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# Potential Therapeutic Benefits of Dipyridamole in COVID-19 Patients

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## Abstract

**Background:** COVID-19 pandemic is caused by coronavirus also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The viral infection continues to impact the globe with no vaccine to prevent the infection or highly effective therapeutics to treat the millions of infected people around the world. The disease starts as a respiratory infection, yet it may also be associated with a hypercoagulable state, severe inflammation owing to excessive cytokines production, and a potentially significant oxidative stress. The disease may progress to multiorgan failure and eventually death.

**Objective:** In this article, we summarize the potential of dipyridamole as an adjunct therapy for COVID-19.

**Methods:** We reviewed the literature describing the biological activities of dipyridamole in various settings of testing. Data were retrieved from PubMed, SciFinder-CAS, and Web of Science. The review concisely covered relevant studies starting from 1977.

**Results:** Dipyridamole is an approved antiplatelet drug, that has been used to prevent stroke, among other indications. Besides its antithrombotic activity, the literature indicates that dipyridamole also promotes a host of other biological activities including antiviral, anti-inflammatory, and antioxidant ones.

**Conclusion:** Dipyridamole may substantially help improve the clinical outcomes of COVID-19 treatment. The pharmacokinetics profile of the drug is well established which makes it easier to design an appropriate therapeutic course. The drug is also generally safe, affordable, and available worldwide. Initial clinical trials have shown a substantial promise for dipyridamole in treating critically ill COVID-19 patients, yet larger randomized and controlled trials are needed to confirm this promise.

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AUTHORS' CONTRIBUTIONS

RAAH: Conceptualized the project; RAAH & KFA: Reviewed the relevant literature; KFA: Wrote the first draft; RAAH: Supervised, revised, and finalized the manuscript; RAAH: Provided all resources; RAAH: Visualized project aspect.

CONFLICT OF INTEREST

The authors declare no financial interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

**Keywords**

COVID-19; SARS-CoV-2; dipyridamole; coagulopathy; cytokine storm

## 1. INTRODUCTION

Throughout history, infectious diseases have imposed an existential threat to living creatures including humans. This is particularly true because most often these diseases are easy to spread. We have yet to hear about a condition in which cancer, hypertension, or diabetes has been transmitted by coughing, sneezing, hugging, kissing, or handshaking. Nevertheless, infectious diseases, and in this time viral infections, do so. Not only that but the ability of microorganisms including viruses to change and adapt is also challenging in a way that complicates the search for long-lasting effective vaccines and/or cures. Thus, drug discovery and development in the area of infectious diseases is and should always be a very active research area.

On December 31, 2019, the health authorities in China informed the World Health Organization (WHO) about a cluster of viral pneumonia cases of unknown cause in Wuhan, Hubei. On January 30, 2020, the WHO declared the outbreak as a Public Health Emergency of International Concern [1, 2]. Subsequently, the WHO recognized the viral outbreak as a global pandemic on March 11, 2020 [3]. The outbreak has been caused by, yet another coronavirus and the disease is labeled as coronavirus disease of 2019 (COVID-19). The disease is caused by severe acute respiratory syndrome coronavirus-2 that is abbreviated as SARS-CoV-2. Thus far, the virus has infected more than 23 million individuals worldwide with more than 800 thousand patients have died because of the infection and/or its complications [4].

Coronaviruses are RNA viruses that cause diseases in humans as well as animals. In humans, they cause respiratory tract infections among other illnesses. The infections can be mild as in the common cold which is predominantly caused by rhinoviruses. However, the infections can also be severe and deadly as in the cases of the severe acute respiratory syndrome (SARS) caused by SARS--CoV (200–2004 outbreak) and SARS-CoV-2 (current pandemic) or in the case of the Middle East respiratory syndrome (MERS) caused by MERS-CoV (2012-) [5, 6]. Unfortunately, despite recommendations and approvals of compassionate use of few potential therapeutics, there is no vaccine to protect from COVID-19, and indeed, no highly effective approved therapeutics are currently available. Yet, knowledge pertaining to the virus life cycle and its pathogenicity continue to evolve. There are enormous ongoing efforts to repurpose existing therapeutics to treat COVID-19 patients, particularly the critically ill ones. In this direction, dipyridamole may present a promising opportunity as prophylaxis and/or supportive treatment to be considered in COVID-19 patients.

Dipyridamole is a synthetic small molecule and a tetra-substituted derivative of pyrimido-pyrimidine. The drug was first approved by the United States Food and Drug Administration (U.S. FDA) in 1961. In the U.S., its labelled indications were the oral adjunctive prophylaxis use against thromboembolism with cardiac valve replacement as well as the parenteral use

during the evaluation of coronary artery disease. It was also off label prescribed in combination with aspirin to prevent stroke [7]. Currently, an extended-release combination of dipyridamole and aspirin is available to prevent stroke, treat patients with symptomatic carotid artery stenosis, and/or to improve hemodialysis graft patency [8]. However, studies also show that dipyridamole may exert additional antiviral activity, anti-inflammatory effects, and antioxidant properties. In this review, we summarize the studies that describe the other biological activities of dipyridamole to establish its potential utility in COVID-19 patients.

## 2. COVID-19: THE VIRUS AND THE DISEASE

Coronaviruses are enveloped, positive-sense, and single-stranded RNA viruses. They infect a wide variety of host species including humans. Based on their genomic structures, there are four known types of coronaviruses i.e, α, β, γ, and δ [9]. SARS-CoV-2 is classified as β-coronavirus and has ~79% genome sequence similarity with SARS-CoV and ~50% genome sequence similarity with MERS-CoV [10, 11]. The viral life cycle follows the typical stages of adsorption (attachment), fusion and uncoating, replication and biosynthesis, processing and assembly, and release. The important viral and host proteins in this cycle are the viral spike protein (S) to attach the viral particle to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell, the host furin, and transmembrane protease serine-2 (TMPSS2) to facilitate the virus-host fusion, the viral RNA-dependent RNA polymerase for replication, and the viral main protease (Mpro) for viral glycoproteins processing/maturation, and others [9].

The virus uses ACE2 surface protein as its main receptor to get into the host cells. The receptor is broadly expressed in vascular endothelium, respiratory epithelium, alveolar monocytes, macrophages [12]. The main transmission route of SARS-CoV-2 appears to be respiratory tract exposure-mediated, given the virus active ability to replicate in the upper respiratory tissues [13]. Subsequently, the viral replication may progress to the lower respiratory tract, followed by an extensive attack against other organs that express ACE2 such as the ileum, heart, kidney, and bladder [14]. While the majority of COVID-19 cases are described as mild illnesses, COVID-19 can become a deadly illness in the elderly and individuals with co-morbidities. Two distinctive features have been observed in severe and critically ill patients: excessive inflammation and hypercoagulable state [15].

On one hand, immune-mediated inflammation appears to play an important role in the pathogenesis of COVID-19. The progression of COVID-19 has been found to be associated with a continuous decrease in lymphocytes number and a substantial increase in neutrophils number. A number of inflammatory markers are reported to significantly increase during the severe stage of the illness including C-reactive protein, ferritin, interleukin-6 (IL-6), C-X-C motif chemokine-10 (CXCL-10; also known as interferon gamma-induced protein-10 (IP-10)), granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP-1), chemokine C-C motif ligand 3 (CCL3; also known as macrophage inflammatory protein-1α (MIP-1α)), and tissue necrosis factor-α (TNF-α) [16, 17]. Furthermore, some analyses also reported the up-regulation of apoptosis, autophagy, and p53 pathways in peripheral blood mononuclear cells of COVID-19 patients [18]. Others

suggested functional exhaustion of natural killer and CD8+ T lymphocyte cells with increased expression of natural killer G2A in COVID-19 patients [19]. Collectively, such excessive inflammation response has been described as a cytokine release syndrome (also known as cytokine storm) which appears to have led to acute lung injury/acute respiratory distress syndrome, multiple organ failure, and ultimately death [20]. On the other hand, some COVID-19 patients exhibited a hypercoagulable state represented by elevated levels of D-dimer and fibrinogen as well as prolonged prothrombin time [21]. Reports indicated that some patients had disseminated intravascular coagulation [22] while others had pulmonary embolism [23] or even stroke [24]. These coagulopathies have been linked to poor clinical outcomes and death [25]. Importantly, the crosstalk between the two responses [26], i.e. inflammation and coagulation has further worsened the clinical outcome in critically ill patients.

Furthermore, several reports have suggested oxidative stress as a key player in COVID-19 and the associated respiratory distress syndrome as well as the acute cardiac injury [27, 28]. Given the extended period of the illness, neutrophils and macrophages can produce several highly reactive oxygen species (ROS) including hydroxyl, superoxide, and oxygen radicals [29–31]. While a certain level of ROS is a part of the host response to pathogens including viruses, but excessive ROS may oxidize proteins and lipids and destroy both the virus-infected cells and the normal cells in the lung and heart leading to multiple organ failure [27, 28]. Together, excessive inflammation, coagulopathies, and potentially oxidative stress appear to play significant roles in the pathogenesis of COVID-19, particularly in severe cases and critically ill patients (Fig. 1A).

Given the clinical features of COVID-19, a therapeutic agent with multiple potentials is perhaps needed. In this direction, the antiviral, antithrombotic, anti-inflammatory, and antioxidant activities of dipyridamole can be beneficial (Fig. 1B). In the following sections, we review the literature that describes each of these effects.

## 3. THE ANTIVIRAL ACTIVITY OF DIPYRIDAMOLE

The antiviral effects of dipyridamole have been reported as early as 1977. The antiviral properties were studied in the chick embryo, human diploid, and FL cell cultures by the agar diffusion plaque inhibition and plaque reduction tests and one-step growth cycle experiments. Dipyridamole was found to significantly inhibit the replication of a wide range of viral families including *Picornaviridae, Togaviridae, Orthomyxoviridae, Paramyxoviridae, Herpetoviridae, Poxviridae*, and *Chlamydiaceae* [32]. Its derivatives also demonstrated significant antiviral activity against mengovirus, coxsackie B1 virus, fowl plague virus, vaccinia virus, and pseudorabies virus as demonstrated by inhibiting plaque formation and the infectious virus yield [33]. In subsequent studies, dipyridamole was also found to be in vitro 90–99% active against influenza viruses A/England 42/72, A/Bangkok 1/79, and A/fowl plague, although no inhibition was exhibited against influenza virus B/Leningrad 235/74. In infected mice, orally administered dipyridamole exhibited a significant protection rate of 62.5% against influenza virus A/England 42/72 [34].

Furthermore, dipyridamole was found to significantly potentiate the antiviral effects of the phosphonyl-methoxyethyl derivatives of adenine (Fig. 2A) and 2,6-diaminopurine, and those of 3-hydroxy-2-phosphonylmethoxypropyl derivatives of adenine (Fig. 2A) and 3-deazaadenine as well as the antiviral effect of the cyclic derivative of 3-hydroxy-2-phosphonylmethoxypropyl derivative of adenine. A significant decrease in the $IC_{50}$ values of the acyclic nucleoside phosphonates for varicella-zoster virus (in HEL cells), human cytomegalovirus (in HEL cells), or herpes simplex virus (in HEL and Vero cells)-induced cytopathic effect or plaque formation was reported. The results were confirmed by flow cytometry in the case of varicella-zoster virus and virus yield assays in the cases of human cytomegalovirus and herpes simplex virus. Together, this study highlighted that dipyridamole could increase the activity of acyclic nucleoside phosphonates (Fig. 2A) [35]. It is well established that dipyridamole is a nucleoside transport inhibitor. Thus, it appears that dipyridamole treatment permits a faster and more efficient phosphorylation activation of the acyclic nucleoside phosphonate-based antiviral drugs, and that is by indirectly limiting/eliminating the competing intracellular phosphorylation of endogenous nucleosides.

Interestingly, it was shown that dipyridamole (25–50 μM) also inhibited the thymidine-enhanced reactivation from the latency of thymidine kinase-negative herpes simplex virus in explant medium [36]. Dipyridamole was also shown to dose-dependently inhibit the reactivation of the wild-type herpes simplex virus in both standard and explant media. Similar results were obtained in an experimental mouse model of latency [37]. Likewise, dipyridamole was also shown to prevent Epstein-Barr virus reactivation in cells. It repressed viral immediate-early and early genes expression [38]. The antiviral activity of dipyridamole in these settings was also linked to its ability to inhibit nucleoside uptake, i.e. dipyridamole is a nucleoside transport inhibitor.

Dipyridamole was also found to reversibly inhibit mengovirus RNA replication. In detail, mengovirus plaque formation in HeLa or L cells was nearly completely and reversibly inhibited by dipyridamole (80 μM). The inhibition targeted an early step in the replication cycle. Luciferase-expressing mengovirus replicons showed that the effect was likely on RNA synthesis [39]. Earlier, dipyridamole (0.31–10 μM) exhibited antiviral activity against mengovirus in FL and L cells (>57% inhibition) using a series of tests including the agar diffusion plaque inhibition test, plaque reduction test, tube titration test, and virus yield test after one replication cycle. In the same study, dipyridamole failed to show an effect on cellular RNA synthesis in uninfected prelabelled FL cells, however, it did impact the viral RNA synthesis in mengovirus-infected L cells, potentially by inhibiting the transport of uridine into the cells [40]. The effect of dipyridamole on the multiplication of vaccinia virus in RK13 cells was also demonstrated at 25 μM [41].

Along these lines, dipyridamole (0.08–10 μM) was reported to augment the inhibitory effects of 3’-azido-3’-deoxythymidine (zidovudine, AZT) and 2’,3’-dideoxycytidine (Fig. 2B) against human immunodeficiency virus type-1 (HIV-1) in human monocyte--macrophages without potentiating their toxic effects on these cells or on human bone marrow progenitor cells [42]. The effect of dipyridamole was attributed to multiple potential mechanisms including cell surface alterations, interferons induction, reduced CD4 expression, and more importantly nucleoside transport inhibition. Although it is a nucleoside

transport inhibitor, dipyridamole does not inhibit the transport of nucleoside analog antivirals such as zidovudine and lamivudine (Fig. 2B) into the cells. These observations and the reported dipyridamole-mediated inhibition of transport of nucleosides such as thymidine and deoxycytidine, which compete with the antivirals for kinase-mediated phosphorylation, have been suggested as the mechanism by which dipyridamole may potentiate the antiviral effect of the dideoxynucleoside drugs. In fact, in uninfected monocyte-macrophages, dipyridamole significantly inhibited the cellular salvage of [3H]-deoxycytidine without affecting the salvage of [3H]-dideoxycytidine. Similar differential inhibition by dipyridamole for the thymidine salvage as opposed to 3'-azido-3'-deoxythymidine was also reported previously. Together, inhibition of the salvage of competing physiological nucleosides may explain or contribute to the potentiating effect of dipyridamole on the antiviral dideoxynucleoside drugs (Fig. 2B) [43, 44].

Another study in mice showed that dipyridamole is an effective antiviral agent in experimental viral infections with Semliki Forest virus, herpes simplex virus type 1, influenza A/Puerto Rico/8/34 (H1N1), and influenza virus B (Lee strain). The activity was attributed to the drug's ability to induce interferons at oral doses of 12.5–100 mg/kg or intraperitoneal doses of 5.5–50 mg/kg [45]. Dipyridamole-induced interferon production was previously reported in animal models [46–48] as well as in humans [49, 50], which may lend some support for the interferon induction phenomenon as a potential mechanism for dipyridamole's antiviral effects.

The antiviral activity of dipyridamole can also be attributed to its ability to stimulate prostacyclin synthesis which was found to concentration-dependently enhance the action of prostaglandins on cells [51]. Prostaglandins were shown to help mediate cellular inflammatory responses, including antiviral effects against the growth of adenovirus, parainfluenza virus, and measles [52]. Prostaglandins A and J were shown to partially inhibit poliovirus replication in human cells [53]. Another mechanism by which dipyridamole can promote antiviral effects is the alteration of the cyclic-AMP/AMP intracellular ratio. Dipyridamole inhibits phosphodiesterase enzyme which converts cyclic-AMP into AMP. Fluctuations in cellular AMP concentrations were responsible for the drug-dependent changes in picornaviral RNA synthesis rates [54].

With respect to coronaviruses, dipyridamole was identified by virtual screening of FDA approved drug library to bind to the main protease Mpro of SARS-CoV-2 [55]. Subsequently, dipyridamole was found to inhibit the enzyme activity with an $IC_{50}$ value of 0.53 μM. Furthermore, at a concentration of 100 nM, dipyridamole suppressed more than 50% of SARS-CoV-2 replication in Vero E6 cells. The concentration appeared to be significantly less than the reported serum concentration of the drug that is typically used for thromboprophylaxis. The identification of dipyridamole as a potential direct inhibitor of the virus main protease was also reported by others [56, 57]. Very recently, it was shown that low concentrations of dipyridamole enhanced the antiviral efficacy of RNA-dependent RNA polymerase experimental inhibitor on dengue virus replication and cell proliferation in the presence of exogenous uridine [58]. Dipyridamole was also found to inhibit the in vitro replication of feline infectious peritonitis virus, a coronavirus that causes a lethal and immunological illness in exotic as well as domestic cats [59]. Given the fact that SARS-

CoV-2 is associated with pneumonia, it is worth to mention that some studies involving the wild type-Mycoplasma pneumoniae culture demonstrated that dipyridamole also strongly inhibits the uptake and metabolism of hypoxanthine and guanine with MIC values of ~2 μg/mL [60].

Overall, dipyridamole may exert direct or indirect antiviral activities. In fact, several inhibitors of RNA-dependent RNA polymerase are currently being evaluated in clinical trials for SARS--CoV-2. Dipyridamole can potentially offer a synergetic approach in combination with the antiviral agents being tested for COVID-19 which have similar chemical structures to acyclic nucleoside phosphonates or dideoxynucleosides.

## 4. THE ANTITHROMBOTIC ACTIVITY OF DIPYRIDAMOLE

In critically ill COVID-19 patients, elevated D-dimers and fibrin levels as well as prolonged prothrombin time have been reported as baseline characteristics giving rise to a significant risk of thrombotic complications [61, 62]. The latest data revealed that the incidence of thrombotic complications among COVID-19 patients admitted to the intensive care unit is 16–49% [63]. In these patients, venous and arterial thromboembolism happen due to excessive inflammation, hypoxia, endothelial dysfunction, platelet activation, and stasis [64].

A recent retrospective, observational study of data showed that the incidence of stroke among hospitalized patients with COVID-19 was approximately 5% [65]. In fact, large-vessel stroke was reported as a presenting feature of COVID-19 in young patients [66]. Large-vessel stroke was also previously reported with the 2004 SARS-CoV-1 outbreak in Singapore [67]. Furthermore, pulmonary arterial thrombosis was reported in COVID-19 with a fatal outcome [68]. Multiple other studies reported the same presentation of arterial thromboses [69, 70].

Along these lines, dipyridamole (Persantin) has been used as a coronary vasodilator and an antiplatelet drug [7]. It was one of the 50 most widely prescribed drugs in the U.S. Dipyridamole is a relatively weak antiplatelet agent, and today, it is used in an extended-release formulation combined with low-dose aspirin (Aggrenox) for the prevention of stroke in patients with transient ischemic attacks [8]. Mechanistically, dipyridamole is an inhibitor of phosphodiesterase, an enzyme that is responsible for the metabolism of cyclic-AMP. Thus, the use of dipyridamole increases the level of intraplatelet cyclic-AMP which subsequently decreases the intracellular calcium concentration and eventually inhibits platelet activation and aggregation. Dipyridamole also blocks the uptake of adenosine by platelets and other cells leading to excessive stimulation of adenosine A2 receptors, activation of the coupled adenylate cyclase, and ultimately further production of intraplatelet cyclic-AMP from ATP. Dipyridamole also appears to directly stimulate the release of prostacyclin by vascular endothelium, which inhibits the platelet functions. Therapeutic levels of dipyridamole are also reported to inhibit the metabolism of cyclic-GMP by the corresponding phosphodiesterase [71].

In the ESPS2 study [72], aggrenox diminished the risk of stroke by 22.1% compared to aspirin 50 mg/day alone and decreased the risk of stroke by 24.4% compared to an extended-

release form of dipyridamole 400 mg/day alone. Aggrenox also reduced the risk of stroke by 36.8% compared to the placebo. Furthermore, aggrenox decreased the risk of stroke or death by 12.1% compared to aspirin alone and by 10.3% compared to an extended-release dipyridamole alone. The incidence rate of all-cause mortality was 11.3% for aggrenox, 11.0% for aspirin alone, 11.4% for extended-release dipyridamole alone, and 12.3% for placebo alone [72]. Currently, aggrenox is given twice daily. Each capsule contains 200 mg of the extended-release dipyridamole and 25 mg of aspirin.

Overall, given the clinical presentations of COVID-19 and the antiplatelet-based anti-thrombotic activity of dipyridamole, it appears that the drug can be used in treating and/or preventing arterial thrombotic complications in COVID-19 patients.

## 5. THE ANTI-INFLAMMATORY ACTIVITY OF DIPYRIDAMOLE

It is becoming increasingly evident that hospitalized COVID-19 patients may suffer from serious complications of pneumonia, sepsis, respiratory failure, and/or multiorgan failure. As it was mentioned earlier, these patients typically have an elevated level of inflammatory markers such as C-reactive protein, ferritin, IL-6, IP-10, G-CSF, MCP-1, MIP-1α, and TNF-α [16, 17]. Thus, anti-inflammatory therapeutics can benefit COVID-19 patients. Multiple anti-inflammatory small molecules and monoclonal antibodies are under investigation for COVID-19. Along these lines, the anti-inflammatory activity of dipyridamole is well established in cells, animal models, and humans. Importantly, it has been reported that dipyridamole's anti-inflammatory properties are largely independent of its antiplatelet properties.

In lipopolysaccharide (LPS)-activated RAW 264.7 macrophages, dipyridamole was found to inhibit the secretion of IL-6 and MCP-1, the expression of inducible nitric oxide synthase protein, the accumulation of nitrite, and the induction of cyclooxygenase-2 (COX-2). Dipyridamole inhibited NF-κB signaling pathway as well as LPS-stimulated p38 mitogen-activated protein kinase (p38 MAPK) and IkappaB kinase-β (IκBK-β) activities in RAW 264.7 cells. Dipyridamole was also found to activate mitogen-activated protein kinase phosphatase-1 (MKP-1), a potent inhibitor of p38 MAPK. Overall, the study suggested that dipyridamole exerts its anti-inflammatory effect via activation of MKP-1, which dephosphorylates and inactivates p38 MAPK. Inactivation of p38 MAPK, in turn, inhibits IκBK-β activation which subsequently inhibits the NF-κB signaling pathway that mediates LPS-induced COX-2 expression in these cells [73].

Likewise, dipyridamole was also found to inhibit LPS-induced COX-2 and MCP-1 expression and to decrease LPS-induced ROS generation in rat mesangial cells. The effect was attributed dipyridamole's ability to upregulate heme oxygenase-1 [74]. Furthermore, dipyridamole (5 μg/mL) was found to decrease the nuclear translocation of NF-κB, to block the synthesis of MCP-1 at the transcriptional level, and to inhibit the expression of matrix metalloproteinase-9 (MMP-9) in platelet-monocyte system and/or LPS-stimulated monocytes [75]. Later, it was shown that increasing the concentration of dipyridamole (up to 10 μg/mL) reduced TNF-α-induced MMP-9 activity and its release. Dipyridamole also significantly inhibited TNF-α-induced NF-κB activation and nuclear translocation of the

p65 NF-κB subunit via a mechanism involving the inhibition of IκBα degradation and p38 MAPK activation [76]. Dipyridamole (1–5 μM) also significantly attenuated intercellular adhesion molecule-1 (ICAM-1) and MMP-9 levels in human brain endothelial cells exposed to inflammatory insult with TNF-α [77]. Likewise, dipyridamole significantly decreased MMP-9 levels and the cell death of human brain endothelial cells following a metabolic insult by oxygen-glucose deprivation [77].

In a rat model, dipyridamole pre-treatment (20 mg/kg/day, p.o.) substantially prevented gentamicin-induced acute nephrotoxicity. In this model, dipyridamole exerted reno-protective effects by preventing renal structural and functional abnormalities, renal inflammation, and serum uric acid elevation [78]. Moreover, IV-administered dipyridamole, at levels similar to therapeutic levels, was shown to reverse the impairment of spatial working memory in rats subjected to experimental vascular cognitive impairment owing to its anti-inflammatory properties [79]. Treatment with dipyridamole (1 mL of 20 μg/L) was also found to improve cardiac function and to prevent injury in a rat model of hemorrhage owing to its ability to reduce the TNF-α plasma level as well as the number of inflammatory cells [80]. The anti-inflammatory potential of dipyridamole also appeared to ameliorate adjuvant-induced arthritis in rats [81] as well as to attenuate the elevation of several cytokines and chemokines in human microglia [82]. Dipyridamole (2.5–40 mg/kg, subcutaneous) also demonstrated anti-hyperalgesic activity in models of inflammatory pain in guinea pigs [83]. In a cellular model of Crohn's disease, dipyridamole also appeared to suppress TNF-α in a similar fashion to methotrexate, yet it was superior to methotrexate in increasing IL-10 levels [84].

Likewise, in a rat model of acute LPS-induced endotoxemia and delayed-type hypersensitivity, and in chronic models of collagen-induced and adjuvant-induced arthritis, prednisolone and dipyridamole combination produced anti-inflammatory activity that required only a subtherapeutic dose of prednisolone. In fact, the combination was also found to synergistically suppress the release of TNF-α, IL-6, RANTES, MMP-9, and other pro-inflammatory factors, from human peripheral blood mononuclear cells and mouse macrophages [85]. It was further shown that dipyridamole-induced production of nitrite/nitic oxide significantly reduces the inflammatory responses while increasing vascular growth in ischemic tissues [86]. The anti-inflammatory effects of dipyridamole were also deemed beneficial in mitigating the vascular inflammation in atherothrombosis development and acute stroke progression [87–89].

A recent randomized, placebo-controlled, pilot clinical trial in HIV-1 patients receiving virally suppressive therapy showed that dipyridamole (100 mg four times a day for 12 weeks) increased the extracellular levels of adenosine and significantly reduced CD4+T--cell activation [90]. In another randomized, double-blind, placebo--controlled study, healthy male subjects received 2 ng/kg E. coli endotoxin intravenously after a 7-day pretreatment with dipyridamole (200 mg slow release twice daily). The results indicated that dipyridamole augmented the endotoxin-induced increase in IL-10 (anti-inflammatory), yet resulted in a significant decrease in TNF-α and IL-6 levels (pro-inflammatory) [91]. Furthermore, in a masked single-center and placebo-controlled study, the short-term effect of dipyridamole in addition to prednisolone on clinical parameters and serum levels of C-

reactive protein and proinflammatory cytokines in subjects with periodontitis was evaluated [92]. The administration of the combination resulted in a significant decrease in high-sensitivity- C-reactive protein, IL-6, and interferon-γ (IFN-γ), and it had a favorable effect on the levels of TNF-α suggesting a gained benefit. Lastly, patients suffering from primary membranoproliferative glomerulonephritis who received aspirin (1000 mg/day) and dipyridamole (300 mg/day) for 24 months had better clinical outcomes with respect to proteinuria and serum albumin level [93].

## 6. OTHER ACTIVITIES OF DIPYRIDAMOLE

Dipyridamole also possesses significant antioxidant properties that could address the potential ROS-related complications in COVID-19. For example, dipyridamole ($IC_{50}$=17–100 μM) prevented pyrogallol- and ferrous salt-induced platelet aggregation as well as ferrous salt-induced lipid peroxidation by scavenging oxygen-derived free radicals [94]. Likewise, dipyridamole, at therapeutically relevant concentrations, suppressed the formation of ROS in platelets and endothelial cells, suppressed platelet soluble CD40 ligand release, and improved cellular redox status of platelets and endothelial cells, suggesting a significant potential in atherothrombotic diseases [95]. Dipyridamole has also been shown to prevent membrane and mitochondrial lipid peroxidation as well as oxidative modification of low-density lipoprotein by serving as an oxygen-derived free radical scavenger [96, 97]. Dipyridamole was also reported to protect primary neuronal cultures against insults suggesting a potent antioxidant ability [98]. At clinically relevant doses, dipyridamole was shown to spare vitamin E and thiols in red blood cells after oxidative stress [99]. Dipyridamole also inhibited ferrous-induced lipid peroxidation in human lung tissue [100].

Because of its antioxidant properties, dipyridamole was found to reverse peripheral ischemia and to induce angiogenesis in the Db/Db diabetic mouse hind-limb model [101], to stimulate the proliferation of aorta smooth muscle cells [102], and to attenuate cerebral oxidative stress [103]. Dipyridamole also potently inhibited HIV-1 gp120-induced oxidative damage with an apparent $IC_{50}$ of 1.0 μM [104]. In this case, dipyridamole activity against ROS production was put forward to prevent HIV-1-associated neurotoxicity.

Dipyridamole also promotes potential antifibrotic effects which were illustrated by a number of studies. For example, dipyridamole was shown to in vitro inhibit human peritoneal mesothelial cell proliferation and to attenuate peritoneal fibrosis in rats [105]. Dipyridamole (17 μg/mL) appeared to inhibit platelet-derived growth factor-stimulated human peritoneal mesothelial cell proliferation, and therefore, it was presented as a potential therapy to prevent or alleviate peritoneal fibrosis [106]. Dipyridamole also appeared to mitigate bleomycin-induced pulmonary fibrosis in mice [107]. Pharmacological approaches that increase cyclic-AMP have also been suggested to block or reverse tissue fibrosis [108].

## 7. DIPYRIDAMOLE: PHARMACOKINETICS, TOXICITY, AND DRUG-DRUG INTERACTIONS

The pharmacokinetics of dipyridamole is well established. Following oral administration, dipyridamole is readily absorbed. The time to peak concentration is 2–2.5 hours. Its reported

volume of distribution is 2–3 L/kg in adults. It binds extensively (91–99%) to plasma proteins. It is hepatically metabolized by phase II glucuronidation with the resulting O-glucuronide metabolites being eliminated in feces. Its terminal elimination half-life is about 10 hours. No dose adjustment is reported by the manufacturer in renal or hepatic impairment [7, 109].

Dipyridamole is generally safe and well-tolerated. Adverse reactions at therapeutic doses are minimal and temporary. Because dipyridamole has vasodilatory effects, it must be used with caution in patients with coronary artery disease. Gastrointestinal effects, facial flushing, headache, dizziness, and hypotension can also occur, yet frequency is very low, and none is permanent. No evidence of drug-related carcinogenicity, mutagenicity, or fertility impairment is reported. In animals, no teratogenic effect was observed in mice, rabbits, or rats at oral dipyridamole doses of up to 125 mg/kg, 40 mg/kg, and 1000 mg/kg, respectively [7, 109]. Given its effect on platelets, there may be a risk of bleeding, but the risk is the lowest among known antiplatelets [110]. No serious drug-drug interaction problems have been reported with antiviral agents in use, but this can be attributed to the lack of relevant studies.

## 8. STUDIES IN COVID-19 PATIENTS

In a proof-of-concept trial involving 31 patients with COVID-19, two groups were considered: a placebo group (17 patients) and a dipyridamole group (14 patients receiving 50 mg oral tablet three times a day for 14 consecutive days) [55]. All patients received ribavirin, glucocorticoids, and oxygen therapy. Dipyridamole supplementation significantly decreased concentrations of D-dimers and increased lymphocyte and platelet recovery in the circulation. It substantially improved clinical outcomes in comparison to the control patients. According to the study, all severely ill patients treated with dipyridamole showed remarkable improvement with 87.5% of patients reported to achieve a clinical cure and were discharged from the hospitals, while the remaining patients were in clinical remission [55]. Currently, dipyridamole (100 mg given orally four times a day for 14 consecutive days) is being evaluated in phase 2 randomized, placebo-controlled, single-blinded, single-center trial to prevent coronavirus exacerbation of respiratory status in COVID-19 patients (DICER, NCT04391179). Furthermore, aggrenox (dipyridamole ER 200 mg and aspirin 25 mg given two times a day for two weeks) plus standard care is also being evaluated in phase 3 randomized controlled, open-label trial to evaluate the outcomes in patients with SARS-CoV-2 infection (ATTAC-19, NCT04410328). A third randomized, open-label trial has also been initiated to evaluate dipyridamole (100 mg given orally three times a day for 7 days) in treating respiratory tract infection and circulatory dysfunction due to SARS-CoV-2 coronavirus in hospitalized CVID-19 patients (TOLD, NCT04424901).

## CONCLUSION

The potential benefits of dipyridamole as an adjunct treatment for COVID-19 infection and/or its complications can be attributed to its antiviral, antithrombotic, anti-inflammatory, and antioxidant properties. These properties have been supported by a myriad number of studies in cellular settings, animal models, and even in humans. Owing to these properties,

dipyridamole may potentially assist in halting viral replication, coagulopathy, inflammation, and oxidative stress. The encouraging aspect is also the safety profile of dipyridamole. Nevertheless, the direct benefits to COVID-19 patients will have to be clinically evaluated in large, randomized, double-blinded, placebo-controlled, and perhaps multicenter, clinical trials to ascertain the benefits in this illness. Initial results from small studies have just been reported [55].

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ACE2** | Angiotensin-Converting Enzyme-2 |
| **CoV** | Coronavirus |
| **COVID-19** | Coronavirus Disease of 2019 |
| **COX-2** | Cyclooxygenase-2 |
| **G-CSF** | Granulocyte-Colony Stimulating Factor |
| **HIV-1** | Human Immunodeficiency Virus-1 |
| **IκBK-β** | IkappaB Kinase-β |
| **IP-10** | Interferon Gamma-Induced Protein-10 |
| **IL-6** | Interleukin-6 |
| **LPS** | Lipopolysaccharide |
| **MIP-1α** | Macrophage Inflammatory Protein-1α |
| **MERS** | Middle East Respiratory Syndrome |
| **MKP-1** | Mitogen-Activated Protein Kinase Phosphatase-1 |
| **Mpro** | Main protease |
| **p38 MAPK** | p38 Mitogen-Activated Protein Kinase |
| **SARS** | Severe Acute Respiratory Syndrome |
| **TNF-α** | Tissue Necrosis Factor-A |
| **TMPSS2** | Transmembrane Protease Serine-2 |
| **WHO** | World Health Organization |

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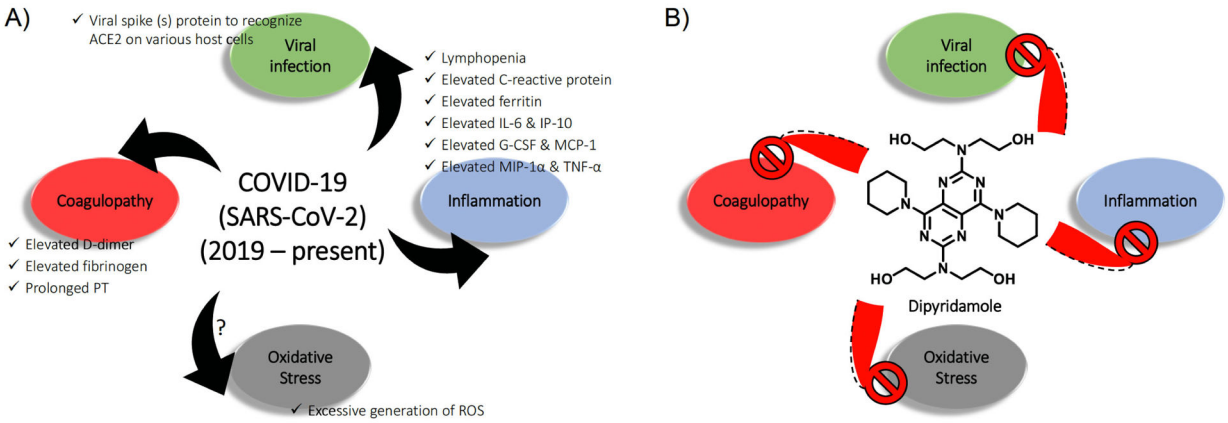


**Fig. (1).**

**A**) The clinical presentations of COVID-19: respiratory infection, excessive inflammation (cytokine storm or cytokine release syndrome), hypercoagulation state, and potentially oxidative stress. **B**) The potential therapeutic benefits of dipyridamole owing to its antiviral, antithrombotic, anti-inflammatory, and antioxidant properties.

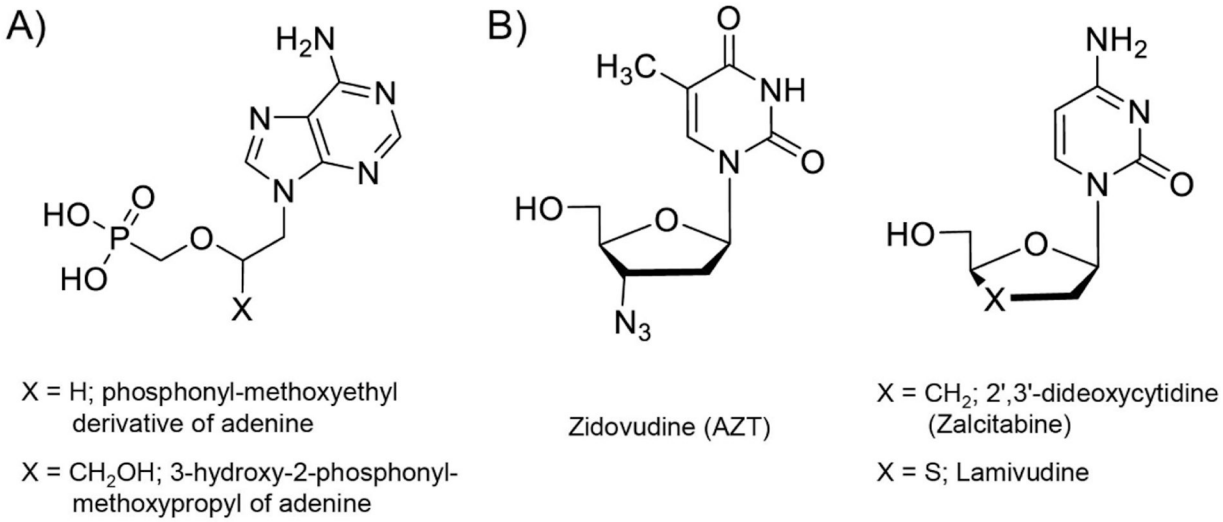


**Fig. (2).**

The chemical structures of **A)** acyclic nucleoside phosphonates and **B)** dideoxynucleosides. Dipyridamole may potentially offer a synergetic approach to enhance the efficacy of acyclic nucleoside phosphonate-based or dideoxynucleoside-based antiviral agents.