiratory diseases, with infection of the respiration system (e.g., pneumonia or bronchitis) [4]. Compared to the other members of the coronavirus family, such as SARS and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV-2 has higher transmissibility. The significance of this fact is that this virus can engage a higher number of people through contact with an infected patient [5].

COVID-19 infection results in acute upper respiration symptoms, such as sneezing, sore throat, fever, dry coughs, fatigue, sputum, dyspnea, and headache [6, 7]. Severe cases of this disease are marked by pneumonia, metabolic acidosis, septic shock, and hemorrhage [8]. The laboratory results of most cases indicate a reduction in the number of white blood cells and lymphocytes [6, 9]. In acute cases, neutrophil counts, urea, and creatinine levels also show a significant rise while the number of lymphocytes is reduced. Inflammatory factors, such as interleukin 6 and 17, and necrosis factors, such as tumor necrosis factor (TNF-α), often increase [10]. The current anti-virus treatments target human cells or the virus itself. Currently, there are

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eight approved treatments for use in the European Union, and this field is rapidly evolving [11]. In addition to investigating the effect of the chemical-pharmaceutical agents on the pathogenicity of the virus, several studies have addressed the influence of phytochemicals on coronavirus due to evidence of the antiviral efficacy of some plant-based compounds. Some phytochemicals have also been found to boost the immune system against various diseases through diverse cellular mechanisms [12, 13].

Curcumin is an important phytochemical compound that is extracted from the rhizome of Curcuma longa, also known as the turmeric plant. Turmeric includes an extensive spectrum of phytochemicals, such as curcumin, demethoxycurcumin, zingiberene, curcumenol, eugenol, triethyl curcumin, and turmerones. However, most of the therapeutic features of turmeric have been ascribed to curcumin [14]. Numerous studies have confirmed curcumin's antioxidant and anti-inflammatory effects, making it a viable candidate for treating diseases marked by disturbances in these pathways [15–28]. The anti-inflammatory effects of curcumin are comparable with those of anti-inflammatory steroids and non-steroid drugs [29] and appear to be mediated by inhibition and suppression of the prostaglandins synthesis and inhibition of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), as well as suppression of the production of cytokines, such as gamma interferon (INFγ) and tumor necrosis factor-alpha (TNFα) and activation of transcription factors such as nuclear factor-κB (NF-κB) [30]. Some studies have confirmed the role of curcumin in the inhibition of the proliferation of some viruses, such as human papillomavirus (HPV) and human immunodeficiency virus (HIV) [31]. Antiviral effects have also been proven against COVID-19 disease [32, 33]. Hence, curcumin appears to be a potential phytochemical for preventing and treating COVID-19 infection.

Recently, phytochemical investigations have been conducted to unveil the various molecular effects and pharmacological properties involved in their mechanisms of action [34]. This is important as some patients do not respond to particular drug therapy or suffer from adverse effects limiting the drug development process [35, 36]. Therefore, validated biomarkers that predict the effects of drugs and establish optimal therapeutic dosages are urgently needed [37]. In addition, the emergence of systems biology techniques has brought dawn to researchers in COVID-19 medication, and there are also many new technologies and strategies for drug design that can promote research in this field [38]. Accordingly, this study was conducted to review the molecular mechanisms and methods used in the study of curcumin and its derivatives in the prevention and treatment of COVID-19.

2 Methods

This review was carried out in a narrative manner by searching the databases PubMed, Web of Science, and Science Direct using coronavirus-19, COVID-19, SARS-CoV-2, curcumin, nanocurcumin, turmeric, nutraceutical, and phytochemical keywords without any limiting search items. The main objective was to report on the clinical trials which have investigated the effects of various forms of curcumin in the treatment of COVID-19 patients (Table 21.1).

Table 21.1 Characteristics and results of the studied articles on clinical trials for protective effects of curcumin on COVID-19 disease

Authors [Ref.]	Objective	Methods	Results
Valizadeh et al. [57]	Investigation of the effect of nanocurcumin on modulation of inflammatory cytokines in COVID-19 patients	Intervention groups: 40 healthy controls and 40 COVID-19 patients Intervention: Group 1 received nanocurcumin (160 mg nano-curcumin for 14 days) Group 2 received a placebo Biomarker techniques used to monitor treatment: Assessment mRNA expression and secretion IL-1β, IL-6, TFN-α, IL-18 by real-time PCR and ELISA	Significant decrease after treatment with nanocurcumin in expression and secretion of IL-6 and IL1β
Hassaniazad et al. [59]	Investigation of the effect of nanocurcumin on clinical variations of cellular immunity subgroups of COVID-19	Intervention groups: 40 patients divided into two groups Intervention: Group 1 received nanocucumin capsules (40 mg) 4/day for 2 weeks Group 2 received placebo over the same schedule Biomarker techniques used to monitor treatment: mRNA expression levels measured by PCR Serum levels of cytokines measured on days 0, 7, and 14	TBX21 and FOXP3 mRNA levels were decreased and increased, respectively, between nanocurcumin and placebo groups on day 7 Reduced serum levels of IFN-γ and IL-17 in the nanocurcumin group Increased serum levels of IL-4 and TGF-β in the nanocurcumin group on day 14 compared to the placebo
Pawar et al. [72]	Determining the effect of curcumin / piperine (to optimize absorption) on symptoms in COVID-19 patients	Intervention groups: 140 patients in two groups of case and control Intervention: The case group received curcumin (525 mg) along with piperine (2.5 mg) in tablet form twice a day Biomarker techniques used to monitor treatment: None	Early symptomatic recovery (fever, cough, sore throat, and breathlessness) and better clinical outcomes in patients who received curcumin/piperine

(continued)

Table 21.1 (continued)

Authors [Ref.]	Objective	Methods	Results
Tahmasebi et al. [67]	Investigation of the therapeutic effects of nanocurcumin on frequency and response of Th17 cells in mild and severe COVID-19 patients	Intervention groups: 40 severe COVID-19 patients (admitted to ICU) 40 mild COVID-19 patients Intervention: Prescription nanocurcumin (80 mg 2/day) or placebo Biomarker techniques used to monitor treatment: Measuring frequency of RNA expression of Th17-relevant factors, and serum levels of inflammatory cytokines Flow cytometry used to measure frequency of the Th17 cell population with monoclonal antibodies against surface and intracellular markers	Decreased number of Th17 cells, Th17-related factors, and Th-17-related cytokines levels in the mild and severe COVID-19 patients treated by nanocurcumin
Askari et al. [73]	Investigation of the efficacy of curcumin/piperine on clinical symptoms, duration, severity, and inflammatory factors of COVID-19 patients	Intervention group: 46 COVID-19 patients (23 in each group of case and control) Intervention: Two curcumin/piperine capsules (500 mg curcumin/5 mg piperine) or placebo for 14 days Biomarker techniques used to monitor treatment: Auto-analyzer used to measure CBC, FBS, serum cholesterol, TG, LDL, HDL, VLDL, ALT, AST, LDH, creatinine, BUN, and CRP using commercial kits	Curcumin/piperine co-supplementation in COVID-19 patients significantly reduced weakness, but not other biochemical and clinical indices

(continued)

Table 21.1 (continued)

Authors [Ref.]	Objective	Methods	Results
Asadirad et al. [68]	Evaluation of the effect of nanocurcumin on inflammatory cytokines of hospitalized mild to moderate COVID-19 patients	Intervention group: 60 COVID-19 patients (two groups receiving nanocurcumin or placebo) Intervention: 240 mg nanocurcumin for 7 days Biomarker techniques used to monitor treatment: Record clinical signs and laboratory parameters on days 0 and 7 Measure serum levels of TNF-α, IL-1β, and IL-6 using ELISA kits	Improved clinical manifestations and laboratory parameters by nanocurcumin treatment Decreased IFN-γ and TNF-α mRNAs by nanocurcumin treatment

A secondary objective was to report on the molecular techniques used in these studies as biomarkers of efficacy or toxicities.

3 Results

Results of the studies on the mechanisms of action showed the effect of curcumin on the prevention and treatment of COVID-19 at four stages of the virus life cycle, including entry into the cell, viral replication, cytokine storm effects, and involvement of the renin-angiotensin system. It should be noted that all the hypotheses mentioned in this study are based on the assumption that the immune response against COVID-19 is similar to that caused by other coronaviruses, which should be confirmed with further studies. This is important to aid preparedness for future coronavirus pandemics. These four stages are discussed in the following sections.

3.1 Cellular Entry of SARS-CoV-2 and Curcumin

Angiotensin-converting enzyme 2 (ACE2) receptor on host cell surface acts as an attachment and entry port for the SARS-CoV-2 virus. The SARS-COV-2 spike glycoprotein has two structural subunits (S1 and S2), which play separate roles in identifying and binding to the receptor and promoting fusion with the host cell membrane [39]. The attachment stage occurs through the binding of the receptor-binding

domain (RBD) in the S1 subunit to ACE2 on the target cells [40]. Studies have shown that curcumin interacts with and can block this stage of SARS-COV-2 infection [41]. Various amino acid residues of ACE2 (e.g., alanine 348, asparagine 394, glutamate 402, histidine 378, and Tyrosine 385) have been identified as being in the active binding site in the interaction with curcumin [41]. Also, curcumin reduces the expression of TMPRSS-2 [42], which is one of the main activating proteases of host cells, permitting entry of the SARS-Cov-2 virus [39]. This enzyme cleaves the spike glycoprotein between the S1 and S2 domains to allow the fusion of the S2 subunit with the host cell membrane. Moreover, curcumin has a high binding affinity to the SARS-CoV-2 nucleocapsid proteins, which regulates replication of the viral RNA, inhibits protein translation, alters the cell cycle, and promotes apoptosis in host cells [43]. Thus, some of the antiviral properties of curcumin might arise by blocking the actions of this protein.

3.2 SARS-CoV-2 Proliferation and Curcumin

A large number of studies have investigated the key factors and enzymes involved in SARS-CoV-2 replication. Most of these have been carried out on the RNA-dependent RNA polymerase (RdRp) and the main protease (MPro; a 3CL-like enzyme). The MPro enzyme is responsible for the proteolytic cleavage of the viral polyprotein into distinct active peptides and the RdRp, which is also known as non-structural protein 12 (NSP12), is responsible for catalyzing the synthesis of the new viral RNA as part of the replication and transcription process [44]. In silico molecular docking studies have suggested that curcumin can bind directly to the MPro enzyme and the RdRp [45–47]. Other molecular docking studies have shown the effects of curcumin in blocking SARS-CoV-2 reproduction by targeting NSP9 of the viral replicase. NSP9 binds to single-stranded RNA and works in concert with the RdRp complex in the replication process [48]. Although a number of drugs have now been identified which can inhibit the activity of the RdRp complex, as well as the MPro enzyme and NSP9 [49], these will require further in vitro and in vivo validation. However, as curcumin has shown inhibitory properties against the viral replication cycle, it is possible that it achieves these effects by targeting some or all of the above SARS-CoV-2 proteins [50, 51]. Thus, curcumin has the potential to interfere with the process of replication of SARS-CoV-2 RNA in the generation of new virus particles.

3.3 COVID-19, the Cytokine Storm, and Curcumin

In any type of viral infection, inflammatory cytokines such as IL-1, IL-6, and TNF-α are actively released by immune cells into the bloodstream [51]. The release of large amounts of cytokines into the systemic circulation is often referred to as a cytokine

storm [52]. Such an increase in cytokine levels in COVID-19 cases is associated with conditions related to acute respiratory distress syndrome (ARDS) and multiple organ damage, which can lead to a poorer prognosis [53, 54]. Curcumin also shows promise as a novel and effective treatment of the cytokine storm effects as the immunomodulatory activities of this molecule have been well established in different studies [32, 55, 56]. The ability of curcumin to suppress the cytokine storm and its potential in treating viral disorders, including those caused by coronaviruses, supports the case that it may be an effective treatment for COVID-19 [32]. The inflammatory factors released in the cytokine storm include IL-1, IL-2, IL-6, IL-10, transforming growth factor-β (TGF-β), interferons (IFNs), and TNF-α. The expression of IL-6 and TNF-α is mainly associated with COVID-19-related ARDS, which may contribute to organ damage in severe cases [53, 54]. Curcumin has a suppressive effect on IFN-α, and its lowering effect on inflammatory cytokines has been attributed to the inhibition of NF-κB signaling [55]. In a study conducted on the effects of nanocurcumin on the modulation of the inflammatory cytokines in COVID-19 patients, curcumin was found to temper the virus-related increase in inflammatory cytokines at both the mRNA and protein levels [57]. In another study of mild and severe nanocurcumin-treated COVID-19 patients, a significant decrease was observed in the number of inflammatory markers, including pro-inflammatory Th17-related cytokines [58]. Hassaniazad et al. also investigated the effect of curcumin nanomicelles in a clinical study on the cellular immune response in COVID-19 patients [59]. This revealed a rise in the levels of the anti-inflammatory cytokines IL-4 and TGF-β in the group receiving nanocurcumin, compared to the placebo group on the day 14.

The effect of curcumin to stimulate the production of anti-inflammatory factors may aid in at least a partial restoration of the cytokine balance by modulating key regulatory elements of immune and inflammatory pathways, thereby reducing the cytokine storm response to viral infection and minimizing the potentially damaging oxidizing effects of excessive reactive oxygen species (ROS) production [32].

3.4 Renin-Angiotensin System, SARS-CoV-2, and Curcumin

ACE2 present on the surface of host cells provides a target for the spike glycoprotein of SARS-CoV-2 as an entry point for viral infection via endocytosis [40]. Simultaneous internalization of ACE2 has been reported during cellular entry of SARS coronaviruses, including SARS-CoV-2 [39, 60]. As ACE2 normally acts to inactivate angiotensin II (AngII), a decrease in cell surface ACE2 levels can lead to the accumulation of this peptide hormone and high levels of AngII have been associated with acute lung injury in COVID-19 patients [54]. The mechanism of this is likely due to the fact that AngII is a peptide hormone that acts as a vasoconstrictor, which can lead to high blood pressure and trigger an inflammatory response. High AngII levels can stimulate the AT1 angiotensin receptor, which can have multiple adverse effects on physiology, including those mentioned above, as well as fibrosis and ARDS [61].

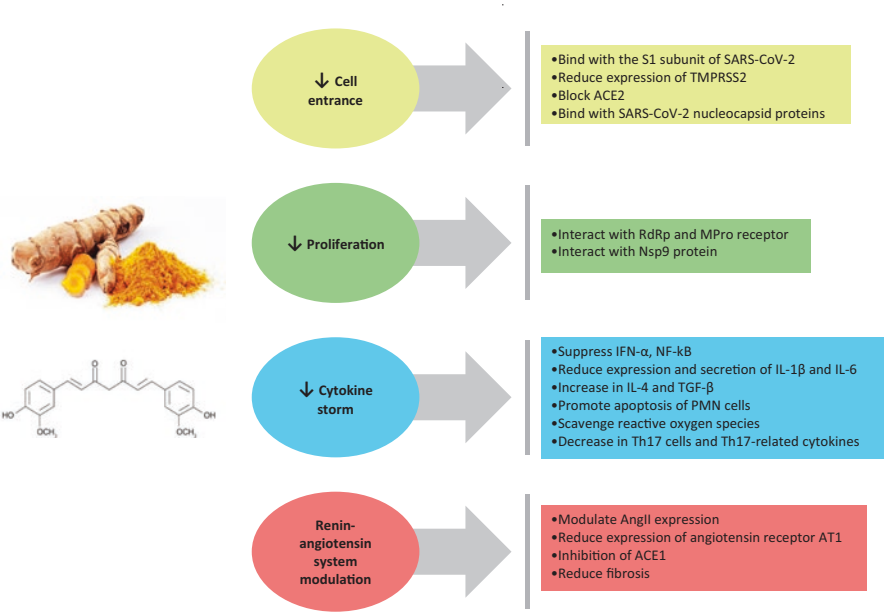

Fig. 21.1 The potential inhibitory mechanisms of curcumin on COVID-19 prevention and treatment

Curcumin has been reported to modulate the level of AngII expression and prevent inflammation-associated fibrosis [62]. Furthermore, the modulation of ACE2 levels by curcumin has also been documented [62, 63]. Such modulation of ACE2 expression by curcumin could lead to reduced AngII cell signaling and the subsequent damage and pathological consequences. Furthermore, curcumin has been found to inhibit high blood pressure by lowering the expression of angiotensin 1 converting enzyme (ACE1) in a rat model of hypertension [64]. Curcumin has also been found to reduce the expression of the angiotensin receptor AT1 in an AngII infusion model of fibrosis in rats [62]. Consistent with this, curcumin treatment was found to reduce AngII-induced hypertension in a mouse model [65].

Taken together, these findings indicate that treatment with curcumin can be used in the treatment of COVID-19 disease effects via multiple complementary pathways (Fig. 21.1).

4 Cellular and Molecular Profiling Techniques Used in the Assessment of Curcumin Efficacy in the Treatment of COVID-19 Disease

Different cellular and molecular profiling techniques were used to evaluate the biomarkers linked with the mechanism of action of curcumin treatment in the above studies. Valizadeh et al. used both real-time PCR and an enzyme-linked

immunosorbent assay (ELISA) approach for evaluating the effects of curcumin on the production of the IL-1β, IL-6, IL-18, and TNF-α in peripheral blood mononuclear cells (PBMCs) and serum from COVID-19 patients [57]. The real-time quantitative PCR method allowed simultaneous multiplex detection of the different cytokines through the use of nucleotide probes linked with different fluorescent tags, as described by Hawkins and Guest [66]. In a similar manner, Hassaniazad et al. used real-time PCR analysis to examine immune response gene expression changes in the transcription factors TBX21, GATA-3, FOXP3, and RAR-related orphan receptor γt (ROR-γT) and ELISA to measure the serum levels of IFN-γ, IL-4, IL-17, and TGF-β cytokines in investigating the effects of curcumin nanomicelles on clinical cellular immune responses in COVID-19 patients [59]. Tahmasbi et al. used a flow cytometry technique to measure the frequency of circulating Th17 cells in patients with COVID-19 and healthy subjects using monoclonal antibodies against surface and intracellular markers [67]. They also evaluated mRNA expression profiles of Th17 cell-related factors RORγt, IL-17, IL-21, IL-23, using real-time PCR and the secreted levels of serum IL-17, IL-21, IL-23, and granulocyte-macrophage colony-stimulating factor (GM-CSF) via ELISA. Similar approaches were employed by Asadirad et al. in the measurement of TNF-α, IL-1β, IL-6, and IFN-γ inflammatory cytokines by the real-time PCR method and analyses of serum levels of TNF-α, IL-1β, and IL-6 using cytokine ELISA kits [68].

Other multiple analyte probing techniques have also been described, which can also be applied in the study of risk factors for COVID-19 and for assessing the effects of this disease in cells and circulation, and also for monitoring the response to various pharmaceutical and phytochemical treatments such as curcumin. These techniques include multiplex immunoassay [69] and biochip arrays [70] for the simultaneous measurement of multiple analytes such as inflammation- and immune-related factors. Given the multi-faceted nature of COVID-19 disease, the multiplex biomarker technologies listed above enable the simultaneous analysis of numerous analytes for interrogation of disease and treatment effects on specific protein pathways such as inflammation and oxidative damage. There are also methods for measuring effects on entire protein pathways, such as kits developed for determining total antioxidant capacity and coagulation status [71] in blood samples. Figure 21.2 indicates some of the main multiplex molecular profiling technologies employed in studying the effects of curcumin on COVID-19 disease.

5 Conclusions and Future Perspectives

In this chapter, we have summarized the disrupted molecular pathways that are potentially targeted by the phytochemical curcumin in COVID-19 disease prevention and treatment. We have also described the main methods which have been used to investigate these effects, with a focus on multiplex molecular profiling techniques such as real-time PCR and multi-analyte immunoassay. Curcumin has protective effects in preventing viruses from entering the cells, reducing virus proliferation,

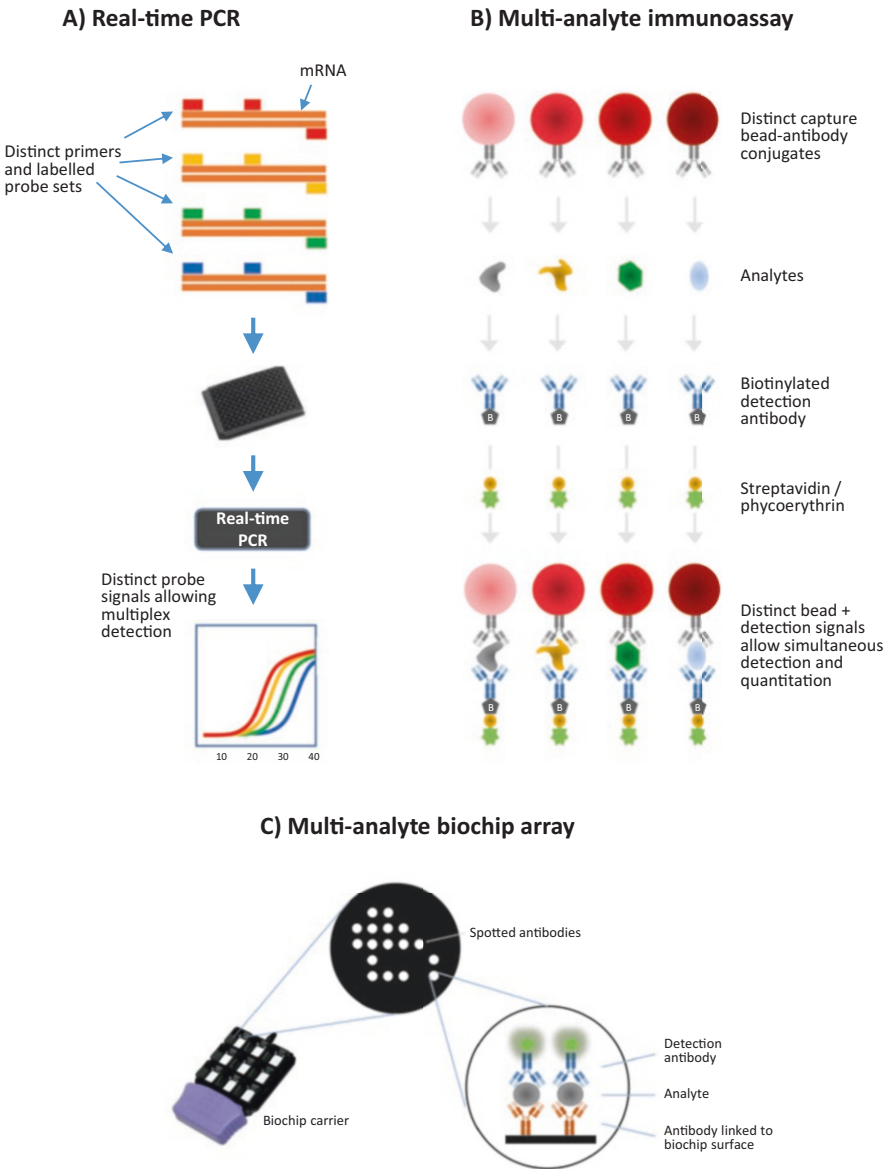

Fig. 21.2 Multiplex molecular profiling technologies employed in studying the effects of curcumin on COVID-19 disease. (**a**) Real-time PCR. (**b**) Multi-analyte immunoassay. (**c**) Multiplex biochip array

decreasing the cytokine storm effects, and modulating the renin-angiotensin pathway. Further studies on the possible use of natural compounds such as curcumin and the application of the appropriate molecular profiling approaches to monitor disease and treatment effects can lead to improved management of coronavirus and other viral infections during the current pandemic and future outbreaks.

Competing Interests MM is the founder of Sami-Sabinsa group of companies.

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