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New Understandings to Improve Acyclovir-Based Therapeutics for the Treatment of Herpes virus infections

Esmat Mohamed Kamel[1*], Azza A. A. Galal[1], Sawsan M. A. El-Sheikh[1], Fatma M. Abdalla[2], and Tarek Khamis[1]

[1]Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt.

[2]Department of Virology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt.

Corresponding author: Esmat Mohamed Kamel

Email: esmatelsalamony@gmail.com

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Abstract: Because of its hydrophilicity, acyclovir is an antiviral medication with a low oral bioavailability of about 20% and is poorly absorbed in the gastrointestinal tract. Herpes simplex encephalitis (HSE) is treated with acyclovir; nonetheless, the disease has a terrible prognosis, especially if therapy is delayed, with fatality rates as high as 70% if treatment is not received. Therefore, in adults with normal renal function, substantial doses of acyclovir are given via intravenous (IV) infusion, often at a dosage of 10 mg kg−1 8 hourly. Nonetheless, the death rate associated with HSE treated with acyclovir is still high (~20%), and reports of long-term effects (~50%) are typical after a year. Novel discoveries that attempt to improve drug bioavailability—such as acyclovir or its prodrugs—were evaluated. This could result in the medicine being targeted for systemic distribution. Much research has been done to enhance antiviral therapy. Specifically, efforts have been made to find delivery systems that can increase the bioavailability of acyclovir using non-invasive pathways like the nasal and oral pathways, or through parenterally delivered nanotechnology-based systems that can target specific drugs. Nanocarriers, albeit not yet produced on an industrial scale, are viable solutions for treating HSE when supplied through non-invasive channels.

Keywords: *Acyclovir, antivirals, pharmacokinetics, and pharmacodynamics.*

Introduction

Acyclovir, an acyclic guanosine nucleoside analogue is an antiviral agent that is active against herpes virus infections **(Rogers et al., 1983).** The use of acyclovir (ACV) has become an established part of clinical practice, it is also being increasingly used in the treatment of herpes simplex and cytomegalovirus diseases in immunocompromised host **(Dos Santos et al.,1997).**

Athough herpes zoster is not a fatal disease, it can cause severe zoster-related pain including both acute zoster pain and chronic pain of post herpetic neuralgia (PHN).

Severe zoster related pain can cause physical disability and emotional distress, impair quality of life, and create an economic burden on the individual and society. It is well known that antiviral treatments are available to ameliorate acute zoster pain and to prevent it **(Kim et al., 2012).**

Acyclovir's activity is greatest against herpes 1 and herpes 2, less against varicella zoster, even less against Epstein-Barr, and very little against cytomegalovirus also It is an antiviral drug approved by FDA for the treatment of herpes virus infection **(Talluri et al., 2008)**.

In pediatric patients with herpes simplex **(HSV)** keratitis, oral acyclovir and topical steroids have been demonstrated to help treat infection **(Bodack, 2019).**

Acyclovir is the drug of choice for the treatment of neonatal HSV infections, including mucocutaneous, skin, mouth, and eye infections, and disseminated or CNS infections. It is also the drug of choice for prophylaxis against HSV recurrence in hematopoietic stem cell transplant (HSCT) recipients seropositive for HSV; such prophylaxis is not recommended in those seronegative for HSV **(Anon, 2005).**

When acyclovir is prescribed orally, its absorption is poor and only 15 to 30% of the drug is absorbed. However, when given intravenously the total dose enters the circulation, it is picked up by herpes-infected cells, and converted to an active form, acyclovir triphosphate, incorporated into cell nuclei where it inhibits DNA polymerases. It is widely distributed in body fluids, and it is excreted through glomerular filtration and tubular secretion **(Rogers et al., 1983).**

Although acyclovir is prescribed in the management of herpes simplex encephalitis (HSE), the disease has a poor prognosis, particularly if the treatment is delayed, reaching mortality rates of 70% if left untreated. Thus, high acyclovir doses are administered by intravenous infusion, usually at a dosage of 10 mg kg every 8 hours in adults with normal renal function. However, the mortality related to HSE treated with acyclovir remains high (~20%) **(Assis et al., 2021)**.

Acyclovir treatment options for herpes infections currently include oral, parenteral, and topical administration **(Cortesi and Esposito, 2008)**. However, topical therapy is thought to be less effective due to acyclovir's low skin permeability into the target site **(Spruance et al., 2002)**. Oral drug delivery, on the other hand, is the most appropriate and patient-compliant method because it offers several advantages and is preferred over other routes. Following oral therapy, acyclovir absorption was found to be slow, variable, and incomplete, with low oral bioavailability (15–30%) **(Arnal et al., 2008)**. As a result, oral therapy for this drug necessitated frequent administration of high doses of acyclovir, which could result in systemic adverse effects such as acute renal failure as well as neurotoxicity **(Johnson et al., 1994)**. Drug discovery groups, on the other hand, have synthesized acyclovir prodrugs to improve therapeutic efficacy **(De Clercq ,2006)**. Microemulsions and self-emulsifying drug delivery systems were also tried to improve acyclovir oral bioavailability **(Cortesi and Esposito, 2008 and Paul et al., 2013)**. Effective acyclovir oral therapy is still elusive **(Nair et al., 2014)**.

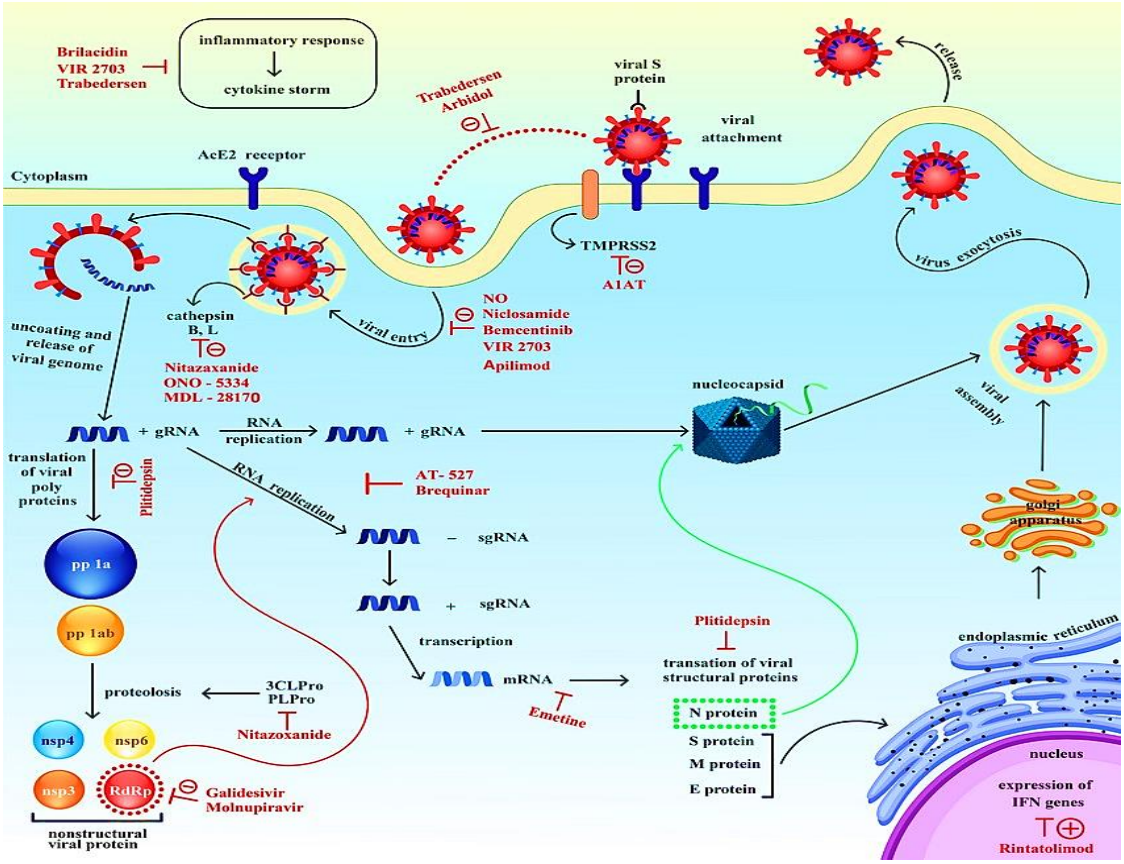

Figure (1) molecular targets for the antiviral drugs

Mechanism of Action:

The inhibitory activity of ACV is highly selective due to its affinity

for the enzyme thymidine kinase (TK) encoded by HSV and VZV. Upon absorption into the virus-infected cell, ACV undergoes a series of phosphorylations to generate ACV triphosphate which is an active metabolite that inhibits viral DNA replication. In the virus-infected cell, viral TK selectively converts ACV into ACV monophosphate a nucleotide analog.

The monophosphate undergoes further phosphorylation into diphosphate by cellular guanylate kinase. The last phosphorylation to ACV triphosphate (acycloguanosine triphosphate) is catalyzed by several cellular enzymes **(Talluri et al., 2008)**. Acyclovir would mildly interfere with the host cells replication as it inhibits viral DNA replication way more than cellular DNA **(Narayana, 2008).** Acyclovir is phosphorylated intracellularly by viral kinases, and the resultant triphosphate competes with guanosine for incorporation into viral DNA blocking viral DNA polymerase activity (**National Institute of Diabetes and Digestive and Kidney Diseases, 2012)**. **Kukhanova et al., (2014)** stated that Acyclovir triphosphate inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate for viral DNA polymerase and thus gets incorporated into viral DNA, resulting in chain termination This can be accomplished in 3 ways:.

1) Competitive inhibition of viral DNA polymerase

2) Incorporation into and termination of the growing viral DNA chain

3) Inactivation of the viral DNA polymerase **Figure (2).**

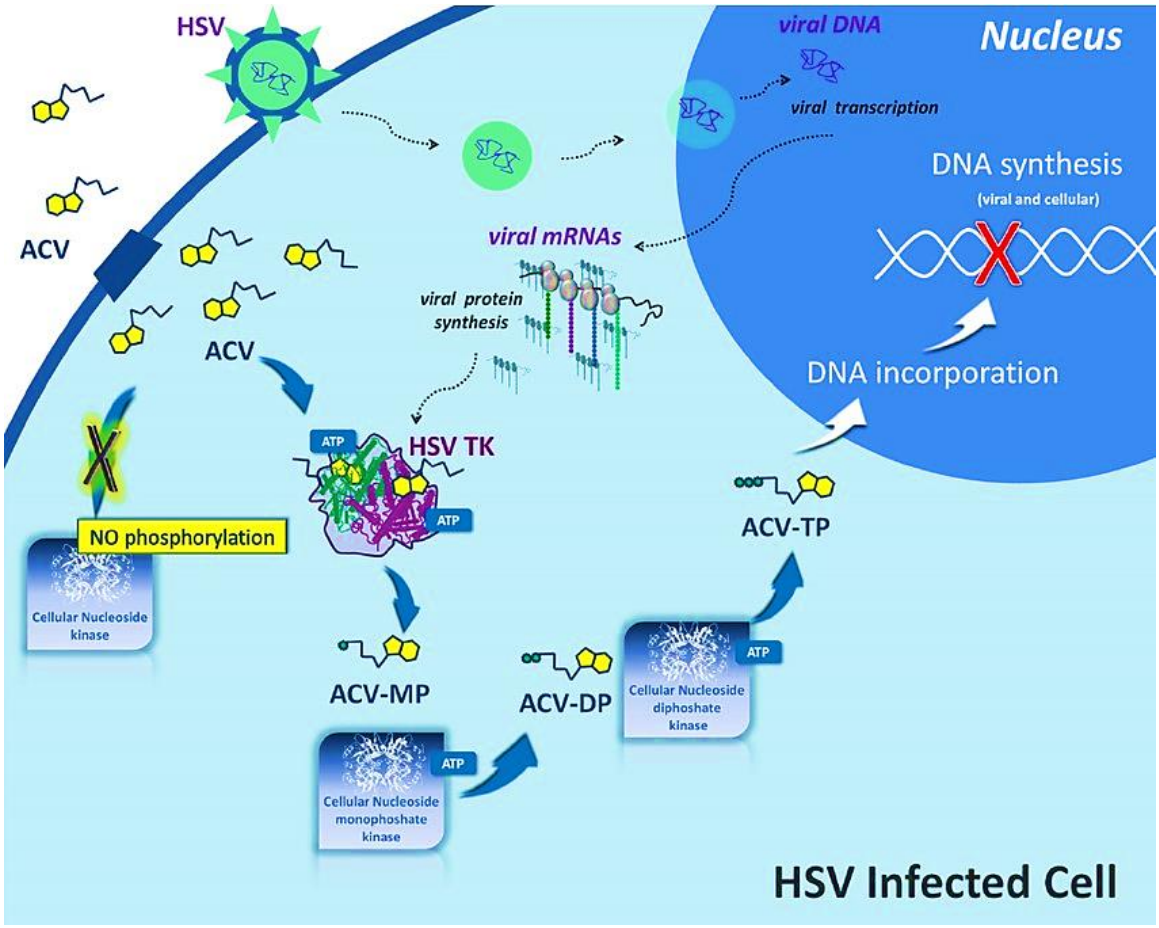

Figure (2) Mechanism of action of Acyclovir.

Acyclovir is proposed to act by preventing the binding of interleukin- 12 (IL-12) to the IL-12 receptor This is promising for the treatment of COVID-19 by treating the high levels of serum cytokines, inhibiting the cytokine storm inflammatory response (**German, et al., 2023).**

Pharmacokinetics of Acyclovir:

Absorption

Acyclovir is poorly absorbed from the gastrointestinal tract following oral administration. The oral bioavailability ranges from 10 to 20%. It is a hydrophilic molecule with poor solubility and cellular permeability **(Talluri et al., 2008 and Assis et al., 2021).**

Metabolic disposition and pharmacokinetics in mice, rats, and dogs indicated acyclovir distribution into all the tissues, without extensive drug binding to plasma proteins and with little biotransformation in vivo **(Assis et al., 2021).**

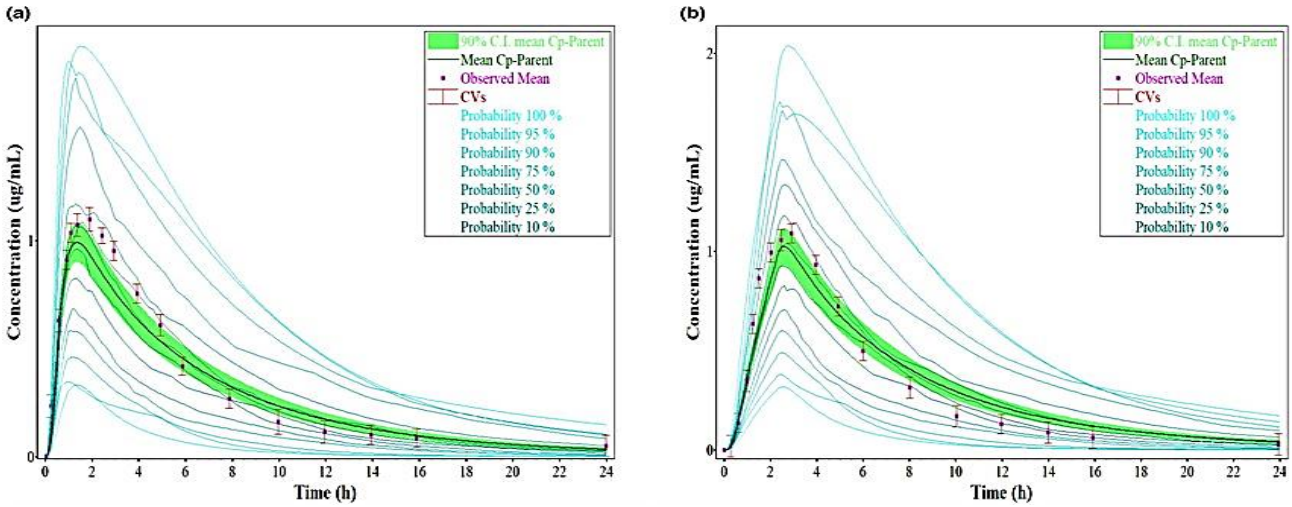

Figure (2) peak plasma concentration of acyclovir

A study has been done by **Steingrimsdottir et al., (2000)** on 12 patients with malignant hematological diseases with leukopenia after chemotherapy to examine the acyclovir bioavailability after oral administration. It was found that the median bioavailability was 21.5% **(Figure 3).**

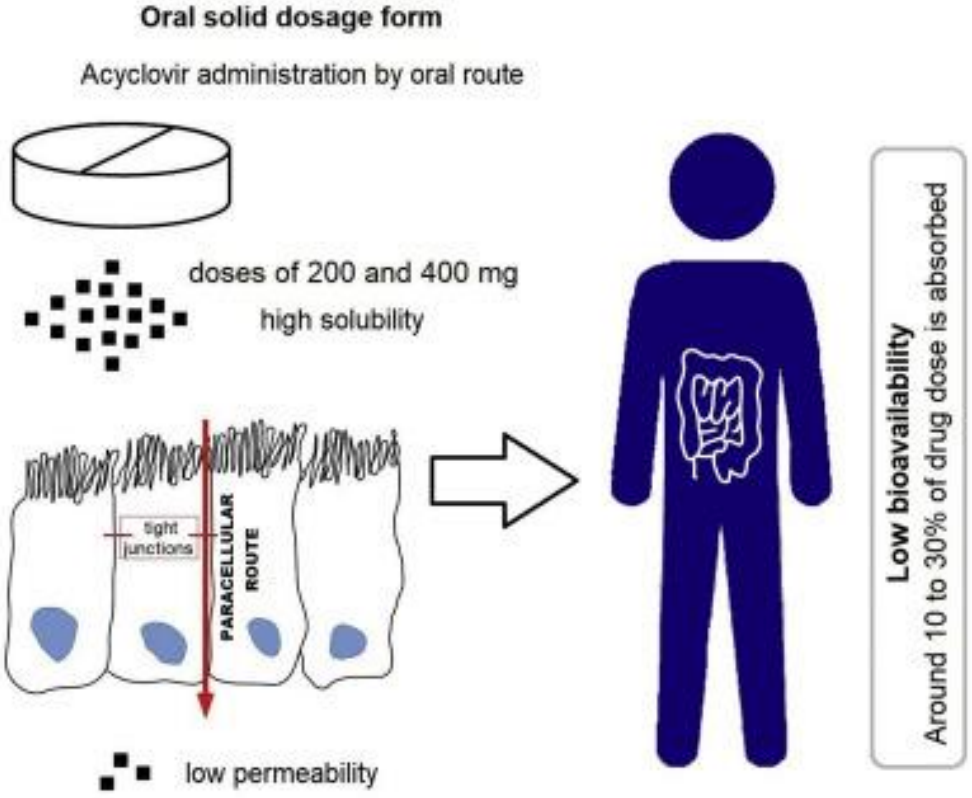

Figure (3) oral bioavailability of acyclovir.

Metabolism

Acyclovir is oxidized by alcohol dehydrogenase and aldehyde dehydrogenase to 9-carboxymethoxymethylguanine, also aldehyde oxidase acyclovir to 8-hydroxy-acyclovir **(Smith et al., 2010).** After oral administration, ACV has a very low bioavailability, around 15–30% of the administered dose. Protein binding of ACV is in the range of 9% to 33%. The volume of distribution of the ACV molecule is large allowing

good tissue penetration, including the central nervous system (CNS) where high concentrations in the cerebrospinal fluid (CSF) are reached. In humans, ACV is subjected to minimal metabolism.

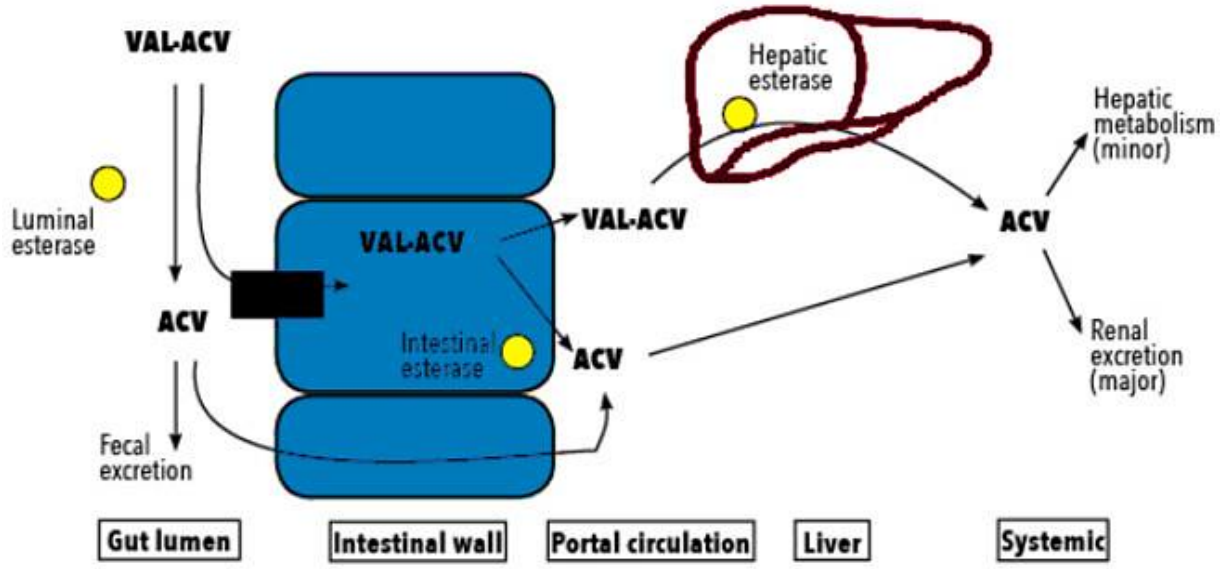

Figure (4) metabolism of acyclovir

Approximately 5–15% of ACV are metabolized in the liver by alcohol dehydrogenase (ADH) to an ACV-aldehyde which is subsequently metabolized via aldehyde dehydrogenase (ALDH) to the main metabolite 9-(carboxymethoxymethyl)guanine (CMMG). Aldehyde oxidase metabolizes ACV into 8-hydroxy-9-(- 2-hydroxyethoxymethyl)guanine (8-OH-ACV) **(Kacirova et al., 2023).** Acyclovir is minimally (15%) protein-bound only a small percentage (15%) of the intravenous dose is metabolized in persons with normal renal function. Acyclovir is excreted primarily by glomerular filtration, with only minor excretion secretion. The toxicity of acyclovir appears to be acceptable **(Lietman et al.,1982)**.

Excretion

Acyclovir, a potent anti-herpesvirus agent, is eliminated mainly by the renal excretion of unchanged drug, where the renal clearance of Acyclovir is about 75–80% of the total body clearance renal clearance of Acyclovir is approximately three times greater than the glomerular filtration rate, renal excretion of Acyclovir has a significant tubular secretion component **(Laskin et al., 1982).**

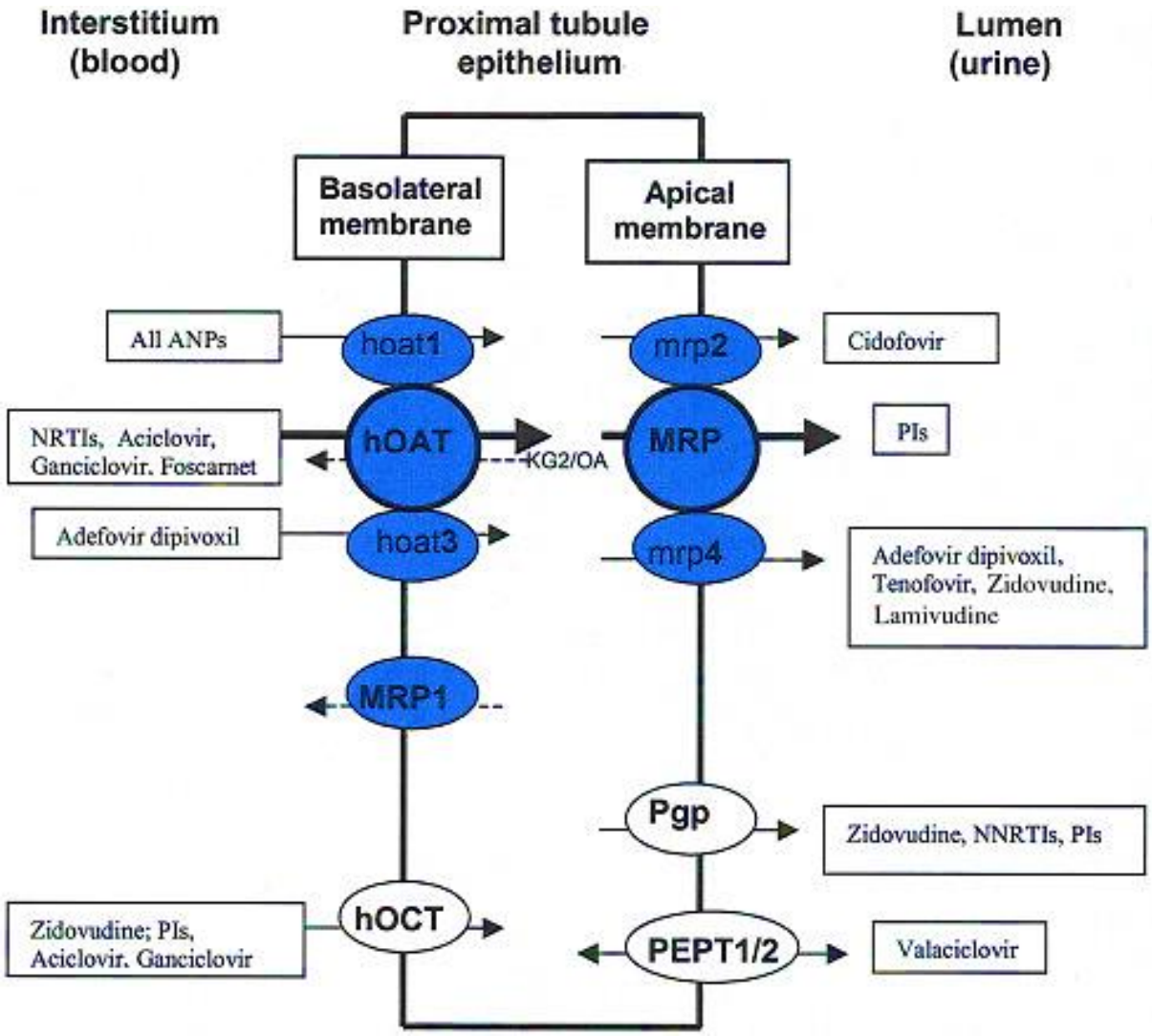

Figure (5) excretion of Acyclovir

Acyclovir is primarily excreted via both glomerular filtration and tubular excretion and is eliminated mostly as unchanged drug **(Gnann et al., 1983).**

In patients without renal failure, 62.1–91.0% of intravenous ACV are excreted in urine in an unchanged form, 8.5–14.1% as CMMG, and less than 0.2% as 8-OH-ACV metabolite. The main route of ACV elimination is renal excretion **(Kacirova et al., 2023).**

Excretion of acyclovir an antiviral agent, occurs predominantly through the kidney (glomerular filtration and tubular secretion). Its normal plasma half-life is 2 - 3 hours; dosage modifications are obligatory in renal insufficiency **(Onuigbo et al., 2009).**

Acyclovir is almost entirely eliminated by the kidneys and has a terminal plasma half-life (t1/2) of 2 to 3 hr in subjects with normal renal function Acyclovir is insoluble in urin and capable of precipitating in the form of intratubular crystals, causing tubular obstruction and inflammation, which caused the acute renal damage **(Coscojuela Otto et al., 2020).** Acyclovir is primarily excreted via both glomerular filtration and tubular excretion and is eliminated mostly as unchanged drug. **(Downes et al., 2020).**

Only about 10% to 30% of acyclovir is absorbed after oral administration, and 60% to 90% of it is excreted by the kidneys through glomerular filtration and tubular secretion. It has a half-life of 2 to 3 h in individuals with normal kidney function and 20 h in patients with ESRD]. Its protein binding is in the range of 9% to 33%. It

distributes widely in body fluids and is concentrated in the kidney (100%), cerebrospinal fluid (50%), breast milk (324%), and amniotic fluid and placenta (300% to 600%). With increasing renal failure, systemic and renal clearance of acyclovir is reduced and a linear relationship between acyclovir and creatinine clearances has been demonstrated, **(Laskin et ai., 1983**). The main pathway of ACV elimination from the body is renal elimination by kidneys via glomerular filtration and tubular secretion. About 62% to 90% is observed in urine as either unchanged drug or its metabolites The plasma elimination half-life of ACV ranges from 2.5 to 3.3 hours in patients with normal renal function, as it is primarily eliminated by kidneys the half-life and total body clearance are dependent on renal function **(Tallur et al., 2008)**. Acyclovir is predominantly excreted via the kidneys. Thus, caution must be used when prescribing to those with kidney disease **(German, et al., 2023).**

Therapeutic uses for Acyclovir

Acyclovir is the drug of choice in the treatment of initial and recurrent mucocutaneous HSV-1 and HSV-2 infections (e.g., orofacial, esophageal, genital, nasal, labial) in immunocompromised adults, adolescents, and children, including HIV-infected individuals **(Anon, 2005).** Acyclovir can be used as a safe and effective treatment for COVID-19 neurologic symptoms for patients with long-term symptoms and unusual presentations of the virus, such as encephalopathy or coagulopathy (**German et al., 2023).** Acyclovir is unsuccessful or slightly helpful in preventing herpes labialis recurrence in immunocompetent persons, eczema herpeticum treatment in patients with a previous diagnosis of atopic dermatitis and HSV keratitis in HIV-infected individuals **(Anon, 2005)**. Acyclovir is an antivirus drug that has good in vitro activity against hepatitis B virus. But because of the low solubility and low distribution in the liver, the clinical application of acyclovir in hepatitis B was limited **(Tu et al., 2004).**

Acyclovir, an acrylic purine nucleoside analog, is a highly potent inhibitor of herpes simplex virus, types 1 and 2, varicella-zoster, virus, Epstein Barr virus (EBV), cytomegalovirus (CMV) and herpes B viruses and has extremely low toxicity for the normal host cells **(Talluri et al., 2008)**. Acyclovir is used for treating adults and adolescents, including HIV- infected individuals, for their first episodes of genital herpes and the recurrent ones. It is also used in treatment of the first episodes of herpes proctitis. It can be used as chronic suppressive therapy for recurrent genital herpes outbreaks in adults and adolescents, including HIV-infected patients. The Centers for Disease Control and Prevention (CDC) and others recommend oral acyclovir, oral famciclovir, or oral valacyclovir as first-line treatments for genital herpes, as well as episodic treatment or chronic suppressive therapy for recurrent genital herpes **(Anon, 2005).** The greater antiviral activity of ACV against HSV compared to VZV is due to its more affinity towards viral Thymidine kinase Which results in efficient phosphorylation to monophosphate **(Talluri et al., 2008)**.

Acyclovir is the drug of choice used for the treatment of Varicella (chickenpox) and Herpes zoster (shingles, zoster) in immunocompromised and immunocompetent adults, adolescents, and children, including HIV-infected patients. As Varicella is often a self-limiting condition in otherwise healthy people, the function of acyclovir for therapy in these people is controversial also Acyclovir is used in the treatment of Herpes zoster ophthalmicus in HIV-infected patients and dermatomal herpes zoster in immunocompromised individuals, such as transplant recipients and HIV patients. In HSCT patients, Acyclovir is an alternative to varicella-zoster immune globulin (VZIG) for post-exposure prevention of VZV infection. Although long-term prophylaxis is not commonly advised for the prevention of recurrent VZV infections in HSCT recipients, it may be explored in individuals with severe, long-term immunodeficiency **(Anon, 2005).** Acyclovir is used in (CMV) disease prevention in transplant Recipients, it has been used to protect form CMV disease in solid organ transplant recipients and bone marrow transplant patients at risk for the disease. It has been used to prevent CMV illness in HSCT patients; In adults, adolescents, and children **(Bailey et al., 1997).**

Approaches for improving kinetics and dynamics of Acyclovir.

More than thirty years have passed since acyclovir was first used in the clinic, and its poor oral absorption still presents difficulties in daily practice. It is the preferred treatment for HSE, however, to get meaningful levels of acyclovir in the central nervous system (CNS), large dosages of the medication are required, which is done by

IV administration. Acyclovir side effects are more severe in individuals suffering from renal impairment, notwithstanding reports of local responses brought on by the high pH of IV acyclovir infusion. In spite of this, a lot of research has been done to enhance antiviral therapy, looking for ways to deliver acyclovir or its prodrugs in a way that significantly increases medication targeting or bioavailability. Several formulations were previously studied such as Polymeric nanoparticles based on Eudragit® with ammonium groups were prepared as colloidal suspensions for oral administration of acyclovir, Thin planar poly(methyl methacrylate) microdevices were tested to enhance the oral bioavailability of acyclovir, Liposomes were prepared from egg phosphatidylcholine alone (neutral liposome) or mixed with egg phosphatidylglycerol (negatively charged liposomes), Buccal films (ethylcellulose dispersion with dibutyl phthalate) with polymeric nanospheres (Eudragit® RL 100, hydroxypropyl methylcellulose K15, and Carbopol® 974P) for acyclovir release were prepared by double emulsion solvent evaporation technique, Thiolated xyloglucan polysaccharide nanoparticles with acyclovir were prepared to enhance drug oral bioavailability, designing colloidal carriers with increased bioadhesion, and Bilosomes for oral absorption of acyclovir were prepared by thin-film hydration technique as nanocarriers resistant to digestive enzymes disruption (Gurgel Assis et al., 2021).

Conclusion

There are new discoveries aimed at increasing acyclovir bioavailability through non-invasive methods. Nevertheless, these approaches are primarily focused on drug-containing nanocarriers and have not yet advanced to the stage of pharmaceutical manufacture. Several challenges, including large-scale production, scaling up industrial batch manufacturing, and regulatory concerns related to drug safety, need to be resolved before an incremental strategy may lead to clinical application for acyclovir in nanocarriers. Following that, it might be possible to produce an acyclovir formulation that can be administered in a non-invasive manner to treat HSE.

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Author contribution: all authors contributed equally.

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