Biological Forum – An International Journal **15(5a): 681-689(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Viral Endocytosis: Mechanistic Insights and Therapeutic Targets

Ravdeep Kaur[1], Joginder Singh Panwar[2] and Kongara Hanumantha Rao[3]*

[1]Department of Biotechnology, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara (Punjab), India.
[2]Department of Botany, Nagaland University, Zunheboto (Nagaland), India.
[3]Department of Biochemistry and Bioinformatics, GITAM School of Sciences, GITAM University, Visakhapatnam (Andhra Pradesh), India.

(Corresponding author: Kongara Hanumantha Rao)*
(Received: 06 March 2023; Revised: 29 April 2023; Accepted: 05 May 2023; Published: 15 May 2023)
(Published by Research Trend)

ABSTRACT: Endocytosis process is utilized for various cell processes including cell-cell interactions, signal responses, homeostasis and even for virus internalization, by the eukaryotic cells. Among all the endocytic mechanisms such as Phagocytosis, Pinocytosis, Caveolin dependent & independent pathway; Clathrin dependent and receptor mediated is the most commonly hijacked by the human viruses such as Human Papilloma Virus, Adenovirus, ZIKA virus and Hepatitis-B virus. The selection basis for these four viruses is non-availability of high efficacy drugs, vaccines and other treatments as compared to the other human viruses. As per the evolutionary knowledge, host cells themselves are contributing towards the viral internalization and infection. However, the mechanisms and factors involved in the viral uptake are still not properly understood. Advances in the understanding of the uptake, transmission and infection process will facilitate the researchers to design the targeted therapeutic approaches and in prevention of the infection to the naïve host cells in the human body. In this review, we have addressed the current knowledge of endocytic mechanisms, host cell factors & host-virus interactions; employed by the Human Papilloma virus, ZIKA virus, Adenovirus and Hepatitis-B virus. We have attempted to summarize the drugs, plant and microbes' based compounds & therapies developed from the currently available researches along with their targets in the infected host cells and the drugs, therapeutic treatments and vaccines under the clinical trials that can be possibly available in the future against the concerned viruses.

Keywords: Endocytosis, Human Papilloma Virus, Hepatitis – B Virus, ZIKA Virus, Adenovirus, Antivirals.

INTRODUCTION

Endocytosis is a crucial mechanism in eukaryotic cells for entry of micro and macro-molecules within the cell, Cell-cell communication, body homeostasis, responses to the signals and antigen presentation, cellular adhesion and uptake of nutrients (Kaksonen and Roux 2018). Pathogens, including viruses and their toxins, use different endocytic pathways, to have access inside the cells. Phagocytosis and Clathrin dependent & receptor mediated endocytosis are the most extensively studied ones.

Clathrin, a protein composed of 3 heavy (approx. 190 kDa) & 3 light chains (25 kDa) that together forms triskelion, a framework of pentagons and hexagons (Shi *et al.*, 2021). It is associated with Assembly peptides or AP's (Adaptor proteins). The formation of coated pits on plasma membrane leaflet is still unclear, but it is believed to be result of receptor aggregation process (Duncan, 2022). The mechanism behind joining of the ends of the coated pits from the plasma membrane and their pinching off is still unclear (Sochacki and Taraska 2019).

Clathrin dependent & receptor mediated endocytosis happens within the nucleated cells, primarily used by viruses to enter and leave host cells. This pathway is utilized by the lipid bound ligands (Nestic *et al.*, 2021). This selective pathway clears cell surface bound proteins and increases their amount in coated vesicles. An example is the uptake of *Shiga* toxin from *Shigella dysenteriae* L. Here, glycosphingolipid receptors help in receptor concentration elevation and vesicles to endocytose (Chan and Ng 2016). Various endocytic mechanisms can be differentiated as discussed in (Fig. 1).

Viruses, derived from a Latin word which means "poison" are major contributors to genetic diversity on Earth. They are known as the obligate (species specific) intracellular (functional and active only inside the host organism) parasites with large genome size and genes acquired from hosts. Three main lineages of +RNA viruses are – flavivirus, picorniavirus and alpha virus superfamilies' based on the genes and gene arrangements (Koonin *et al.*, 2015). They possess simple structure and complex interaction mechanisms with host cells (Belov, 2014). They make the use of the host cell's metabolic machinery to form virions and spread infection inside the host body.

They have built the abilities to cause infection by entering host cell, binding to surface proteins and activating intracellular signaling pathways such as antiviral responses, rearrangements in the cell cytoskeleton (Herrscher *et al.,* 2020). Still, the most common mechanism hijacked for viral entry is Endocytosis, which can be either Clathrin-mediated or Caveolin- mediated (Herrscher *et al.,* 2020). Once inside, virion assembly transport viral components to a specific intracellular location to complete the remaining assembly process (Boulant *et al*., 2015).

This review explores virus entry into mammalian cells, their internalization pathways, and distribution mechanisms; especially for HPV, HBV, ZIKA and adenovirus due to the non-availability of the potential therapeutics against them till now to cure the patients. It also discusses potential drugs and therapies to prevent virus internalization, replication, and infection by the studied viruses.

Evolution of virus to more virulent strains. The easy entry and infection of viruses into humans can be attributed to evolutionary pressures, such as Human herpes virus shows convergence of phylogenetic trees with humans. Origin of 8% of human genome from RNA viruses, makes viruses to easily evade host (Wolf *et al*., 2018). Viruses have 10x high mutation rates due to the lack of proof-reading activity of RNA-dependent-RNA polymerases (Khan *et al*., 2022). Insertions and deletions cause high mutation with evolution. Frequent viral infections is the disability of the human DNA polymerase enzyme to replicate the genome, leading to new viruses with unique properties (Humphreys, 2018).

Mechanisms of entry into host cells by various viruses. The viral entry and its genome replication differs based on the type of cell infected by virus, type of viral genome and virion structures. There are two phases included in the replication cycle of a virus – entry and genome replication (Aksoy *et al*., 2017).

1. Human Papillomavirus (HPV). HPV, a non-enveloped, ds-circular DNA viruses causing several types of cancer such as cervical, head&neck, anal cancer. The most studied type is HPV16, responsible for majority of cancers (Boda *et al*., 2018). It causes infection via capsid proteins – major protein (L1), forming 72 pentamers for the capsid and minor protein (L2), exposing N-terminal on viral capsid surface. Thus, the initial interactions take place with the L1 protein only. It infects epithelial basal cells. It binds to basal membrane and interacts with cell surface protein, HSPGs or Heparan sulfate proteoglycans (Aksoy *et al.,* 2017). Syndecan-1 is an essential receptor for viral attachment due to its highest expression in the keratinocytes of the epithelium (Holzhauser, 2018). *In vivo* studies have shown that furin inhibitors can prevent HPV16 from attaching to cell surface, But *in vitro* studies showed that furin is essentially required for viral escape from the late endosomes (Aksoy *et al.,* 2017). There are still contradictions about the presence of the furin on the human cell surfaces and its role in the viral entry.

HPV16 uses pathways such as Clathrin-mediated, caveolin-mediated or both simultaneously (DiGiuseppe *et al.,* 2016). Studies showed that CD151 recruitment at TEMs and its interaction with the laminin-binding Integrins is essential for HPV16 endocytosis. The HPV16-CD151 complex moves laterally before viral internalization, directing virus towards cell entry (Scheffer *et al.,* 2013). A new endocytic pathway for viral entry which is independent of clathrin, caveolin, dynamin, flotillin and cholesterol and is related to macro pinocytosis but different in terms of absence of small & even vesicles and protrusions of membrane. Despite extensive information on HPV16 infection, the mechanisms of infection remain a subject of scientific debate due to the diverse results (Schelhaas *et al.,* 2012).

Drugs and therapies against Human Papilloma Virus. Cervical cancer, primarily in females, is the leading HPV-related cancer, with 7.5% mortality in 2018 (Bray *et al.,* 2018). Rapid screening (Pap smear) and vaccine application have reduced death rates, but survival rates remain low (Zhu *et al*., 2016). Various agents interfering apoptosis have been implied for cervical cancer therapy, with surgery and chemotherapy being the standard treatments (Liu *et al.,* 2021) (Table 1).

Advanced cancerous stage require radiation treatment with Cisplatin-based chemotherapy (Brown *et al.,* 2018), while Systemic drug treatment are proven to be less effective (Liu *et al.,* 2021). Pembrolizumab, a checkpoint inhibitor, has been approved against malignant melanoma (Poole, 2014). Inhibitors - Durvalumab (Tan *et al.,* 2018) and drugs – Atezolizumab, Nivolumab and Cemiplimab have completed the Phase III trials.

Plant secondary metabolites. The active compounds extracted from many edible and medicinal plants have proven to be effective against cervical cancer (Table 2).

Compounds Extracted From Microorganisms. Microorganisms, particularly actinomycetes, some bacteria, and fungi, are crucial sources for discovering new therapeutic substances with anticancer activities (Table 3).

2. ZIKA virus. ZIKA virus, belonging to family Flaviviridae, was first isolated from sentinel Rhesus monkey's blood serum at a forest, Zika, Uganda in 1947 (Polonio *et al.,* 2017). It causes various diseases - (Guillain-Barre Syndrome in adults) in infants and fetuses - microcephaly. It is an enveloped virus possessing RNA from mosquitoes. Its 10.7 kb codes for single long structure that codes for polyprotein which is cleaved into different components such as prM (precursor or premembrane protein), E (envelope protein), C (capsid protein) and 7 NS (Non –structural proteins) Its entry mechanism is endocytosis mediated via Clathrin, followed by conformational changes in the viral envelope, viral fusion with the host cell membrane and viral genome release inside the host cell. During infection, virus attaches to GAGs via its envelope proteins and diffuses towards the clathrin coated pits, encapsulating it and releasing the viral genome in the cell cytoplasm (Rumlova and Ruml 2018). The homodimer of envelope protein make multiple interactions with host surface receptors to increase avidity and stronger binding (Agrelli *et al*., 2019). Studies have shown that virus entry can be mediated by

negatively charged plasma membrane lipids like phosphatidylserine that interact with positively charged phosphatidylserine receptors - TIM and TAM. TAMs bind via Growth arrest specific 6 or GAS-6, also known as protein S (Heinz and Stiasny 2017). This process is "apoptotic mimicry" (Amara and Mercer 2015), used to infect skin, neural, placental and endothelial cells. Further research is needed to understand the infection process (Tabata *et al.,* 2016).

Drugs and therapies against ZIKA virus – Various technologies and strategies are being developed to develop inhibitors against ZIKA virus including– virus replication based screening, screening of virus protein and drug repurposing. However, no virus–specific vaccines or therapeutic drugs are available (Alam *et al.,* 2017). Currently the main focus for treatment is drug repurposing due its cost effectiveness & rapid strategy as bioinformatics is involved (Diamond *et al.,* 2019). Chloroquine (1934), mefloquine, hydroxychloroquine, amodiaquine have shown antiviral activities (Delvecchio *et al.,* 2016).

Chloroquine (CQ) has ability to reverse the phenotypic changes by virus in the neurospheres of mouse (Delvecchio *et al*., 2016). CQ blocks virus internalization process (Zhu *et al.,* 2017). Being FDA-approved drug (C-class) can be beneficial towards therapies for pregnant women (Shiryaev *et al.,* 2017). HCQ (Hydroxychloroquine) has much better pharmacokinetic properties as compared to CQ due to higher concentration in brain as compared to blood plasma (Compter *et al.,* 2021). HCQ inhibits virus entry and also blocks protein glycosylation via alkalization of acidic cell organelles (Faraone *et al.,* 2020). HCQ prevents placental damage in fetus heads and limits ZIKA virus transmission. However, ongoing studies are not sufficient to determine the fetotoxicity (Kaplan *et al.,* 2016). Mefloquine is better at crossing the blood-brain barrier but cytotoxic against the hNPCs (Barrows *et al.,* 2016). Amodiaquine or AQ has shown *in vivo* inhibition of ZIKA virus in mouse brain having SCID-beige (Zhou *et al*., 2017). AQ works by targeting virus at early step of entry and viral replication same as of HCQ (Han *et al.,* 2018), but proven to be effective during pregnancy with toxic effects on liver and blood (Parhizgar *et al.,* 2017). Further investigation is still required.

Antibiotics. Two antibiotics –macrolide and cyclic lipopeptide, are in use (Azithromycin - AZ and Daptomycin) without affecting pregnant women and fetal development, but *in vivo* action mechanism still need to be addressed (Li *et al.,* 2019). AZ inhibits the ZIKA virus production and also induces the virus-mediated cell death (Retallack *et al.,* 2016). Daptomycin has inhibitory effects in Huh-7 cells but very poor effects in the HeLa cell and JEG3 cell lines, with reduction in replication of virus in both the hNSCs and hAECs (human Amnion Epithelial Cells) (Barrows *et al.,* 2016).

Natural products. Labyrinthopeptins (Laby A1 and A2) are the peptides working as antibiotics, produced by bacteria – Actinomycetes specifically *Actinomadura namibiensis (*DSM 6313). This peptide directly binds to the ZIKA viral particle, leading to virolysis (Prochnow *et al.,* 2020). The crude extracts of *Dictyota menstrualis*, a Brazilian Brown Seaweed, has shown the anti-ZIKA viral activity (Cirne-Santos *et al*., 2019) by inhibiting >90% viral activity when its FAc-2 fraction was used at concentration of 20 µg per ml and when the fraction f-6 from the same extract was used, it reduced the adsorption of viruses on to the host cells, thus indirectly reducing viral activity. Green tea's flavanol compound, EGCG i.e. Epigallocatechin gallate (Carneiro *et al.,* 2016) and red grapes' Resveratrol: reduced the foci formation by 93% and showed the direct virucidal activity (Fong and Chu 2022).

Others – Emricasan (a selective inhibitor of pan-caspase) inhibits the death of neural cells (Dhani *et al.,* 2021) but failed to stop viral replication. Inhibitor PHA-690509 (cyclic dependent kinase) possess better potential to inhibit the proliferation of the ZIKA virus ((Barreyro *et al.,* 2015). 774 FDA- approved drugs were screened and only Mefloquine, Sertraline & Mycophenolic acid (an immunosuppressant drug) proved to be effective against ZIKA virus in Huh-7, JEG3 and HeLa cells (Devillers, 2018).

Associated risks still need to be investigated for pregnant women and newborns (Yuan *et al*., 2017).

3. Hepatitis-B virus. HBV is an enveloped virus that mainly infects the liver cells in humans and other primates. The Dane particle, is infectious form, consists of circular, partially dsDNA molecule with polymerase enzyme, a nucleocapsid and 3 proteins of viral envelope– S, M and L as small, medium and large proteins (Lamontagne, 2016). These proteins share a common C-terminal domain - S domain, while the M protein contains preS2 domain (N –terminal domain), L protein consists preS1, preS2 and S domains (Pastor *et al.,* 2019). These are essential for viral attachment to the hepatocytes or liver cells to cause infection. Two non-infectious sub forms; known as SVPs (Sub viral particles) contain envelope proteins and are secreted in excessive quantities (Hu and Liu 2017). 25% of the weight of these SVPs is formed by lipids like cholesterol, cholesterol ester, phosphatidylcholine and triglycerides. The role of these SVPs is unclear but thought to protect the Dane particles from the host's humoral response and the detailed information is lacking due to HBV's cccDNA or existence of its viral genome in the form of a Minichromosome. HBV require strong binding to the highly sulfated Heparan Sulfate Proteoglycans present abundantly on liver cells to initiate the infection process. Recent studies show that HBV primarily infects hepatocytes with HSPG named Glypican (Verrier *et al.,* 2016). The major interaction between HSPGs on liver cells and positively charged amino acids – Arg122 and Lys141 present of S domain's antigenic loop, present in all the HBVs (Herrscher *et al.,* 2020); promotes high affinity binding to viral receptor. An 11 amino acid mutation (i.e. deletion) in preS1 domain enhances the infectivity of the HBVs, helping them to bind to various liver cell receptors (Sargiacomo, 2018). Gene expression of HepaRG cells has demonstrated that knocking down of NTCP ((Sodium taurocholate co-transporting polypeptide) receptor has blocked the HBV infection (Ni *et al.,* 2014). Studies suggest that NTCP is not

sufficient for infection; EGFR also facilitates HBV internalization into host cells, accounting for low infection rate (Iwamoto *et al.,* 2019).

As per a study, cell polarization is an efficient mechanism for easy cellular HBV uptake (Linfield *et al.,* 2021). A 2018 study revealed that a drug named Silibinin has inhibited the Clathrin-mediated endocytosis of HBV particles in HepG2-NTCP cells (Umetsu *et al.,* 2018). Following this research, a new study has investigated that silencing of this pathway, dynamin-2, AP-2 has resulted in huge decline in the HBV entry and infection (Herrscher *et al.,* 2020). Several studies shows that Clathrin-mediated endocytosis is the major entry route in the hepatocytes. Cell treatment with Bafilomycin A1 (inhibitor of vacuolar proton ATPase's) and silencing of the GTPases (Rab5 and Rab7) responsible for transport of cargo from early endosomes to late endosomes and then to lysosomes; also inhibit the HBV infection. EGFR plays role in internalization of HBV bound to NTCP receptor through its own endocytic/sorting pathway (Iwamoto *et al*., 2020).

Inhibition of HBV entry with available treatments- Recent study has shown that extracellular vesicle miRNAs play crucial in antiviral function, suggesting that HBV maintains its replication by secreting anti-HBV intracellular miRNAs, potentially offers therapeutic advantages (Chu *et al.,* 2022). HBIGs or Hepatitis B Immunoglobulins of blood plasma are the only "inhibitors of HBV entry" till now, targeted against the AGL loop of S domain of viral envelope, as they neutralize virions in circulation (Jhajharia *et al.,* 2022). However, treatment is quite expensive, time consuming Ab purification process, limited supply due to lack of vaccinated donors and lack of efficacy due to mutations in the S domain's AGL loop. "Monoclonal antibodies" specifically targeting the PreS1 domain has shown promising results during the preclinical trials (Wi *et al.,* 2017), but limited for transplantation and to prevent mother to child transmission (Eke *et al.,* 2017). Alternative approaches include blocking viral attachment to naïve hepatocytes; using HSPG substrates like suramin, heparin, and sulfated dextrans (Herrscher *et al.,* 2020). Interferon alpha inducible soluble factors bind to HSPG and inhibits the HBV binding; a novel approach as an entry inhibitor (Xia *et al.,* 2017). Approaches targeting the NTCP may lead to the removal of cccDNA and infection by the host's immune system, a natural hepatocyte process. NTCP substrates such as taurocholate along with its derivatives and Ezetimibe have been tested, but long term treatment can have several side effects (Veloso *et al.,* 2015).

4. Adenovirus. Adenoviruses are naked and non-oncogenic DNA viruses, produces virions within the host cell's nucleus and releases them upon cell lysis. Ad2 and Ad5 are responsible for causing respiratory tract infections and are majorly used as vectors for gene delivery (Ison and Hayden, 2016). Viral structure consists of outer capsid, inner core consisting of 36 kbp DNA molecule along with terminal proteins, condensing proteins (V and VII) (Kulanayake and Tikoo 2021). Viral chromosome contains 10 copies of Cys protease (p23), connected to capsid via protein VI; stabilized by IIIa, VIII, IX proteins. RGD domain and fiber protein protruding over the virus surface aid in virus attachment to target cell (Nemerow and Stewart 2016). Adenovirus species except B species bind to the CAR receptor (Coxsackie virus B Ad receptor), of prime importance for Ad entry into respiratory tract. Human CAR is a trans-membrane protein (type-1), folds into V-like Ig fold and C2- like fold. The viral fibers distort the Adheren junctions and helps virus in lumen of airways, indicating the CAR working as an exit receptor also (Ortiz-Zapater *et al.,* 2017).

Most recent studies have revealed that Ad2 and Ad5 makes the use of Clathrin- mediated endocytic pathway for entry into respiratory tract epithelial cells (Huang *et al.,* 2015), utilizing K44A-dynamin, Eps15 and clathrin fragments (Nestic *et al.,* 2021). Integrins also support viral entry as Integrin αV gets activated as Ad makes contact with CAR on target cell surface; triggering viral endocytosis. This activation also requires large and small GTPases (such as Dynamin, PI3K & Rac1, Rab5 and Cdc42). After endocytosis, Ad escapes from acidic conditions to cytoplasm. It uses Protein kinase A and MAPK/p38 pathway to boost microtubule and dynactin/dynein – dependent transport to the target cell nucleus; where it binds to the nuclear receptor CAN/Nup214 (Flatt and Greber 2017). Within the nucleus, it recruits histone protein H1 along with its import factors – importin 7 & β (Hennig and O'Hare 2015). Recent study has revealed the use of Signal-mediated macro pinocytosis by Ad2 and Ad5 simultaneously with Clathrin-mediated endocytosis; depending only on PKC (Protein Kinase C) and EIPA {Na^+/H^+ exchange inhibitor 5-(N-ethyl-N-isopropyl)amiloride} (Nestic *et al.,* 2021).

Viral escape, an essential step for better infectivity, occurs immediately after viral endocytosis. Low pH and $\alpha_V\beta_5$ integrin has emerged as crucial factors for the viral escape from endosomes to cytoplasm (Kremer and Nemerow 2015).

Treatments available against the adenoviruses. Despite usage of adenoviruses as vectors for development of vaccines and gene therapies, there are no US-FDA approved antiviral drugs (Lopez *et al.,* 2018). This has created an urgent demand for development of such antiviral drugs to prevent the infections in patients receiving these treatments. Current attractive strategy is drug repositioning (Pushpakom *et al.,* 2019). Using the cell based assay, new antiviral inhibitors were identified against the AdV3 & AdV5 in the *in vitro* studies (Liu *et al.,* 2022). These hit compounds were targeting the host factors like Heat Shock Proteins (HSPs) mainly Hsp90, mTOR (mammalian target of rapamycin), PTKs (protein Tyrosine Kinases) (Liu *et al.,* 2022). Among these inhibitors, KPT-335 and 17-AAG were reported to play role in the inhibition of the adenovirus replication (Dalidowska *et al*., 2021).

Antivirals are involved in the inhibition of the DNA and RNA synthesis process such as ganciclovir, cidofovir, and ribavirin (Khanal *et al.,* 2018). However, Brincidofovir, conjugate of cidofovir, has received the fast track status from FDA and is under clinical trials, with advantages like higher cellular uptake & oral

delivery, but has caused gastrointestinal toxicity in some of the patients (Ramsay *et al*., 2017). Immunotherapies that assess the virus-specific T lymphocytes are also under consideration (Florescu *et al*., 2019).

Table 1: Chemotherapy involves the following drugs in use (Liu *et al*., 2021).

Target of the drug	Drugs in use
Cell cycle drugs (non-specific)	Cisplatin, Carboplatin,Oxaliplatin
Cell cycle drugs (specific)	Paclitaxel, Vincristine, Gemcitabine,5-fluorouracil
Targets VEGF	Bevacizumab, Sildenib, Sunitinib, Pazopanib
Targets EGFR	Cetuximab, Lapatinib, Gefitinib, Erlotinib
Blocks Signal Transduction	CCI-779, Gendicine
Targets Programmed Death Ligand-1	Pembrolizumab

Table 2: Source of plant secondary metabolites and their mode of action against cervical cancer.

Plant secondary metabolites against cervical cancer	Activity of secondary metabolites	References
Luteoloside and Carnosic acid (obtained from Chinese medicinal herbs)	— Induces apoptosis via modulation of mitochondrial pathways and ROS (Reactive Oxygen Species) — Activates mTOR and protein p53	Shao *et al*. (2018)
Tanshinone IIA (extracted from *Salvia miltiorrhiza*) and Realgar	— Represses HPV oncogenes — Induce apoptosis via activation of p53 dependent pathway	Ding *et al*. (2018)
Tanshinone IIA alone (extracted from *Salvia miltiorrhiza*)	— Cervical cancer cell death via inhibition of glucose metabolism	Liu *et al*. (2019)

Table 3: The Compounds derived from microorganisms and their mode of action in treatment against cervical cancer.

Microorganism	Compounds	Anticancer activity	References
Trichothecium roseum	Rosoloactone	Endoplasmic Reticulum Stress associated Pro-apoptotic activity and apoptosis via mitochondrial pathway.	Zhou *et al.* (2017)
Penicillium sclerotiorum	PSE	Apoptosis via mitochondrial pathway, anti angiogenic and antioxidant properties.	Kuriakose *et al.* (2018)
Streptomyces sp OA293	Streptomyces metabolites	Activation of 4E-BP1 and P70S6K (Downstream signals of mTORC1 inhibitor) along with expression of Akt.	Dan *et al.* (2018)

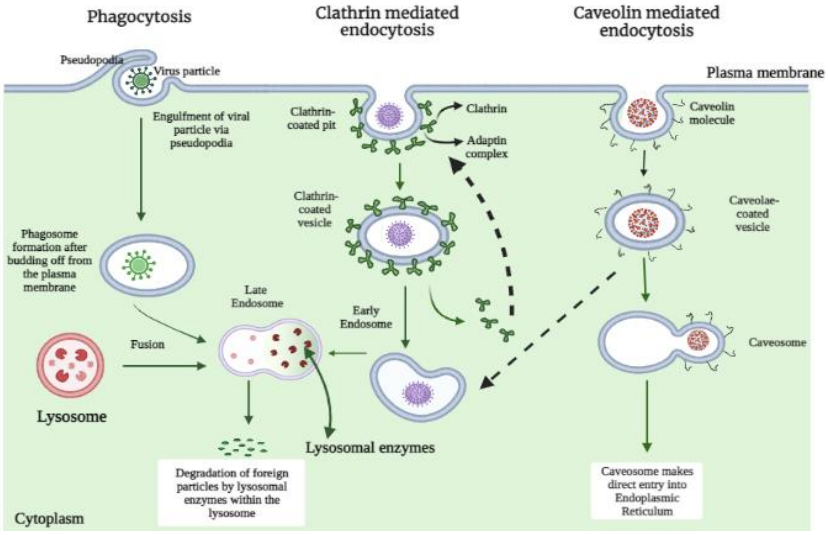

Fig. 1. Diagrammatic representation of different endocytic mechanisms including – Phagocytosis, Clathrin – and Caveolin - mediated endocytosis. Phagocytosis involves engulfing foreign particles through plasma membrane invaginations, while Clathrin- and Caveolin-mediated endocytosis involves clathrin and caveolin molecules coating mammalian plasma lemma's inner leaflet. These processes involve endosome fusion to lysosomes, leading to particle degradation.

CONCLUSIONS

This review explore endocytic mechanisms and drugs against four human viruses: Human Papilloma Virus, Zika virus, Hepatitis B Virus and Adenovirus. Introduction of viral genes in human hosts contribute to viral infection spread, affecting the understanding of endocytic mechanisms & development of viral protein inhibitors and vaccines. The various pathways of endocytosis employed by the viruses to enter the host cell, replicate and cause infection, still forms a unique tool that is necessary to uncover the other new virus transportation and endocytic pathways, in order to develop a remarkable drug against the definitive virus.

FUTURE SCOPE

Diversified drugs for dissimilar diseases, are ahead in consideration for drug repurposing due to time consuming and laborious new drug development process. Therefore, various plant metabolites with multiple therapeutic properties are preferred for viral infection treatments. They are able to produce several synergistic effects with superior therapeutic results, despite challenges during discovery process. The drug ability of plant metabolites in therapeutics is a major obstacle, influenced by pharmacokinetic parameters such as drug absorption, distribution to target, metabolism and elimination from body. Fortunately, the advancement in the area of nanotechnology and novel targeted drug delivery systems, have enlightened the hope for developing plant metabolites as first candidates for potential drug and treatment against viral activities. Challenges in drug development include plant material authentication, the necessity to develop high-throughput screening bioassays, complications in isolation, purification and scaling-up process of bioactive plant–derived compounds as they are relatively complex ones; and disappointing failures at the clinical trials during drug development (Phu *et al.*, 2020).

Acknowledgements. This review was compiled by the authors after reviewing the published literature. There is a great work done in this field and we apologize if any literature has been overlooked.

Conflict of Interest. None.

REFERENCES

Agrelli, A., de Moura, R. R., Crovella, S., & Brandão, L. A. C. (2019). ZIKA virus entry mechanisms in human cells. *Infection, genetics and evolution: journal of molecular epidemiology and evolutionary genetics in infectious diseases*, *69*, 22–29.

Aksoy, P., Gottschalk, E. Y., & Meneses, P. I. (2017). HPV entry into cells. *Mutation research. Reviews in mutation research*, *772*, 13–22.

Alam, A., Imam, N., Farooqui, A., Ali, S., Malik, M. Z., & Ishrat, R. (2017). Recent trends in ZikV research: A step away from cure. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *91*, 1152–1159.

Amara, A., & Mercer, J. (2015). Viral apoptotic mimicry. *Nature reviews. Microbiology*, *13*(8), 461–469.

Barreyro, F. J., Holod, S., Finocchietto, P. V., Camino, A. M., Aquino, J. B., Avagnina, A., Carreras, M. C., Poderoso, J. J., & Gores, G. J. (2015). The pan-caspase inhibitor Emricasan (IDN-6556) decreases liver injury and fibrosis in a murine model of non-alcoholic steatohepatitis. *Liver international : official journal of the International Association for the Study of the Liver*, *35*(3), 953–966.

Barrows, N. J., Campos, R. K., Powell, S. T., Prasanth, K. R., Schott-Lerner, G., Soto-Acosta, R., Galarza-Muñoz, G., McGrath, E. L., Urrabaz-Garza, R., Gao, J., Wu, P., Menon, R., Saade, G., Fernandez-Salas, I., Rossi, S. L., Vasilakis, N., Routh, A., Bradrick, S. S., & Garcia-Blanco, M. A. (2016). A Screen of FDA-Approved Drugs for Inhibitors of Zika Virus Infection. *Cell host & microbe*, *20*(2), 259–270.

Belov G. A. (2014). Modulation of lipid synthesis and trafficking pathways by picornaviruses. *Current opinion in virology*, *9*, 19–23.

Boda, D., Docea, A. O., Calina, D., Ilie, M. A., Caruntu, C., Zurac, S., Neagu, M., Constantin, C., Branisteanu, D. E., Voiculescu, V., Mamoulakis, C., Tzanakakis, G., Spandidos, D. A., Drakoulis, N., & Tsatsakis, A. M. (2018). Human papilloma virus: Apprehending the link with carcinogenesis and unveiling new research avenues (Review). *International journal of oncology*, *52*(3), 637–655.

Boulant, S., Stanifer, M., & Lozach, P. Y. (2015). Dynamics of virus-receptor interactions in virus binding, signaling, and endocytosis. *Viruses*, *7*(6), 2794–2815.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: *a cancer journal for clinicians*, *68*(6), 394–424.

Brown, A., Kumar, S., & Tchounwou, P. B. (2019). Cisplatin-Based Chemotherapy of Human Cancers. *Journal of cancer science & therapy*, *11*(4), 97.

Carneiro, B. M., Batista, M. N., Braga, A. C. S., Nogueira, M. L., & Rahal, P. (2016). The green tea molecule EGCG inhibits Zika virus entry. *Virology*, *496*, 215–218.

Chan, Y. S., & Ng, T. B. (2016). Shiga toxins: from structure and mechanism to applications. *Applied microbiology and biotechnology*, *100*(4), 1597–1610.

Chu, Q., Li, J., Chen, J., & Yuan, Z. (2022). HBV induced the discharge of intrinsic antiviral miRNAs in HBV-replicating hepatocytes via extracellular vesicles to facilitate its replication. The Journal of general virology, 103(5), 10.1099/jgv.0.001744.

Cirne-Santos, C. C., Barros, C. D., Gomes, M. W., Gomes, R., Cavalcanti, D. N., Obando, J. M., Ramos, C. J., Villaça, R. C., Teixeira, V. L., Paixão, I. C. (2019). *In vitro* antiviral activity against zika virus from a natural product of the Brazilian brown seaweed *Dictyota menstrualis*. *Natural Product Communications. 14*(7), 1934578X19859128.

Compter, I., Eekers, D. B. P., Hoeben, A., Rouschop, K. M. A., Reymen, B., Ackermans, L., Beckervordersantforth, J., Bauer, N. J. C., Anten, M. M., Wesseling, P., Postma, A. A., De Ruysscher, D., & Lambin, P. (2021). Chloroquine combined with concurrent radiotherapy and temozolomide for newly diagnosed glioblastoma: a phase IB trial. *Autophagy*, *17*(9), 2604–2612.

Dalidowska, I., Gazi, O., Sulejczak, D., Przybylski, M., & Bieganowski, P. (2021). Heat Shock Protein 90 Chaperones E1A Early Protein of Adenovirus 5 and Is Essential for Replication of the Virus. *International journal of molecular sciences*, *22*(4), 2020.

Dan, V. M., Muralikrishnan, B., Sanawar, R., J S, V., Burkul, B. B., Srinivas, K. P., Lekshmi, A., Pradeep, N. S., Dastager, S. G., Santhakumari, B., Santhoshkumar, T.

R., Kumar, R. A., & Pillai, M. R. (2018). Streptomyces sp metabolite(s) promotes Bax mediated intrinsic apoptosis and autophagy involving inhibition of mTOR pathway in cervical cancer cell lines. *Scientific reports*, *8*(1), 2810.

Delvecchio, R., Higa, L. M., Pezzuto, P., Valadão, A. L., Garcez, P. P., Monteiro, F. L., Loiola, E. C., Dias, A. A., Silva, F. J., Aliota, M. T., Caine, E. A., Osorio, J. E., Bellio, M., O'Connor, D. H., Rehen, S., de Aguiar, R. S., Savarino, A., Campanati, L., & Tanuri, A. (2016). Chloroquine, an Endocytosis Blocking Agent, Inhibits Zika Virus Infection in Different Cell Models. *Viruses*, *8*(12), 322.

Devillers, J. (2018). Repurposing drugs for use against Zika virus infection. *SAR and QSAR in environmental research*, *29*(2), 103–115.

Dhani, S., Zhao, Y., & Zhivotovsky, B. (2021). A long way to go: caspase inhibitors in clinical use. *Cell death & disease*, *12*(10), 949.

Diamond, M. S., Ledgerwood, J. E., & Pierson, T. C. (2019). Zika Virus Vaccine Development: Progress in the Face of New Challenges. *Annual review of medicine*, *70*, 121–135.

DiGiuseppe, S., Bienkowska-Haba, M., & Sapp, M. (2016). Human Papillomavirus Entry: Hiding in a Bubble. *Journal of virology*, *90*(18), 8032–8035.

Ding, W., Ji, T., Xiong, W., Li, T., Pu, D., & Liu, R. (2018). Realgar, a traditional Chinese medicine, induces apoptosis of HPV16-positive cervical cells through a HPV16 E7-related pathway. *Drug design, development and therapy*, *12*, 3459–3469.

Duncan M. C. (2022). New directions for the clathrin adaptor AP-1 in cell biology and human disease. *Current opinion in cell biology*, *76*, 102079.

Eke, A. C., Eleje, G. U., Eke, U. A., Xia, Y., & Liu, J. (2017). Hepatitis B immunoglobulin during pregnancy for prevention of mother-to-child transmission of hepatitis B virus. *The Cochrane database of systematic reviews*, *2*(2), CD008545.

Faraone, I., Labanca, F., Ponticelli, M., De Tommasi, N., & Milella, L. (2020). Recent Clinical and Preclinical Studies of Hydroxychloroquine on RNA Viruses and Chronic Diseases: A Systematic Review. *Molecules (Basel, Switzerland)*, *25*(22), 5318.

Flatt, J. W., & Greber, U. F. (2017). Viral mechanisms for docking and delivering at nuclear pore complexes. *Seminars in cell & developmental biology*, *68*, 59–71.

Fong, Y. D., & Chu, J. J. H. (2022). Natural products as Zika antivirals. *Medicinal research reviews*, *42*(5), 1739–1780.

Han, Y., Mesplède, T., Xu, H., Quan, Y., &Wainberg, M. A. (2018). The antimalarial drug amodiaquine possesses anti-ZIKA virus activities. *Journal of medical virology*, *90*(5), 796–802.

Heinz, F. X., & Stiasny, K. (2017). The Antigenic Structure of Zika Virus and Its Relation to Other Flaviviruses: Implications for Infection and Immunoprophylaxis. *Microbiology and molecular biology reviews : MMBR*, *81*(1), e00055-16.

Hennig, T., & O'Hare, P. (2015). Viruses and the nuclear envelope. *Current opinion in cell biology*, *34*, 113–121.

Herrscher, C., Pastor, F., Burlaud-Gaillard, J., Dumans, A., Seigneuret, F., Moreau, A., Patient, R., Eymieux, S., de Rocquigny, H., Hourioux, C., Roingeard, P., & Blanchard, E. (2020). Hepatitis B virus entry into HepG2-NTCP cells requires clathrin-mediated endocytosis. *Cellular microbiology*, *22*(8), e13205.

Herrscher, C., Roingeard, P., & Blanchard, E. (2020). Hepatitis B Virus Entry into Cells. *Cells*, *9*(6), 1486.

Herrscher, C., Pastor, F., Burlaud-Gaillard, J., Dumans, A., Seigneuret, F., Moreau, A., Patient, R., Eymieux, S., de Rocquigny, H., Hourioux, C., Roingeard, P., & Blanchard, E. (2020). Hepatitis B virus entry into HepG2-NTCP cells requires clathrin-mediated endocytosis. *Cellular microbiology*, *22*(8), e13205.

Holzhauser, S. (2018). *Effect of ionising radiation on HPV-positive and HPV-negative oropharyngeal cancer cell lines* (Doctoral dissertation, Cardiff University).

Hu, J., & Liu, K. (2017). Complete and Incomplete Hepatitis B Virus Particles: Formation, Function, and Application. *Viruses*, *9*(3), 56.

Hu, Q., Zhang, F., Duan, L., Wang, B., Ye, Y., Li, P., Li, D., Yang, S., Zhou, L., & Chen, W. (2020). E-cadherin Plays a Role in Hepatitis B Virus Entry Through Affecting Glycosylated Sodium-Taurocholate Cotransporting Polypeptide Distribution. *Frontiers in cellular and infection microbiology*, *10*, 74.

Huang, J., Tan, D., Wang, Y., Liu, C., Xu, J., & Wang, J. (2015). Egg drop syndrome virus enters duck embryonic fibroblast cells via clathrin-mediated endocytosis. *Virus research*, *210*, 69–76.

Humphreys M. (2018). The influenza of 1918: Evolutionary perspectives in a historical context. *Evolution, medicine, and public health*, *2018*(1), 219–229.

Ison, M. G., & Hayden, R. T. (2016). Adenovirus. *Microbiology spectrum*, *4*(4), 10.1128/microbiolspec.DMIH2-0020-2015.

Iwamoto, M., Saso, W., Nishioka, K., Ohashi, H., Sugiyama, R., Ryo, A., Ohki, M., Yun, J. H., Park, S. Y., Ohshima, T., Suzuki, R., Aizaki, H., Muramatsu, M., Matano, T., Iwami, S., Sureau, C., Wakita, T., & Watashi, K. (2020). The machinery for endocytosis of epidermal growth factor receptor coordinates the transport of incoming hepatitis B virus to the endosomal network. *The Journal of biological chemistry*, *295*(3), 800–807.

Iwamoto, M., Saso, W., Sugiyama, R., Ishii, K., Ohki, M., Nagamori, S., Suzuki, R., Aizaki, H., Ryo, A., Yun, J. H., Park, S. Y., Ohtani, N., Muramatsu, M., Iwami, S., Tanaka, Y., Sureau, C., Wakita, T., & Watashi, K. (2019). Epidermal growth factor receptor is a host-entry cofactor triggering hepatitis B virus internalization. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(17), 8487–8492.

Jhajharia, S., Lai, F., Low, H. B., Purushotorman, K., Shunmuganathan, B. D., Chan, C. E. Z., Hammond, R., Netter, H. J., Chen, Q., Lim, S. G., & MacAry, P. A. (2022). Defining the specificity and function of a human neutralizing antibody for Hepatitis B virus. *NPJ vaccines*, *7*(1), 121.

Kaksonen, M., & Roux, A. (2018). Mechanisms of clathrin-mediated endocytosis. *Nature reviews. Molecular cell biology*, *19*(5), 313–326.

Kaplan, Y. C., Ozsarfati, J., Nickel, C., & Koren, G. (2016). Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. *British journal of clinical pharmacology*, *81*(5), 835–848.

Khan, M. Z. I., Nazli, A., Al-Furas, H., Asad, M. I., Ajmal, I., Khan, D., Shah, J., Farooq, M. A., & Jiang, W. (2022). An overview of viral mutagenesis and the impact on pathogenesis of SARS-CoV-2 variants. *Frontiers in immunology*, *13*, 1034444.

Khanal, S., Ghimire, P., & Dhamoon, A. S. (2018). The Repertoire of Adenovirus in Human Disease: The Innocuous to the Deadly. *Biomedicines*, *6*(1), 30.

Koonin, E. V., Dolja, V. V., & Krupovic, M. (2015). Origins and evolution of viruses of eukaryotes: The ultimate modularity. *Virology*, *479-480*, 2–25.

Kremer, E. J., & Nemerow, G. R. (2015). Adenovirus tales: from the cell surface to the nuclear pore complex. *PLoS pathogens*, *11*(6), e1004821.

Kulanayake, S., & Tikoo, S. K. (2021). Adenovirus Core Proteins: Structure and Function. *Viruses*, *13*(3), 388. https://doi.org/10.3390/v13030388

Kuriakose, G. C., Lakshmanan M, D., Bp, A., Rs, H. K., Th, A. K., Ananthaswamy, K., & C, J. (2018). Extract of Penicillium sclerotiorum an endophytic fungus isolated from Cassia fistula L. induces cell cycle arrest leading to apoptosis through mitochondrial membrane depolarization in human cervical cancer cells. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *105*, 1062–1071.

Lamontagne, R. J., Bagga, S., & Bouchard, M. J. (2016). Hepatitis B virus molecular biology and pathogenesis. *Hepatoma research*, *2*, 163–186.

Li, C., Zu, S., Deng, Y. Q., Li, D., Parvatiyar, K., Quanquin, N., Shang, J., Sun, N., Su, J., Liu, Z., Wang, M., Aliyari, S. R., Li, X. F., Wu, A., Ma, F., Shi, Y., Nielsevn-Saines, K., Jung, J. U., Qin, F. X., Qin, C. F. and Cheng, G. (2019). Azithromycin Protects against Zika virus Infection by Upregulating virus-induced Type I and III Interferon Responses. *Antimicrobial agents and chemotherapy*, *63*(12), e00394-19. Advance online publication.

Linfield, D. T., Raduka, A., Aghapour, M., & Rezaee, F. (2021). Airway tight junctions as targets of viral infections. *Tissue barriers*, *9*(2), 1883965.

Liu, L., Wang, M., Li, X., Yin, S., & Wang, B. (2021). An Overview of Novel Agents for Cervical Cancer Treatment by Inducing Apoptosis: Emerging Drugs Ongoing Clinical Trials and Preclinical Studies. *Frontiers in medicine*, *8*, 682366.

Liu, M., Jiang, L., Cao, W., Wu, J., & Chen, X. (2022). Identification of Inhibitors and Drug Targets for Human Adenovirus Infections. *Viruses*, *14*(5), 959.

Liu, Z., Zhu, W., Kong, X., Chen, X., Sun, X., Zhang, W., & Zhang, R. (2019). Tanshinone IIA inhibits glucose metabolism leading to apoptosis in cervical cancer. *Oncology reports*, *42*(5), 1893–1903.

Lopez, S. M. C., Michaels, M. G., & Green, M. (2018). Adenovirus infection in pediatric transplant recipients: are effective antiviral agents coming our way?. *Current opinion in organ transplantation*, *23*(4), 395–399.

Nestić, D., Božinović, K., Pehar, I., Wallace, R., Parker, A. L., & Majhen, D. (2021). The Revolving Door of Adenovirus Cell Entry: Not All Pathways Are Equal. *Pharmaceutics*, *13*(10), 1585.

Ni, Y., Lempp, F. A., Mehrle, S., Nkongolo, S., Kaufman, C., Fälth, M., Stindt, J., Königer, C., Nassal, M., Kubitz, R. (2014). Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. *Gastroenterology*, *146*, 1070–1083.

Ortiz-Zapater, E., Santis, G., & Parsons, M. (2017). CAR: A key regulator of adhesion and inflammation. *The international journal of biochemistry & cell biology*, *89*, 1–5.

Parhizgar, A. R., & Tahghighi, A. (2017). Introducing New Antimalarial Analogues of Chloroquine and Amodiaquine: A Narrative Review. *Iranian journal of medical sciences*, *42*(2), 115–128.

Pastor, F., Herrscher, C., Patient, R., Eymieux, S., Moreau, A., Burlaud-Gaillard, J., Seigneuret, F., de Rocquigny, H., Roingeard, P., & Hourioux, C. (2019). Direct interaction between the hepatitis B virus core and envelope proteins analyzed in a cellular context. *Scientific reports*, *9*(1), 16178.

Phu, H. T., Thuan, D. T. B., Nguyen, T. H. D., Posadino, A. M., Eid, A. H., & Pintus, G. (2020). Herbal Medicine for Slowing Aging and Aging-associated Conditions: Efficacy, Mechanisms and Safety. *Current vascular pharmacology*, *18*(4), 369–393.

Polonio, C. M., de Freitas, C. L., Zanluqui, N. G., & Peron, J. P. S. (2017). Zika virus congenital syndrome: experimental models and clinical aspects. *The journal of venomous animals and toxins including tropical diseases*, *23*, 41.

Poole R. M. (2014). Pembrolizumab: first global approval. *Drugs*, *74*(16), 1973–1981.

Prochnow, H., Rox, K., Birudukota, N. V. S., Weichert, L., Hotop, S. K., Klahn, P., Mohr, K., Franz, S., Banda, D. H., Blockus, S., Schreiber, J., Haid, S., Oeyen, M., Martinez, J. P., Süssmuth, R. D., Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris, A., Sanseau, P., Cavalla, D., & Pirmohamed, M. (2019). Drug repurposing: progress, challenges and recommendations. *Nature reviews. Drug discovery*, *18*(1), 41–58.

Ramsay, I. D., Attwood, C., Irish, D., Griffiths, P. D., Kyriakou, C., & Lowe, D. M. (2017). Disseminated adenovirus infection after allogeneic stem cell transplant and the potential role of brincidofovir - Case series and 10 year experience of management in an adult transplant cohort. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*, *96*, 73–79.

Retallack, H., Di Lullo, E., Arias, C., Knopp, K. A., Laurie, M. T., Sandoval-Espinosa, C., Mancia Leon, W. R., Krencik, R., Ullian, E. M., Spatazza, J., Pollen, A. A., Mandel-Brehm, C., Nowakowski, T. J., Kriegstein, A. R., &DeRisi, J. L. (2016). Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(50), 14408–14413.

Rumlová, M., & Ruml, T. (2018). In vitro methods for testing antiviral drugs. *Biotechnology advances*, *36*(3), 557–576.

Sargiacomo, C. (2018). *Role of NTCP in HBV infection of mesenchymal stem cells derived hepatocytes and relevance of its ontogenesis for liver diseases* (Doctoral dissertation, UCL-UniversitéCatholique de Louvain)

Scheffer, K. D., Gawlitza, A., Spoden, G. A., Zhang, X. A., Lambert, C., Berditchevski, F., & Florin, L. (2013). Tetraspanin CD151 mediates papillomavirus type 16 endocytosis. *Journal of virology*, *87*(6), 3435–3446.

Schelhaas, M., Shah, B., Holzer, M., Blattmann, P., Kühling, L., Day, P. M., Schiller, J. T., &Helenius, A. (2012). Entry of human papillomavirus type 16 by actin-dependent, clathrin- and lipid raft-independent endocytosis. *PLoS pathogens*, *8*(4), e1002657.

Shao, J., Wang, C., Li, L., Liang, H., Dai, J., Ling, X., & Tang, H. (2018). Luteoloside Inhibits Proliferation and Promotes Intrinsic and Extrinsic Pathway-Mediated Apoptosis Involving MAPK and mTOR Signaling Pathways in Human Cervical Cancer Cells. *International journal of molecular sciences*, *19*(6), 1664.

Shi, R., Hou, L., Wei, L., & Liu, J. (2021). Involvement of adaptor proteins in clathrin-mediated endocytosis of virus entry. *Microbial pathogenesis*, *161*(Pt A), 105278.

Shiryaev, S. A., Mesci, P., Pinto, A., Fernandes, I., Sheets, N., Shresta, S., Farhy, C., Huang, C. T., Strongin, A. Y., Muotri, A. R., &Terskikh, A. V. (2017). Repurposing of the anti-malaria drug chloroquine for Zika Virus treatment and prophylaxis. *Scientific reports*, *7*(1), 15771.

Sochacki, K. A., &Taraska, J. W. (2019). From Flat to Curved Clathrin: Controlling a Plastic Ratchet. *Trends in cell biology*, *29*(3), 241–256.

Stasiak, A. C., & Stehle, T. (2020). Human adenovirus binding to host cell receptors: a structural view. *Medical microbiology and immunology*, *209*(3), 325–333.

Tabata, T., Petitt, M., Puerta-Guardo, H., Michlmayr, D., Wang, C., Fang-Hoover, J., Harris, E., & Pereira, L. (2016). Zika Virus Targets Different Primary Human Placental Cells, Suggesting Two Routes for Vertical Transmission. *Cell host & microbe*, *20*(2), 155–166.

Tan, S., Liu, K., Chai, Y., Zhang, C. W., Gao, S., Gao, G. F., & Qi, J. (2018). Distinct PD-L1 binding characteristics of therapeutic monoclonal antibody durvalumab. *Protein & cell*, *9*(1), 135–139.

Umetsu, T., Inoue, J., Kogure, T., Kakazu, E., Ninomiya, M., Iwata, T., Takai, S., Nakamura, T., Sano, A., &Shimosegawa, T. (2018). Inhibitory effect of silibinin on hepatitis B virus entry. *Biochemistry and biophysics reports*, *14*, 20–25.

Veloso Alves Pereira, I., Buchmann, B., Sandmann, L., Sprinzl, K., Schlaphoff, V., Döhner, K., Vondran, F., Sarrazin, C., Manns, M. P., Pinto Marques Souza de Oliveira, C., Sodeik, B., Ciesek, S., & von Hahn, T. (2015). Primary biliary acids inhibit hepatitis D virus (HDV) entry into human hepatoma cells expressing the sodium-taurocholate cotransporting polypeptide (NTCP). *PloS one*, *10*(2), e0117152. 2

Verrier, E. R., Colpitts, C. C., Bach, C., Heydmann, L., Weiss, A., Renaud, M., Durand, S. C., Habersetzer, F., Durantel, D., Abou-Jaoudé, G., López Ledesma, M. M., Felmlee, D. J., Soumillon, M., Croonenborghs, T., Pochet, N., Nassal, M., Schuster, C., Brino, L., Sureau, C., Zeisel, M. B., Baumert, T. F. (2016). A targeted functional RNA interference screen uncovers glypican 5 as an entry factor for hepatitis B and D viruses. *Hepatology (Baltimore, Md.)*, *63*(1), 35–48.

Wi, J., Jeong, M. S., & Hong, H. J. (2017). Construction and Characterization of an Anti-Hepatitis B Virus preS1 Humanized Antibody that Binds to the Essential Receptor Binding Site. *Journal of microbiology and biotechnology*, *27*(7), 1336–1344.

Wolf, Y. I., Kazlauskas, D., Iranzo, J., Lucía-Sanz, A., Kuhn, J. H., Krupovic, M., Dolja, V. V., & Koonin, E. V. (2018). Origins and Evolution of the Global RNA Virome. *mBio*, *9*(6), e02329-18.

Xia, Y., Cheng, X., Blossey, C. K., Wisskirchen, K., Esser, K., & Protzer, U. (2017). Secreted Interferon-Inducible Factors Restrict Hepatitis B and C Virus Entry In Vitro. *Journal of immunology research*, *2017*, 4828936.

Yuan, S., Chan, J. F., den-Haan, H., Chik, K. K., Zhang, A. J., Chan, C. C., Poon, V. K., Yip, C. C., Mak, W. W., Zhu, Z., Zou, Z., Tee, K. M., Cai, J. P., Chan, K. H., de la Peña, J., Pérez-Sánchez, H., Cerón-Carrasco, J. P., & Yuen, K. Y. (2017). Structure-based discovery of clinically approved drugs as Zika virus NS2B-NS3 protease inhibitors that potently inhibit Zika virus infection in vitro and in vivo. *Antiviral research*, *145*, 33–43.

Zhou, L., Qin, J., Ma, L., Li, H., Li, L., Ning, C., Gao, W., Yu, H., & Han, L. (2017). Rosoloactone: A natural diterpenoid inducing apoptosis in human cervical cancer cells through endoplasmic reticulum stress and mitochondrial damage. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *95*, 355–362.

Zhou, T., Tan, L., Cederquist, G. Y., Fan, Y., Hartley, B. J., Mukherjee, S., Tomishima, M., Brennand, K. J., Zhang, Q., Schwartz, R. E., Evans, T., Studer, L., & Chen, S. (2017). High-Content Screening in hPSC-Neural Progenitors Identifies Drug Candidates that Inhibit Zika Virus Infection in Fetal-like Organoids and Adult Brain. *Cell stem cell*, *21*(2), 274–283.e5.

Zhu, H., Luo, H., Zhang, W., Shen, Z., Hu, X., & Zhu, X. (2016). Molecular mechanisms of cisplatin resistance in cervical cancer. *Drug design, development and therapy*, *10*, 1885–1895.

Zhu, Y., Lin, Y., Liu, X., Hu, W., & Wang, Y. (2017). Identification of AcAP5 as a novel factor Xa inhibitor with both direct and allosteric inhibition. *Biochemical and biophysical research communications*, *483*(1), 495–501.

How to cite this article: Ravdeep Kaur, Joginder Singh Panwar and Kongara Hanumantha Rao (2023). Viral Endocytosis: Mechanistic Insights and Therapeutic Targets. *Biological Forum – An International Journal*, *15*(5a): 681-689.