The antiviral effect of phytochemical compounds of medicinal plants: Applications and drug delivery strategies

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Introduction

Viral infections remain a major worldwide cause of morbidity and mortality. Among the most aggressive viral infections are Ebola, AIDS (acquired immunodeficiency syndrome), influenza, and SARS (severe acute respiratory syndrome). For in stance, influenza is responsible for over 3 million new cases of severe disease, and between 300,000–500,000 deaths yearly. Alarmingly, the number of patients diagnosed with viral infections is increasing every year with more blood transfusions, organ transplantations, and the use of hypodermic syringes. Classic antiviral drugs such as interferon and ribavirin are effective *in vitro* against most viruses, but often are ineffective in patients. Ninety different antiviral agents available today

only treat a selection of viruses; these viruses include HIV (human immunodeficiency virus), herpes viruses, including HSV (herpes simplex virus), hCMV (human cytomegalovirus), VZV (varicella zoster virus), influenza viruses, and the hepatitis viruses. Currently, there is no approved remedy for many types or viruses, and vaccination is limited to hepatitis A virus, mumps, and varicella. In addition, these agents are often costly and ineffective due to viral resistance and cause side effects.

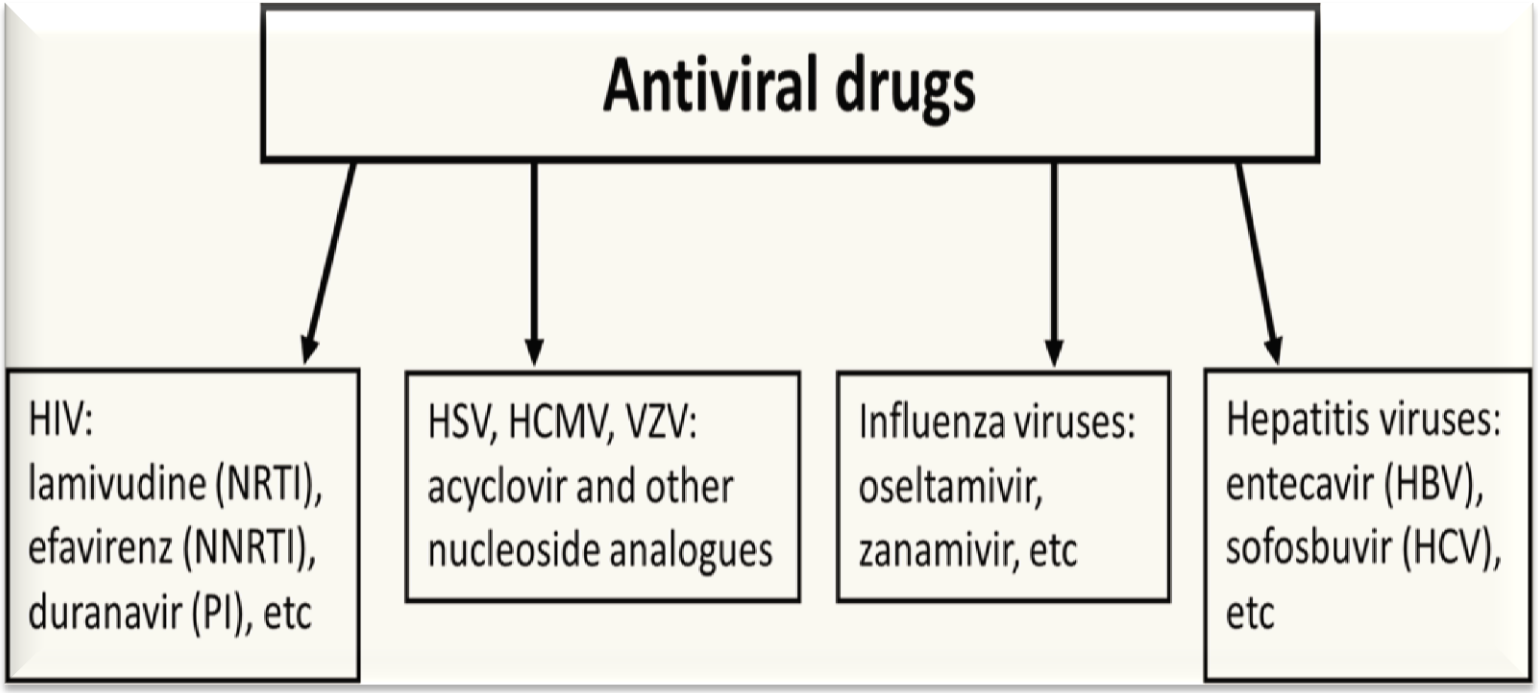

Figure Antiviral drugs. The antiviral drugs are used for HIV (human immunodeficiency virus), herpes viruses, influenza A and B viruses, and the HBV (hepatitis B) and HCV (hepatitis C) viruses. Some of the commonly prescribed antiviral drugs are given. NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Thus, it is necessary to further examine the topic of antiviral phytochemicals, highlighting drug delivery applications in overcoming the multiple biological barriers existing for antiviral agents to successfully reach their intended site(s) of action. The present review focuses on the antiviral properties of herb extracts and bioactive constituent isolates from medicinal plants, and the efforts to obtain their efficient delivery.

Antiviral medicinal plants

Various plants have been used in medicine since ancient times and are known for their strong therapeutic effect. In traditional medicine, diseases of possible viral origin have been treated by many of these plants. The main findings related to antiviral plant extracts are collected in Table 1. Included extracts were tested in cell culture, and some extracts were also studied *in vivo*

Table 1 Antiviral properties of plant extracts

Plant	Kind of extract	Virus	Chemical compounds
Camellia sinensis	Aqueous extract	HBV	Epigallocathechin-3-gallate
Cassine xylocarpa	Aqueous extract	HIV	Pentacyclic lupane-type triterpenoids
Curcuma longa	Aqueous extract	HSV-1	Curcumin
Cyperus rotundus	Hydro-alcoholic extract	, HBV HSV-1	cyperene-3, 8-dione, 14-hydroxy cyperotundone,

Plant	Kind of extract	Virus	Chemical compounds
Daphne gnidium	Hydro-alcoholic extract	HIV	Daphnetoxin, gnidicin
Diospyros kaki	Aqueous extract	Human rotavirus	Licocoumarone, licoflavonol
Ficus benjamina	Ethanol extract	HSV-1, HSV-2	Rutin, kaempferol 3-O-rutinoside
Leucojum vernum	Methanolic extract	HIV-1	Homolycorine and 2-O-acetyllycorine
Panax ginseng	Methanolic extract	Human rotavirus	Epigallocatechin gallate, theaflavin
Phyllanthus acidus	Aqueous extract	HBV	sesquiterpenoids, phyllanthacidoid acid methyl ester

Plant	Kind of extract	Virus	Chemical compounds
Phyllanthus emblica	Aqueous extract	Influenza A virus strain H3N2	Sesquiterpenoids Sesquiterpenoid glycoside dimers
Viola diffusa	Ethanol extract	HBV	2β-hydroxy-3, 4-seco-friedelolactone-27-oic acid,
Vitis labrusca	Methanol extract	(SA-11) and human (HCR3) rotaviruses	Resveratrol, piceatannol
Vitis macrocarpon	Methanolic extract	(SA-11) and human (HCR3) rotaviruses	Abietic acid, all-trans-retinoic acid
Zataria multiflora	Methanolic extract	HSV-1	Rosmarinic acid

Phytochemicals compounds

Various phytochemicals were isolated, purified, and identified from the crude extracts of alkaloids, terpenes, flavonoids, various glycosides, and proteins.

- Quercetin, an aglycone of rutin, is a phytochemical abundant in plants and may diminish the replication of many viruses: highly pathogenic influenza virus, dengue virus type-2, HSV-1, poliovirus , adenovirus, Epstein-Barr virus.

- Baicalin 5 ,6,7- trihydroxyflavone all effectively inhibited reverse transcriptases from Rauscher murine leukemia virus (RLV) and HIV

- Myricetin, is abundant in wild plants, nuts, fruits, berries, and vegetables. were active in cell cultures against different subtypes of influenza viruses

- **Apigenin** (4′,5,7-trihydroxyflavone), an aglycone of the flavone class, is found in many plants and has broad antiviral activities against enterovirus-71, foot and mouth disease virus, HCV, African swine fever virus (ASFV), and influenza A virus . Of note, many flavonoids of plant origin have known antiviral properties.

- **The triterpenoids** oleanolic acid and ursolic acid are abundant in the plant kingdom, may be effective against HCV by reducing HCV NS5B RdRp virulence, and can also inhibit entero- virus 71 replication. Lastly, *Sambucus nigra* L. is an active ingredient in a standardized elderberry extract, effectively used in the treatment of fever, colds, and influenza A and B.

Delivery of herbal extracts

- Introducing pharmaceutical nanotechnology into the field of natural medicine is useful and promising. New strategies for the delivery of poorly soluble phytochemicals and plant extracts allow improved pharmacokinetic and clinical outcomes.
- Commonly used approached such as phytosomes, nano-particles, hydrogels, microspheres, transferosomes and ethosomes, self-microemulsifying drug delivery systems (SMEDDS), and self-nanoemulsifying drug delivery systems (SNEDDS) have been applied for the delivery of antiviral plant agents (Table 2).
- These antiviral technologies may be preferred over older phytochemical drug formulations due to enhanced solubility and oral absorption, systemic bioavailability, safety, delayed metabolism, and better overall antiviral activity.

Table 2 Summary of the different applied delivery systems for antiviral phytochemicals

Phytochemical	Virus	Delivery system/method
Myricetin	HIV, RLV, influenza	SNEDDS.nanogel, mixed micelles, nanosuspension, cocrystal, nanoencapsulation
Apigenin	Enterovirus 71, FMDV, HCV, ASFV, influenza A	W/O/W emulsion, O/W microemulsion, solid dispersion, mixed micelles, phospholipid phytosome, pellets, SMEDDS
Baicalin	Influenza, NDV, enterovirus 71, DENV, RSV, HIV, HBV	Liposome, mixed micelles, polymeric micelles, SNEDDS, nanoemulsion, inclusion complex, solid dispersion, nanoparticles, nanocrystals, SMEDDS

HIV human immunodeficiency virus, *RLV* rhesus lymphocryptovirus, *FMDV* foot and mouth disease virus, *HCV* hepatitis C virus, *ASFV* African swine fever virus, *NDV* Newcastle disease virus, *DENV* dengue virus, *RSV* respiratory syncytial virus, *HBV* hepatitis B virus, *JEV* Japanese encephalitis virus, *EBV* Epstein–Barr virus, *MAYV* Mayaro virus, *RV* rhinovirus, *CHIKV* Chikungunya virus, *HPV* human papilloma virus, *HSV* herpes simplex virus, *ZIKV* Zika virus, *CMV* cytomegalovirus, *EV*enterovirus, *SNEDDS* self-nanoemulsifying drug delivery system, *W/O/W* water-in-oil-in-water, *O/W* oil-in-water, *SMEDDS* self-microemulsifying drug delivery system

Phytochemical	Virus	Delivery system/method
Quercetin	JEV, influenza A, EBV, MAYV, RV, HCV	Nanocrystal , nanoparticles, phytosome, nanoliposome, mixed micelles, SNEDDS, nanocarrier , nanoemulsion, nanosuspension
Fructus Forsythiae extracts	Influenza, RSV	chito-oligosaccharide
Flos Lonicerae extracts	Influenza, RSV, HIV, NDV	chito-oligosaccharide

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Phytochemical	Virus	Delivery system/method
Andrographolide	DENV, CHIKV, HPV16 pseudovirus, influenza, HBV, HCV, HSV1, EBV, HIV	SMEDDS, microspheres, nanosuspension, self-nanodispersion, nanoparticles, inclusion complex
Curcumin	Influenza, RSV, HBV, HCV, ZIKV, CHIKV, norovirus, HIV, HPV, CMV, EV71, DENV type-2	Mixed micelles, nanoparticles, solid dispersion , SNEDDS , SMEDDS, lipid carrier, copolymeric micelles, exosomes

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Phytochemical	Virus	Delivery system/method
Naringenin	DENV, HCV	SNEDDS, solid dispersion, nanoparticles, liposome, nanosuspension , cyclodextrin complex
Honokiol	DENV, HCV	Inclusion complex, conjugate micelles, nanoparticles
Oleanolic acid	Acute and chronic hepatitis	SMEDDS, nanoparticles, nanosuspensions , SNEDDS

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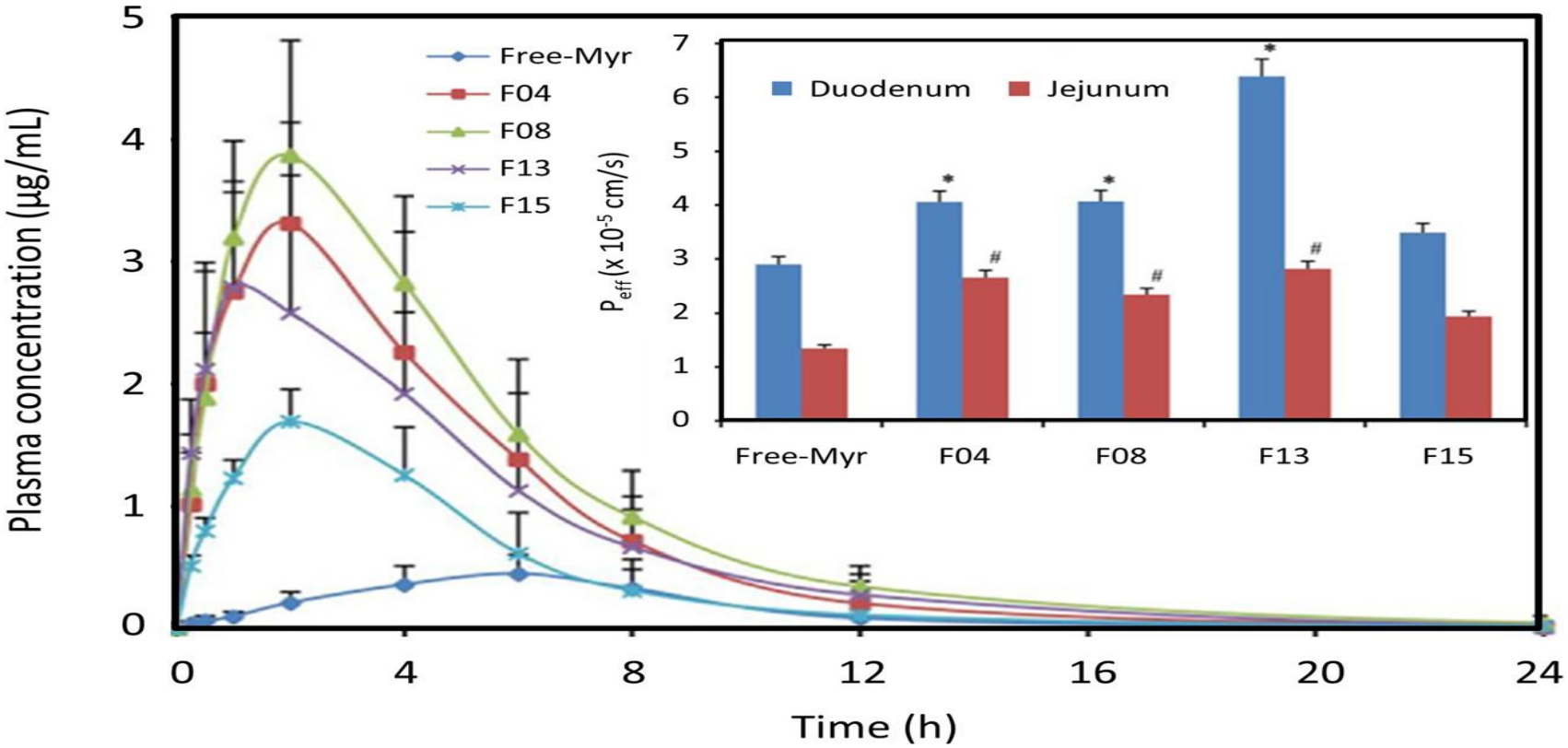

Figure Myricetin blood levels in rats after oral administration of 20 mg/kg free myricetin or any of four different SNEDDS formulations (n = 6); upper right: permeability coefficient (P_{eff}) of myricetin in single-pass intestinal perfusion model (n = 3); F04, Capryol 90/Cremophor RH 40/ PEG 400 4:3:3; F08, Capryol 90/ Cremophor RH 40/1,2- propanediol 4:3:3; F13, Capryol 90/Cremophor EL/Transcutol HP 4:3:3 and F15, Capryol 90/ Cremophor RH 40/Transcutol HP 2:7:1. Reproduced from [79] with permission

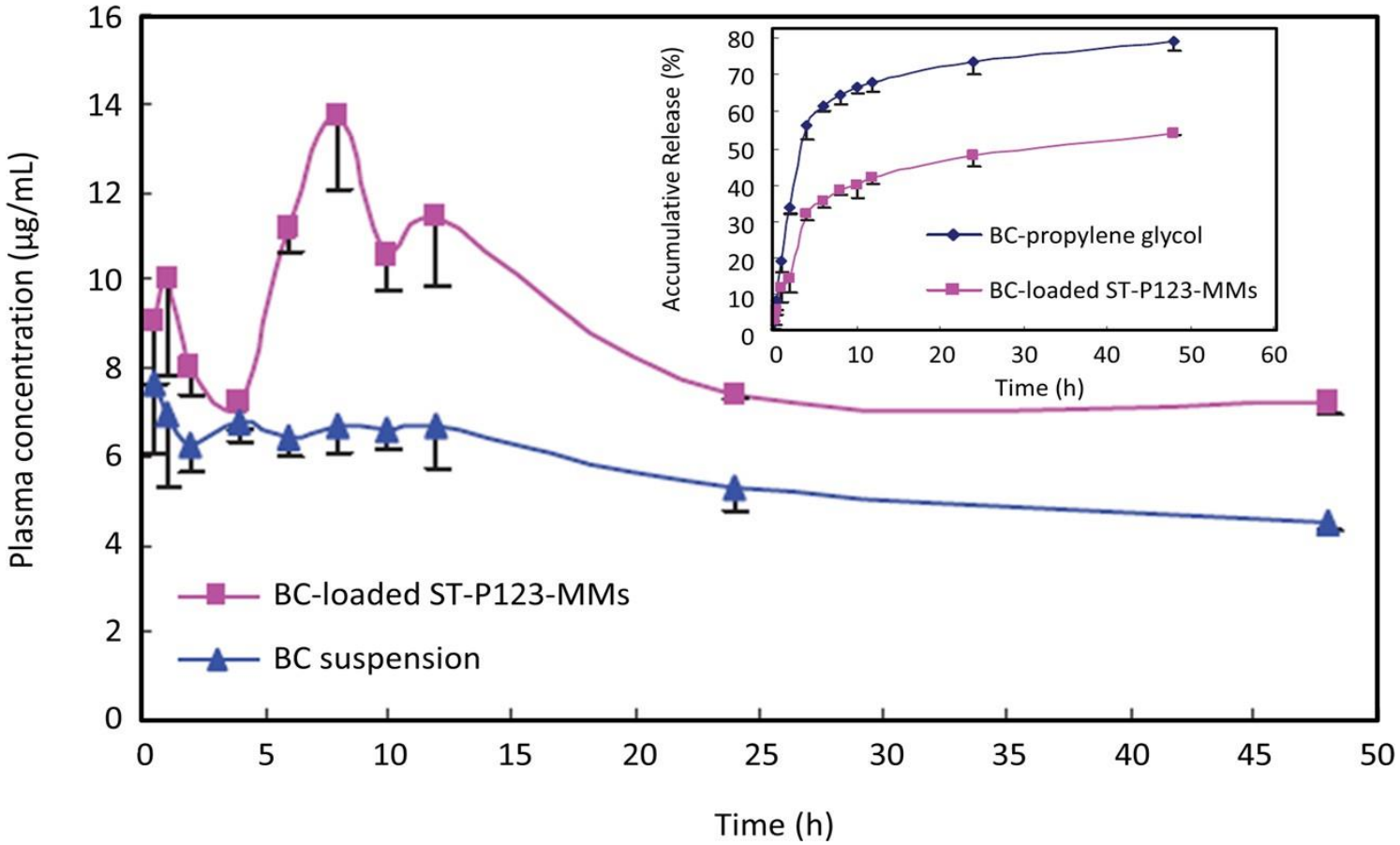

Fig. 3 Baicalin blood levels after oral administration of baicalin (BC) and BC-loaded ST-P123- MMs (P123, an amphipathic polymer and sodium taurocholate as a carrier); upper right: drug release of baicalin. Reproduced from with permission

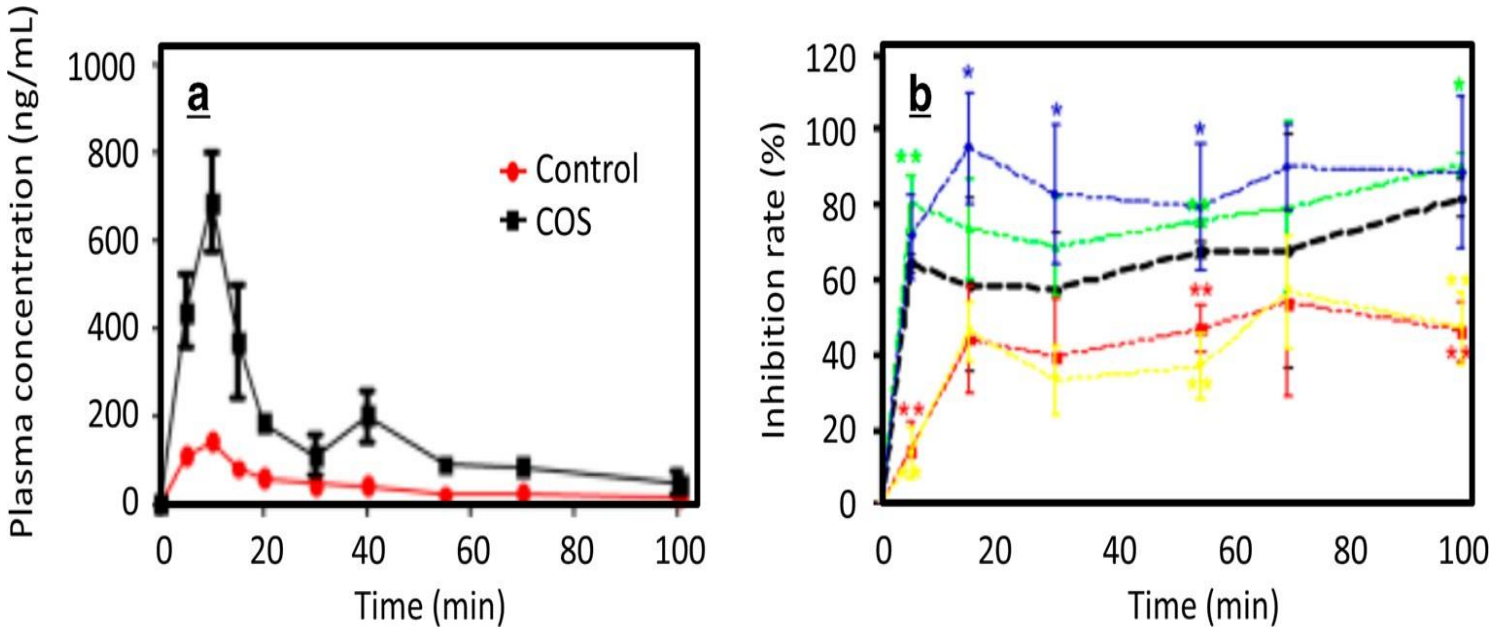

Figure Effect of COS (chito-oligosaccharide) on the pharmacokinetic (panel a) and pharmacodynamics (inhibition of influenza virus; panel b) of caffeic acid derivative after oral administration of preparation containing *Flos Lonicerae Japonicae* and Fructus, forsythia extracts. Black, 1:1:2-fold of *Flos Lonicerae Japonicae*, Fructus Forsythiae Radix Scutellariae, respectively; red, only Radix Scutellariae; green,

2:2:2-fold of *Flos Lonicerae Japonicae*, Fructus Forsythiae, and Radix Scutellariae, respectively; yellow, COS with added Radix Scutellariae only; blue, COS with added 1:1:2-fold of *Flos Lonicerae Japonicae*, Fructus Forsythiae, and Radix Scutellariae, respectively ($n = 6$). Reproduced from [122] with permission

Conclusions

- Medicinal plants have promising therapeutic potential, especially in the case of herb products against viral infections. Further research on the mechanisms by which phytochemicals exhibit their antiviral effect will allow the developing of successful target-specific drug delivery systems.

- Pharmaceutical nanotechnologies and targeting strategies that can avoid cellular defenses, transport drugs to targeted intracellular sites, and release the drugs in response to specific molecular signals.

- Literature also lacks randomized clinical trials to discern the strength of new herbal antiviral drug delivery systems. It is our hope that in the future more high quality clinically relevant studies

Thank you