Review Article

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TANAFFOS

Plant-Derived Antioxidants for Management of COVID-19: A Comprehensive Review of Molecular Mechanisms

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We aimed to review the literature to introduce some effective plant-derived antioxidants to prevent and treat COVID-19. Natural products from plants are excellent sources to be used for such discoveries. Among different plant-derived bioactive substances, components including luteolin, quercetin, glycyrrhizin, andrographolide, patchouli alcohol, baicalin, and baicalein were investigated for several viral infections as well as SARS-COV-2. The mechanisms of effects detected for these agents were related to their antiviral activity through inhibition of viral entry and/or suppuration of virus function. Also, the majority of components exert anti-inflammatory effects and reduce the cytokine storm induced by virus infection. The data from different studies confirmed that these agents may play a critical role against SARS-COVID-2 via direct (antiviral activity) and indirect (antioxidant and anti-inflammatory) mechanisms, suggesting that natural products are a potential option for management of patients with COVID-19 due to the lower side effects and high efficiency.

Keywords: Coronavirus Disease 2019; Angiotensin-Converting Enzyme2; Inflammation; Herbal Antioxidants; Antiviral

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan City, Hubei, China and led to coronavirus disease 2019 (Covid-19) pandemic (1). This coronavirus has a single-stranded, non-segmented, large positive-sense RNA genome which belongs to the Coronaviridae family (2, 3). The flue-like manifestations, including fever and dry cough, were the frequent manifestations among the COVID-19 patients (4). These mild symptoms can be changed into severe illness and progress as dyspnea, hypoxemia, and acute respiratory distress syndrome (ARDS) in one week after the onset of the disease. It is responsible for the higher mortality rate of COVID-19 followed by multi-organ impairment (5). The origin of SARS-COV-2 has a 79.5% similarity of genomic sequences to SARS-CoV (6). Structural proteins of the virus

including spike (S)-, matrix (M)-, envelope (E)-, and nucleocapsid (N)-proteins are translated from this genome. To invade the host cells, the S-protein binds to angiotensin-converting enzyme2 (ACE2) receptor (7).

There is no specific antiviral agent or vaccine against SARS-CoV-2 particularly in severe cases (8). Recently, some therapeutic approaches were suggested to develop a vaccine or drug including the production of an S-protein-based vaccine, inhibition of the ACE2 receptor, inhibition of transmembrane serine protease 2 activity, and soluble ACE2 delivery on large scale (9). Currently, using herbal medications for the treatment of patients with COVID-19 along with chemical medicines attracts clinicians' attention (10). Up to now, China and South Korea have prepared guidelines to use traditional medicine to prevent and treat SRAS-CoV-2 infection (11).

In the present study, we aimed to review the literature to investigate the effects of antioxidants extracted from medical herbs and their underlying mechanisms against COVID-19.

SARS-COV-2 INFECTION: PATHOGENIC FEATURES

SARS-CoV-2 can apply the injury through direct and indirect pathways:

Direct mechanisms

SARS-CoV-2 may bind to cells' ACE2 receptor, a monocarboxypeptidase on the host cell via S-protein (12). Respiratory diseases are the most common characteristics of COVID-19 due to the high concentration of ACE2 in the respiratory system (9). The different cell types of the respiratory system have been reported to express this receptor including type II alveolar epithelial cells, epithelial cells of bronchioles, and lung vascular cells including endothelium and arterial smooth muscle cells. However, the involvement of other organs in critically ill patients has been reported. The distribution of this receptor in other vital organs may contribute to the pathogenesis of the non-respiratory manifestation (12). The ACE2 expression was confirmed on other cell types, including myocardial cells, epithelial cells of ileum and esophagus, different cell types of the kidney (proximal and distal tubular cells, parietal and visceral epithelial cells of glomerulus), and urothelium of the bladder (13, 14). Furthermore, the vascular components, such as smooth muscle cells and endothelium of interlobular arteries were revealed to express the ACE2 receptor (15). Serine protease ACE2 also can be found in mast cells which converts Ang I into Ang II (16). Moreover, mast cells release some serine proteases (17), particularly the mast cell-serine protease tryptase, which plays an essential role in infection by SARS-CoV-2 (18). In addition to ACE2, the serine protease type 2 transmembrane serine protease (TMPRSS2) is an important factor for invading the host cell by this virus (19).

Indirect mechanisms

Cytokine storm: Unregulated overexpression of chemokines and cytokines following the viral infections has been reported resulting in the situation so-called "cytokine storm" and subsequent "hyperinflammation syndrome"; what is detected as a major leading cause of COVID-19 pathophysiology induces multi-organ dysfunction in infected patients (20). The direct viral attack of the lung epithelial cells, dendritic cells, and macrophages leads to the systemic cytokine storm, and microcirculation dysfunctions in other organs which induce the viral sepsis (21). This complex condition is responsible for symptoms of COVID-19 in severe patients e.g., ARDS and respiratory failure, renal and hepatic dysfunctions, and increasing the risk of death in infected patients (12). The higher levels of proinflammatory factors including tumor necrosis factor (TNF)-α, interleukins (ILs), interferon (IFN)-γ, inducible protein-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1α were recorded in COVID-19 patients, correlated with the severity of disease (22). Inflammasomes complex which activates IL-1β by stimulation of caspase-1 (23), has been revealed to be important in the progress of viral illness (24).

Activation of mast cells: Mast cells are migrant cells of mucosal and connective tissues containing the histamine and heparin-rich granules. The pulmonary mast cells are activated and degranulated during the infection and provide innate and adaptive immune responses to respiratory pathogens. These cells are responsible for respiratory pathologic conditions such as asthma, pulmonary hypertension, and fibrosis (25). The secretion of leukotrienes from these cells leads to bronchoconstriction which can be exhausted by mast cells-induced renin-Ang generating system activation in the lungs (26). SARS-CoV-2 activates the mast cells placed in the sub-mucosa of the respiratory system by inducing the cross-linking of the IgE-FcεRI or toll-like receptors signaling pathways (27). In the early phases of mast-cell activation, degranulation results in releasing histamine and proteases. Lately, activated cells produce proinflammatory cytokines, contributing to cytokine storm development (22). The over-activation of mast cells may involve in pulmonary fibrosis in COVID-19 which plays an essential role in the induction of chronic lung disease in recovered patients (10).

Oxidative stress: The imbalance between the antioxidant system and free radicals, leads to oxidative stress (OS) (28). OS has been presented to be a key player in SARS-CoV and SARS-CoV-2 infection (29). Generally, viral infections results in enhanced free radicals and an antioxidant system depletion (30, 31). The sources of free radicals are associated with mitochondrial dysfunction as a result of the invasion of the virus into the host cell. Besides, the relationship between inflammation and OS has been established well (32). The cytokines can induce the nitric oxide synthetase (NOs) isoforms and stimulate the synthesis of NO (33). Thus, the regulation of OS potentially can be investigated as a new therapeutic approach for improving the outcomes of COVID-19.

NATURAL ANTIOXIDANTS

The bioactive components of medical plans are suggested to be effective for the prevention and treatment of COVID-19. Here, we tried to summarize the effects of some famous bioactive components on outcome of SARS-CoV-2 infection.

Luteolin

Luteolin (LUT, 3',4',5,7-tetrahydroxyflavone) is a common flavone and biologically active agent (34). It exerts therapeutic characteristics including antioxidant, anti-inflammatory, anticancer, autophagic-regulatory, and metabolic effects (35). As a dietary source compound, LUT has been demonstrated to be a potential antiviral drug, particularly against respiratory viruses such as influenza A virus (IAV). LUT inhibits the virus function by blocking the virus life cycle in the early phase, inhibiting the replication, and regulating host proteins (36). Moreover, LUT extracted from the "heat clearing" class of herbs limits the replication of the dengue virus via suppression of the proprotein convertase furin (37). LUT was demonstrated to play an antiviral role against the Epstein-Barr virus via the suppression of the lytic cycle (38). Serine proteases of viruses can be targeted by LUT, required for viral infectivity (39). Furthermore, the protease activity of dengue virus NS2B/NS3 was affected by LUT (40). LUT, isolated from Torreya Nucifera, can inhibit the SARS-CoV 3-chymotrypsin-like cysteine protease ($3CL^{pro}$) that is critical for the life cycle of the virus by regulation of its replication (41). Due to the sequence similarity of SARS-CoV-2 $3CL^{pro}$ to SARS-CoV (42, 43), LUT may have antiviral features against SARS-CoV-2. In a study using molecular docking, the high affinity of LUT to the main protease sites of SARS-CoV-2 was recorded (44). Furthermore, the SARS-COV-2-induced cytokine storm can be controlled by LUT due to its anti-inflammatory responses. Also, LUT can suppress mast cells activation (45, 46). Methoxyluteolin, a novel LUT analog, inhibits the secretion of the proinflammatory cytokines TNF and IL-1 as well as the mast cells-derived chemokines such as CCL2 and CCL5 (47-49).

Enrichment data from *in silico* molecular modeling method showed that LUT is a potential inhibitor of SARS-CoV-2 (50). In addition, the results of bioinformatics analysis and system pharmacology reported that LUT was a practical approach for determining its biological mechanism against comorbid asthma in COVID-19

patients (51). A discovery on possible drug targets and curative mechanisms revealed the anti-inflammatory effects of LUT. The elevation of immunity and promotion of metabolism were introduced as the main mechanism and functions of LUT in treating prostate cancer and COVID-19. Furthermore, the computational analysis demonstrated that *MPO* and *FOS* were core drug targets of LUT (52). Taken together, LUT is a potential antiviral agent for the management of COVID-19. However, *in vivo* and *in vitro* studies should be performed to determine the efficacy and to establish the mechanism of action.

Quercetin

Quercetin (QRT, 3,3′,4′5,7-pentahydroxyflavone) can be found in various types of vegetables, seeds, leaves, and grains. QRT exerts diverse pharmacological features such as anti-oxidant, anti-viral, anti-cancer, antihypertensive, anti-allergic, anti-inflammatory, and anti-depressive effects (53-56). Studies have found that the antiviral features of QRT against different viruses such as Hepatitis C Virus (57), Enterovirus (58), IAV (54), and SARS-CoV (59). The promising antiviral effects of QRT is associated with different mechanisms such as suppression of DNA and RNA polymerases (60), reverse transcriptase (61), proteases (62), and binding viral capsid proteins (63). The Houttuynia cordata extracted QRT 3-rhamnoside was reported to show antiviral effects on influenza A/WS/33 via suppression of virus replication in the early phase of infection (55). Moreover, the finding of enzyme inhibition assays confirmed that QRT had inhibitory features against SARS-CoV $3CL^{pro}$ (41). QRT-3β-galactoside may inhibit the proteolytic effects of SARS-CoV $3CL^{pro}$ by attaching to its binding sites (59). QRT was revealed to suppress the expression of SARS-CoV 3CLpro in Pichia pastoris (80%), suggesting that QRT may also exert anti-SARS-CoV-2 features (64). According to the molecular modeling and Q189A mutation, this suppression of $3CL^{pro}$ was related to the QRT hydroxyl group which detected that QRT binds to the Gln189 site on $3CL^{pro}$ (59). With lower cytotoxicity and a half-effective concentration, QRT also has been recognized as a substance capable to inhibit SARS-CoV invasion into the host cell (65). QRT may block influenza virus strains (including H1N1 and H3N2) entry into the host cell via interfering with the hemagglutinin protein (68). Recently, hydroxyl groups of QRT were reported to be able to bind SARS-CoV-2 $3CL^{pro}$ (59), the same Gln189 site of SARS-CoV $3CL^{pro}$ (67). Additionally, QRT exerts anti-inflammatory properties in viral infections and significantly regulates the production of chemokines, cytokines, and NO in virus-induced macrophages through the calcium-STAT signaling pathway (68). In a review article, the synergistic therapy with QRT and vitamin C was recommended to prevent and treat COVID-19, due to their overlapping immunomodulatory and antiviral features (69). Findings from a pilot clinical trial revealed that QRT was a potential clinical approach for the management of SARS-CoV-2 infection in the early stage (70). In another prospective, randomized, controlled, and open-label study, adjuvant QRT was shown to be a possible therapeutic approach for the treatment of COVID-19 patients in the early-stage of the disease (71). According to the findings, QRT is a promising therapeutic approach with antiviral and anti-inflammatory effects which can be investigated for patients with COVID-19. However, existing evidence on the beneficial effects of QRT in treating and preventing SARS-CoV-2 infection is inadequate.

Glycyrrhizin

Glycyrrhizin (GRZ) is a major ingredient of licorice root. It has various biological properties, including anti-tumor, antioxidant, anti-inflammatory, antiviral, and neuroprotective activities (72). Licorice and its derivatives were introduced as a promising herbal medication for treatment and protection against inflammation-induced damage in the lung, particularly following SARS disease (73). In a study, the efficacy of usual antiviral drugs (such as pyrazofurin, ribavirin, mycophenolic acid, and 6-aziridine) and GRZ were compared on COVID-19 and the findings reported that GRZ had a good antiviral effect via inhibition of viral adsorption and penetration (74). GRZ was also recorded to suppress virus growth and inactivate

the virus particles (75). It seems that GRZ may have anti-SARS-CoV-2 effects due to its structural similarities to SARS-CoV (74). Additionally, GRZ can boost the production of IFN-γ by T cells (76). Recent studies have shown that GRZ can bind to ACE-2 receptors to suppress the SARS-CoV entry into the host cell, suggesting that GRZ may have improved COVID-19 consequences (77). In a pharmacoinformatics study on the bioactive substances from *Glycyrrhiza glabra*, glycerin-A and GRZ were identified as potential and useful agents against SARS-CoV-2 infection via inhibition of S- protein and Nsp15 (78). GRZ may inhibit the progress of cytokine storms and development of immune hyperactivation (79). Moreover, GRZ and its systemically active metabolite, glycyrrhetinic acid (GA), may directly target viral infection by decreasing the gene expression of TMPRSS2, which is required for SARS-CoV-2 cell entry (80). In another study, it has been reported that the besides exhibiting antioxidant, immunomodulatory, and anti-inflammatory properties, antiviral effects of GRZ and licorice extract are associated with their attachment to viral entry proteins. Thus, it can disrupt virus-cell fusion and control the infection (81). In a randomized clinical trial, it was shown that the combination of GRZ and boswellic acids, an inexpensive, safe, immunomodulating, anti-inflammatory, and antiviral supplement, was beneficial for the treatment of mild to moderate COVID-19 (81). Another open-label randomized clinical trial developed a protocol to investigate the effects of licorice root extract on the manifestation and laboratory findings of moderately ill COVID-19 patients with pneumonia (82). Overall, GRZ can be utilized for the prevention or treatment of patients with COVID-19 in clinical studies.

Andrographolide

Andrographolide (AGP), a major active component extracted from *Andrographis paniculata*, is recorded to have several pharmacological features e.g., immune regulation, anti-cancer, hepatoprotection, anti-hyperglycemia, antivirus, anti-parasite, and anti-bacteria (83). Several studies have demonstrated APG can inhibit various viral infections such as IAV, dengue virus, Chikungunya virus, HIV, and Enterovirus D68 via a wide range of mechanisms interacting with cellular pathways such as autophagy, OS, unfolded protein response pathway, etc. (84). The investigations further detected that the anti-dengue virus activity of APG is associated with its interaction on 78-kDa glucose-regulated protein, a main mediator of unfolded protein response (85). Moreover, the anti-H1N1 activity of APG is related to the suppression of activated RLRs pathways and subsequently improves virus-induced cell death (86). Docking of the APG with major targets has demonstrated that APG can bind well to S-protein, $3CL^{pro}$, ACE2, papain-like protease (PL^{pro}), and RNA-dependent RNA polymerase (RdRp) indicating that APG has potential efficacy against SARS-CoV-2. According to the results of an *in silico* study, APG was proven to have a potency of SARS-CoV-2 $3CL^{pro}$ inhibition (87). According to the network pharmacology analysis, APG and its derivative, 14-deoxy-11,12-didehydroandrographolide, can be effective in the treatment of COVID-19. These active components exhibit immunomodulatory properties via targeting chemokine signaling (i.e., Rap1 signaling), mitogen-activated protein kinase (MAPK or MAP kinase) signaling, cytokine/cytokine receptor interaction, nuclear factor kappa B (NF-κB) signaling, p53 signaling, RAS signaling, hypoxia-inducible factor-1 (HIF-1) signaling, and cytotoxicity mediated by natural killer cell (88). In addition, computational methods have identified APG to be a potential component for the inhibition of SARS-CoV-2-triggered cytokine storm by binding with NFkB1 and TNF proteins (89). Findings of an *in silico* approach demonstrated that APG with appropriate solubility, pharmacodynamics properties, and target accuracy could successfully attach to the binding site of the virus, blocking the entry of SARS-CoV-2 entry into the host cell (87). In a similar investigation, AGP derivatives could bind the active site of SARS-CoV-2, including main protease (M^{pro}), spike glycoprotein (S), PL^{pro}, NSP15 endoribonuclease, and RdRp (90). Of note, as a novel herbal source medication with wide distribution, low cytotoxicity, and antiviral

properties, APG is a good candidate to be used as an anti-SARS-CoV-2 agent, recommending to be further investigated in the clinic.

Patchouli alcohol

Patchouli alcohol (PA, $C_{15}H_{26}O$), a natural constituent from the Pogostemon (patchouli) leaves and oils is a tricyclic sesquiterpene (91). Several pharmacological and biological properties including anti-inflammatory, antioxidant, antiviral, anti-bacterial, immunomodulatory, and antitumor activities were reported for PA (91, 92). In an *in vitro* study, PA was found to show an anti-IAV effect while the most sensitive virus to PA was influenza virus H1N1 (93). In an *in vitro* study, the plaque-forming assay was used to investigate the anti-influenza virus H1N1 effects; findings indicated that administration of PA reduced the number of plaques dose-dependently (94). Moreover, the anti-IAV effect of PA was found to be related to the intracellular ERK/MAPK and PI3K/Akt pathways; PA significantly suppresses the *in vitro* proliferation of different IAVes recommending that PA can block IAV infection by directly interfering with some early stages of life cycle after viral adsorption and disturbing the viral particles (95). The anti-H2N2 activity of PA was reported to be associated with the suppression of neuraminidase functions due to the spatial and energetic criteria (96). PA also promoted the protection against IAV via attenuating pulmonary and systemic inflammation and enhancing host immune responses, confirming that PA can protect the human against viruses via both antiviral and anti-inflammatory mechanisms in mice models (97). Based on molecular interaction studies, patchouli alcohol, ergosterol, and shionone were reported to introduce as novel drug choice for the treatment of SARS-CoV-2 (98). Molecular docking and molecular dynamics simulation studies reported that PA exhibited a high affinity for SARS-CoV-2 enzymes, including PL^{pro}, $3CL^{pro}$, and NSP15, inhibiting the virus to invade host cells (99). Accordingly, PA may have a beneficial protective effect as anti-inflammatory and antiviral agent for SARS-CoV-2 infection.

Baicalin

Baicalin (BC, baicalein7-O-β-D-glucuronic acid) is the most abundant compound of *Scutellaria baicalensis* Georgi (100). It is well-known to exhibit beneficial biological properties e.g., anti-oxidative, anti-tumor, anti-inflammatory, antiviral, sensitization, and anti-apoptotic activities (101). The anti-HIV-1 effects of BC were shown to be applied via two mechanisms at the levels of cell entry by interfering with cellular receptors and inhibiting of viral reverse transcriptase (102). The anti-IAV effects of BC were shown to be related to the inhibition of viral replication via stimulation of the IFN type I signaling pathway (103). BC also could suppress influenza virus H1N1 (A/PR/8/34) replication via stimulation of IFN-γ production in major IFN-γ producing cells, such as natural killer cells and cytotoxic and helper T cells via activation of the JAK/STAT-1 pathway (104).

The anti-SARS-CoV activity of BC has been proven using plaque reduction assays (102). It seems that BC may also play an anti-SARS-CoV-2 effect due to its high sequence similarities to SARS-CoV. Furthermore, the inhibitory activity of BC *in vitro* against the ACE was evaluated via UV spectrophotometry: ACE was suppressed via this bioactive substance (105). Based on isothermal titration calorimetry data, BC was detected as a noncovalent and nonpeptidomimetic inhibitor of SARS-CoV-2 $3CL^{pro}$ with high efficiency to bind specifically to proteases (106). In an *in vitro* study, the inhibitory effects of BC on the SARS-CoV-2 proteases including $3CL^{pro}$, PL^{pro}, and RdRp, were proven. In addition, the pathway analysis showed that the antiviral effects of BC were associated with signaling pathways of proinflammatory mediator, e.g., chemokine and cytokine (107). BC with lower cytotoxicity can be developed as an efficient therapeutic substance to prevent or treat COVID-19 via further investigations.

Baicalein

Baicalein (BE, 5,6,7-trihydroxyflavone) similar to BC is a principal component found in *Scutellaria baicalensis* Georgi roots (108). BE has effective biological features e.g.,

antioxidant, anti-inflammatory, anti-apoptotic, and anti-excitotoxicity effects. It can protect the mitochondria and promote cytoprotection (109). The derivatives of *S. baicalensis* have exhibited a wide range of antiviral activities against viral infections (110). Among six compounds including apigenin, BE, biochanin A, kaempferol, LUT, and naringenin, BE exerts the best potency as anti-H5N1 by interfering with virus replication and virus-induced cytokine expression (inhibition of IL-6 and IL-8) (111).

In mice-infected models of IAV strain FM1, the BE could improve the lung index, survival, and inflammatory alterations with high doses (112). In cell culture, BE was reported to inhibit the A/FM1/1/47 (H1N1) in a dose-dependent manner via interaction with mRNA synthesis in the mid-late phase (113). The synthetic analogs of BE were demonstrated to have more antiviral potency against H1N1 Tamiflu-resistant (114). Low-dose of BE could suppress the neuraminidase enzymatic function in seasonal IAV and H1N1(115). Oral administration of BE dose-dependently exerts anti-influenza H1N1 (A/FM1/1/47) effects and increases the mean time to death in a mice model via reducing the lung viral titer and inhibiting the lung consolidation (116). Recently, in an *in vitro* study using BE at microM concentration, the major components of *Scutellaria baicalensis* was recorded to suppress the SARS-CoV-2 $3CL^{pro}$ and viral replication (117). Cell-based and biochemical studies showed that BE could directly inhibit SARS-CoV-2 RdRp; however, it was less effective compared with BC (118). In a preclinical study, BE was reported to suppress SARS-CoV-2-induced cell injury in Vero E6 cells.

In addition, BE reversed the body weight loss, suppressed viral replication, and improved lung tissue in transgenic mice expressing human ACE2 (hACE2) infected with SARS-CoV-2. Furthermore, BE relieved the respiratory dysfunction, suppressed infiltration of inflammatory cells into the lung tissue, and reduced the serum levels of IL-1β and lipopolysaccharides (LPS)-induced acute lung injury (ALI) in mice (119). BE also was recognized to suppress SARS-CoV-2 replication by affecting oxidative phosphorylation in mitochondria in a mPTP dependent manner (120). In another research, *Scutellaria baicalensis* extract and BE were illustrated to suppress viral replication and block SARS-CoV-2 enzyme $3CL^{pro}$ activity (117) Given efficiency, the development of clinical trials to investigate BC anti-SARS-CoV-2 effects is suggested.

CONCLUSION

Natural substances extracted from plants serve as a good source of biodiversity for developing novel and effective strategies against SARS-CoV-2. Many herbal ingredients including LUT, quercetin, GRZ, APG, PA, BC, and BE have been observed to demonstrate antiviral activities against respiratory viruses suggesting that their discoveries can further help develop therapeutic approaches. Considering the aforementioned, the natural products are safe and inexpensive agents that can mainly apply their effects against SARS-CoV-2 via three main pathways: 1) Direct inhibition of viral replication and cytotoxicity, 2) Direct suppression of viral entry into the host cell via high affinity for SARS-CoV-2 enzymes (i.e. 3CLpro, RdRp, and PLpro), and 3) immunomodulatory and anti-inflammatory activity via blockage of cytokine storm .

Further studies also should be conducted to evaluate the probability of natural agents' combination therapies with chemical drugs to the synergy risk of generating drug-resistant viruses. It seems that natural products will continue to increase the efficiency of co-treatment and decrease the adverse effects of chemical agents. Taken together, natural products alone or combined with other approaches could play a critical role and contribute to the development of antiviral drugs against SARS-CoV-2 infection.

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