Golden Pigment Curcumin: An Inspiring Antiviral Molecular Model for COVID-19 Drug Design

Altın Pigment Kurkumin: COVID-19 için İlham Veren Antiviral Bir Moleküler Model

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ABSTRACT

COVID-19 caused by a new type of coronavirus (SARS-CoV-2) originated in China has speedily become a frightening pandemic all over the world. Despite of intense efforts relevant to experimental and clinical studies since the start of the COVID-19 pandemic, no disease-specific drug or vaccine is available, yet. Several treatment strategies including already known antiviral drugs, interpherons, interleukin inhibitors, and other drugs acting through different mechanims are being implemented in COVID-19 patients. On the other hand, natural products especially pythocompounds have been proven to be lead molecules for drug design and development research. Among them, curcumin as the main constituent of *Curcuma longa* L. (turmeric), is the reputed compound displaying remarkable biological activities for human health. It has been shown to have a inhibiting effect against a wide range of viruses such as HCV, HIV, PEDV, HSV, Ebola, dengue, influenza, Zika, SARS-CoV, etc. Therefore, curcumin could be considered as a structural model for designing new molecules against COVID-19. In the present review, antiviral activity of curcumin is scrutinized thorugh the literature data relevant to its enzyme and receptor interactions, *in vitro*, *in vivo*, *in silico*, and cell-based assays.

Key Words: COVID-19, coronavirus, curcumin, antiviral activity

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ÖZET

Çin menşeli yeni bir tür koronavirüs (SARS-CoV-2) nedenli COVID-19 hızla tüm dünyada korkutucu bir salgın haline gelmiştir. COVID-19 pandemisinin başlangıcından bu yana deneysel ve klinik çalışmalarla ilgili yoğun çabalara rağmen, henüz hastalığa özgü bir ilaç veya aşı mevcut değildir. COVID-19 hastalarında halihazırda bilinen antiviral ilaçlar, interferonlar, interlökin inhibitörleri ve farklı mekanizmalarla etki eden diğer ilaçlar dahil olmak üzere çeşitli tedavi stratejileri uygulanmaktadır. Öte yandan, özellikle bitkisel bileşikler gibi doğal ürünlerin ilaç tasarımı ve geliştirme araştırmaları için öncü moleküller oldukları kanıtlanmıştır. Bunların arasında, *Curcuma longa* L.'nin (zerdeçal) ana bileşeni olan kurkumin, insan sağlığı için dikkate değer biyolojik aktiviteler sergileyen meşhur bir bileşiktir. HCV, HIV, PEDV, HSV, Ebola, dang, grip, Zika, SARS-CoV, vb. gibi çeşitli virüslere karşı inhibitör etkiye sahip olduğu gösterilmiştir. Bu nedenle, kurkumin COVID-19'a karşı yeni moleküller tasarlamak için yapısal bir model olarak düşünülebilir. Bu derlemede, kurkuminin antiviral aktivitesi, enzim ve reseptör etkileşimleri, *in vitro*, *in vivo*, *in silico* ve hücre-temelli yöntemler ile ilgili literatür verileri üzerinden irdelenmektedir.

Anahtar Sözcükler: COVID-19, coronavirus, kurkumin, antiviral aktivite

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INTRODUCTION

A new type of coronavirus known as SARS-CoV-2 is the cause of coronavirus virus disease (COVID-19) which has become a worldwide pandemic as proclaimed by World Health Organization (WHO) in January 30th, 2020. The disease firstly emerged in Wuhan city of China in the end of December, 2019 and then rapidly spread out. SARS-CoV-2 targets respiratory system acting through angiotensin-converting enzyme-2 (ACE-2) receptors and trans membrane serine protease-2 (TMPRSS-2) co-receptors to enter into lung alveolar cells for viral replication (1). For viral invasion, spike (S) glycoprotein of SARS-CoV-2 having a furin-cleavage site interacts mainly with the binding region (318-510aa) of ACE-2 receptors (2). Relevantly, Ala251-His641 residues of (S) glycoprotein of SARS-CoV play a crucial role in viral penetration (3). Airborne transmission is the main route for SARS-CoV-2, which causes such symptoms as cough, fewer, muscle pain, respiratory deficiency, severe acute respiratory disease (SARS), organ failure, and finally death. Clearly, there is no new drug developed towards COVID-19 so far and the known antiviral drugs, *e.g.* lopinavir/ritonavir, ribavirin, favipiravir, arbidol, darunavir/umifenovir, remdesivir, other drugs such as hydroxychloroquine, azithromycin, interpherones, interleukine inhibitors (tocilizumab, sarilizumab) as well as convalescent plasma treatment have been currently applied in the treatment (4).

Coronaviruses are of zoonotic origin and belong to order *Nidovirales*, family *Coronaviridae*, and subfamily *Orthocoronavirinae.* Four coronavirus families are known as α, β, γ and δ (5). SARS-CoV-2 has been found to possess 79% similarity to that of SARS-CoV and about 50% to that of Middle East respiratory disease coronavirus (MERS-CoV) in their genome sequencing and COVID-19 looks like to SARS considering their viral replication mechanisms (6). SARS-CoV and MERS-CoV genomes, from the betacoronaviruses family like SARS-CoV-1, are translated into two polyproteins known as papain-like protease (PL^{pro}) and 3C-like protease (CL^{pro}, also called M-pro). Among them, particularly CL^{pro} is vital for viral replication (7). Several other human coronaviruses (HCoV) including HCoV-229E, HCoV-NL63, and HCoV-OC43 with milder infectious effect are also present and they contain common positive-strand RNA genomes similar to those of SARS-CoV-1, -2, and MERS-CoV. Therefore, inhibition of PL^{pro} and CL^{pro} is important to find new inhibitors against SARS-CoV-2 and a number of natural products have been tested against these two proteases (8). In addition, natural compounds with antiviral effect against other human pathogenic viruses including human immunodeficiency virus (HIV), influenza viruses (IFV), etc may give a tip and be molecular frameworks for scientists to develop novel effective drugs against COVID-19. In this regard, curcumin [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane] (Fig. 1), found in the rhizomes of *Curcuma longa* L. (turmeric, Zingiberaceae), is a shining natural molecule with a diarylheptanoid structure. Countless number of studies are going on this molecule considering its promising pharmacological activities including its antiviral activity. The aim of the current review is to cover and provide a basis for antiviral activity of curcumin (named as golden spice, Indian solid gold) through the specific studies in order to scrutinize its probable protective role against COVID-19. On this purpose, we searched literature *via* PubMed, Scopus, and Web of Science (WoS) using the keywords "curcumin, antiviral activity, and coronavirus". The studies on *C. longa* were excluded to focus only curcumin itself in the current review.

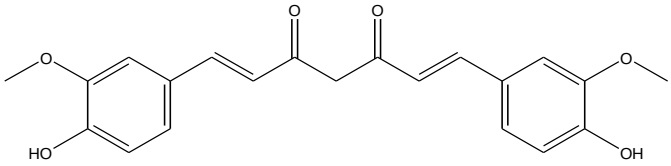

Figure 1. Chemical structure of curcumin

Antiviral activity of curcumin by enzyme inhibition mechanisms

a. Angiotensin-converting enzyme (ACE) inhibitory activity

Since it is a hot topic nowadays, activity of curcumin has been recently reviewed against SARS-CoV-2 by Rocha and de Assis (9) and only inhibition of ACE was evaluated as the most remarkable mechanism targeted by SARS-CoV-2 in the first place. Hence, the studies on ACE inhibition-related and enzyme inhibition-related to viruses (excluding PL^{pro} and CL^{pro}) of directly curcumin and/or its analogues were mentioned followingly.

When a number of natural products were tested for their ACE inhibitory activity potential, curcumin had a mild level of inhibitory effect characterized by IC_{50} value of 0.83 ± 0.04 mM, where IC_{50} value of enalapril as the reference drug was 0.071 ± 0.04 mM (10). Consistently, curcumin, known with disadvantage of its high lipophilicity and low bioavailability (11), was reported to have a very low ACE inhibitory effect, when compared with that of captopril (12). Nevertheless, ACE inhibitory activity of curcumin was found to enhance in its nanoemulsion formulation in the same study. Bhullar et al. synthesized 16 novel carboxylic analogues of curcumin and tested against ACE (13). Curcumin showed 76.86% of inhibition, while 9 of its structural analogs displayed ACE inhibition over 50% ranging between 51.96 and 93.89%. In fact, 4 of them had even superior inhibition than that of curcumin. The structure-activity relation (SAR) among the analogs of the aforementioned curcumin series revealed that location of electron-releasing groups on aromatic ring and increasing hydrophylic-hydroxyl groups caused a better inhibition potency against ACE. In a similar study performed by Zhuang et al. with other type of the synthesized curcumin analogues, the compounds were demonstrated to have lower inhibition shown by their IC_{50} values ranging between 1.23 and 131.14 μM than that of captopril (IC_{50}= 0.094 μM) (14). A new *in silico* study also reported that curcumin had a marked binding affinity to ACE-2 receptors to prevent attachment of the new type coronavirus using 3 target proteins, *e.g.* SARS-CoV-2 protease, spike glycoprotein-RBD, and PD-ACE2 (15).

Curcumin was reported to lead to down-regulation of ACE gene expression in rats (16). In another work, curcumin treatment at daily dose of 150 mg/kg in Sprague-Dawley rats decreased ACE level and its expression determined using Western blot analysis (17). Curcumin was found to inhibit ACE activity significantly in the brain, when compared to the control and perindopril groups in 5-week old male ICR rats (18). Besides ACE mRNA was also expressed significantly lower in the curcumin group than control group. However, it should be noted that ACE inhibitory activity of curcumin has been observed to occur through different mechanisms in *in vivo* conditions.

b. Aminopeptidase N (APN)/CD13 inhibition

Aminopeptidase N (APN)/CD13 is known to be a transmembrane protease type of receptor for coronaviruses, found in endothelial and epithelial tissues, fibroblasts, and leukocytes (19). Curcumin was reported to be an irreversible inhibitor of APN/CD13 using combination of surface plasmon resonance analysis and an APN-specific antibody competition assay (20).

b. Neuraminidase inhibition

Neuraminidase is the enzyme located in envelope part of influenza virus. The reputed inhibitory drugs of the enzyme are amantadine, oseltamivir, and zanamivir. Five derivatives of curcumin (IC_{50}= 450.27 μM) were shown to lessen in H1N1-induced neuraminidase activation in lung epithelial Madin–Darby canine kidney (MDCK) cells (21). Corresponding IC_{50} values of the active derivatives including demethylcurcumin, demethoxycurcumin, bisdemethoxycurcumin, tetramethylcurcumin, and dihydrocurcumin were established as 62.77, 199.64, 70.12, 225.8, and 219.15 μM.

d. Inosine monophosphate dehydrogenase (IMDPH) inhibition

Inosine monophosphate dehydrogenase (IMDPH), which is a crucial enzyme for *de novo* purine nucleotide biosynthesis, is another validated target for antiviral activity (22). IMDPH inhibitors such as ribavirin, mizoribine, mycophenolate, mofetil, and tiazofurin have been so far implemented in clinical use. In screening of several plant polyphenols against IMDPH, curcumin was elucidated to be the most active inhibitor with 68% of inhibition, followed by epigallocatechin gallate (47%), whereas resveratrol, genistein, eugenol, gingerol, naringenin, naringin, and caffeic acid had no inhibition (23). Its IC_{50} value was determined as 43.0 μM.

e. Protein phosphotase-1 (PP1) inhibition

Inhibition of protein phosphatase-1 (PP1) is another approach for determining antiviral effect. PP-1 catalyzes and regulates transcription of HIV-1 and ebola virus (24, 25) and curcumin and its some analogs were reported to endorse proteosomal (PP-1) deprivation of Tat protein leading to the inhibition of Tat-induced HIV-1 transcription and lessening of virion creation through interfering with cellular RNA (26). On the other hand, HIV protease inhibitory activity of curcumin was examined by *in silico* experiments and found to interact with Asp25, Asp29, Asp30, Gly27', Asp29', and Asp30' residues in the protease active site (27). SAR analysis point to important role of *o*-hydroxyl and/or keto-enol moieties of curcumin as well as its symmetric structure.

f. PL^{pro} and 3-CL^{pro} inhibition

As abovementioned, SARS-CoV PL^{pro} and 3-CL^{pro} are important enzymes as the drug targets. Wen et al. screened 221 compounds of herbal origin against SARS using cytopathogenic effect (CPE) induced by SARS-CoV in Vero E6 cells as well as 3CL^{pro} inhibition assay (28). Among them, curcumin was revealed to exhibit moderate level of inhibition in viral replication and 3CL^{pro} having IC_{50} value of 40 μM. In a recent study, strong binding affinity of curcumin against COVID-19 3CL^{pro}/M^{pro} was demonstrated to occur through H bonding with the amino acid residues Leu141, Gly143, Ser144, Cys145, and Thr190 (29). M-pro (3-CL^{pro}) crystal structure has been the first protease identified for COVID-19, which was evidenced to share high similarity to those of SARS-CoV and MERS-CoV. A virtual screening of compounds using Schrodinger glide docking module indicated that curcumin was the potent inhibitor of SARS M-pro with the IC_{50} value of 0.0235 μM (30).

g. RNA polymerase II inhibition

Anti-HSV-1 activity of curcumin was demonstrated to occur *via* diminishing activity of RNA polymerase II mediated by the viral transactivator protein VP16 (31).

h. Protease and integrase inhibition

Curcumin was earlier shown to inhibit proteases of HIV-1 (IC_{50} = 100 μM) and 2 (IC_{50} = 250 μM) moderately (32), where it was also able to block integrase of the same virus (IC_{50} = 40 μM) (33). On the other hand, curcumin and its several analogs successfully inhibited by interacting NS2B-NS3 protease of dengue virus supported by molecular docking simulations (34-38).

Antiviral effect of curcumin by cellular assays and molecular docking analyses

Curcumin was previously reported to inhibit several viral species, *e.g.* Zika and Chikungunya viruses, both of which are mosquito-borne, as well as dengue virus, hepatitis C virus (HCV), ebola virus, herpes simplex virus (HSV), vesicular stomatitis virus (VSV), human immunodeficiency virus (HIV), and Coxsackievirus B3 (CVB3) (38-45). It effectively inhibited avian influenza virus (AIV), a type of orthomyxoviridae virus, in turkeys synergistically acting with thymoquinone, which also led to less expression of cytokine genes (46). Curcumin was also able to block human influenza virus PR8 *via* inhibition of plaque formation in MDCK cells (47). In a separate study, mechanism of anti-influenza action of curcumin was demonstrated to befall through its contact with the receptor binding region of viral haemagglutination (HA) protein to prevent viral entry (48). The SAR study pointed out to importance of presence of the double bonds in the central seven-carbon chain in the compound. Consistently, Dai et al. found antiviral effect of curcumin on influenza A virus (IAV) replication through suppressing oxidative stress induced by IAV, increasing production of Nrf2, HO-1, NQO1, GSTA3, and IFN-β, and inhibiting IAV-induced activation of TLR2/4/7, Akt, p38/JNK MAPK, and NF-κB pathways (49). Besides, the compound led to escalation in survival rate of mice, whereas it caused a reduction in lung index and levels of inflammatory cytokines.

Curcumin was described to inhibit HCV replication in dose-dependent manner using luciferase reporter gene assay, RNA detection, and protein analysis in HCV in human hepatoma cell line (50). The results underlined that inhibition of PI3K-AKT along with heme oxygenase-1 induction was the mechanisms for the compound in preventing replication of HCV, in consistent with outcomes of an earlier study reporting curcumin as heme oxygenase-1 inducer (51). The authors suggested curcumin as adjuvant to anti-HCV medication.

A similar study indicated that curcumin did not exhibit a direct inhibition on HCV RNA replication or viral release, while co-incubation of curcumin with HCV led to complete inhibition of viral entry of all HCV genotypes (52). Relevantly, Kim et al. reported that curcumin diminished gene expression of HCV by supressing activation of Akt-sterol regulatory element binding protein-1 (SREBP-1) that induces viral replication as a lipogenic factor (53).

Curcumin was strongly effective in Vero cells in inhibiting human enterovirus 71 (EV71), which causes hand, foot, and mouth disease (HFMD) in children (54). The synthesis of viral RNA, the expression of viral protein, and the complete assembly of viral progeny was successfully blocked by curcumin. Moreover, production of reactive oxygen species (ROS) due to viral infection as well as activity of viral proteasomes was also suppressed by curcumin at early stage of viral infection. Strong antiviral activity of curcumin was disclosed against Japanese encephalitis virus (JEV) acting through mainly its antioxidative effect (55).

Curcumin and its derivative curcumin A exhibited a marked inhibition against HIV-1 in primary peripheral blood mononuclear cells, where curcumin A (IC_{50}= 2 μM) had a higher activity than that of curcumin (IC_{50}= 12 μM) (56). Curcumin A prevented reverse transcription of HIV-1, while it did not exhibit inhibition on Tat-induced transcription of the virus. Another mechanism for anti-HIV-1 effect of curcumin was formerly proposed to occur *via* inhibiting activity of its viral long terminal repeat (LTR) (57).

Antiviral effect of curcumin against human cytomegalovirus (HCMV) was shown *in vitro* and tested later against HCMV infection in Balb/c mice which supported the *in vitro* data. Its protective effect against HCMV was suggested to happen through its antioxidant and anti-inflammatory actions (58). Curcumin and its derivatives (bisdemethoxycurcumin, demethoxycurcumin, and tetrahydrocurcumin) were tested against Ebola viral receptor proteins (VP40, VP35, VP30, and VP24) as the drug targets for this virus using molecular docking simulations. In this work, bisdemethoxycurcumin was revealed to possess higher binding activities against these receptor proteins than curcumin, while tetrahydrocurcumin had identical activity to that of curcumin (59). In a similar study, molecular docking studies indicated that curcumin displayed a good connection with binding pocket of V30 receptor protein of Ebola virus (60). Replication of Rift Valley fever virus (RVFV, MP12 strain) was shown to be inhibited by curcumin, where it led to down-regulated extracellular infectious virus levels (61). Curcumin was revealed to exert antiviral activity against PEDV as another type of coronavirus by inhibiting its replication through reducing plaque numbers and virus titers (62).

CONCLUSION

Curcumin is one of the star molecules amongst natural products with a great potential of various biological activities desired for human health. Hence, curcumin-containing preparations are broadly in demand by consumers in the world. During COVID-19 pandemic, it has attracted a special interest due to its antiviral activity. Our literature survey related to curcumin underlined again its antiviral activity towards the human-threatening viruses including HIV, HCV, HSV, etc by various mechanisms of action. Besides some of its derivatives were demonstrated to possess even better levels of antiviral activity than that of curcumin. Referring to its higher antiviral capacity of those derivatives, curcumin may serve as a bright molecular framework for rational designing of novel antivirals and holds promise as a prophylactic agent for COVID-19 to some extent.

Conflict of interest

No conflict of interest was declared by the authors.

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