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# AN OVERVIEW OF REMDESIVIR AND ASPIRIN TREATMENT IN COVID-19

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**Abstract**

The SARS-CoV-2 causes disease COVID-19, which is being spread worldwide with critical illnesses, respiratory syndrome and thromboembolism. To overcome this pandemic hassle in urgent, use "specific conventional drug" because there is no specific authorized antiviral drugs for COVID-19. The Gilead Science identified that Remdesivir most favorable treatment for COVID, as reduced fatality in people. Remdesivir is a trial agent with broad spectrum antiviral drug against SARS-CoV and MERS, potently inhibition of RdRp is identified as mode of action. However, there is urgent need to improve the efficacy and safety of these diagnostic investigations. The initial use of aspirin in COVID-19 patients is expected to reduce the incidence complications, shorten period of hospital duration and reduce the incidence of cardiovascular problems and its effects are recognized to inhibit COX, PGE2 in macrophages, fusion AcCoA to E1A-associated protein p300 and NF-kB factors pathway.

**Keywords:** Thromboembolism, Acetylsalicylic, Anticoagulant, Anti- platelet aggregation Myocardial infarction and Ischemic stroke, Remdesivir

## INTRODUCTION

Since 2019, December, a novel human infectious coronavirus, formally named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is occurred in China and extent speedily in instant of time. Researchers have reserved short move of detection gene sequencing of this novel emerged virus and possible to develop treatments. Consequently, it is not possible in short time to explore vaccines or drugs thus it is improbable to be useful "conventional drugs" to patients with urgent need. The SARS-CoV-2 shows 80% similarities with SARS-CoV-1, which emerged in 2002 in China and some enzymes is similar greater than 90% (Wang et al., 2020). The complete genome sequencing of SARS-CoV-2 is 40% homologous to MERS and shows more compatibility with SARS-CoV-1 greater than 80% similarities (Zhou et al., 2020). Subsequently, it is presuming to apply drugs for the remedy of COVID-19 from the familiarity of few drugs consisting of interferon corticosteroids, Lopinavir and Ribavirin, used in patients with SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome) (Wang et al., 2020). A broad-spectrum antiviral drug, Remdesivir, has verified power in trials correlated to MERS-CoV and Ebola viral infection. This has been persuaded publically that Remdesivir could emerge as a new unique drug for COVID-19 when the first COVID19 patient in United States with 24 hours Remdesivir treatment has exposed substantial progress in clinical symptoms (Li et al., 2020).

### REMDESIVIR

Remdesivir is a broad-spectrum medication and was formerly mediated by Gilead Sciences in 2009 and was initially generated for hepatitis C treatment, then tried against Ebola and Marburg viral infection as potential treatment (Warren et al., 2016). It is being tested as a precise drug for COVID-19 in 2020, and has been approved for urgent practice in Japan for patients with severe symptoms (Qaseem et al., 2021) and ratified in the US, India, (Qaseem et al., 2021) and Singapore, (Tsvetov et al., 2020). It may takes less time to recover from the infection (COVID, 2020).

Remdesivir (GS-5734) is a nucleoside analogues treatment with significant antiviral action and effective drug for lethal Ebola and Nipah viral infection in primates (Lo et al., 2019). It can inhibit replication of various coronaviruses in epithelial cells as RNA-dependent RNA polymerase (RdRp). A latest study testified, Remdesivir contests with natural ATP.

Remdesivir cannot cause inhibit immediately when brought into the rising chain (I position) and on other aspect, it stops strand at (I+3) position to extend three more nucleotides down (Gordon, Tchesnokov, Feng, et al., 2020).

## 1. Chemical structure and pharmacokinetics

The chemical formula of Remdesivir is $C_{27}H_{35}N_6O_8P$ and molecular mass 602.6 g/mol (Figure 1). In several human cells, Remdesivir can metabolized to nucleoside triphosphate in active form (Wang et al., 2016).

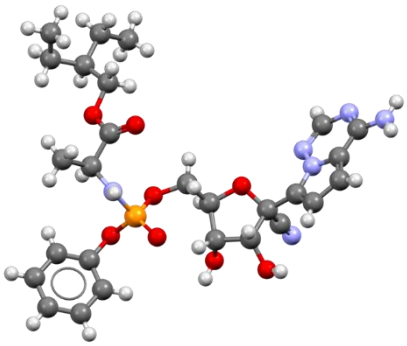


Figure 1. Chemical structure of Remdesivir

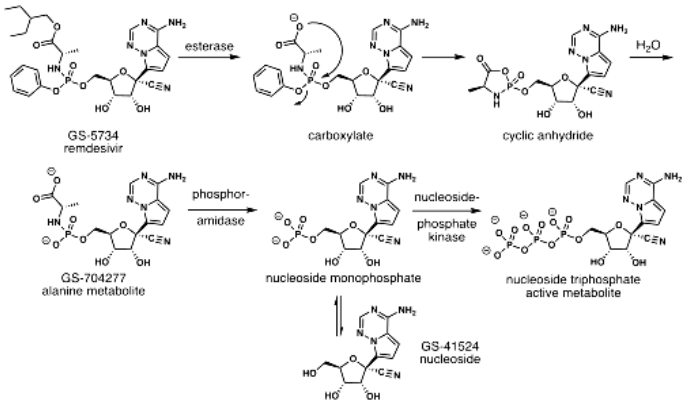



Figure 2. Activation of Triphosphate Metabolite (Wang et al., 2016)

Remdesivir (GS-5734), is a prodrug an adenosine C–nucleoside analogue that is converted into GS-441525 monophosphate by the action of enzymes such as esterase and phosphoamidase when competent to diffuse into cells and then further phosphorylated by nucleoside phosphate kinases to its active metabolite triphosphate (Figure 2) (Gordon, Tchesnokov, Woolner, et al., 2020). In vitro study revealed that nucleoside triphosphate mechanism is absorption opponent with adenosine triphosphate, actions as delayed RNA

chain terminator against Ebola virus and complicate viral RdRp (Tchesnokov et al., 2019; Warren et al., 2016), stop proofreading by viral exoribonuclease (ExoN), and decline RNA replication in virus (Agostini et al., 2018). Lately, antiviral action of Remdesivir confirmed at step when virus enter into E6 cells, supports as a nucleotide analogue (Wang et al., 2020).

## 2. Remdesivir and COVID-19

The etiologic cause of COVID-19 is SARS-CoV-2, with the incidence of the SARS-CoV-2, we requisite an effective antiviral drug to be competent to pauses outburst. It has been encouraged that Remdesivir possibly a selection for treatment in COVID-19 patients. Gilead Science instigated laboratory checking out for Remdesivir against SARS-CoV-2 in January 2020, testifying that Remdesivir had been revealed to be active against (SARS) and (MERS). The Wuhan Institute of Virology testifies a Chinese "use patient", for treating COVID-19 on 21st January 2020 with Remdesivir (Lo et al., 2019).

In a report study, Remdesivir therapy was started intravenously in COVID-19 patients on day 7 (Morse et al., 2020). Remdesivir were demonstrated as broad spectrum anti- CoV activities in clinical studies; randomized, controlled, double sightless clinical trial estimate efficiency and cure to Remdesivir with slight or sensible respiratory disease in COVID-19 patients. The 308 patients were randomized to Remdesivir with 200 mg dose on first day then observed 100 mg daily for 9 days intravenously. Other continuing study in 452 hospitalized adult sufferers with extreme covid-19 is comparing the efficacy and protection of Remdesivir (Holshue et al., 2020).

## 3. Mode of action of Remdesivir

Though SARS-CoV-1 and SARS-CoV-2 shares 82 % RNA and 96% RdRp homologous sequences (Morse et al., 2020). Therefore, drugs targeting viral RdRp protein and are expected to be powerful for SARS-CoV2. There are some prospective drugs such as Favipiravir, Penciclovir, Remdesivir, Galidesivir, Acyclovir Fleximer, Ribavirin, and 6-Fluorinated Aristeromycin that targeting RdRp in the members of Beta coronavirus (Guangdi, 2019). The active metabolite of Remdesivir as an adenosine nucleoside triphosphate analogue restricts with the action of viral RdRp and affecting a drop in RNA production by avoids proofreading by viral ExoN (Agostini et al., 2018). In respiratory syndrome virus causes to inhibit RdRp but this is not instant preventing process, it occurring after adding five additional subsequent nucleotides to the growing RNA chain

(Tchesnokov et al., 2019). To stop RNA production in MERS-CoV, SARS-CoV-1, and SARS-CoV-2 occurs after incorporation of three additional nucleotides to growing chain. So Remdesivir is labeled as an instantaneous-appearing antiviral drug that acts as delay chain terminator (Gordon, Tchesnokov, Woolner, et al., 2020). Figure 3 shows mechanism of Remdesivir.

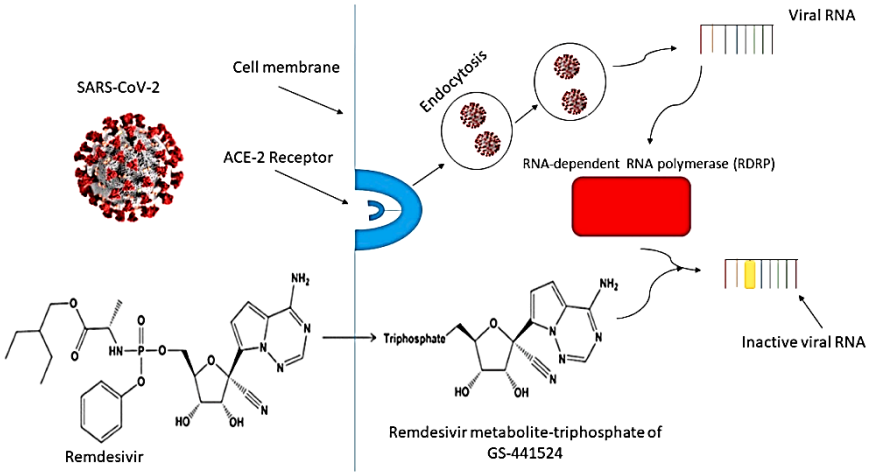



Figure 3. Mechanism of Remdesivir

## ASPIRIN

Aspirin (acetylsalicylate) is a chemical drug of salicylate and formula is $C_9H_8O_4$, molecular mass 180.159g/mol (Figure 4). Today, aspirin is one the most broadly used medications worldwide as non-steriodal anti-inflammatory therapy and is used for the prevention of ischemic stroke, coronary heart assault and blood clots.

### 1. Chemical structure of Aspirin and Pharmacokinetics

Epidemiological research suggested that lengthy-standing consumption with aspirin is associated to decrease of carcinomas, gasterointestinal cancer and cardiovascular morbidity and mortality (Thun et al., 2012). Acetylsalicylic is a weak acid and is quickly absorbed through cell membrane due to increase pH and large surface area of small intestine. Salicylate is bounded to albumin protein in the blood with about 50 to 80% and saturation of more binding sites causes toxicity. About 80% of its doses are metabolized in liver and conjugate with glucuroic acid forms glucuronide esters, glycine forms salicyluric acid, acetyl group forms acyl glucuronide and deacetyl forms phenolic glucuronide. With less amount salicylic acid are hydroxylated in gentisic acid and large dose become saturated as metabolic

pathways. Its increasingly critical renal excretion with salicylic acid becomes highly sensitive to change in urinary pH (Levy & Tsuchiya, 1972).

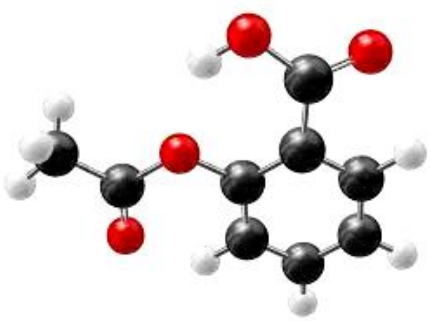


Figure 4. Chemical structure of Aspirin

## 2. Aspirin and COVID-19

The COVID-19 can develop critical infection with acute respiratory suffering and disseminated intravascular coagulation (DIC). SARS-CoV-2 relates to reduced thrombocyte creation in inflamed hematopoietic marrow and causes thrombocytopenia with increase intake by DIC and damage capillaries and lungs tissue (Yang et al., 2005). In the early SARS epidemic, thrombocytopenia had been testified in 20–55% patients and SARS-CoV-2 pandemic are reported with rate of thrombocytopenia between 5% and 41.7% of cases (Lippi et al., 2020).

So COVID-19 is producing critical medical and social problems lead probably risky complications by SARS-CoV-2, which increase need of mechanical ventilation or intensive care units (ICU). However, not only lung damage, other organs consisting kidney, heart can be critically damaged which motive for the excessive fatality risk. It is stated that COVID-19 is a multi-organ disease such as complex pneumonia, which is thought to be associated with systemic infection and thrombotic associated ailment consisting of ischemic stroke and myocardial infarction (Violi et al., 2017). Patients may experience systematic or local thrombosis in the coronary circulation during early phase of disease when pneumonia shows change in clotting and platelet activation, which causes systemic or local thrombosis (Clerkin et al., 2020). Contrariwise, there are many studies recording that platelet count and clotting in COVID-19 patients is indicative of hypercoagulation event as clinical manifestation and severity in COVID-19. It is suggested that Aspirin has numerous properties of inhibiting viral replication, anti-inflammatory, anticoagulant, anti- platelet

aggregation, and against lung injury. The initial use of aspirin in covid-19 sufferers is predicted to lessen the prevalence of severity and complication, reduce the period of hospital duration and decrease the occurrence of cardiovascular risks (Wang et al., 2020). In this evaluation we conclude various clotting variables, liable with severity of the disease.

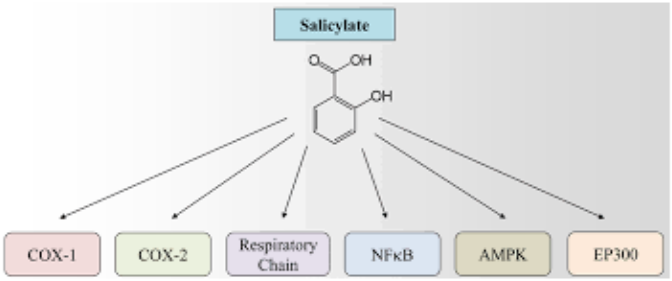
## 3. Mode of mechanism of aspirin

Although much research has been carried out information on the modes of action of aspirin about action against virus, for example antiviral activity against HCV RNA is protein expression via Cyclooxygenase (COX-2) signaling pathway (Trujillo-Murillo et al., 2008), against varicella zoster and cytomegalo virus (Speir et al., 1998; Walz-Cicconi & Weller, 1984) and antiviral activity against influenza virus was inhibition of the NF-ϰB-pathway (Mazur et al., 2007). Figure 6 shows mechanism of Aspirin.

The main mechanism of action of aspirin was assumed to suppress the manufacture of prostaglandins, pro- inflammatory, thromboxanes and thrombocyte, occurring during in irreversible inhibition of prostaglandin-endoperoxide synthase (PTGS1) such as cyclooxygenase (COX-1) and PTGS2 as COX-2 (Vane & Botting, 2003).

The failure of COX-1 and COX-2 inhibitors base on prevention of pro-inflammatory transcription component NF-kB and activation of AMP-activated kinase (AMPK) and separation of aerobic respiration through proton transmission on the inner membrane of mitochondria, Lately, there is another mechanism of action of aspirin and its metabolite salicylate. Certainly, salicylate competitively prevents fusion of acetyl co-enzyme A (AcCoA) with E1A-associated protein p300 (adenovirus early region1A), referred as EP300. By virtue of preventing EP300 stops acetyl-transferase action and autophagy is induced. Accordingly, aspirin to lose its proautophagic when mutation in EP300 causing reduction in salicylate fusion. Figure 5 shows primary the approach of action of Salicylate.

Aspirin can action to inhibit viral replication by blocking Prostaglandin E2 (PGE2) in macrophages and active regulation of interferon (type 1) production. Outcome of non-steroidal agent against inflammation (Aspirin) on PGE2 creation by COX-2 from endogenous and exogenous arachidonic acid in rat peritoneal macrophages motivated with lipo-polysaccharide (Hawley et al., 2012; Petrescu & Tarba, 1997).




The aspirin active metabolite salicylate can modulate the activity of several molecular targets including cyclooxygenase 1 (COX-1), cyclooxygenase 2 (COX2), mitochondrial respiratory chain, NFκB (nuclear factor kappa-B), AMP-activated protein kinase (AMPK) and histone acetyltransferase p300 (EP300).)

Figure 5. Mechanisms describes primary the approach of action of Salicylate

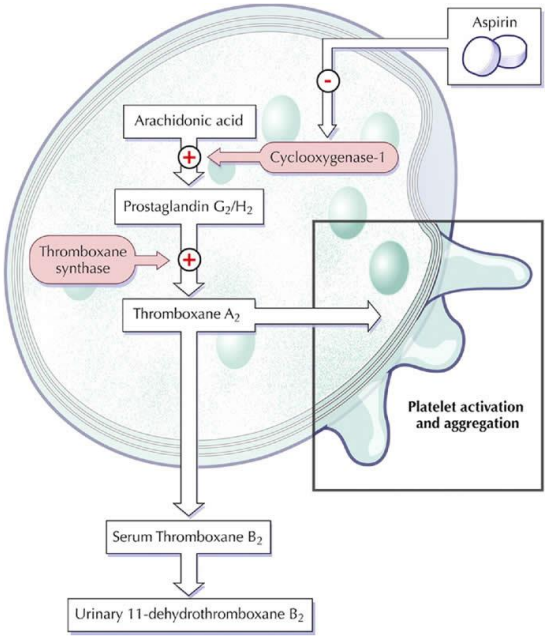



Figure 6. Mechanism of Aspirin

## CONCLUSION

As a consequence, we executed an overview of COVID-19 literature reporting trials critical conditions with probability treatment trails with Remdesivir and Aspirin, moreover, we conferred the clinical possibility of the thrombotic complications in SARS-CoV-2 and the capacity use of an anti-thrombotic treatment. In this review we determine variations to

clotting evaluate if fluctuations are measurable and dependent on the severity of disease. This study presents the action of potential antiviral drugs with mechanism and efficacy to control COVID-19 complications.

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