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A REVIEW ON THE THERAPEUTIC POTENTIAL OF DIPYRIDAMOLE IN THE TREATMENT OF COVID-19

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ABSTRACT

Dipyridamole (DIP) belongs to the class of antiplatelet drugs and functions as a phosphodiesterase 3 & 5 (PDE3 and PDE5) inhibitor that enhances intracellular cAMP/cGMP concentrations. Besides the well-established platelet agglutination inhibition activity, DIP may offer advantageous therapeutic actions to patients suffering from COVID-19. Various clinical and experimental studies have indicated that DIP possesses broad-spectrum antiviral actions, and its administration has shown to suppress SARS-CoV-2 replication in Vero E6 cells. Moreover, it has been reported that DIP suppress inflammation, possess anti-oxidative properties and enhances nitric oxide mediated cellular pathways. Experimental evidences have shown that DIP may protect acute damage and progressive fibrosis of the renal, cardiac, and hepatic tissues. Here we provide evidence advocating DIP as a possible therapy against major COVID-19 complications such as acute kidney injury, acute respiratory distress syndrome, and acute liver injury encompassing the pieces of evidence directly from DIP.

Keywords **:** Dipyridamole, COVID-19, Phosphodiesterase, cAMP, Acute Liver Injury, Acute Respiratory Distress Syndrome, Acute Liver Injury

Introduction

In December 2019, Wuhan (China) had an outbreak with deadly virus disease having symptoms similar to the pneumonia which was later on identified as new type of coronavirus i.e. SARS-COV-2 (Severe Acute Respiratory Syndrome). In 2020, WHO has designed it as COVID-19 (Fei Zhou, Jay J, Xialou Tang). Within nine months, the total number of cases was 38.1 Million and among them 1.09 Million deaths have been reported, therefore it reported to it as a global pandemic. Slowly, the cases began to increase and limited patients had no travel narration to the seafood marketplace, suggesting a potential human-to-human transmission (Zhou *et al*., 2020). SARS-coronavirus-2 (SARS-CoV-2) retains the characteristic coronavirus structural features such as the occurrence of spike protein and action of various nucleoproteins, polypeptides, and cell membrane peptides like RNA polymerase, main protease (M^{pro}), RNA helicases, glycoprotein, and auxiliary proteins (Wu *et al*., 2020).

Dipyridamole (DIP), a traditional anti-platelet drug has been indicated to possess possesses broad-spectrum antiviral actions, especially effective in opposition to the positive-stranded RNA viruses (Szebeni *et al*., 1989; Tenser *et al*., 2001). Moreover, it has shown great promise in prevention of tissue injuries to cardiac, hepatic and bronchial tissues. In this review, we provide and correlate experimental evidences with established DIP's actions to advocate DIP's use as an adjunctive therapy in COVID-19.

Major Therapeutic actions of Dipyridamole

(i) Adenosine and platelet inhibition

In the beginning, DIP was found to enhance adenosine extracellular levels by blocking red blood cell adenosine absorption, contributing to platelet aggregation inhibition (Best *et al*., 1979). Adenosine is discharged as a disintegration product of adenosine triphosphate (ATP) from epithelial vascular cells and thrombocytes into extracellular space. Adenine nucleotides released are quickly transformed by nucleases to adenosine. Unrestricted adenosine is quickly extracted from blood through a particular adenosine transporter into erythrocytes in circulating blood. DIP blocks adenosine acceptance by red blood cells by 90 percent at therapeutically significant doses and raises plasma adenosine levels by 60 percent (Dresse *et al*., 1982). Adenosine, functioning via adenosine receptors, stimulates platelet adenylyl cyclase and raises cyclic adenosine monophosphate (cAMP) intracellular levels, thereby indicating that is a strong platelet activation inhibitor (BORN & CROSS, 1963). It must be observed that DIP may also enhance intracellular amounts of cAMP in platelets by protecting PDE mediated disintegration of cAMP (Mills & Smith, 1971). Indeed, DIP has been presented to suppress platelet aggregation in-vitro in whole plasma and increase the effect in-vitro antiaggregatory effect of adenosine (Gresele *et al*., 1986).

(ii) Vasodilation and perfusion

DIP increases cGMP-dependent downstream vasodilatory actions in vascular smooth muscle by blocking cyclic guanine monophosphate (cGMP) degrading PDE (Schoeffter *et al*., 1987). DIP may also activate the development of prostacyclin (PGI2) by enhancing intracellular levels of cAMP (BLASS *et al*., 1980). PGI2 is a powerful inhibitor of platelet agglutination and also a dilator of vessels. In many cells, which includes endothelial cells, PGI2 is produced by a cyclooxygenase-dependent pathway (Mehta & Mehta, 1982). Finally, by enhancing local adenosine levels, DIP can increase the effect of vasodilation. DIP can also be responsible for direct as well as indirect vasodilatory actions on vascular smooth muscle. Due to its vasodilatory characteristics, DIP is usually employed to detect underlying coronary ischemia in combination with electrocardiographic or imaging studies (Harker & Kadatz, 1983). The support of these experiments is to increase the divergence in myocardial perfusion, i.e., cardiac steal syndrome, compared to fixed rate-regulating lesions, via non-rate-limiting atherosclerotic coronary arteries. Myocardial DIP imaging tests are done with an IV DIP injection, resulting in 5 times more acute DIP concentrations in the blood than can be obtained with an oral dosage. With sustained-release oral DIP, there is a minor enhancement in myocardial perfusion, indicating increased hyperaemic heart muscles plasma flow and left ventricular systolic operation in patients with ischemic cardiomyopathy (Akhtar *et al*., 2007).

(iii) Antioxidant activity

DIP's molecular structure enables it to accept electrons, thereby acting as an antioxidant and free radical scavenger. DIP was discovered to hunt hydrophilic as well as hydrophobic radicals by the use of lipid oxidation assays which is generally reliant on the production of peroxy radicals by azo chemical compounds (Iuliano, 1995). In comparison with vitamin C, alpha-tocopherol, and biphenabid, DIP was more successful in blocking chemically or cellularly stimulated low-density lipoprotein (LDL) oxidation as determined via diene formation, hydroperoxide evolution, and DIP prevents erythrocyte membranes from oxidation at clinically appropriate concentrations and saves the antioxidant capacity of erythrocytes (Kusmic, 2000). Also, DIP inhibits oxygen-free radicals production in platelets and endothelial cells and increases tissue redox status (Chakrabarti *et al*., 2005). These kinds of anti-oxidative effects of DIP can increase the half-life and enhance the bioavailability of vascular protective endothelium-derived nitric oxide (NO).

(iv) Anti-inflammatory activity

In addition to the indirect anti-inflammatory effects of DIP through adenosine and PGI2, by blocking platelet-monocyte combination, DIP can also responsible for direct anti-inflammatory effects. Activated platelets, for example, bind to and induce monocytes, allowing monocytes to discharge monocyte chemotactic protein-1 (MCP-1) and gelatinase B (Weyrich *et al*., 2005). Management of stimulated platelets with DIP, protected the release of monocytes with MCP-1, and MCP-9, (Brozna *et al*., 1990). DIP has also been shown to block vascular endothelium adhesion of neutrophils in patients with ischaemic stroke by the unique downregulation of MAC-1 (Macrophage-1 antigen) (Hallevi *et al*., 2007). Besides, DIP blocks the lymphocyte recruitment, stimulation, and release of proinflammatory mediators (Coeugniet *et al*., 2009). The possible anti-inflammatory actions of DIP could therefore lead to few of its clinical advantages.

(v) Potentiation of NO-mediated pathways

DIP might increase most of the downstream signaling transduction pathways of NO by raising intracellular concentrations of cGMP. Decrease of endothelium obtained NO function contributing to decreased levels of intracellular cGMP leads to compromised vascular reactions (Liao *et al*., 1991), increased platelet agglutination (Radomski *et al*., 1992), and propagation of vascular smooth muscles (Garg & Hassid, 1989). Blockage of endothelial NO development by the blocker of endothelial NO synthase (eNOS), N-monomethyl-l-arginine (l-NMA), induces constriction of vessels (Kurose *et al*., 1993) and vascular inflammation by encouraging vascular inflammation and endothelial-white blood cell adhesion (De Caterina *et al*., 1995). Indeed, decreased vascular cGMP concentrations are correlated with systemic and pulmonary hypertension in mutant mice lacking eNOS (Huang *et al*., 1995), a higher inclination for intimal smooth muscle propagation in reaction to vascular cuff injury (Moroi *et al*., 1998), and greater stroke magnitudes in reaction to cerebral ischemia (Huang *et al*., 1996). Therefore, DIP can potentiate the downstream effects of NO by blocking cGMP degrading PDE. DIP has been demonstrated to potentiate vasodilatory and platelet antiaggregatory effects of NO/cGMP (Aktas *et al*., 2003), to improve ischemia-induced angiogenesis (Kawasaki *et al*., 2003), to enhancee myocardial perfusion in cardiac failure and stable atherosclerotic heart disease (Jagathesan *et al*., 2006), and to improve the severity of ischemic strokes through effects mediated by NO and adenosine.

Suppression of SARS-CoV-2 replication by DIP in Vero E6 cells

Liu and colleagues assessed the virtual U.S. The Food and Drug Administration accepted drug library and discovered that the SARS-CoV-2 protease M^{pro} was attached to DIP. The key stimulators for the interaction between DIP and M^{pro} are hydrophobic and hydrogen bond (H-bond) interactions. The binding free energy of ΔG_{pred} was calculated to be −8.60 kcal/mol with a projected $IC_{50,\ pred}$ value of 490 nmol/L encompassing the relation $\Delta G_{pred} = -RT \ln (IC_{50,\ pred})$ by free energy perturbation calculations. An enzymatic assay encompassing a beforehand reported method was subsequently performed on the inhibitory potential of DIP against M^{pro}. As a consequence, DIP had an $IC_{50,exp}$ value of 530 ± 10 nmol/L, that was compatible with the literary $IC_{50,\ pred}$ forecast (Jin *et al*., 2020).

The scientists calculated viral titers making use of a prone cell line, the Vero E6 cells, to explicitly validate that DIP suppresses SARS-CoV-2 replication in-vitro. As a positive regulation, chloroquine was used. Remarkably, DIP had suppressed more than 50 percent of SARS-CoV-2 replication at a concentration of 100 nmol/L. This was 4 folds fewer than the expected and empirically calculated IC_{50} to inhibit the action of M^{pro}, that was in line with the previous findings that indicate additional antiviral effects of DIP (Fata-Hartley & Palmenberg, 2005; Szebeni *et al*., 1989). For the prevention of hypercoagulability, DIP (50 mg oral TID) (Bjornsson & Mahony, 1983) was used in patients and serum drug concentrations were stated to be around 3 μmol/L

(Serebruany *et al*., 2009). Collectively, these results indicate that SARS-CoV-2 replication in infected patients could theoretically be suppressed by the medicinally approved therapeutic concentrations of DIP used to attenuate hypercoagulability.

Experimental shreds of evidence of Dipyridamole effectiveness in major COVID-19 complications

(i) Acute respiratory distress syndrome (ARDS)

ARDS is accompanied with an extensive range of precipitating elements and has a high mortality, often not specifically affecting the lung. ARDS is approximately always happened with sepsis, either as an originating cause or as a resulting complication that enhances the expression of several complement-activating cytokines and coagulation cascades through the action of bacterial lipopolysaccharides. Such modifications have an effect on many cellular systems, which involves circulating and resident phagocytic pulmonary cells. This process leads to the discharge of free radicals and the reactive oxygen species (ROS) to stimulate neutrophils sequestered in the pulmonary circulation, which is considered to be crucial in controlling the pulmonary vascular endothelial injury through lipid oxidation. The major clinical manifestations of Acute liver injury/ARDS are responsible for the subsequent endothelial dysfunction and disturbance (Chabot *et al*., 1998). In the treatment of acute liver injury/ARDS, numerous radical controllers, such as superoxide dismutase (SOD) (Maybauer *et al*., 2005), N-acetylcysteine (Koksel *et al*., 2004), have been used.

Therefore, an investigation was conducted to examine whether DIP, given as a liposomal preparation, would improve acute lung injury or ARDS caused by lipopolysaccharides (LPS). Important antioxidant activity has also been reported for DIP, a pyridopyrimidine compound with antithrombotic and vasodilating activities (Pedulli *et al*., 1999). Past investigations have shown that DIP has an repressing action on lipid peroxidation, in addition to being superoxide and hydroxyl radical scavenger (Kusmic, 2000).

DIP was inserted into liposomes because the DIP does not dissolve in its free form in the solution for intravenous injection, and antioxidation may result from ionization used to solubilize DIP. The extremely insoluble DIP, on the other hand, can be conveniently inserted into liposomes, enabling its administration and distribution to the body. DIP liposomes were made and characterized first in this study. Then, compared to DIP injection, the bronchial targeting profile and therapeutic efficacy were analyzed for LPS-induced ALI /ARDS of DIP liposomes. The results revealed that DIP liposomes have a relatively high efficiency of entrapment and a satisfactory particle size. The liposomes enhanced the buildup of DIP in the lungs on a large-level correlate with DIP injection. Besides, DIP liposomes have greatly improved the Acute liver injury (ALI) happened by LPS. All of the findings indicated that because of their apparent lung targeting, DIP liposomes have the potential effectiveness in treating ALI/ARDS. For example, vasodilation, anticoagulation, and PDE 5 inhibition are different pharmacological activities of the drug DIP. Consequently, except for antioxidation, it may be able to deal with ALI/ ARDS in numerous respects (Ziegler *et al*., 1995). The possible efficacy of liposomal DIP has not been identified in the management of ALI/ARDS and the related complications and should be considered for in-depth studies.

(ii) Acute liver injury (ALI)

In many tissues, adenosine, which is the metabolism product of ATP's cleavage in ischemia, is recorded to reduce ischemia and reperfusion injury. A nucleoside transport suppressor that increases the levels of endogenous adenosine is DIP.

A research study explored whether DIP can reduce damage to hepatic I/R. DIP was added to a two-hour complete liver vascular exclusion model in dogs for this reason. DIP importantly enhanced hepatic blood flow and energy metabolism postreperfusion, the weakened release of hepatic enzymes and development of purine catabolites, and increased levels of cAMP. Platelet aggregation decreased by the medium dose of DIP, development of thromboxane B2, and infiltration of polymorphonuclear neutrophils and enhanced survival (Taniguchi *et al*., 2004).

Through moderate inhibition of Polymorphonuclear cells (PMN) infiltration into liver tissue, DIP might exert its hepatoprotective impact. The existence and extent of infiltration of PMNs are essential parts of hepatic ischemia and reperfusion injury (TOLEDO-PEREYRA *et al*., 1993). Oxidants, elastase and other proteases discharged from infiltrated PMNs lead to post-ischemic damage; these proteolytic proteins function to generate reperfusion injury in synergy with free radicals. Pinsky and coworkers (Pinsky *et al*., 1993) showed that dibutyryl cyclic analog of cAMP, Inhibition of intracellular calcium rise, and stimulation of PKC in PMN is reported to inhibit cAMP, causing direct decline of PMN activation, proteolytic enzyme discharge , and NADPH oxidase system (Mitsuyama *et al*., 1993). As a result, inhibition of cAMP reduction by DIP seems to minimize PMN infiltration and to reduce liver injury.

DIP can have hepatoprotective effects by protecting the formation of free radicals. DIP blocked the transport of adenosine into endothelial cells; thus, the formation of superoxide anion by the xanthine oxidase system was inhibited. Adenosine in endothelial cells is converted to hypoxanthine during ischemia. Hypoxanthine is oxidized into xanthine in the presence of molecular oxygen and free radical superoxide. Nucleoporin oxidation is catalyzed by endothelial xanthine oxidase (Knabb *et al*., 1984). It has been shown that due to a poorly evolved protection mechanism, nonparenchymal sinusoidal cells like the endothelial cells are more susceptible to oxidative stress in comparison to parenchymal hepatic cells (Parks & Granger, 1983). In this analysis, management with DIP certainly reduced the levels of purine catabolites in the ischaemic liver, suggesting inhibition of nucleoside transport and reduced development of purine catabolites in endothelial cells. Consequently, the endothelial cells were preserved in response to oxidative stress by DIP.

Another potential elucidation correlates to the improvement of microcirculatory disruption by the DIP vasodilator function, which prevented the decline in cAMP. In this analysis, DIP therapy restored blood flow from postischemic hepatic tissue to three to five times that of ischaemic function. Both vascular smooth muscle cells and sinusoidal Ito cells control hepatic blood flow. By stimulating the Ca^{2+}-activated K receptor, cAMP induces calcium efflux in vascular smooth muscles (Minami *et al*., 1993). As a result of vasorelaxation, the decrease in intracellular calcium triggers vasodilation, and cAMP also

relaxes Ito cells (Kawada & Inoue, 1994). Subsequently, cAMP plays a major role in maintaining the flow of hepatic blood.

(iii) Acute kidney injury

The function of adenosine receptors in DIP controlled defense in the case of ischemia reperfusion stimulated AKI in rats was examined in an experimental study. Bilateral renal ischemia was noticed in rats for 30-40 minutes, succeeded by reperfusion for 24 hours. Creatinine clearance tests, plasma urea nitrogen, uric acid, blood potassium, fractional sodium removal, and microproteinuria in rats were used to determine renal damage that happened by ischemia-reperfusion injury. Via quantification of thiobarbituric acid-reactive substances, superoxide anion production, and decreased glutathione levels, oxidative stress was examined in renal tissues. To determine histopathological variations in renal tissues, hematoxylin-eosin staining was taken out. DIP (10 and 30 mg/kg, i.p.) was given 30 minutes before renal ischemia-reperfusion injury was administered to the rats. Caffeine (50 mg/kg, i.p.), an adenosinergic A1/A2A receptor competitor, was given with and devoid of DIP treatment in different groups before the rats were exposed to kidney ischemia-reperfusion injury. Important recuperations in serum and urinary parameters, elevated oxidative stress, and histopathological alterations in kidney tissues had indicated the ischemia reperfusion-induced AKI. Defense against AKI was demonstrated by the administration of DIP. DIP controlled kidney protection showing the function of A1 and A2A adenosine receptors in DIP controlled kidney protection in rats was prohibited by prior caffeine management. Adenosine receptors had been concluded to have a definite role in DIP-mediated anti-oxidative and reno-protective effects against AKI-induced ischemia-reperfusion (Puri *et al*., 2016).

In another study, Hung and colleagues with hindsight examined an observational cohort of more than 3000 Chronic Kidney Disorder (CKD) stage 3-5 participants from southern Taiwan, of whom 871 (28.30%) obtained DIP administration of ≥ 50 mg/d for 90 days and further than half of the scrutiny period. The average age was 63.60 years, and 25.50 mL/min/1.73m^2 was the mean approximate glomerular filtration rate (eGFR). There were no discrepancies between the DIP-treated and untreated groups following the inverse likelihood of management weighted adjustment by propensity ranking. Management with DIP was happened with reduced chances of rapid eGFR deterioration [odds ratio, 0.755; 95 % confidence interval (CI), 0.595–0.958; p = 0.007] and urinary protein-to-creatinine ratio progression (odds ratio, 0.655; 95 % CI, 0.517–0.832; p = 0.002). The group treated with DIP was also happened with a decreased danger of last-stage kidney disease (hazard ratio, 0.847; 95 % CI, 0.733–0.980; p = 0.011) and all-cause deaths (hazard ratio, 0.765; 95 % CI, 0.606–0.971; p = 0.001) in the survival study, but not concerning cardiovascular actions. The examinations indicated that management with DIP in patients with CKD stage 3-5 had considerably happened with improved kidney outcomes and patient survival. Many underlying mechanisms can responsible for their renoprotective effects by DIP. First, by enhancing the adenosine level and inhibiting cAMP-PDE (Harker & Kadatz, 1983), DIP can suppress platelet activation and aggregation. Also, by increasing the NO pathway, it can induce vasodilation (Bult *et al*., 1991) and also act as an antioxidant (Nepomuceno *et al*., 1999). Furthermore, DIP can produce their renoprotective effects by suppressing the cellular proliferation of human mesangial and renal fibroblast cells and an increase of extracellular matrices (Hewitson *et al*., 2002). In-vivo, DIP alone or in combination with ACEI had been shown to attenuate renal progression and microalbuminuria through enhanced efficient renal plasma flow in rats with decreased renal mass (Buranakarl *et al*., 2003) and increased NO expression in rats with diabetes induced by streptozotocin (Onozato *et al*., 2003).

Conclusion

DIP's major pharmacodynamic properties such as antioxidative, anti-inflammatory, anti-platelet, vasodilation, and potential of NO-mediated pathways adds to the potential of DIPs possible usage in controlling COVID-19 complications. Recently it was observed that it stopped the replication of SARS-COV-2. Owing to its actions such as PDE3/PDE5 inhibition, enhancement of cAMP/cGMP/PKA levels, it has shown a great therapeutic potential in management of the major complications of COVID-19 such as Acute respiratory distress syndrome, Acute kidney injury and Acute liver injury. Moreover, the past experiments on the use of Dipyridamole has validated its therapeutic potential in the treatment of above-mentioned complications. Therefore, through this Review We would like to propose that Dipyridamole should be clinically tested to decipher its direct actions of attenuation of these complications of the COVID-19.

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