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Exploring the Triad of Remdesivir: Pharmacological, Pharmaceutical and Analytical Perspectives

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ABSTRACT: Remdesivir, a nucleotide analogue prodrug, has garnered significant attention in the realm of antiviral therapeutics, particularly amid the COVID-19 pandemic. The pharmacological profile of Remdesivir encompasses its potent inhibitory activity against viral RNA-dependent RNA polymerases, pivotal in impeding viral replication. This mechanism underscores its therapeutic efficacy against a spectrum of RNA viruses, including coronaviruses like SARS-CoV-2. Analytically, Remdesivir poses challenges due to its complex chemical structure and the need for sensitive and selective quantification in biological matrices. Various chromatographic techniques and mass spectrometry have emerged as indispensable tools for Remdesivir analysis, facilitating accurate determination in plasma, tissues, and pharmaceutical formulations. On the pharmaceutical front, formulation approaches play a crucial role in enhancing Remdesivir's stability, solubility, and bioavailability, thereby augmenting its therapeutic efficacy. Formulation strategies such as lipid-based delivery systems, nanoparticle formulations, and prodrug derivatives have been explored to overcome challenges associated with Remdesivir's physicochemical properties and to optimize its pharmacokinetic profile.

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INTRODUCTION:

Remdesivir, classified as a broad-spectrum antiviral, was developed by the US biopharmaceutical company Gilead Sciences. Its potential as a treatment for COVID-19 gained prominence in April 2020, leading to its inclusion in international solidarity and European discovery trials alongside three other treatments. Laboratory testing against SARS-CoV-2 commenced in January 2020, with previous preclinical trials demonstrating activity against SARS and MERS. Despite initial optimism, trials in China from February to March 2020 revealed Remdesivir's ineffectiveness against COVID-19,

prompting termination due to adverse effects and fatalities.

On March 18, 2020, the WHO initiated trials, including a group treated with Remdesivir. Preliminary data from multi-center, placebo-controlled trials by the US National Institute of Health suggested its effectiveness in reducing COVID-19 recovery time from 15 to 11 days. The ACTT trials announced on April 29, 2020, confirmed Remdesivir's superiority over placebo in reducing recovery time. However, it became evident that antiviral treatment alone might not suffice, necessitating further research.

In April 2020, the European Medicines Agency began a "rolling review" of Remdesivir data, completing it in May. Indian companies like Cipla, Jubilant Life Sciences, and Hetero Labs entered agreements with Gilead for drug production, with Dr. Reddy's and Jairus Cuedila joining later. The Committee for Medicinal Products for Human Use (CHMP) of the EMA commenced evaluating Remdesivir for marketing authorization in June 2020, following Gilead's application. Subsequently, on June 21, 2020, Remdesivir received approval from the Drugs Controller General of India (DCGI) [1]. The objective of the work is to summarise the pharmaceutical, pharmacological, and analytical profiles of the selected drug.

CLASS OF REMDESIVIR:

Remdesivir (Fig 1) belongs to the category of medications known as antivirals, which function by halting the spread of the virus within the body.

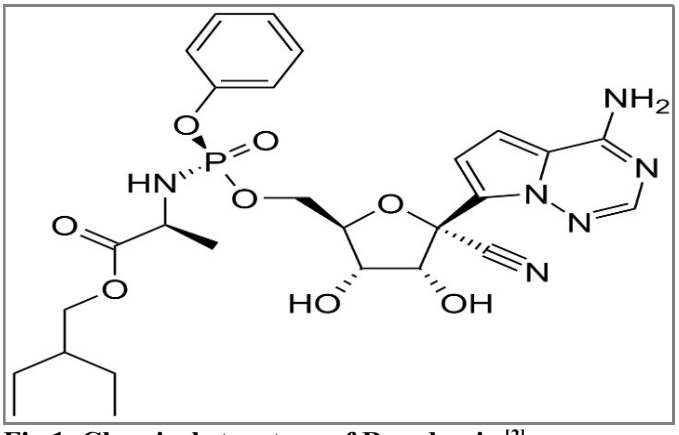

Fig 1. Chemical structure of Remdesvir [2].

These drugs encompass various classifications, including antivirals, anti-SARS-CoV-2 antibody agents (such as monoclonal antibodies, convalescent plasma, and immunoglobulins), anti-inflammatory drugs, and immunomodulators. Specifically, Remdesivir is a phosphor amidite prodrug of a 1'-cyano-substituted adenosine nucleotide analog. It competes with ATP for integration into newly synthesized viral RNA by the corresponding RdRp complex. Antiviral medications like Remdesivir inhibit viral entry via the ACE2 receptor and TMPRSS2, viral membrane fusion and endocytosis, or viral proteases and RdRp. This class of drugs plays a crucial role in impeding the progression of COVID-19 illness, particularly during early infection stages when viral replication is more active. By interfering with viral replication mechanisms, antiviral drugs like Remdesivir contribute significantly to limiting the severity and duration of the illness.

Table 1. Drug profile of Remdesivir [3].

Drug	Remdesivir
IUPAC name	2-ethyl butyl(2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-{4-aminopyrrolo [2,1-f][1,2,4]triazin-7-yl}-5-cyano-3,4-dihydroxyoxolan-2 yl]methoxy}(phenoxy)phosphoryl]amino}propanoate
Chemical formula	$C_{27}H_{35}N_6O_8P$
Molecular mass	602.585 g/mol
Melting point	133 °C
Physical state	Solid
Solubility	Water: insoluble, DMSO: soluble, Ethanol: soluble
LogP	2.01
Color	White
$T_{1/2}$	25 h

Pharmacokinetics:

In non-human primates, the plasma half-life of the prodrug is 20 minutes, with the main metabolite being the nucleoside, GS-441524. Two hours post-injection, the main metabolite GS-441524 is present at micromolar concentrations, whilst intact Remdesivir is no longer detectable. Because of this rapid extracellular conversion to the nucleoside GS-441524, some researchers have questioned whether the active nucleotide triphosphate is truly derived from Remdesivir pro-drug removal or whether it occurs by GS-441524 phosphorylation, and whether direct administration of GS-441524 would constitute a cheaper and easier to administer COVID-19 drug compared to Remdesivir. The activated nucleotide triphosphate form has sustained intracellular levels in PBMC and presumably in other cells as well [5].

Table 2. Chemical toxicity [4].

Description	This compound belongs to the class of organic compounds known as alpha amino acid esters. These are ester derivatives of alpha amino acids.
Kingdom	Organic compounds
Superclass	Organic acids and derivatives
Class	Carboxylic acids and derivatives
Subclass	Amino acids, peptides, and analogs.
Direct parent	Alpha-amino acid esters
Alternative parents	C-glycosyl compounds/Alanine and derivatives/Phenoxy compounds/ Organic phosphoramides etc.
Substituents	1,2,4-triazine / 1,2-diol / Alanine or derivatives / Alcohol / Alpha-amino acid ester / Amine / Aromatic heteropolycyclic compound / Azacycle / Benzenoid / C-glycosyl compound etc..
Molecular framework	Aromatic hetero polycyclic compounds

***Absorption*:**

Remdesivir is absorbed quickly; maximal plasma concentrations following a single 30-minute intravenous infusion are reached within 0.67 to 0.68 h (T_{max}). Repeated dosing yields a C_{max} (coefficient of variation as a percent) of 2229 (19.2) ng/ml and an AUC_{tau} of 1585 (16.6) ng×h/ml. Remdesivir metabolite GS-441524 has measured values: T_{max} 1.51 to 2.00 h, C_{max} 145 (19.3) ng/ml, AUC_{tau} 2229 (18.4) ng×h/ml, and C_{trough} 69.2 (18.2) ng/ml. Another metabolite, GS-704277, has measured values: T_{max} 0.75 h, C_{max} 246 (33.9) ng/ml, AUC_{tau} 462 (31.4) ng×h/mL, and an undetermined C_{trough}. A 10mg/kg intravenous dose given to cynomolgus monkeys distributes to the testes, epididymis, eyes, and brain within 4 h [6].

***Metabolism*:**

Remdesivir is a phosphoramidate prodrug that must be metabolized within host cells to its triphosphate metabolite to be therapeutically active. Upon cell entry, remdesivir is presumed to undergo first esterase-mediated hydrolysis to a carboxylate form followed by cyclization to eject the phenoxide moiety and finally hydrolysis of the cyclic anhydride to yield the detectable alanine metabolite (GS-704277). The alanine metabolite is subsequently hydrolyzed to yield the monophosphate form of remdesivir, which is either hydrolyzed again to yield the bare nucleoside metabolite GS-441524 or phosphorylated by cellular kinases to yield the active triphosphate form.

***Route of elimination*:**

Remdesivir is 74 % eliminated in the urine and 18% eliminated in the feces. About 49 % of the recovered dose is in the form of the metabolite GS-441524, and 10 % is recovered as the unmetabolized parent compound. A small amount (0.5 %) of the GS-441524 metabolite is found in faeces [7].

***Biological half-life*:**

Remdesivir has an elimination half-life of 1 h following a single 30-minute intravenous infusion. Under the same conditions, the elimination half-lives of the remdesivir metabolites [GS-441524] and GS-704277 are 27 and 1.3 h respectively. A 10 mg/kg intravenous dose in non-human primates has a plasma half-life of 0.39 h. The nucleoside triphosphate metabolite has a half-life of 14 h in non-human primates. The nucleoside triphosphate metabolite has a half-life of approximately 20 h in humans [8].

***Plasma protein binding*:**

Remdesivir is 88 to 94 % bound to plasma proteins; GS-441524 and GS-704277 are 2 and 1% bound to plasma proteins, respectively [9].

Pharmacodynamics:

Remdesivir is a nucleoside analogue used to inhibit the action of RNA polymerase. The duration of action is moderate, as it is given once daily. Due to the much higher selectivity of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase, for ATP over remdesivir triphosphate, remdesivir is not a significant inhibitor of these enzymes, which contributes to its overall tolerability and safety profile. Despite this, remdesivir carries risks for hypersensitivity reactions, including anaphylaxis and other infusion-related reactions, elevated transaminase levels, and potential decreased efficacy when combined with hydroxychloroquine or chloroquine [10].

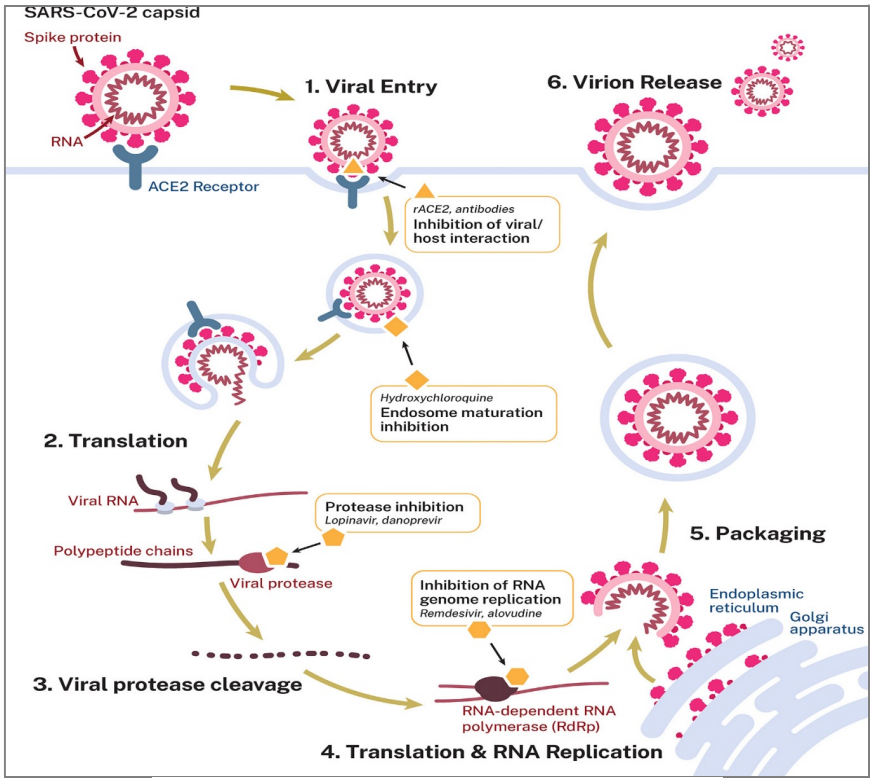

Fig 2. Mechanism of Action of Remdesivir [11].

Table 3. Drug interactions [12].

Drug	Interaction
Acyclovir	The excretion of Acyclovir can be decreased when combined with Remdesivir.
Albendazole	The metabolism of Albendazole can be decreased when combined with Remdesivir.
Alprazolam	The metabolism of Alprazolam can be decreased when combined with Remdesivir.
BCG vaccine	The therapeutic efficacy of the BCG vaccine can be decreased when used in combination with Remdesivir.
Carbamazepine	The metabolism of Carbamazepine can be decreased when combined with Remdesivir.
Digitoxin	The metabolism of Digitoxin can be decreased when combined with Remdesivir.
Erythromycin	The serum concentration of Remdesivir can be increased when it is combined with Erythromycin.
Fluconazole	The metabolism of Remdesivir can be decreased when combined with Fluconazole.
Guanidine	The excretion of Guanidine can be decreased when combined with Remdesivir.
Isoniazid	The metabolism of Remdesivir can be decreased when combined with Isoniazid.
Ketoconazole	The metabolism of Remdesivir can be decreased when combined with Ketoconazole.
Liothyronine	The excretion of Liothyronine can be decreased when combined with Remdesivir.
Metformin	The excretion of Metformin can be decreased when combined with Remdesivir.

Table 4. Available Marketed Formulation of Remdesivir [15].

Trade name	Company name	Formu-lation	Dosage form
Veklury	Gilead Sciences	Inj.	100 mg 100 mg/ 20 ml (5 mg/ml)
Covifor	Hetro Labs Limited	Inj.	5 mg/ml
Desrem	Reliance Life Sciences	Inj.	100 mg
Remda	Zydus Cadila	Inj.	100 mg
Redyx	Dr. Reddys Laboratories	Tablets	50 mg
Remdacta	Cipla	Inj.	100 mg
Resof	Dr.Reddys Laboratories	Tablet	400 mg/ 100 mg

Remdesivir Mylan	Mylan Pharmaceuticals	Inj.	100 mg
Remdesivir Hetero	Hetro Labs Limited	Inj.	100 mg/ 20 ml
Cipremi	Cipla	Inj.	100 mg

Table 5. List of Analytical methods (UV Spectroscopy) available for Remdesivir Estimation.

Sl. No.	Wavelength (nm)	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Correlation coefficient
1[16]	CLS 220-400 PCR 220-400 PLS 220-400	1-17 1-17 1-17	0.356 0.215 0.177	1.079 0.177 0.537	- - -
2[17]	239	1-60	0.2613	0.871	0.9981
3[18]	244-405	1.0-65.0 ng/ml	0.287 ng/ml	0.871 ng/ml	-
4[19]	90	0.10-1.10	0.01	0.03	0.9999
5[20]	Method I: 244 Method II: 248 Method III: 244-207.3 Method IV: 272-340 Method V: 280	1-10 1-10 1-10 1-10 1-10	0.05 0.14 0.20 0.26 0.26	0.16 0.48 0.60 0.78 0.80	0.9999 0.9999 0.9997 0.9997 0.9997
6[21]	245.5	2-12	0.23	0.69	0.999
7[22]	245	3.77-2.41	3.57	10.83	0.9997
8[23]	418	2-12	-	-	0.9998
9[24]	247-249	10-60	-	-	-
10[25]	247	10-60	3.00	9.00	0.9996

Table 6. List of Analytical methods (HPLC) available for Remdesivir Estimation.

Sl. No.	Column type	Mobile phase	Run time (min)	RT (min)	Flow rate (ml/min)	Wave-length (nm)	LR (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	CC
1[26]	RP-C18 column Kinetix® (5 µm, 150 × 4.6 mm)	water, MeOH (50:50, v/v)	-	8.5	1	244	5.0–100.0	0.5	2.0 µg mL−1	0.999
2[27]	Zorbax Eclipse plus C18 (4.6 mm x 150 mm, 5.0 µm)	acetonitrile and 0.1 % formic acid in water (45:55, v/v)	-	3.296	0.7	245	2 – 100	0.57	1.73	≥0.999
3[28]	a reversed-phase Agilent C18 (150 mm × 4.6 mm, 3 µm)	A: water acidified with orthophosphoric acid B: acetonitrile (70:30, v/v)	6	9.80	1	245	0.02−15		0.02	0.9996
4[29]	ODS (C18) RP Column, 250 mm x 4.6 mm, 5µm	Phosphate Buffer (0.02M) and Acetonitrile in the ratio of 48: 52	8	3.665	1.0	248	30-70	0.09	0.27	0.999
5[30]	Inert Sustain C18 (4.6 mm × 100 mm i.e., 3 µm particle size)	A Water: Acetonitrile (50:50 % v/v) B (60:40 % v/v) Methanol and		4.5	1	245	10-90			0.9997

		Water								
6[31]	X-Bridge phenyl (150x4.6mm , 3.5µ)	Acetonitrile: 0.1% Triethylamine, TEA (70:30)	1		1	235	50–300	6.0	20	0.9989

CC - Correlation coefficient, RT - Retention time, LR - Linearity range.

Table 7. List of Analytical methods (LC-MS) available for Remdesivir Estimation.

Sl. No.	M/Z Value	Ionization method	CT (° C)	IV (V)	Solvent mixture	MS used	Run time (min)
1[32]	603 → 200	heated electrospray ionization	270	4300 spray voltage	90%:10% acetonitrile: water	Thermo Fisher Scientific TSQ Altis triple quadrupole MS	1.2
2[33]	603.3 → 402.2	Turbo Ion Spray	650	4500	Acetonitrile: Dime ethyl Sulfoxide at 50:50 (v: v)	Triple Quadrupole MS	3.4
3[34]	603.4	electrospray ionization	150	-	methanol-water (1:1; v/v)	Triple Quadrupole MS	5.0
4[35]	603.3 → 200.0 and 229.0	electrospray ionization	350	-	0.1% formic acid (A) and acetonitrile (B) starting from 0% of (B) to 100%	TSQ Endura triplequadrupole mass spectrometer (ThermoFisher)	5.0
5[36]	603.2333	electrospray ionization	-	1000	0.1% formic acid in water (solvent A) and acetonitrile (solvent B)	quadrupole time-of-flight tandem mass spectrometer	19
6[37]	603.3 → m/z 200.0 (35%) and m/z 229.0 (23%)	electrospray ionization	350	3500	10 mM sodium formate buffer in 0.1% formic acid (A) and acetonitrile (B)	Triple Quandrupole MS	5
7[38]	607.9 → 204.9	electrospray ionization	150	-	% formic acid (v/v) in acetonitrile	Waters Xevo® TQ-S micro tandem quadrupole mass spectrometer	4

CT - Capillary temperature, IV - Ionization voltage, IM - Ionization method.

Mechanism of Action:

As an adenosine nucleoside triphosphate analog (GS-443902) [33] the active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase. It evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production [15,34]. In some viruses, such as the respiratory syncytial virus, it causes the RNA-dependent RNA polymerases to pause, but its predominant effect (as in Ebola) is to induce an irreversible chain termination. Unlike with many other chain terminators, this is not mediated by preventing the addition of the immediately subsequent nucleotide but is instead delayed, occurring after five additional bases have been added to the growing RNA chain [35]. For the RNA-Dependent RNA Polymerase of MERS-CoV, SARS-CoV-1, and SARS-CoV-2, the arrest of RNA synthesis occurs after the incorporation of three additional nucleotides [32,36]. Hence, remdesivir is classified as a direct-acting antiviral agent that works as a delayed chain terminator.

CONCLUSION:

The triad of pharmacological, pharmaceutical, and analytical perspectives provides a comprehensive understanding of Remdesivir's therapeutic potential and challenges. By elucidating its pharmacological mechanisms, optimizing pharmaceutical formulations, and developing robust analytical methodologies, researchers aim to harness the full therapeutic benefits of

Remdesivir in combating viral infections and addressing unmet medical needs.

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