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REVIEW PAPER

Curcumin and Its Analogs as a Therapeutic Strategy in Infections Caused by RNA Genome Viruses

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Abstract

The use of natural resources for the prevention and treatment of diseases considered fatal to humanity has evolved. Several medicinal plants have nutritional and pharmacological potential in the prevention and treatment of viral infections, among them, turmeric, which is recognized for its biological properties associated with curcuminoids, mainly represented by curcumin, and found mostly in rhizomes. The purpose of this review was to compile the pharmacological activities of curcumin and its analogs, aiming at stimulating their use as a therapeutic strategy to treat infections caused by RNA genome viruses. We revisited its historical application as an anti-inflammatory, antioxidant, and antiviral agent that combined with low toxicity, motivated research against viruses affecting the population for decades. Most findings concentrate particularly on arboviruses, HIV, and the recent SARS-CoV-2. As one of the main conclusions, associating curcuminoids with nanomaterials increases solubility, bioavailability, and antiviral effects, characterized by blocking the entry of the virus into the cell or by inhibiting key enzymes in viral replication and transcription.

Keywords *Curcuma longa* L. · Curcumin · RNA virus · Antiviral activity · Viral infections

Introduction

Viruses generally enter organisms through contact with their cells on body surfaces. Common entry sites include the mucous membranes of the respiratory, gastrointestinal, and urogenital systems, conjunctiva, and skin (Santos et al., 2015). The respiratory system is probably the most common route (Louten, 2016). Respiratory viruses are responsible for various clinical syndromes, including common cold, flu, pharyngitis, laryngitis, sinusitis, bronchiolitis, asthma exacerbations, and chronic obstructive pulmonary disease (Nelson et al., 2020). Most respiratory infections and other diseases considered fatal to humanity are caused by viruses consisting of a single-stranded ribonucleic acid (RNA) genome, which are subdivided into positive and negative polarity (Louten, 2016).

RNA genome viruses undergo high mutation rates that contribute to their viral genetic variability and natural selection, enabling fast evolution and more resistant strains (Sanjuán & Domingo-Calap, 2016). Several medicinal plants, especially turmeric (*Curcuma longa* L.), used as food have bioactive compounds capable of stimulating the immune system, a nutritional and pharmacological strategy for the prevention and treatment of viral infections (Ciavarella et al., 2020).

Native to Asia, turmeric is a plant from the Zingiberaceae family recognized for its biological properties associated with curcuminoids (polyphenols), such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin, mostly present in rhizomes. Throughout its multi-millennial medicinal use, turmeric proved therapeutic due to numerous activities against various diseases (Aggarwal et al., 2007). Longitudinal studies have shown curcumin, the main chemical

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constituent, and its analogs to have anti-inflammatory (Mukhopadhyay et al., 1982), anticancer (Brouet & Ohshima, 1995; Goel et al., 2008), immunomodulatory (Srivastava et al., 2011) and antioxidant properties (Ahsan et al., 1999), in addition to its antibacterial, antifungal, and antiviral activities (Zorofchian Moghadamtousi et al., 2014).

Evidence of the therapeutic potential of curcumin in the prevention or treatment of diseases is often related to its ability to positively or negatively regulate multiple molecular targets, such as inter and intracellular cell-signaling pathways, phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), matrix metalloproteinases-9 (MMP-9), nuclear factor-kappa B (NF-κB), tumor necrosis factor alpha (TNF-α), interleukin-1 and 6 (IL-1, IL-6) (Anand et al., 2008). Although the effects of curcumin and its analogs have been demonstrated against several diseases, its use is limited in the clinic because of its low oral bioavailability (Oglah et al., 2020), which makes its approval and the approval of its analogs as antiviral agents difficult. In this sense, considering we found that the association of curcuminoids with nanomaterials increases solubility, bioavailability, and antiviral effect, one of our aspirations for this review was to explore this aspect as a potential fix for that limitation. This study seeks to combine the pharmacological activities of curcumin and its analogs, aiming at stimulating their use as a therapeutic strategy against infections caused by RNA genome viruses.

Methods

Search Strategy and Selection Criteria

PubMed scientific database (www.pubmed.org) was searched for relevant studies between 2000 and 2020, using the combined terms "curcumin" or "turmeric" or "*C. longa* L." and "viral", "antiviral effect" and "inhibits viruses", "interferon alpha", "MERS", "SARS", "COVID-19", "coronavirus", "SARS-CoV-2", and "cytokines storm". The inclusion criteria were publications referring to the activities of *C. longa*, curcumin and analogs against human viruses and trials that investigated their therapeutic properties. The exclusion criteria were as follows: papers on other species of the genus *Curcuma*, non-human viruses, and viruses with a DNA genome.

Data Selection and Theoretical Underpinning

The search strategy identified 1,047 papers and 386 were excluded (duplicates). There were 661 selected by title and/or abstract, for partial reading, of which 555 were excluded for not meeting the selection criteria. Therefore, 106 papers were examined in detail, remaining 56 that met the research objectives. Additional papers were used as theoretical underpinning for this study.

Results

Table 1 shows the resulting analyses of the selected references, totaling 14 RNA genome viruses: Severe Acute Respiratory Syndrome Coronavirus (SARS-COV and SARS-COV-2); Human Respiratory Syncytial Virus (HRSV); Influenza A Virus (IAV); Ebola Virus (EBOV); Dengue Virus (DENV); Japanese Encephalitis Virus (JEV); Zika Virus (ZIKV); Chikungunya Virus (CHIKV); Coxsackie Virus B (CVB); Enterovirus 71 (EV71); Murine Norovirus (MNV); Hepatitis C Virus (HCV); and Human Immunodeficiency Virus (HIV). Several authors have mentioned tests of nanomaterials from curcumin and analogs such as curcumin-silver nanoparticles (Yang et al., 2016b), carbon quantum dots (Lin et al., 2019), curcumin-loaded β-cyclodextrin-functionalized graphene oxide composite (Yang et al., 2017), curcumin-chitosan nanocomposites (Loutfy et al., 2020), and nanoemulsions (Nabila et al., 2020). It appears that it is necessary to improve and standardize the formulations to guarantee the bioavailability of curcumin and its analogs as an antiviral agent (Praditya et al., 2019). Chemical structures of curcumin and of some of its analogs found in the papers are shown in Fig. 1.

Activity Against Coxsackievirus

Coxsackie viruses belong to the genus *Enterovirus* (Picornaviridae). They are characterized by their size (diameter of approximately 30 nm), not having an envelope and presenting a capsid with icosahedral symmetry. The capsid contains four structural proteins (VP1, VP2, VP3, and VP4). The genome is composed of linear, single-stranded RNA with a positive polarity of approximately 7.4 kb (Jacobs et al., 2013). Coxsackievirus B (CVB) has six subtypes that induce myocarditis in mice and humans (Wessely et al., 2001). The cardiotropic coxsackievirus B subtype 3 (CVB3) is recognized as the main etiologic agent of acute and chronic myocarditis and viral meningitis (Martino et al., 1994).

Experiments with BALB/c mice demonstrated the protective effect of curcumin (100 mg/kg) against myocarditis caused by CVB3 through the inhibition of the PI3K/Akt and NF-κB signaling pathways, thereby inhibiting the production of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) in mouse serum. According to the authors, the use of curcumin can be a therapeutic strategy for the treatment of acute myocarditis induced by CVB3 (Song et al., 2013). Another study indicated the ability of curcumin to reduce the synthesis of viral capsid protein (VP1) in HeLa cells (cells originating from epithelial carcinoma of the

Table 1 Antiviral activity in silico, in vitro, in vivo, and in clinical tests described for curcumin and analogs

Virus (Family)	Curcumin/analogs	Kind of study	Antiviral activity	References
Coxsackie virus B3 (Picornaviridae)	Curcumin	In vitro	Reduction of VP1 protein synthesis and viral titer by more than 20-fold through UPS dysregulation	Si et al. (2007)
	Curcumin	In vivo	Protective action on myocarditis in mice through the inhibition of the PI3K/Akt/NF-kB pathway and the pro-inflammatory cytokines TNF-α, IL-6 and IL-1β	Song et al. (2013)
Enterovirus 71 (Picornaviridae)	Curcumin	In vitro	Inhibition of viral replication by the suppression of RNA synthesis and viral protein expression; inhibition of the production of GBF1proteasomes and the PI4KB pathway	Qin et al. (2014)
	Curcumin	In vitro	Suppression of viral RNA replication in early stage of infection; inhibition of PKCδ	Huang et al. (2018)
	Curcumin functionalized carbon quantum dots (Cur-CQD) nanoparticles curcumin	In vivo In vitro	Inhibition of the expression of VP1, RNA polymerase (3Dpol) and viral protease (3CDpro); survival rate was 100% in mice treated with Cur-CQD (25 mg/kg) lower viral inhibition and higher cytotoxicity of curcumin (> 34-fold and > 1000-fold, respectively) when compared with Cur-CQD	Lin et al. (2019)
Murine norovirus (Caliciviridae)	Curcumin	In vitro	High percentage (91%) of neutralized virus in assays with RAW 264.7 cells	Yang et al. (2016a)
SARS-CoV (Coronaviridae)	Curcumin	In vivo In vitro	Mild inhibition of 3CL protease and of viral replication	Wen et al. (2007)
SARS-CoV-2 (Coronaviridae)	Curcumin + 24 analogs	In silico	Best level of inhibition of the proteases Mpro, Spike and RdRp (compared to the test drugs) by 1-(4-hydroxyphenyl)-7-(3,4-dihydroxyphenyl)-1,6-heptadiene-3,5-dione	Emirik (2020)
	Curcumin	In silico	Strong binding affinity (-9.2 kcal/mol) with Mpro	Ibrahim et al. (2020)
	C. longa L. five from 19 curcuminoids (C1-C5) with higher levels of activity	In silico	Strong binding affinity (-9.08 and -8.07 kcal/mol) with Mpro [relative to lopinavir (-5.4 kcal/mol)] by compounds C1 [(1E,6E)-1,2,6,7-tetrahydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione] and C2 [(4Z,6E)-1,5-dihydroxy-1,7-bis(4-hydroxyphenyl) hepta-4,6-dien-3-one], respectively	Gupta et al. (2020)
	Curcumin vitamin C glycyrrhizic acid	In silico	Inhibition of PI3K/AKT, NF-kB and MAPK signaling pathways by the combination of these compounds	Chen et al. (2020)
	Combined extracts of turmeric and black pepper	In silico In vitro	Strong binding affinity (from -6 to -9.7 kcal/mol) with Spike RBD and with P50 of main compounds (including curcumin); viral inhibition of 88% to 92% at the concentrations range from 0.1 to 0.4 µg/mL	Roshdy et al. (2020)
	Curcumin	In silico	High interaction with Spike protein (-141.36 kcal/mol) and ACE2 receptor (-142.647 kcal/mol)	Maurya et al. (2020)
	Compound similar to curcumin	In silico	Better binding energy at the active site of Mpro (-8.72 kcal/mol) compared to curcumin (-6.90 kcal/mol)	Basu et al. (2020)
	Curcumin	In silico	Strong binding capacity with the nsp15 (-7.26 kcal/mol)	Kumar et al. (2021)
	Curcumin	In silico	Formation of the most stable complex with Mpro (-7.1 kcal/mol) when compared to other drugs	Huynh et al. (2020)
	Curcumin	In silico	Binding affinity with Mpro (position 334 of 488 investigated molecules)	Kandeel and Al-Nazawi (2020)
SARS-CoV-2 (Coronaviridae)	Nanocurcumin	*Clinical*	Significant decrease in IL-6 expression and secretion and IL-1β gene expression in serum and supernatant in 20 patients with COVID-19	Valizadeh et al. (2020)

Table 1 (continued)

Virus (Family)	Curcumin/analogs	Kind of study	Antiviral activity	References
Influenza A virus (Orthomyxoviridae)	Curcumin	In silico	Interference with the binding site between RNA and NP-Y148	Liu et al. (2016)
	Curcumin	In vitro In vivo	Repression of H1N1 replication in lung cells by 15%; inhibition of viral replication in mice; induction of HO-1 expression and inhibition of NF-κB	Han et al. (2018)
	Curcumin	in vitro In vivo	Inhibition of viral replication in the adsorption stage; inhibition of Nrf2 pathways; p38/JNK MAPK and Toll-like receptors (TLR2/4) increase in mice survival rate; reduction of lung index, inflammatory cytokines and lung viral titer; improvement of pulmonary histopathological changes after viral infection	Dai et al. (2018)
	Curcumin + 10 analogs	In vivo	Inhibition of neuraminidase; decrease in TNF-α, IL-6 and IFN-γ levels in mice lung homogenates; inhibition by curcumin of viral activity in H1N1-infected mice	Lai et al. (2020)
	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	In silico	Strong binding affinity with the H1, H2, H3 protein subtypes of the virus;	Kannan and Kolandaivel (2017)
	Curcumin tetrahydrocurcumin	In silico In vitro	Interaction of curcumin with the hemagglutinin receptor binding region; reduction of the production of viral progenies by curcumin and tetrahydrocurcumin	Ou et al. (2013)
	Curcumin monoacetylcurcumin (MAC)	In silico In vitro	Potentiation of inhibition of viral replication by curcumin in association with MAC; suppression of PI3K/Akt pathway and reduction of viral replication by MAC	Richart et al. (2018)
	Curcumin	In vitro	Irreversibly prevention of viral replication by disrupting the integrity of the viral envelope membrane	Chen et al. (2013)
	Curcumin	In vivo	Inhibition of the secretion of pro-inflammatory cytokines (TNF-α, IFN- α and IL-6) in BAL from mice infected with H1N1	Xu and Liu (2017)
Respiratory syncytial virus (Pneumoviridae)	Curcumin-silver nanoparticles	In vitro	Inhibition by direct virus inactivation; reduction of viral titers	Yang et al. (2016b)
	Curcumin nanocomposite of β-cyclodextrin-functionalized graphene oxide	In vitro	Direct virus inactivation, inhibiting viral attachment to host cells and interfering with virus replication	Yang et al. (2017)
Ebola virus (Filoviridae)	Curcumin demethoxycurcumin bisdemethoxycurcumin tetrahydrocurcumin	In silico	Better binding energies of tetrahydrocurcumin than of curcumin with target proteins VP35, GP and VP30	Baikerikar (2017)
	Curcumin	In silico	Good binding energy with VP30 (-9.6 kcal/mol) when compared to the Reference antiviral drug BCX4430 (-7.6 kcal/mol)	Setlur et al. (2017)
Dengue virus (Flaviviridae)	Curcumin bisdemethoxycurcumin CC3,CC4 and CC5	In vitro	Higher inhibition of NS2B/NS3 protease of DENV-2 by synthetic analogs (CC3, CC4, and CC5)	Balasubramanian et al. (2019)
	Curcumin solution curcumin nanoemulsion	In vitro	Greater reduction of viral titers of DENV-1 and DENV-2 in comparison to curcumin solution	Nabila et al. (2020)
	Curcumin	In vitro	Inhibition of the production of viral particles from DENV-2; increase in the level of ubiquitin-conjugated proteins Lys48; disorganization of actin filaments of the cytoskeleton; apoptosis	Padilla-S et al. (2014)
Japanese encephalitis virus (Flaviviridae)	Curcumin	In vitro	Reduction of reactive oxygen species (antioxidant action); recovery of cell membrane integrity; decrease in the signals of pro-apoptotic molecules; reduction of the production of infectious viral particles in Neuro-2a cells; likely inhibition by UPS dysregulation	Dutta et al. (2009)
Chikungunya virus (Togaviridae)	Curcumin demethoxycurcumin bisdemethoxycurcumin	In vitro	Reduction of genome and viral titer	Mounce et al. (2017)
Zika virus (Flaviviridae)	Curcumin	In vitro	Reduction of genome and viral titer	Mounce et al. (2017)
	Curcumin	In vitro	Inhibition of viral infection (75 to 100%) in the early stages of adsorption	Gao et al. (2019)

Table 1 (continued)

Virus (Family)	Curcumin/analogs	Kind of study	Antiviral activity	References
Hepatitis C virus (Flaviviridae)	Curcumin	In vitro	Inhibition of viral replication (by inducing HO-1 expression) and of the PI3K-Akt pathway	Chen et al. (2012)
	Curcumin desmethoxycurcumin bisdemethoxycurcumin tetrahydrocurcumin	In vitro	Inhibition of the entry of virus genotypes into cells by curcuminoids (except tetrahydrocurcumin)	Colpitts et al. (2014)
	Curcumin	In vitro	Reduction of viral replication by suppressing the Akt/SREBP-1 pathway	Kim et al. (2010)
	Curcumin curcumin-chitosan (CuCs) nanoparticles	In silico In vitro	Higher binding affinity to NS3 protease and NS5A polymerase by curcumin; reduction of viral titer by 100% (CuCs) and 95% (curcumin)	Loutfy et al. (2020)
Human immunodeficiency virus (Retroviridae)	Curcumin	In vitro	Degradation of Tat protein; inhibition of activation of the LTR promoter	Ali and Banerjea (2016)
	Curcumin iron-phenanthroline (NCIP) nanocomplex	In vitro	Decrease of the expression of HIV-p24 and of inflammatory mediators NF-α, IL-8 and NO	Sharma et al. (2019)
	Curcumin A (synthetic analog)	In vitro	Inhibition of viral reverse transcription; induction of HO-1 expression; reduction of the progression of the viral infectious cycle	Kumari et al. (2015)
	Tetrahydrocurcumin microemulsion gel	In silico In vitro	Inhibition of binding between gp120 and the CD4 receptor; prevention of virus entry into the target cell; inhibition (> 50%) of the p24 antigen	Mirani et al. (2019)
	Curcumin curcumin-silver nanoparticles (Cur-AgNP)	In vitro	Decrease in the expression of the viral LTR gene (-73% by Cur-AgNP and -33% by curcumin); reduction (by Cur-AgNP) of viral replication by inhibiting NF-κB and pro-inflammatory cytokines IL-1β, TNF-α and IL-6	Sharma et al. (2017)
	Curcumin solid dispersion	In vivo	Increase in the intravenous pharmacokinetics parameters of saquinavir for the oral exposure in rats	Kim et al. (2013)
	Multidrug nanoparticles (ritonavir, atazanavir and curcumin)	In vitro	Reduction of viral replication, by inhibiting the production of viral p24 protein up to 36 times	Singh et al. (2020)

DENV-1, DENV-2 serotypes of dengue virus, *HCV* hepatitis C virus, *HIV-1* human immunodeficiency virus type 1, *H1, H2, H3* subtypes of HA (hemagglutinin), *HO-1* Heme oxygenase inducible isoform, *IL-8* interleukin-8β, *IL-6* interleukin-6, *IL-1β* interleukin-1β, *IFN* interferon, *LTR* long terminal repeat, *Lys48* lysine residues, *MAPK* mitogen-activated protein kinase, *NF-κB* nuclear factor-kappa B, *NO* nitric oxide, pro-inflammatory mediator, *NP-Y148* viral nucleoprotein, *Nsp15* non-structural protein 15, *p24* HIV antigen, a viral protein, *PI3K/Akt* phosphatidylinositol 3-kinase/protein kinase B, *RBD* receptor binding domain, *SREBP-1* sterol regulatory element-binding protein 1, *Tat protein* trans-activator of transcription protein, *TLR2/4* Toll-like receptor 2/4, *TNF-α* tumor necrosis factor alpha, *UPS* ubiquitin–proteasome system, *VP1* capsid viral protein 1, *VP30* viral protein 30

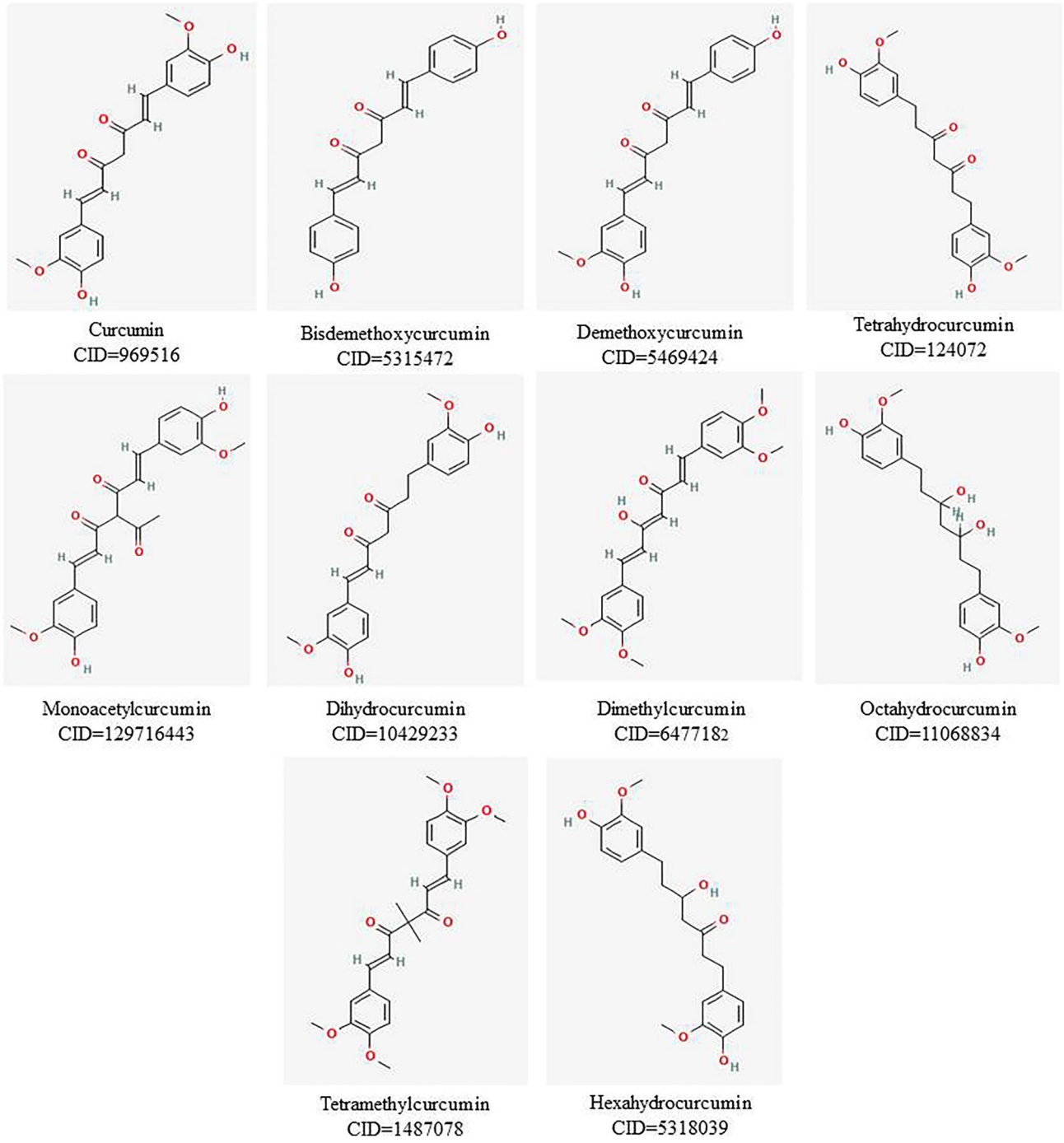

Fig. 1 Chemical structures of curcumin and analogs

human cervix) infected with CVB3 (Si et al., 2007). Curcumin decreases viral titer by more than 20-fold through dysregulation of the ubiquitin–proteasome system (UPS).

Activity Against Enterovirus 71

The Enterovirus 71 serotype (EV71), family Picornaviridae, *Enterovirus A* species, mainly affects children, harming hands, feet, and mouth with neurological and systemic complications (Solomon et al., 2010). The antiviral potential

of curcumin against this virus was demonstrated in vitro by suppressing RNA synthesis and viral protein expression (Qin et al., 2014). Another mechanism is the reduction in the activity of the GBF1 (Golgi brefeldin A resistant guanine nucleotide exchange factor 1) proteasome induced by viral infection. Therefore, by inhibiting the production of proteasomes and the PI4KB (phosphatidylinositol 4-kinase beta) pathway, it interferes with viral replication.

Similar results were observed in an investigation into a human colon adenocarcinoma cell line (HT29) treated with curcumin and then infected with EV71 (Huang et al., 2018). After treatment, viral RNA replication was suppressed during the early stage of infection, in addition to the inhibition of protein kinase C delta (PKCδ), which plays a role in viral translation in EV71-infected intestinal epithelial cells as a consequence of reduced phosphorylation of this enzyme. Thus, the authors suggest that ingestion of this polyphenol may protect against enteroviral infections.

Another study on EV71 used curcumin derived carbon quantum dot (Cur-CQD) nanoparticles and compared it to natural curcumin (Lin et al., 2019). The antiviral activity of Cur-CQD was confirmed by plaque reduction assay. In the treatment, virus replication was inhibited, probably due to the inhibition of the production of the VP1 capsid protein, the expression of RNA polymerase 3Dpol, and the protease 3CDpro. The survival rate was 100% for mice infected with a mouse-adapted EV71 strain (EV-A71/4643/MP4) and treated with Cur-CQD (25 mg/kg), thus confirming the protective effect on morbidity. It is noteworthy that the association of curcuminoids with nanomaterials contributes to increased solubility, bioavailability, and bioactivity, making them promising candidates for the treatment of infections caused by EV71. Curcumin, however, had much lower activity and higher cytotoxicity (> 34-fold lower and > 1000-fold higher, respectively) when compared with Cur-CQD, indicating far superior antiviral capabilities and high biocompatibility of the nanoparticles.

Activity Against Murine Norovirus

Murine norovirus (MNV), family Caliciviridae, has positive polarity single-stranded RNA genomes (Vinjé et al., 2019). MNV is closely related to human norovirus (HuNov), which is clinically more relevant as it is an etiologic agent of acute gastroenteritis. The importance of combating HuNov lies in its high infectivity and environmental persistence, in addition to its high genetic variability (Teunis et al., 2020). Since HuNovs cannot be routinely propagated, cultivable substitutes such as feline calicivirus (FCV) and MNV are commonly used as experimental models to assess viral inactivation by bioactives in the control of enteric diseases (D'Souza, 2014). The antiviral effects of 18 active ingredients from plants were investigated in assays with MNV (RAW 264.7 cells), and curcumin stood out for its high percentage (91%) of neutralized virus when compared to the control. The authors indicated curcumin as a potential anti-noroviral agent, either in the prevention or treatment of foodborne disease outbreaks (Yang et al., 2016a). Another study investigated the activity of photoactivated curcumin using cultivable FCVs and MNVs (Randazzo et al., 2016). It was observed that photoactivated curcumin (50 µg/mL), after incubation at 37 °C for 30 min, reduced FCV titers by almost 5 logs. Under the same conditions, the authors reported lower antiviral activity of curcumin against MNV (0.73 log $TCID_{50}$/mL reduction).

Activity Against SARS-CoV and SARS-CoV-2

Coronaviruses (CoVs), Coronaviridae family, are capable of causing diseases in animals and humans and are considered zoonoses of great medical importance (Weiss & Navas-Martin, 2005). They cause respiratory infections ranging from a common cold to more serious illnesses such as Middle Eastern respiratory syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and coronavirus disease-2019 (COVID-19), whose transmissibility can occur from animal to human or from human to human, resulting in a major epidemic (Gorbalenya et al., 2020). Before the discovery of the new SARS-CoV-2, Wen et al. (2007) investigated the specific cytopathogenic effect of 221 chemical constituents against SARS-CoV in Vero-E6 cell culture. Among them, 20 substances (ten diterpenoids, two sesquiterpenes, two triterpenes, five lignoids, and curcumin) at concentrations of 3–10 µM exhibited an anti-SARS-CoV effect. Compared to the other compounds, curcumin showed mild activity against SARS-CoV replication and inhibition of 3CLpro (chymotrypsin-like main protease). These findings already signaled a direction for the development of antiviral therapeutic agents from medicinal plants.

SARS-CoV-2 is a virus with a linear, single-stranded RNA genome and positive polarity coated with a lipoprotein envelope and a genome of approximately 30 kb (Naqvi et al., 2020; Wang et al., 2020). It has a set of proteins related to the regulation of viral function and structure: spike glycoprotein (S, Spike), envelope glycoprotein (E), membrane glycoprotein (M), and nucleocapsid protein (N), which are closely linked to viral RNA (Naqvi et al., 2020; Vellingiri et al., 2020). Currently, the non-structural proteins (nsps) refer to 16 proteins that are involved in the replication–transcription complex. Special attention has been given in antiviral activity studies to: nsp3—called PLpro (papain-like protease); nsp5—called Mpro (main protease) or 3CLpro (chymotrypsin-like main protease); and nsp15—called NendoU (Nidovirus uridylate-specific endoribonuclease) (Parks & Smith, 2020; Yan et al., 2020).

SARS-CoV-2 is a potent agent that induces the production of inflammatory cytokines by immune cells and pulmonary vascular endothelial cells, a process known as "cytokine storm", which causes damage to the affected organs, especially the lungs (Jiang et al., 2020). Coronavirus infection results in the activation of monocytes, macrophages, and dendritic cells, resulting in increased systemic production of cytokines that contributes to the severe pathophysiology of COVID-19. Thus, blocking or inhibiting the production of interleukin-6 (IL-6), a cytokine involved in the inflammatory response, can help in the treatment of patients with severe conditions (Moore & June, 2020; Zhang et al., 2020).

The rapid global spread of the SARS-CoV-2 virus has resulted in urgent vaccine development, concomitant with the investigation of other therapies, such as drug repositioning strategies (Rosa & Santos, 2020), passive immunization of hyperimmune globulin in horses (Cunha et al., 2020) and the search for natural products that inhibit coronavirus proteases. Evidence gathered on botanical drugs and immunomodulatory supplements to help prevent and treat viral infections demonstrated that turmeric exhibited improved immune response parameters; thus, the so-called adaptogenic herbal medicines mitigate the adverse effects of physical and psychological stress and improve immunological function. Therefore, they are useful in the prevention of and convalescence from respiratory viral infections (Brendler et al. 2021).

Curcumin as a dietary supplement can help stimulate the immune system, prevent viruses from spreading, prevent disease progression to the severe stage, and further suppress hyperinflammation, providing prophylactic and therapeutic support against COVID-19 (Mrityunjaya et al., 2020). It can prevent SARS-CoV-2 replication, as well as prevent and repair damage to pneumocytes, renal cells, cardiomyocytes, hematopoietic stem cells, and other damage associated with COVID-19 (Soni et al., 2020). This published evidence provides a basis for the clinical assessment of curcumin in the therapeutic management of SARS-CoV-2 infection.

A literature review on non-clinical studies in animal models of lethal respiratory virus-induced pneumonia showed that curcumin exerts a protective effect by regulating the expression of pro- and anti-inflammatory factors (IL-6, IL-8, IL-10, and COX-2) and the elimination of reactive oxygen species (ROS) (Liu & Ying, 2020). The low toxicity of curcumin and its antiviral, antioxidant, and inhibitory effects on the cytokine storm contribute to the clinical investigation of curcumin as a therapeutic agent in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2.

Another review reports the potential therapeutic effects of 159 natural compounds in the treatment of lung injuries, from which curcumin stands out for its ability to regulate several molecular targets. According to the authors, the evidence gathered justify clinical investigations in patients infected with coronavirus, particularly when aggravated by ALI or ARDS (He et al., 2020).

The combination of three bioactive compounds, including vitamin C, curcumin, and glycyrrhizic acid (VCG Plus), was investigated for its capacity to regulate the immune response to infections associated with the coronavirus (Chen et al., 2020). Using system biology tools, the VCG Plus has shown the potential to regulate responses through Toll-like (TLRs) and NOD-like receptors (NLRs), inhibiting interferon (IFN) and phosphatidylinositol 3-kinase (PI3K) pathway; protein kinase B (Akt); Nuclear factor-κB (NF-kB); and mitogen-activated protein kinase (MAPK). The authors emphasized the need for in vitro, in vivo, and clinical studies to validate its effectiveness to hinder the cytokine storm.

Another study evaluated a combination of turmeric and black pepper extracts, an immunomodulatory herbal product with promising activity against SARS-CoV-2 infection (Roshdy et al., 2020). Its effect was attributed to two reasons: the inhibition of NF-κB p50 nuclear translocation attenuates the cytokine storm associated with SARS-CoV-2 infection; and an in vitro antiviral effect on SARS-CoV-2 in Huh-7 cell lines. Docking analyses of the main compounds (including curcumin) with Spike receptor binding domain (RBD) and with P50 proteins provided strong binding affinity (from − 6 to − 9.7 kcal/mol) with both for all (except lupeol). In in vitro tests, the concentration range from 0.1 to 0.4 µg/mL showed 88% to 92% viral inhibition. The product antagonizes the NF-κB pathway in in silico and in vitro studies, preventing the release of IL-6 and TNF-α, and decreasing cytokine production.

To identify the effects of nanocurcumin on the modulation of inflammatory cytokines in patients with COVID-19, one study evaluated 40 patients with COVID-19 and 40 healthy controls for the expression and secretion of inflammatory cytokines (Valizadeh et al., 2020). Subsequently, patients with COVID-19 were divided into two groups: 20 patients receiving nanocurcumin and 20 patients receiving placebo. The mRNA expression and cytokine secretion levels of IL-1β, IL-6, TNF-α, and IL-18 were evaluated by real-time Polymerase Chain Reaction (PCR) and Enzyme-linked Immunosorbent Assay (ELISA), respectively. The primary results indicated that mRNA expression and cytokine secretion of IL-1β, IL-6, TNF-α, and IL-18 in patients with COVID-19 significantly increased compared to those in the healthy control group. Following treatment with nanocurcumin, a significant decrease was observed in IL-6 expression and secretion in the serum and supernatant ($P = 0.0003$, 0.0038, and 0.0001, respectively), and in IL-1β gene expression and secretion levels in the serum and supernatant ($P = 0.0017$, 0.0082, and 0.0041, respectively).

However, IL-18 mRNA expression and TNF-α concentrations were not influenced by nanocurcumin.

In silico predictive models are promising for obtaining new antivirals against SARS-CoV-2 infections. Studies have been considering papain-like protease (PLpro), RNA-dependent RNA polymerase (RpRd), and the main protease (Mpro/3CLpro) attractive targets for antiviral therapies (Anand et al., 2003; Dai et al., 2020).

Analyzing a set of 19 commercial drugs to investigate the possibility of repositioning drugs already used in clinical practice, Huynh et al. (2020) performed docking studies and molecular dynamics (MD) simulation to identify which drugs had a high potential for Mpro (3CLpro) inhibition. The results revealed highly promising molecules, such as the antiretroviral drug nelfinavir, used in HIV therapy. Of these molecules, curcumin formed the most stable complex with the Mpro of SARS-CoV-2 (− 7.1 kcal/mol), having high binding affinity, and a score similar to that of the peptide-type ligand (N3) used as a control. This newly discovered mechanism paves the way for the optimization of new inhibitors with high affinity binding to Mpro.

Kandeel and Al-Nazawi (2020) performed a virtual screening study against SARS-CoV-2 Mpro (3CLpro) aiming to reposition FDA approved drugs by selecting molecules for their high binding affinity. Among the antivirals, ribavirin and telbivudine stood out, and had the second and third best docking scores, respectively. Curcumin, recognized for its inhibitory activity against SARS-CoV-2, was ranked at position 334 in this study, out of a total of 488 investigated molecules.

Recently, curcumin was chosen in a study as a reference to screen analogous compounds since it has antiviral activity and a safe toxicity profile (Basu et al., 2020). From 400 substances examined, a cyclohexanone derivative with high similarity to curcumin was investigated and exhibited better binding energy at the active site of Mpro (3CLpro) (− 8.72 kcal/mol) compared to curcumin (− 6.90 kcal/mol) and other drugs that were tested: lopinavir (− 8.29), a protease inhibitor; remdesivir (− 6.18), nucleoside analog; hydroxychloroquine (− 6.36), an antimalarial drug. The results of this study encourage experimental applications based on medicinal chemistry and pharmacokinetics against COVID-19.

Emirik (2020) investigated the potential therapeutic effects of the chemical constituents of *C. longa* compared to experimental drugs against COVID-19. Thirty compounds from the plant and nine drugs were evaluated (atazanavir, brecanavir, favipiravir, chloroquine, hydroxychloroquine, lopinavir, remdesivir, ribavirin, and ritonavir) and analyzed by docking studies against the viral proteins of SARS-CoV-2 (Mpro, Spike, and RdRp). The results showed that 1-(4-hydroxyphenyl)-7-(3,4-dihydroxyphenyl)-1,6-heptadiene-3,5-dione showed greater inhibition of proteases than drugs used in experimental therapies for COVID-19.

A in silico screening of 267 chemical constituents of turmeric as Mpro inhibitors was performed through a combination of molecular docking, scoring functions, and MD simulations (Gupta et al., 2020). The results revealed that 05 constituents showed great binding capacity to the active site of Mpro. Two of them stood out: C1 [(1E, 6E)-1,2,6,7-tetrahydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione] and C2 [(4Z,6E)-1,5-dihydroxy-1,7-bis(4-hydroxyphenyl)hepta-4,6-dien-3-one]. They exhibited strong binding to the active site of Mpro (− 9.08 and − 8.07 kcal/mol, respectively), showing greater affinity than lopinavir (ca. − 5.4 kcal/mol), a standard inhibitor of this protease. For the authors, other physicochemical and toxicological properties of C1 and C2 need additional validation in vitro and in vivo for the treatment of coronavirus infection.

Wang et al (2020) selected 10,870 ligands through docking and MD studies to assess the interaction between functional foods and the main SARS-CoV-2 protease, Mpro. The study involved 12 types of active principles of functional foods: curcumin, carbohydrates, fatty acids, phospholipids, vitamins, flavonoids, β-sitosterol, nordihydroguaiaretic acid, nootkatone, β-pinene, and betulinic acid, in addition to its isomers, analogs, and derivatives. Flavonoids had a higher binding energy (− 9.1 kcal/mol) than curcumin (− 7.4 kcal/mol); from them, quercitrin (3-O-rhamnosylquercetin) and its analogs showed greater affinity for Mpro. It is suggested that the protease prefers to interact with polycyclic compounds that have short distances between aromatic rings, such as quercitrin.

Another study investigated 32 isolated constituents of 14 natural spices used in cooking, which were evaluated as Mpro (3CLpro) inhibitors (Ibrahim et al., 2020). Curcumin exhibited the second highest binding affinity (− 9.2 kcal/mol). This potential is attributed to curcumin's ability to form Van der Waals interactions and hydrogen bonds with amino acids proximal to the active site of Mpro. Seeking to evaluate the hypothesis that inhibition of the enzyme NendoU (nsp15) that cleaves the RNA of SARS-CoV-2 would decrease viral replication, Kumar et al. (2021) investigated the potential of binding several active principles of medicinal plants with nsp15. The docking approach was performed using two different software packages, Autodock and Swissdock, having hydroxychloroquine as a positive control. The results demonstrated the binding potential of nsp15 with approximately 50 active principles capable of inhibiting SARS-CoV-2 replication, including curcumin, which exhibited good binding capacity (− 7.26 kcal/mol). The authors emphasize the need for in vitro and in vivo tests to confirm the findings of this study.

Through docking studies, Maurya et al. (2020) demonstrated that natural products used in Ayurvedic medicine, such as curcumin and nimbin, interact with the spike glycoprotein. Both exhibited greater interaction (MolDock score: − 141.36 and − 148.621 kcal/mol), as well as with the angiotensin-converting enzyme 2 (ACE2) receptor (MolDock score: − 142.647 and − 140.108 kcal/mol), and have the potential to block virus entry through interaction with cell receptors.

Regarding the possible mechanisms of action of curcumin and its analogs, evidence shows that the virus entry into cells is blocked; key enzymes in viral replication and transcription, and local inflammatory cytokines are inhibited; and several molecular targets are regulated. Our findings were similar to those reported by Zahedipour et al. (2020), who demonstrated the potential effects of curcumin in the treatment of the coronavirus disease (COVID-19), such as inhibition of virus entry into the cell, of virus encapsulation, and of viral protease, in addition to the ability of curcumin to modulate various pathways of cell-signaling (Table 1).

Activity Against Influenza A virus

The genus *Influenza virus A* (IAV) belongs to the Orthomyxoviridae family and has only one species, divided into serotypes, according to the antigenic properties of its glycoproteins. Hemagglutinin (HA) and neuraminidase (NA), proteins of the envelope, constitute the spikes and play a fundamental role in the multiplication and pathogenesis of these viruses (Fouchier et al., 2005). Type A are the most virulent of the three types of human influenza viruses and also characterized by segmented negative-stranded RNA genomes that require an RNA-dependent RNA polymerase essential for viral replication. This genomic feature allows antigenic variations to occur more frequently, which enables viruses to evade adaptive immune responses in the long term (Bouvier & Palese, 2008).

Such antigenic variations require the development of new antiviral strategies and hence curcumin was evaluated against the IAV (Chen et al., 2013). By pre-incubating A/Puerto Rico/8/1934/H1N1 (PR8) strain with curcumin, plaque formation was inhibited, irreversibly preventing viral replication. The effects of curcumin on viral envelope integrity were then examined. For this, they used a liposome with a lipid structure containing SRB (sulforhodamine B), a fluorescent dye that simulates the viral envelope. Curcumin (30 mM, 60 mM) induced greater leakage of SRB from liposomes (compared to dimethylsulfoxide). These results indicate that curcumin disrupts the integrity of the viral envelope membrane, thereby blocking the infectivity of the virus. For the authors, this interference of curcumin in the function of the envelope protein is due to the hydrophobic characteristic of the membranes that favor the intercalation of curcumin in the lipid bilayer.

The effect of curcumin on IAV was further examined through in vitro and in vivo tests (Han et al., 2018). The first experiment was performed with a cell line (A549), and the second one in BALB/c mice using the PR8 strain. Curcumin (10 μM), in a dose-dependent manner, repressed PR8 replication in lung cells by 15%. In addition, it increased the survival rate and attenuated weight loss in mice. Curcumin (100 mg/kg) significantly inhibited IAV replication in the lungs of infected mice. The study demonstrated the ability of this curcuminoid to induce the HO-1 expression, and suggested that local lung inflammation is inhibited by regulating the immune response through the inhibition of NF-κB signaling in macrophages and other immune cells. Given these results, the authors indicate curcumin as a promising agent against IAV infection, which also helps to prevent damage to lung tissue.

Similar results were observed regarding the antiviral effect of curcumin at different concentrations (25, 12.5, 6.25, and 3.125 μg/mL) in eight IAV strains (Dai et al., 2018), by direct inhibition of viral replication in the adsorption stage. Curcumin also significantly increased the survival rate of mice, reduced lung index, inflammatory cytokines and lung IAV titer, and improved pulmonary histopathological changes after IAV infection. Additionally, inhibition by other pathways was verified, such as oxidative stress pathways, nuclear factor erythroid 2-related factor 2 (Nrf2), and Toll-like receptor signaling (TLR2/4), as well as inhibition of mitogen-activated protein kinases (p38/JNK MAPK).

In view of the ability of curcumin to act on the immune system, the pattern of inflammatory cells in the bronchoalveolar lavage (BAL) of mice infected with PR8 strain was investigated (Xu & Liu, 2017). Curcumin (10–80 μmol/L) dose-dependently inhibited the secretion of pro-inflammatory cytokines (TNF-α, IFN-α, and IL-6) through the inhibition of the NF-kB signaling pathway, evidencing the therapeutic potential of curcumin for acute pulmonary inflammatory diseases. The structure–activity relationship of curcumin and analogs was evaluated in relation to the HA protein, which is responsible for the recognition of binding sites in host cells (Ou et al., 2013). The results revealed that curcumin could interfere with the IAV entry through its interaction with the HA receptor. In a drug addiction time trial, curcumin and tetrahydrocurcumin (30 μM) reduced the production of IAV viral progenies in the first stages of infection. However, tetrahydrocurcumin reduced it to a lesser extent, confirming that the ability to inhibit viral replication is related to the functional groups of curcumin (β-diketone moiety, phenolic groups, conjugated double bonds), which act as Michael acceptors (Michael-type addition reaction).

This structural feature is responsible for the inhibitory effects of curcuminoids.

A similar result was observed by Richart et al. (2018), who analyzed monoacetylcurcumin (MAC). This structural analog of curcumin was able to suppress the PI3K/Akt signaling pathway, reducing the IAV replication in cells. The association of MAC and curcumin potentiated the inhibitory effect on viral replication, confirming the importance of further studies on the synergistic effect of curcuminoids. Kannan and Kolandaivel (2017) evaluated the binding affinity of 16 compounds in the search for natural substances that act on the IAV surface structures. Curcumin and its derivatives (bisdemethoxycurcumin and demethoxycurcumin) showed potent binding affinity for all subtypes of the virus HA protein (1918 H1, 2009 H1, 1957 H2, 1968 H3, and 2005 H5) when compared to the other compounds evaluated, which may be due to the structural similarity between curcuminoids.

Another study demonstrated that curcumin interferes with the binding site between RNA and viral nucleoprotein Y148 (NP-Y148), making the IAV viral replication difficult (Liu et al., 2016). However, it did not demonstrate antiviral capacity in computer screening performed with 177 active ingredients from medicinal plants, of which 12 were considered potentially effective against all H1N1 proteins (Saikia et al., 2019).

The antiviral activity of curcumin and its analogs bisdemethoxycurcumin, demethoxycurcumin, demethylcurcumin, dimethylcurcumin, dihydrocurcumin, octahydrocurcumin, hexahydrocurcumin, tetrahydrocurcumin, and tetramethylcurcumin was investigated as potential inhibitors of H1N1 viral neuraminidase (NA), enzyme that enables the virus to be released from the host cell (Lai et al., 2020). The authors combined methodologies for assessing the quantitative structure–activity relationship and docking studies. Most of the selected compounds showed an inhibitory effect on the NA in different ways, depending on their structure and binding mode, thereby preventing the release of virions from infected cells. The effects of curcumin and its analogs were also verified, in different doses, in mice lung homogenates, and they significantly decreased the levels of TNF-α, IL-6, and IFN-γ. The administration of curcumin at 50 mg/kg/day inhibited influenza activity in H1N1-infected mice, improving the lung index inhibition rate at 36% when compared to ribavirin at 70 mg/kg/day (43%). It also prolonged the average survival time, and reduced death rate.

Activity Against Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) belongs to the Pneumoviridae family and contains a genome composed of non-segmented single-stranded RNA and negative polarity (Rima et al., 2017). It is one of the main viral agents of severe pediatric respiratory tract diseases (Collins & Graham, 2008).

The effects of curcumin on RSV were evaluated in infected human nasal epithelial cells (Obata et al., 2013). Curcumin (0.1–10 µg/ml) inhibits the activation of NF-kB, proteasome, and cyclooxygenase 2 (COX-2), as well as suppresses expression of proteins from the surface (G and M2-1), hence inhibiting viral replication. In this study, curcumin did not affect replication of RSV in human lung adenocarcinoma cell line A549 infected with RSV.

Yang et al. (2016b) developed functionalized silver nanoparticles (cAgNPs) from curcumin, which were stable, monodisperse, and showed good bioavailability on tests. The inhibitory effect on RSV corresponded to a significant reduction in viral titer, as a result of cAgNPs directly inactivating the virus before entering the cell, which makes this product a promising agent against RSV. Following the same line of research, Yang et al. (2017) prepared a curcumin nanocomposite of β-cyclodextrin-functionalized graphene oxide, and evaluated its antiviral activity against RSV. They verified the reduction of viral titers, which can be attributed to direct virus inactivation, inhibition of viral binding to host cells, and possible interference with viral replication. These results open a new perspective for the use of products that combine nanotechnology and natural products in the development of innovative therapeutic agents.

Activity Against Ebola Virus

The Ebola virus (EBOV), genus *Ebolavirus*, family Filoviridae, has a negative polarity linear, non-segmented RNA genome with high virulence (Kuhn et al., 2019). EBOV attacks macrophages and dendritic immune cells, triggering an immune response characterized by a storm of pro-inflammatory cytokines (Falasca et al., 2015). Given the ability of curcumin to suppress the release of cytokines, its potential in the treatment of EBOV was evaluated (Setlur et al., 2017). In silico studies with 150 active ingredients from plants showed that curcumin was able to bind to four of the main structural proteins of EBOV (VP24, VP30, VP35, and VP40). Regarding VP30, curcumin exhibited good binding energy (− 9.6 kcal/mol) when compared to the reference antiviral drug BCX4430 (− 7.6 kcal/mol). According to the authors, this result provides a basis for future experimental studies on the utility of plant-based ligands as lead compound candidates against EBOV targets. Baikerikar (2017) evaluated the antiviral potential of curcumin and its analogs against EBOV proteins (VP40, VP30, VP35, VP24, GP, and NP) through MD and docking studies. When comparing the docking scores of all target proteins, it was found that bisdemethoxycurcumin showed better binding affinity than curcumin. In targets VP35, GP, and VP30, tetrahydrocurcumin exhibited better binding energy than curcumin. These results

indicate the need for further studies on curcuminoids as possible antiviral agents against EBOV.

Activity Against Arboviruses

Diseases caused by arboviruses (arthropod-borne viruses) are affected by the bite of an arthropod vector. Some of the infections that affect humans caused by *Flavivirus* (Flaviviridae) include yellow fever virus (YFV), West Nile virus (WNV), Dengue virus (DENV), Zika virus (ZIKV), and Japanese encephalitis virus (JEV). The *Flavivirus* genome is formed by positive polarity single-stranded RNA, approximately 11 kb in length. The genome encodes a polyprotein that gives rise to three structural proteins: capsid protein (C), precursor membrane protein (prM), and envelope protein (E), and seven non-structural proteins—NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Simmonds et al., 2017).

Activity Against Dengue Virus

Most of the studies retrieved in our review on arboviruses were related to Dengue virus (DENV). Padilla-S et al. (2014) found out that curcumin (10, 15, and 20 μM) inhibited the production of viral particles in a dose-dependent manner in cultures of BHK-21 cells (derived from hamster kidney) or Vero cells infected with the DENV-2 serotype. According to the authors, this interference may not occur due to direct effects on the production of viral particles but result from the effects of curcumin on various cell systems, such as the ubiquitin–proteasome system (UPS), by increasing the level of ubiquitin-conjugated proteins Lys48 or the disorganization of actin filaments of the cytoskeleton, resulting in apoptosis.

However, when investigating the antiviral and immunomodulatory properties of curcumin associated or not with other polyphenols in human macrophages (U937-DC-SIGN) infected with DENV serotypes 2 or 3, Jasso-Miranda et al. (2019) observed that curcumin was not able to significantly inhibit infections induced by DENV serotypes 2 and 3 in the absence of polyphenols. This indicates that the combination potentiates the effect of curcumin. Another in vitro study compared the activity of curcuminoids (curcumin and bisdemethoxycurcumin) and their three synthesized analogs (replacing the β-diketone moiety with penta- and hexacyclic structures—cyclopentanone CC4 and cyclohexanone CC5, and with a monoketone moiety—acyclic analog CC3) in inhibiting the non-structural proteins of DENV-2 (NS2B/NS3) (Balasubramanian et al., 2019). The results of the plaque assays revealed that curcumin had a weak inhibitory potential when compared to its analogs. Curcuminoids act by inhibiting the metabolism of lipids by preventing lipogenesis and, consequently, viral replication of DENV-2.

Lim et al. (2020) also demonstrated that curcumin inhibits its NS2B-NS3 protease allosterically by binding to a cavity with no overlap with the active site. The importance of this study lies in the fact that NS2B-NS3 protease also belongs to other viruses of the genus, such as Zika. Therefore, the authors suggest that curcumin could be used directly to treat flaviviral infections and as a starting point for the development of potent allosteric inhibitors.

The antiviral activity of curcumin in solution and as a nanoemulsion (nanocurcumin) was investigated against four DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) in the A549 cell line plaque assays (Nabila et al. 2020). Nanocurcumin showed greater cytotoxicity compared to curcumin solution, due to its better cellular absorption, although no significant anti-DENV difference was observed between curcumin solution and nanoemulsion. Regarding the reduction of the viral titers of DENV-1 and DENV-2, nanocurcumin also excels because of its improved bioavailability and, therefore, greater antiviral potential.

Activity Against Japanese Encephalitis Virus

The role of curcumin as a protective agent for neural cells and against cell death caused by JEV was investigated in vitro (Dutta et al., 2009). Mouse neuroblastoma (Neuro-2a) cells were infected with JEV and treated with varying doses of curcumin (5–10 μM). The neuroprotective action as antioxidant was observed by reducing reactive oxygen species, recovering cell membrane integrity, and decreasing the signals of pro-apoptotic molecules. A reduction of infectious viral particles was also observed in Neuro-2a cells. The authors suggest that this inhibition is probably due to dysregulation of the UPS. The antioxidant potential of curcumin was confirmed by Zhang et al. (2014) in reducing viral load and JEV replication, as well as inhibiting neuronal death, secondary inflammation, and oxidative stress mediated by reactive microglia.

Activity Against Zika and Chikungunya Viruses

The antiviral effects of curcumin, demethoxycurcumin and bisdemethoxycurcumin against Zika virus (ZIKV) and Chikungunya virus (CHIKV) (Togaviridae, genus *Alphavirus*) were demonstrated in vitro in HeLa, BHK-21, and Vero-E6 cells (Mounce et al., 2017), showing their effectivity in different cells. Treatment with curcumin in a dose-dependent manner (1–5 μM) reduced the viral titer of both viruses, an effect corroborated by the reduction of the viral genome, confirming the reduction of the infectivity of enveloped viruses. Therefore, curcuminoids proved promising in the treatment of outbreaks of viruses such as CHIKV and ZIKV.

These effects were confirmed by virtual screening studies after analyzing the inhibitory capacity of 720 natural products against ZIKV (Gao et al., 2019), from which the authors selected gossypol, a polyphenolic substance present

in cottonseed (*Gossypium hirsutum*) and curcumin, for further in vitro analyses, including six epidemic human strains. Gossypol exhibits potent inhibitory activity against ZIKV strains. Curcumin (30 μM) inhibited (75–100%) viral infection in the early stages of adsorption.

Activity Against hepatitis C Virus

The hepatitis C virus (HCV) belongs to the genus *Hepacivirus*, family Flaviviridae, showing similarities and differences with the hepatitis B virus. Although both have a single-stranded RNA genome and positive polarity, are enveloped, and transmitted parenterally, the evolution of their respective pathologies is different (Rehermann & Nascimbeni, 2005).

Natural products with anti-inflammatory and hepatoprotective potential, especially curcumin, were evaluated against HCV (Lovelace & Polyak, 2015). Curcumin acts on several signaling pathways, activating adenosine monophosphate kinase (AMPK) and inhibiting mammalian target of rapamycin (mTOR) and nuclear factor-kappa B (NF-κB), which are important regulators of cellular biosynthetic pathways. These mechanisms influence the inflammatory response and immune system, reducing the infection effects induced by HCV. Kim et al. (2010) demonstrated the ability of curcumin to significantly reduce the replication of HCV, directly or through the suppression of the PKB/SREBP-1 (protein kinase B/sterol regulatory element-binding proteins) pathway, at concentrations that did not affect cell viability. In another study, curcumin (10–20 μM) inhibited HCV replication by inducing HO-1 expression and inhibiting the PI3K/Akt signaling pathway (Chen et al., 2012). Therefore, it has direct effects on the expression of antioxidant proteins that regulate immunity (Ailioaie & Litscher, 2020).

The antiviral activities of curcumin, demethoxycurcumin, bisdemethoxycurcumin, and tetrahydrocurcumin at concentrations of 5 and 20 μM were investigated in cell culture (HCVcc) and in HCV pseudoparticles (HCVpp) in hepatoma cell lines and primary human hepatocytes (Colpitts et al., 2014). The results demonstrated that curcumin treatment had no effect on the HCV RNA replication, viral assembly, or release. However, co-incubation of HCV with curcumin potently inhibited the entry of all major HCV genotypes. Other curcumonoids also had similar antiviral activities, except tetrahydrocurcumin, suggesting the importance of α,β-unsaturated ketone group for this activity.

Loutfy et al. (2020) compared the activity of chitosan nanoparticles encapsulated with curcumin (CuCs) and curcumin (alone) against the HCV genotype 4a (HCV-4a). The docking study showed that curcumin (alone) exhibited a higher binding affinity to NS3 protease and NS5A polymerase than CuCs. However, CuCs exhibited good binding affinity to NS5B polymerase, an essential enzyme for virus replication, compared to curcumin alone. When evaluated in vitro, both inhibited the entry of HCV-4a into Huh-7 cells. CuCs reduced the viral titer by 100% and curcumin alone by almost 95%. The authors indicate that CuCs are potential therapeutic agents against HCV infections.

Activity Against Human Immunodeficiency Virus

Human immunodeficiency virus (HIV), Retroviridae family, has three structural genes (gag, pol, and env) common to retroviruses. It also has proteins with regulatory functions that are composed of two essential elements: Tat, which activates transcription, and Rev, which modulates viral RNA transport. In addition, it has other accessory proteins: Nef (negative regulatory factor), Vif (viral infectivity factor), Vpr (r viral protein), and Vpu (single viral protein) (Votteler & Schubert, 2008). Prasad and Tyagi (2015) mentioned evidence that curcumin and its analogs inhibit the infection and replication of viral genes and the multiplication of HIV. The authors adduce data on inhibitory effect demonstrated for the transactivation of the genome Tat protein (HIV-1 LTR) in proteases, integrases, and inflammatory molecules (interleukins, TNF-α, NF-κB, and COX-2). They summarized reports describing that curcumin increases the effects of conventional drugs and minimizes adverse effects.

The solubility and bioavailability of protease inhibitors are one of the limiting factors for the use of antiretrovirals. Given this fact, the pharmacokinetics of oral and intravenous saquinavir, associated or not with curcumin, was determined in rats (Kim et al., 2013). A solid dispersion (SD) was prepared using Solutol and curcumin to improve the solubility and bioavailability of curcumin. The authors observed that curcumin SD significantly increased the intravenous pharmacokinetics parameters of saquinavir for the oral exposure in rats. However, untreated curcumin did not affect them. These findings suggest that the application of techniques using non-ionic solubilizers with curcumin can increase the oral bioavailability of saquinavir, thereby potentiating the effect of this antiretroviral.

Another strategy used to assess the influence of bioavailability on curcumin activity was to compare it to a synthetic analog, called "curcumin A", and its activity at specific stages of HIV-1 replication was investigated in vitro (Kumari et al., 2015). It was observed that both curcumin and curcumin A showed similar inhibition of one round of HIV-1 infection in cultured lymphoblastoid (also called CEM) T cells. Curcumin A inhibited, at low concentrations, the reverse transcription of HIV-1, but had no effect on the long terminal repeat (LTR), the trans-activator of transcription (Tat) protein, or the transcription factor NF-κB. In the same study, experiments were carried out in lymphoblastoid cell cultures, demonstrating that curcumin A induces the expression of HO-1 and decreases the progression of the HIV-1 infectious cycle. By analyzing this set of activities,

the authors concluded that the maintenance of anti-HIV-1 properties is associated with the improved stability of curcumin A (compared to curcumin), which allows it to be elected as an antiretroviral candidate.

Ali and Banerjea (2016) investigated (in vitro) the effect of curcumin on the rate of degradation of Tat protein. They performed an assay with cycloheximide (CHX), an inhibitor of protein synthesis. Viral producer cells (HEK-293t) were transfected with transcription factors (Myc-Tat) and treated with curcumin. Combining curcumin and CHX provided a rapid degradation of Tat protein, and an inhibition of the activation of the LTR promoter, which resulted in the inhibition of viral replication. According to the authors, one of the main mechanisms behind the anti-HIV activity of curcumin is the degradation of the Tat protein.

A case study evaluated the effect of BIOMOR Curcumin supplementation on the energy metabolism of an adult woman (42 years old) with HIV/AIDS and under antiretroviral therapy (da Silva et al., 2019). The intervention was performed with turmeric extract (500 mg/day) for 27 days. Glycemic and lipid profiles and substrate oxidation (SOxi) at rest were evaluated before and after the supplementation. During the intervention with curcumin, an improvement in the lipid profile and insulin sensitivity was observed, as well as a positive modulation of SOxi at rest. Accordingly, oral curcumin supplementation can positively modulate the energy metabolism of HIV/AIDS patients undergoing antiretroviral therapy. However, the authors suggest that clinical studies are needed to confirm these findings.

Sharma et al. (2017) designed a nanocomplex of curcumin and silver (Cur-AgNP) to evaluate in vitro its immunomodulatory and antiviral effects on HIV-1 infected ACH-2 cells. Comparing to the control, the authors noticed a significant decrease in the expression of the HIV-1 LTR gene (-73%) in cells treated with Cur-AgNP (20–100 μL). The treatment of cells with an equivalent concentration of curcumin reduced the expression of the HIV-1 LTR gene by 33% when compared to that of Cur-AgNP. Furthermore, Cur-AgNPs significantly reduced the expression of HIV-1 viral protein p24 (-58%) and inhibited HIV replication by attenuating NF-κB and other inflammatory mediators (TNF-α, IL-6, and IL-1β).

Following a similar complexation strategy with metal ions, Sharma et al. (2019) developed a nanocomplex of curcumin with iron-phenanthroline (NCIP) and evaluated it in human microglia infected with HIV. NCIP treated HIV-1-infected microglia significantly decreased HIV-p24 expression (41%) and inhibited the pro-inflammatory mediators TNF-α, IL-8, and NO (by 61%, 41%, and 50%, respectively). NCIP also showed antioxidant activity as evidenced by increased catalase gene expression (CAT) and induction of HO-1 expression. The authors suggest that NCIP may be associated with conventional antiretroviral treatment due to its potential to reduce HIV-1-associated neurotoxicity. Such effects help maintain homeostasis and reduce neuroinflammation.

Another study investigated the ability of nanoparticles to cross the blood–brain barrier (BBB) and suppress or eliminate HIV-1 (Singh et al., 2020). Nanoparticles produced in an aqueous medium containing Pluronic F127 and combined by laser ablation with multidrug encapsulation (ritonavir, atazanavir, and curcumin) were analyzed in an in vitro cell model of the BBB. Improved dispersibility of curcumin in aqueous medium by ultra-small size (20–25 nm) nanoparticles, resulting in capability of crossing the BBB, reduced HIV viral replication by inhibiting the production of viral protein p24 up to 36 times.

Considering curcumin's low solubility and its intense yellow–orange color, Mirani et al. (2019) examined tetrahydrocurcumin (THC), a colorless metabolite of *C. longa*, as a potential anti-HIV-1 gynecological microbicide. An in silico study verified that THC is able to inhibit the binding between gp120 (envelope glycoprotein) and the CD4 (cluster of differentiation 4) receptor, preventing the entry of the virus into the target cell. The authors also evaluated the solubility of THC in different oils, surfactants, and co-surfactants, finding better solubility in the oils glycerol monolaurate and propylene glycol monocaprylate; the surfactants Tween 20, Tween 80, and Cremophor EL; and the co-surfactant Transcutol P, and they tested its incorporation into a microemulsion gel. When comparing the anti-HIV activity of THC in solution with it in microemulsion gel p24 antigen assay (viral capsid protein), the microemulsion exhibited more than 50% inhibition of the antigen, indicating THC microemulsion gel as a potential microbicide candidate for early-stage HIV-1 inhibition.

Research Avenues and Concluding Remarks

Reflecting on the outcomes of our review on activities of curcuminoids against RNA genome viruses, it seems clearly evident the lack of research into this. From the 56 selected papers we revised, most of them concentrate on in vitro and in silico studies. Seven examined the effects on laboratory animals (mice/rats) and only one on human patients. These aspects may evidence the incipient stage of these investigations, in spite of the multi-millennial interest in the plant medicinal properties and several decades of research on curcuminoids' health benefits.

It is pertinent though to carefully ponder on constraints associated with clinical studies of curcumin and some of its analogs and how they might hinder progress in this stage. Despite many interesting pharmacological activities, curcumin is rapidly metabolized, has low solubility, limited intestinal absorption, hence reduced systemic availability. Such limitations prompt increasing research in

nanoencapsulation techniques and nanoformulations of curcumin and analogs. This is a manifest trend in recent studies.

We also noticed a new avenue to investigate benefits of curcuminoids when they are studied in combination with antiviral drugs. Besides their already observed direct inhibition of viral activity, they promote immunological response and other vital functions. Such synergistic strategies may contribute to reduced doses and consequential toxicity of commonly used drugs, minimization of side effects, and increased survival rates.

A particular point to consider while assessing the degree of advancement in the studies, aside from reasons of good practice regarding maturity level of knowledge before in vivo tests, is specific test animals' response to certain viral infections. New topics of research in the treatment of infected superior organisms with curcuminoids are constrained by this aspect and further examinations of this topic must regard its implications. Since our findings related to in vivo and clinical tests provide evidence that curcumin exerts positive influence against CVB, Enterovirus 71, HIV, IAV, and SARS-CoV, this might be a promising field of future studies.

There remains plenty to investigate about how curcuminoids interact with varied viral molecular targets on which they are believed to act. Mechanistic features and relationships between the structure of curcumin and its analogs and their antiviral activities are unclear. Taking into account the vast array of pharmacological properties suggested herein, numerous lines of research could develop on this domain.

In view of our initial aspirations for this review, though, another relevant set of unanswered questions takes precedence. As evidenced by revised papers, the association of curcuminoids with nanomaterials increased solubility, bioavailability, and antiviral activities which were confirmed by blocked entry of the virus into cells or by inhibition of key enzymes in viral replication and transcription in in vitro and in vivo experiments. Even expecting this to represent progress, little is known about the risks of curcumin nanoformulations to human health and their toxicological safety. Thus, future scientific exploration of curcuminoids applications must consider these comments simultaneously as cautionary notes and as promising research avenues. We do hope this review will stimulate further studies, resulting in the validation and application of curcumin and analogs as effective, innovative, and sustainable therapeutic agents against medically important viral infections.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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