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REVIEW ARTICLE

Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies

Shimon Ben-Shabat[1] · Ludmila Yarmolinsky[2] · Daniel Porat[1] · Arik Dahan[1]

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Abstract

Viral infections affect three to five million patients annually. While commonly used antivirals often show limited efficacy and serious adverse effects, herbal extracts have been in use for medicinal purposes since ancient times and are known for their antiviral properties and more tolerable side effects. Thus, naturally based pharmacotherapy may be a proper alternative for treating viral diseases. With that in mind, various pharmaceutical formulations and delivery systems including micelles, nanoparticles, nanosuspensions, solid dispersions, microspheres and crystals, self-nanoemulsifying and self-microemulsifying drug delivery systems (SNEDDS and SMEDDS) have been developed and used for antiviral delivery of natural products. These diverse technologies offer effective and reliable delivery of medicinal phytochemicals. Given the challenges and possibilities of antiviral treatment, this review provides the verified data on the medicinal plants and related herbal substances with antiviral activity, as well as applied strategies for the delivery of these plant extracts and biologically active phytochemicals.

Keywords Antiviral · Phytomedicine · Herbal extracts · Flavonoid · Solubility · Oral drug delivery

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 instance, influenza is responsible for over 3 million new cases of severe disease, and between 300,000–500,000 deaths yearly [1, 2]. 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 [3, 4] 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 (Fig. 1). Currently, there is no approved remedy for many types or viruses, and vaccination is limited to hepatitis A virus, mumps, and varicella [2]. In addition, these agents are often costly and ineffective due to viral resistance and cause side effects. With that in mind, naturally based pharmacotherapy may be a proper alternative for treating viral diseases. 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.

✉ Shimon Ben-Shabat
sbs@bgu.ac.il

✉ Arik Dahan
arikd@bgu.ac.il

[1] Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, 8410501 Beer-Sheva, Israel

[2] Eastern R&D Center, Kiryat Arba, Israel

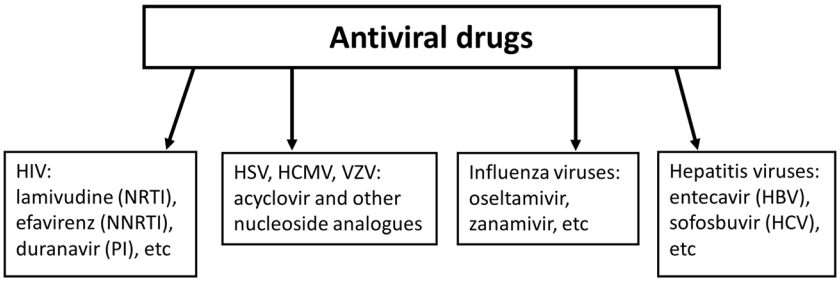

Fig. 1 Antiviral drugs. The antiviral drugs are used for HIV (human immunodeficiency virus), herpes viruses, influenza A and B viruses, and the HBV (hepatitis B) and HCV (hepatitis C) viruses. Some of the commonly prescribed antiviral drugs are given. NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Antiviral medicinal plants and phytochemicals

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* [11, 23, 31, 39].

Various phytochemicals were isolated, purified, and identified from the crude extracts of alkaloids, terpenes, flavonoids, various glycosides, and proteins (Table 1). Compounds with antiviral activity are present in many plants, e.g., rutin, a flavonoid glycoside common in different plants, is effective against avian influenza virus [48], HSV-1, HSV-2 [18], and parainfluenza-3 virus [49].

Quercetin, an aglycone of rutin, is a phytochemical abundant in plants and may diminish the replication of many viruses: highly pathogenic influenza virus [50], rhinovirus [51], dengue virus type-2 [52], HSV-1 [53], poliovirus [54], adenovirus [53], Epstein-Barr virus [55], Mayaro virus [56], Japanese encephalitis virus [57], respiratory syncytial virus [58], and HCV [59, 60]. Its antiviral activity mode was studies in a few cases. Its ability to inhibit HCV by limiting the activity of some heat shock proteins (HSPs) produced by cells in response to exposure to stress which were involved in NS5A (nonstructural protein 5A)-mediated viral IRES (internal ribosome entry site) translation [60] is one well-known mechanism. Another mechanism involved the inhibition of HCV NS3 protease and HCV replication in a subgenomic HCV RNA replicon cell system [59]. Quercetin also inhibits various steps of the rhinoviruses pathogenesis, i.e., endocytosis, viral genome transcription, and protein synthesis [51]. In another case, quercetin was shown to have a more specific mode of action, reducing the replication of dengue virus type-2, but not the processes of viral attachment and entry [52].

In addition, quercetin and three other flavonoids: 3,3′,4′,5,5′,7-hexahydroxyflavone (myricetin), 3,3′,4′,5,6,7-hexahydroxyflavone (quercetagetin), and 5,6,7-trihydroxyflavone (baicalein), all effectively inhibited reverse transcriptases from Rauscher murine leukemia virus (RLV) and HIV; quercetin, myricetin, and quercetagetin were also shown to inhibit different DNA polymerase enzymes [61]. The abovementioned flavonoid, myricetin, is abundant in wild plants, nuts, fruits, berries, and vegetables. Ellagic acid and myricetin (from the aronia fruit) were active in cell cultures against different subtypes of influenza viruses including an oseltamivir-resistant strain, and also effective *in vivo* [62].

Apigenin (4′,5,7-trihydroxyflavone), an aglycone of the flavone class, is found in many plants and has broad antiviral activities against enterovirus-71 [63], foot and mouth disease virus [64], HCV [65], African swine fever virus (ASFV) [66], and influenza A virus [67]. Of note, many flavonoids of plant origin have known antiviral properties. For example, out of 22 different flavonoids, six phytochemicals (apigenin, baicalein, biochanin A, kaempferol, luteolin, naringenin) were active against the avian influenza H5N1 virus in human lung epithelial (A549) cells through inhibiting nucleoprotein production [67]. Baicalin (the glucuronide of baicalein) was also active against a wide range of viruses, including enterovirus [68], dengue virus [69], respiratory syncytial virus [70], Newcastle disease virus [71], human immunodeficiency virus [72], and hepatitis B virus [73], and different mechanisms were suggested for its antiviral actions. For example, baicalin inhibits the production of HBV, the templates for viral proteins and HBV-DNA synthesis [73], and decreases IL-6 and IL-8 production without affecting IP-10 levels, as shown in a study on avian influenza H5N1 virus [67].

The triterpenoids oleanolic acid and ursolic acid are abundant in the plant kingdom, may be effective against HCV by reducing HCV NS5B RdRp virulence [74], and can also inhibit enterovirus 71 replication [75]. 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 [76–78].

Delivery of herbal extracts and phytochemicals

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.

Table 1 Antiviral properties of plant extracts

Plant	Kind of extract	Virus	Phytochemicals	References
Achillea fragrantissima	Hydro-alcoholic extract	Poliomyelitis-1 virus (POLIO)	Unknown	[3]
Aegle marmelos	Aqueous extract	Human coxsackieviruses B1-B6	Unknown	[4]
Aloe vera	Glycerine extract	HSV-2	Unknown	[5]
Artocarpus integrifolia	Aqueous extract	(SA-11) and human (HCR3) rotaviruses	Unknown	[6]
Balanites aegyptiaca	n-Hexane extract	VSV T2	Unknown	[7]
Camellia sinensis	Aqueous extracts	HBV	Epigallocathechin-3-gallate	[8]
Capparis spinosa	Methanolic extract	HSV-2 HIV-1	Unknown Protein	[9]
Cassine xylocarpa	Aqueous extract	HIV	Pentacyclic lupane-type triterpenoids	[10]
Cistus incanus	Polyphenol-rich extract (CYSTUS052)	Avian and human influenza strains of different subtypes HIV-1 and HIV-2	Unknown Unknown	[11, 12] [13]
Curcuma longa	Aqueous extract	HSV-1	Curcumin	[5]
Cyperus rotundus	Hydro-alcoholic extract	HSV-1 HBV	Unknown cyperene-3, 8-dione, 14-hydroxy cyperotundone, 14-acetoxy cyperotundone, 3β-hydroxycyperenoic acid and sugetriol-3, 9-diacetate	[3, 14]
Daphne gnidium	Hydro-alcoholic extract	HIV	Daphnetoxin, gnidicin, gniditrin and excoecariatoxin	[15]
Diospyros kaki	Aqueous extract	Human rotavirus	Licocoumarone, licoflavonol, glyasperin D, 18 β-glycyrrhetinic acid, luteolin, vitexin, apigenin-7-O-glucoside	[6]
Dittrichia viscosa	Aqueous extract	VSV, HSV-1, poliovirus type 1	Unknown	[16]
Euphorbia hirta	Aqueous extracts, methanol extracts	HIV-1, HIV-2, SIV mac 251	Unknown	[17]
Euphorbia spinidens	Methanol extract	HSV-1	Unknown	[5]
Ficus benjamina	Ethanol extract	HSV-1, HSV-2	Rutin, kaempferol 3-O-rutinoside and kaempferol 3-O-robinobioside	[18]
Ficus carica	Aqueous extract The hexanic and hexane-ethyl acetate from latex of fig fruit Hexanic extract	HSV-1 HSV-1, ECV-11 and ADV influenza virus	Unknown	[19] [20] [21]
Globularia arabica	Hydro-alcoholic extract	Poliomyelitis-1 virus (POLIO)	Unknown	[3]
Glycyrrhiza glabra	Methanolic extract	NDV	Unknown	[22]
Glycyrrhiza uralensis	Metabolic extract	Rotavirus diarrhea	Unknown	[23]
Hyssopus officinalis	Methanolic extract	HSV-1	Unknown	[5]
Leucojum vernum	Methanolic extract	HIV-1	Homolycorine and 2-O-acetyllycorine	[24]
Lilium candidum	Ethanol extract	HSV-1, HSV-2	Kaempferol	[25]
Magnolia officinalis	Methanol extract	Dengue virus Type 2	Honokiol	[26]
Maytenus cuzcoina	Aqueous extract	HIV	Pentacyclic lupane-type triterpenoids	[10]
Melissa officinalis	Aqueous extract	HSV-1 HSV-1, HSV-2 HIV	Unknown	[27] [28] [29]
Mentha pulegium	Methanolic extract	HSV-1	Unknown	[30]
Moringa peregrina	Hydro-alcoholic extract	HSV-1	Unknown	[3]
Myristica fragrans	Aqueous extract	Human rotavirus	Unknown	[6]
Olea europaea	Hexanic extract	Influenza virus subtype H9N2	Unknown	[21]
Panax ginseng	Methanolic extract	Human rotavirus	Epigallocatechin gallate, theaflavin digallate, genistein, hesperidin, neohesperidin, diosmin, pectic polysaccharides	[6]

Table 1 (continued)

Plant	Kind of extract	Virus	Phytochemicals	References
Panax notoginseng	Aqueous extract	Influenza A virus	Unknown	[31]
Phyllanthus acidus	Aqueous extract	HBV	Highly oxygenated norbisabolane sesquiterpenoids, phyllanthacidoid acid methyl ester	[32]
Phyllanthus emblica	Aqueous extract	Influenza A virus strain H3N2	Highly oxygenated norbisabolane sesquiterpenoids	[33]
	Aqueous extract	HBV	Sesquiterpenoid glycoside dimers	[34]
Prunella vulgaris	Aqueous extract	HIV-1	Unknown	[35]
		Ebola virus		[36]
Quercus brantii L Acorn.	Ethanol extract	HSV-1	Unknown	[37]
Quercus persica	Hydroalchoholic extract	HSV-1	Unknown	[38]
Salacia reticulata	Aqueous extract	H1N1 influenza	Unknown	[39]
Sanguisorba minor	Aqueous extract	VSV, HSV-1		[16]
		HIV		[40]
Securigera securidaca	Methanol extract	HSV-1, HSV-2	Unknown	[5]
Solanum nigrum	Methanol and chloroform extracts of seeds	HCV	Unknown	[41]
Spondias lutea	Aqueous extract	Human rotavirus	Unknown	[6]
Tamarix nilotica	Hydro-alcoholic extract	HSV-1	Unknown	[3]
Taraxacum officinale	Methanol extract	HCV	Unknown	[42]
	Aqueous extract	Influenza virus type A, H1N1.		[43]
Thymus carmanicus	Methanol extract	HIV-1	Unknown	[44]
Thymus daenensis	Methanol extract	HIV-1	Unknown	[44]
Thymus kotschyanus	Methanol extract	HIV-1	Unknown	[44]
Thymus vulgaris	Methanol extract	HIV-1	Unknown	[44]
Tuberaria lignosa	An aqueous extract	HIV	Ellagic acid derivative	[45]
Viola diffusa	Ethanol extract	HBV	2β-hydroxy-3, 4-seco-friedelolactone-27-oic acid, 2β, 28β-dihydroxy-3,4-seco-friedelolactone-27-oic acid, 2β, 30β-dihydroxy-3,4-seco-friedelolactone-27-lactone and stigmastane, stigmast-25-ene-3β, 5α,6β-triol	[46]
Vitis labrusca	Methanol extract	(SA-11) and human (HCR3) rotaviruses	Resveratrol, piceatannol, trans-arachidin-1 and trans-arachidin-3	[6]
Vitis macrocarpon	Methanol extract	(SA-11) and human (HCR3) rotaviruses	Abietic acid, all-trans-retinoic acid, mangostin, α-glucosyl hesperidin, proanthocyanidins	[6]
Zataria multiflora	Methanolic extract	HSV-1	Rosmarinic acid	[47]

HSV herpes simplex virus, *VSV* vesicular stomatitis virus, *HBV* hepatitis B virus, *HIV* human immunodeficiency virus, *SIV* simian immunodeficiency virus, *ECV* echovirus, *ADV* adenovirus, *NDV* Newcastle disease virus, *HCV* hepatitis C virus

Commonly used approached such as phytosomes, nanoparticles, 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. Yet, very few papers have been published on the topic of antiviral herbal drug delivery, so we wish to display several successful attempts of improving the delivery of phytodrugs with known antiviral activity. Qian et al. [79] attempted to design a self-nanoemulsifying drug delivery system (SNEDDS) to allow greater apparent solubility and oral bioavailability (< 10%) of myricetin. Overall, four formulations were prepared, F04 (Capryol 90/Cremophor RH 40/PEG 400 in a 4:3:3 ratio), 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), and the solubility of myricetin in different excipients was

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

Phytochemical	Viruses	Delivery system/method
Myricetin	HIV, RLV, influenza	SNEDDS [79], nanogel [80], mixed micelles [81], nanosuspension [82], cocrystal [83], nanoencapsulation [84]
Apigenin	Enterovirus 71, FMDV, HCV, ASFV, influenza A	W/O/W emulsion [85], O/W microemulsion [86], solid dispersion [87, 88], mixed micelles [89], phospholipid phytosome [90], pellets [91], SMEDDS [92]
Baicalin	Influenza, NDV, enterovirus 71, DENV, RSV, HIV, HBV	Liposome [93], mixed micelles [94, 95], polymeric micelles [96], SNEDDS [97], nanoemulsion [98], inclusion complex [99], solid dispersion [100], nanoparticles [101], nanocrystals [102, 103], SMEDDS [104]
Quercetin	JEV, influenza A, EBV, MAYV, RV, HCV	Nanocrystal [105], nanoparticles [106–110], phytosome [111], nanoliposome [112], mixed micelles [113, 114], SNEDDS [115, 116], nanocarrier [117, 118], nanoemulsion [119], nanosuspension [120]
Fructus Forsythiae extracts	Influenza, RSV	chito-oligosaccharide [121, 122]
Flos Lonicerae extracts	Influenza, RSV, HIV, NDV	chito-oligosaccharide [122]
Andrographolide	DENV, CHIKV, HPV16 pseudovirus, influenza, HBV, HCV, HSV1, EBV, HIV	SMEDDS [123], microspheres [124], nanosuspension [125], self-nanodispersion [126], nanoparticles [127], inclusion complex [128]
Curcumin	Influenza, RSV, HBV, HCV, ZIKV, CHIKV, norovirus, HIV, HPV, CMV, EV71, DENV type-2	Mixed micelles [129, 130], nanoparticles [131, 132], solid dispersion [133, 134] , SNEDDS [135] , SMEDDS [136], lipid carrier [137], copolymeric micelles [138], exosomes [139]
Naringenin	DENV, HCV	SNEDDS [140], solid dispersion [141], nanoparticles [142, 143] , liposome [144], nanosuspension [145, 146] , cyclodextrin complex [147]
Honokiol	DENV, HCV	Inclusion complex [148], conjugate micelles [149], nanoparticles [150]
Oleanolic acid	Acute and chronic hepatitis	SMEDDS [151], nanoparticles [152], nanosuspensions [153, 154] , SNEDDS [155]

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

studied. The optimized formulations underwent evaluation of release (dissolution), Caco-2 cell cytotoxicity and intestinal permeability studies *in vitro*, following by *in vivo* pharmacokinetics of myricetin-SNEDDS. Three of the four chosen formulations exhibited acceptable cell viability (> 90%), while the fourth formulation was slightly cell-toxic, probably because of high nonionic surfactant content (70%). *In vitro* drug release testing demonstrated that myricetin alone had limited dissolution of 51% after an hour, whereas drug release for all SNEDDS formulations was over 90% after 1 min. Single-pass intestinal perfusion (SPIP) method in rats showed that in the duodenum, the primary absorption site of myricetin, the effective permeability coefficient was significantly higher (1.2–2.2-fold, $p < 0.05$) in all SNEDDS formulations relative to free myricetin, via inhibition of myricetin efflux by nonionic surfactants in SNEDDS (Fig. 2). In animal models, the myricetin-loaded SNEDDS formulations exhibited higher plasma myricetin concentrations in all time points compared to the free myricetin. Formulation No. 13 in Fig. 2 had higher intestinal permeability, but showed lower bioavailability attributed to poor lymphatic transport—a main absorption mechanism of myricetin. Formulation No. 4 and 8, on the other hand, achieved small particle size, required for lymphatic transport (Fig. 2).

Kim et al. [85] tried to increase the oral bioavailability of the low solubility flavonoid apigenin. Different water-in-oil-in-water emulsions of apigenin were studied for their physical characteristics, as well as digestibility using *in vitro* digestion model and *in vivo* pharmacokinetics in rats. An emulsion of soybean oil-Tween 80 was chosen for pharmacokinetic tests in animal model after proving better stability in terms of particle size and zeta potential. Plasma concentrations of apigenin in the water-in-oil emulsion were markedly higher at different time points and maximal concentration was 9-fold higher compared to apigenin suspension [85].

Zhang et al. [94] aimed to improve the oral absorption of baicalin, which has low solubility and poor permeability, by using a micellar formulation comprised of the carriers Pluronic P123 copolymer and sodium taurocholate. Sustained release profile of baicalin-loaded mixed micelles, in *in vitro* drug release experiment, held in several pH conditions, showed 14% drug released after 2 h in gastric conditions and 54% release within 48 h in intestinal conditions, compared to 34% and 79% release

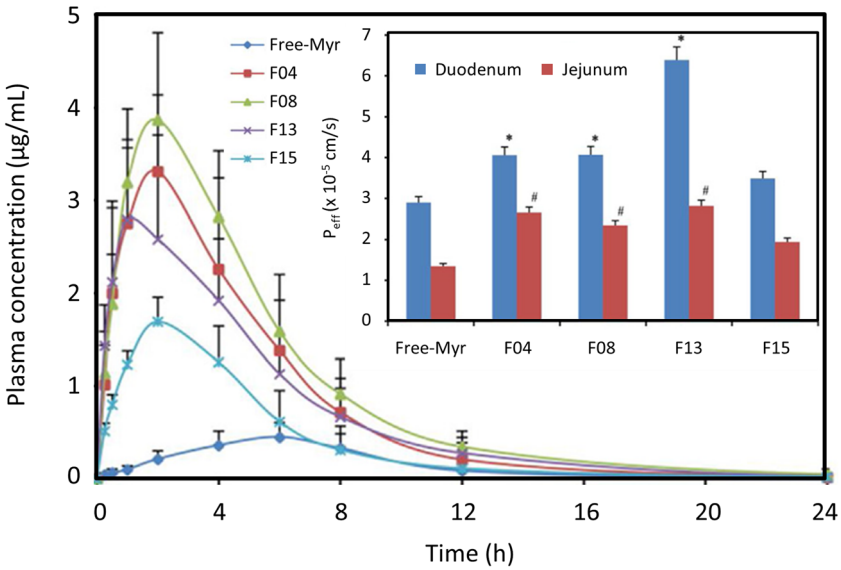

Fig. 2 Myricetin blood levels in rats after oral administration of 20 mg/kg free myricetin or any of four different SNEDDS formulations ($n = 6$); upper right: permeability coefficient (P_{eff}) of myricetin in single-pass intestinal perfusion model ($n = 3$); F04, Capryol 90/Cremophor RH 40/PEG 400 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

from a baicalin suspension, respectively. This observation suggests improved stability afforded by the designed formulation. *In vitro* uptake studies, carried out with a caco-2 cell line, determined the absorption of baicalin within the mixed micelles and verified their internalization ability. Baicalin-loaded ST-P123-MMs formulation achieved high oral bioavailability (Fig. 3). These results are believed to derive from the micellar small size and to Pluronic component, which is a P-glycoprotein inhibitor. In addition, the mixed micelle formulation showed a bimodal presentation, presumably attributed to enterohepatic recirculation, further enhancing the drug's oral bioavailability [94].

Oleanolic acid has low aqueous solubility and systemic bioavailability (0.7% in rats). SMEDDS was developed in an attempt to overcome these limitations. This delivery system consisted of 50% ethyl oleate (oil), 35% Cremophor EL (surfactant), and 15% alcohol (co-surfactant), allowing a great increase in oleanolic acid solubility [151]. *In vitro* studies showed a sustained release behavior from SMEDDS. Systemic rat bioavailability was significantly higher in SMEDDS than in the marketed tablets of oleanolic acid (Fig. 4). The improved drug's oral bioavailability was explained by enhanced solubility and permeability through emulsification and small particle sizes, respectively.

Flos Lonicerae Japonicae and *Fructus forsythia* are used together in Chinese herbal remedies, and both have antiviral, antibacterial, and antiinflammatory properties. An attempt was made to enhance the bioavailability and antiinfluenza properties of the herb combination by chito-oligosaccharide, a chitosan derivative [122]. In a cell culture antiinfluenza assay, chito-oligosaccharide improved the activity of extracts containing *Flos Lonicerae Japonicae* and *Fructus forsythia*, compared to extracts that do not contain the chito-oligosaccharide. The absorption was studied *in vitro* using Caco-2 model, and higher experimentally derived apparent permeability values were obtained with increasing concentrations

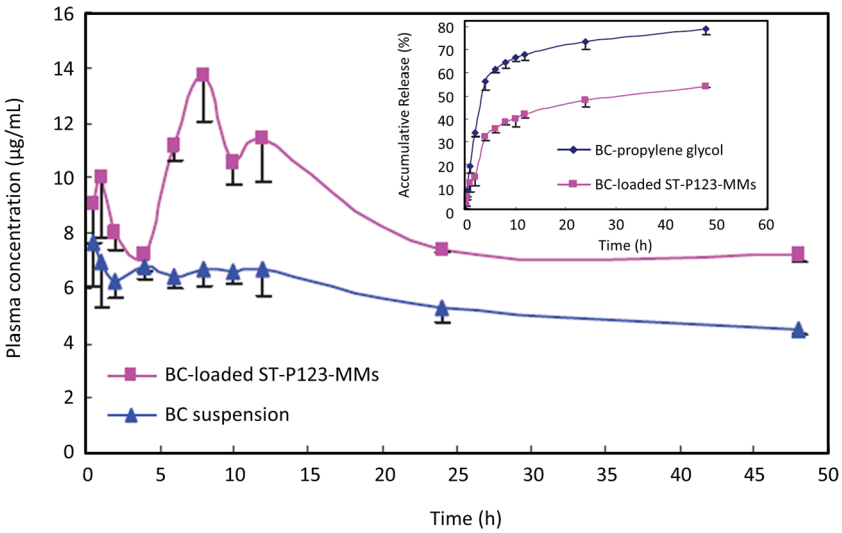

Fig. 3 Baicalin blood levels after oral administration of baicalin (BC) and BC-loaded ST-P123-MMs (P123, an amphipathic polymer and sodium taurocholate as a carrier); upper right: drug release of baicalin. Reproduced from [94] with permission

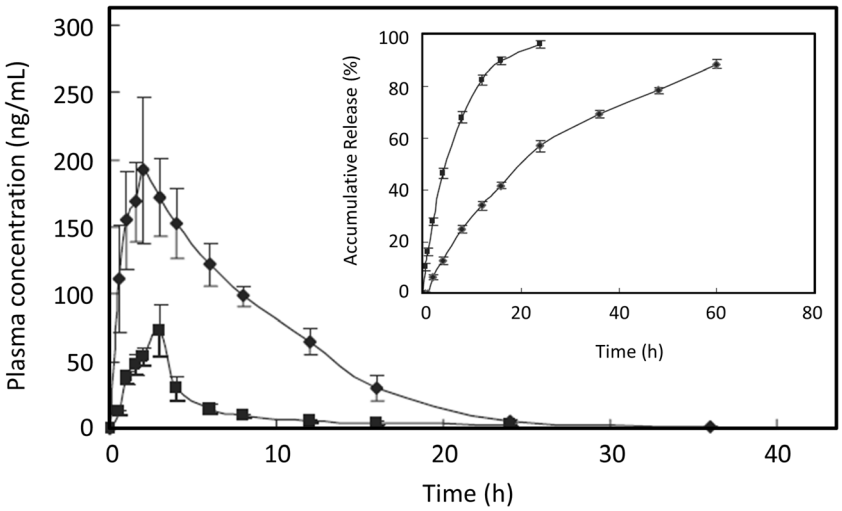

Fig. 4 Oleanolic acid rat blood levels after oral administration of oleanolic acid-loaded SMEDDS (filled diamonds) and marketed drug product (tablet) (filled squares); upper right: accumulative release of oleanolic acid. Reproduced from [151] with permission

of chito-oligosaccharide. *In vivo* pharmacokinetics showed a significant increase in *Flos Lonicerae Japonicae* and *Fructus forsythia* concentrations when co-delivered with chito-oligosaccharide, relative to herb administration alone (Fig. 5a). In addition, enhanced antiviral effect was achieved in four preparations containing chito-oligosaccharide, which was explained by the higher absorption of caffeic acid derivatives (Fig. 5b). This work was unique because it studied the effects of the delivery system on both the pharmacokinetic properties and the antiviral activity of the herbal drug, directly.

An inclusion complex of honokiol and sulfobutyl ether-β-cyclodextrin was made to enhance the solubility and bioavailability of the herbal drug [148]. In a phase solubility experiment, honokiol solubility linearly increased with growing levels of the cyclodextrin. The *in vitro* release study showed that the honokiol/cyclodextrin complex allowed enhanced release rate than either honokiol/cyclodextrin physical mixture or honokiol alone. In rat oral pharmacokinetics, AUC and C_{max} values of the inclusion complex were 1.58 and 1.23 times higher relative to honokiol suspension, respectively. Also, honokiol in suspension had 3 times higher body clearance than complexed honokiol.

Andrographolide is sparingly soluble in water, unstable in very acidic and basic conditions, poorly absorbed, and has low oral bioavailability. PLGA (poly(lactic-co-glycolic acid)) was used to form andrographolide loaded microspheres to overcome these limitations [124]. *In vitro* andrographolide-microsphere formulation exhibited sustained release profile over 9 days, with just 14% andrographolide release over the first 8 h, because of low drug density at the surface of the delivery system, which also allowed a relatively high oral bioavailability of 67.5%. Lastly, fine correlation was obtained between *in vitro* drug release and *in vivo* absorption, indicating that the *in vitro* assay may be a good predictor of drug absorption *in vivo*.

Curcumin, a polyphenolic compound with various medical applications including known antivirus activity, is poorly water-soluble and has low oral bioavailability. With N-acetyl L-cysteine and different levels (20, 50, and 100 mg) of polyethylene glycol (PEG), nanostructured solid lipid carriers were synthesized to obtain curcumin mucoadhesion and mucus penetration

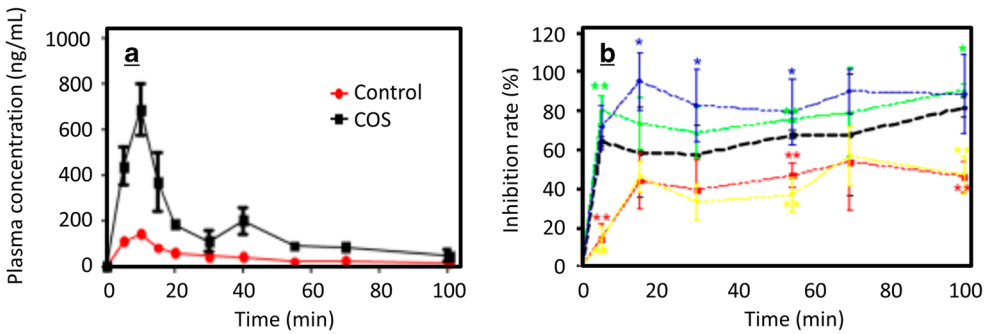

Fig. 5 Effect of COS (chito-oligosaccharide) on the pharmacokinetic (panel **a**) and pharmacodynamics (inhibition of influenza virus; panel **b**) of caffeic acid derivative after oral administration of preparation containing *Flos Lonicerae Japonicae* and Fructus, forsythia extracts. Black, 1:1:2-fold of *Flos Lonicerae Japonicae*, Fructus Forsythiae, and 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

[156]. Drug release was characterized *in vitro* for curcumin solution, curcumin-loaded nanolipid carrier, and curcumin-loaded nanolipid carrier with N-acetyl L-cysteine PEG. From the curcumin solution, 80% of drug was released after 4 h, whereas all the nanolipid formulations allowed sustained curcumin release; the sustained release effect from the modified nanolipid carriers was more pronounced than that of unmodified nanolipids. An SPIP study in rats was then conducted, and results were similar for all three parts of the small intestine: nanolipids allowed enhanced curcumin permeation relative to solution, and so did higher N-acetyl L-cysteine content. Pharmacokinetic study of curcumin solutions (P.O and I.V) and curcumin nanolipid carriers (with N-acetyl L-cysteine PEG content of 0, 20, 50, and 100 mg) was conducted. Similar to the results of the permeability experiment, plasma curcumin concentrations were higher with nanolipid carriers relative to solution (either P.O or I.V) and increased further with higher N-acetyl L-cysteine PEG levels. The area under the curve was substantially larger with the modified nanolipid carriers compared to either curcumin solution or to the unmodified delivery system.

Indeed, modern drug delivery technologies are numerous, and tailoring the most appropriate formulation to the medicinal phytochemical in question is not just a matter of trial and error; rather, the physicochemical properties of the specific natural drug substance determine the delivery issues that the formulator may face, and the excipients that can be used to overcome these challenges [157, 158]. Among the physicochemical properties of importance are log P (a measure of the drug's lipophilicity) and melting point. These parameters will determine the likelihood of the active substance to precipitate in the gastrointestinal lumen, in which case the use of amorphous formulations may be preferred over other oral carriers. Additional important physicochemical properties include the drug's chemical structure and molecular weight; using previously successful formulations to deliver drugs with similar chemical structure may be a wise approach. Also, generally speaking, higher molecular weight substances may be better incorporated into lipid-based drug delivery systems [159–161]. It should be noted that some solubility-enabling formulations may simultaneously decrease the drug's permeability, and overall absorption may be unimproved. This solubility-permeability interplay was shown for formulations based on cyclodextrins [162–164], surfactants [165], cosolvents [166], and hydrotropes [167, 168]. In amorphous solid dispersions (ASD), on the other hand, the solubility increases (via supersaturation) with unchanged permeability, and thus, ASD may be preferred over other carrier systems, given supersaturation can be achieved and maintained for sufficient time [169].

Conclusions

Altogether, the evidence presented in this work supports the notion that 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. At the moment, we cannot ensure the plant phytochemicals directly reach viruses or the correct structures inside cells. Ideally, we would have smart 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 will accumulate in the literature, which will shed light on the full potential of phytochemicals as novel antiviral agents in adequate delivery systems.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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