

Review

Potential of DNA Intercalating Alkaloids and Other Plant Secondary Metabolites against SARS-CoV-2 Causing COVID-19

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Abstract: Many plants produce secondary metabolites (PSMs) with antiviral activities. Among the antiviral PSMs, lipophilic terpenoids in essential oils can disturb the lipid envelope of viruses. Phenols and polyphenols (flavonoids, rosmarinic acid and tannins) attack viral proteins present in the viral membrane or inside the virus particle. Both phenolics and essential oils are active against free viral particles but not—or to a lesser degree—after a virus has entered a host cell. Another group of PSMs is directed against DNA or RNA. These are DNA intercalators such as sanguinarine, berberine, emetine and other isoquinoline alkaloids, β -carboline, and quinoline alkaloids such as quinine, cinchonine, dictamine and skimmianine. The DNA intercalators stabilize double-stranded nucleic acids and inhibit the replication, transcription, and translation of genetic material. These alkaloids can inhibit viral development and viral replication in cells, as shown for SARS-CoV-1 and other viruses. Since chloroquine (which is also a DNA intercalator and a chemical derivative of the alkaloid quinine) is apparently clinically helpful against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, it is assumed that intercalating alkaloids, or the medicinal plants producing them, may be interesting candidates for the development of new antiviral drugs for the treatment of coronavirus disease 2019 (COVID-19).

Keywords: plant secondary metabolites; essential oil; polyphenols; intercalating alkaloids; inhibition of polymerases; inhibition of protein biosynthesis; viral replication; SARS-CoV-1; SARS-CoV-2; COVID-19

1. Introduction—Why Do Plants Produce Antiviral Substances

Terrestrial plants have existed since the Devonian era [1]. When plants evolved, they had to face a crucial challenge from the early beginning. Plant-eating animals (herbivores) and aggressive microbes (bacteria, fungi and viruses) surrounded them. As plants cannot run away from herbivores, they had to develop a new defense strategy. They started to produce defensive chemicals, mostly of low molecular weight (called secondary metabolites or natural products) which would be repellent to or toxic for animals. Plants do not have an adaptive immune system to overcome microbial infections. Their solution was the production of a wide diversity of secondary metabolites with antimicrobial activity. Evolution was ingenious, as many of the antiherbivore substances also exhibit antimicrobial activities. Some of these compounds have a further role in attracting pollinating insects and fruit-dispersing animals [1–4].

Over 100,000 plant secondary metabolites (PSMs) have been characterized. The main groups include those with nitrogen in their structures, such as alkaloids, amines, non-protein amino acids, cyanogenic glucosides and glucosinolates. Major groups without nitrogen are terpenoids and phenolics. Secondary metabolites derive from the primary metabolism of plants and share common precursors.

Nitrogen-containing PSMs derive from one of proteinogenic amino acids or ornithine, terpenes and fatty acids from acetyl-CoA or the methylerythritol phosphate pathway, and phenolics from acetyl-CoA and a moiety of phenylalanine/tyrosine [2,5].

As mentioned before, plants have to face infections from a diversity of viruses, and it is therefore not surprising that a number of PSMs exhibit antiviral activities. As viruses of plants and animals share similar structures, PSMs, which work against plant viruses, can also be useful against human pathogens. Therefore, several extracts from medicinal plants or isolated PSMs are known to have antiviral properties and have been used against bacterial and viral infections (reviews in [6–12]). Thus, plants offer an interesting library of low-molecular-weight compounds with medicinal potential [13].

In this short review, I summarize the experimental evidence for the antiviral activity of PSMs and plant drugs. I then discuss the corresponding potential modes of action, and finally discuss how this information might be used to conduct a targeted search for drugs useful against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). DNA-intercalating alkaloids may be of special interest because they can inhibit viral replication in cells. This review highlights the main findings on antiviral PSMs; it is not intended to completely cover the publications on antiviral plants or PSMs.

2. Antiviral PSM

The structure of viral particles is quite simple when compared to prokaryotic or eukaryotic cells (Figure 1). Many viruses consist of a nucleic acid as the genetic base, which can be RNA or DNA (Table 1). The genetic material is often complexed by nucleic-acid-binding proteins, forming a nucleocapsid. This capsid is surrounded by a membrane envelope derived from the endoplasmic reticulum (ER) of a host cell. Several viral proteins reside in this membrane, which help the viral particle to attach to the cellular receptors of potential host cells in order to be taken up. As an example of the structure of a virus, Figure 1 schematically illustrates the structure of SARS-CoV-2 [14,15].

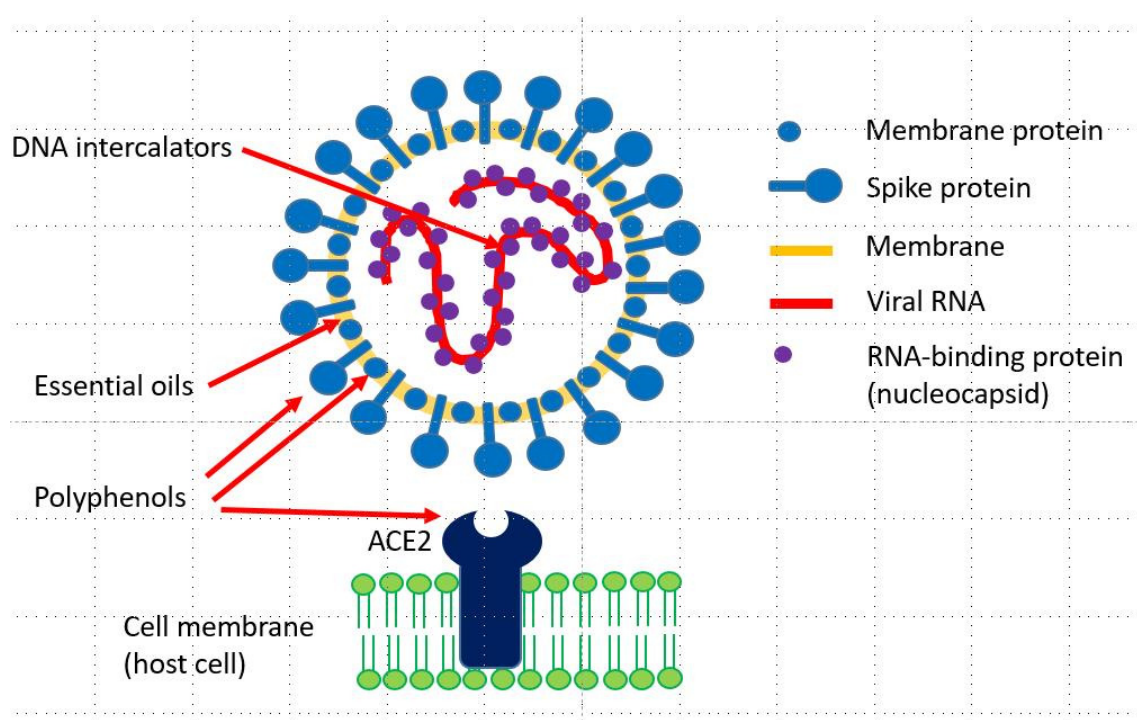


Figure 1. A simplified and schematic structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can bind to a cellular receptor (ACE2) of a host cell with its spike proteins. Targets for antiviral drugs (essential oils, polyphenols and DNA intercalators) are indicated by red arrows.

Table 1. Nucleic acids of main groups of viruses and related health disorders [6,16].

Class	Abbreviation	Example/Disease
I. dsDNA (double-stranded DNA)		
Papilloma virus (Papillomaviridae)	HPV	Papilloma warts, cervical cancer
Adenovirus (Adenoviridae)	HAdV	Infections of the respiratory tract
Herpes simplex virus 1 (Herpesviridae)	HSV-1	HV I (blisters on skin), HV II (blisters on genitals)
Varicella zoster virus (Herpesviridae)	VZV	Chicken pox, shingles
Epstein–Barr virus (Herpesviridae)	EPV	Mononucleosis, Burkitt lymphoma
Smallpox virus (Poxviridae)		Smallpox
II. ssDNA (single/double-stranded DNA)		
Hepatitis B virus (Hepadnaviridae)	HBV	Hepatitis B
III. dsRNA (double-stranded RNA)		
Reoviridae		Diarrhea viruses, diseases of the respiratory tract, tick fever
IV. ssRNA (working as mRNA)		
Coronavirus (Coronaviridae)	SARS-CoV-1, SARS-CoV-2; MERS-CoV	Common cold, respiratory disease; COVID-19
Poliovirus (Picornaviridae)	PV	Poliomyelitis
Rhinovirus (Picornaviridae)		Common cold
Hepatitis A (Picornaviridae)	HAV	Hepatitis A
Hepatitis C virus (Flaviviridae)	HCV	Hepatitis C
Yellow fever (Flaviviridae)		Yellow fever
West Nile virus (Flaviviridae)	WNV	Flu-like symptoms
Zika virus (Flaviviridae)	ZIKV	Flu-like symptoms
Dengue virus (Flaviviridae)	DENV	Dengue fever
V. ssRNA (used as matrix for mRNA synthesis)		
Paramyxovirus (Paramyxoviridae)	PMV	Measles, mumps
Influenza virus (Orthomyxoviridae)	H1N1, H5N1	Influenza
VI. ssRNA (used as matrix for DNA synthesis)		
Retrovirus (Retroviridae)	HIV	RNA tumor viruses, HIV (AIDS)

2.1. Evidence for the Antiviral Activity of PSMs

In most instances, antiviral activities have been described from extracts of medicinal plants or isolated PSMs [6–12]. In general, antiviral activity has been determined *in vitro*, using sensitive cell culture systems (Tables 2 and 3). In the design of such studies, it is important to understand the protocol. Antiviral PSMs can directly interfere with viruses if both are incubated together before they are added to the cells. If cells are already infected, PSMs need to be absorbed by the cell before they can attack viruses intracellularly. Because many PSMs (polyphenols) are polar molecules, which cannot pass biomembranes freely, their absorption into cells is low. Most publications show that extracts with essential oils or phenolics can inhibit free viral particles, but are rather inactive against infected cells [6]. Tannins with many phenolic hydroxyl groups are especially active towards free viral particles, as they can effectively bind to proteins (Table 2). Consequently, most instances of antiviral activity have been recorded when PSMs and viruses are co-incubated, and far less when the cells are already infected. A selection of PSMs or essential oils with antiviral activities is documented in Tables 2 and 3; for more examples and details, see the reviews in [6–12].

Table 2. Antiviral activity of selected plant extracts or plant secondary metabolites (PSMs) [6,7]. For DNA-intercalating alkaloids, see Table 3.

Virus	Class of PSM	Antiviral Activity	Reference(s)
HIV-1	Alkaloids: buchapine, colchicine, schumannificine	IC ₅₀ 0.1–10 µM	[6]
	Coumarins: calonolide A, inophyllum B	IC ₅₀ : 0.04–2 µM	[6]
	Polyphenols: flavonoids, isoflavonoids, lignans, tannins and other phenolic PSMs	IC ₅₀ : 2–60 µg/mL	[6,8,9]
	Triterpenes: betulinic acid, celastrol-B, ursolic acid	IC ₅₀ : 1–20 µg/mL	[6]
HSV-1, HSV-2	Alkaloids: quinolines (acronycine, citrussinine-1); piperidines (rohitukine, schumannificine)	IC ₅₀ : 0.5–10 µg/mL	[6]
	Essential oils: <i>Citrus</i> , <i>Eucalyptus</i> , <i>Hyssopus</i> , <i>Illicium</i> , <i>Leptospermum</i> , <i>Matricaria</i> , <i>Melaleuca</i> , <i>Mentha</i> , <i>Pinus</i> , <i>Santalum</i> , <i>Thymus</i> , <i>Zingiber</i> and other aromatic plants	IC ₅₀ : 0.0003%–0.0001%	[6,8,9]
	Polyphenols: flavonoids (flavans and derivatives, naringenin, tannin, galangin, quercetin, genistein), lignans (podophyllotoxin and derivatives, peltatin), tannins, and other phenolic PSM	IC ₅₀ : 0.03–20 µg/mL	[6,8,9]
	Triterpenes: ursonic acid, dammaradienol, dammaronic acid, hydroxyhopanone	IC ₅₀ : 2–20 µg/mL	[6]
HCMV	Artemisinin and derivatives	Good antiviral activity	[17]
Flaviviridae (JEV, YFV, DV-4)	Alkaloids: isoquinolines (lycorine, narciclasine, pancratistatin, pretazettine)	IC ₅₀ : 0.02–2 µg/mL	[6]
Flaviviridae (bovine viral diarrhoea virus; BVDV)	Water extracts from <i>Alpinia galanga</i> and <i>Alpinia oxyphylla</i> , <i>Celosia cristata</i> , <i>Houttuynia cordata</i> , <i>Ophioglossum vulgatum</i> , and <i>Selaginella tamariscina</i>	Good antiviral activity without cytotoxicity	[17]
Hepadnaviridae (HBV)	Water extracts from <i>Evodia lepta</i> , <i>Glycyrrhiza</i> spp. and <i>Hedyotis diffusa</i>	Good antiviral activity without cytotoxicity	[8,9]
Bunyaviridae (PTV, RVFV)	Alkaloids: isoquinolines (lycorine, narciclasine, pancratistatin, pretazettine)	IC ₅₀ : 0.007–3 µg/mL	[6]
Picornaviridae (HRV-1B, COX)	Flavonoids (flavans and derivatives, galangin)		[6]
Orthomyxoviridae (INFA)	Flavonoids (flavans and derivatives, isoscutellarin)		[6]
Dengue virus	Essential oils: <i>Artemisia</i> , <i>Eupatorium</i>	IC ₅₀ : 60–150 ppm	[6]
Junin virus (Arenaviridae)	Essential oils: <i>Aloysia</i> , <i>Buddleja</i> , <i>Lippia</i> , <i>Heterotheca</i> , <i>Heterothalamus</i> , <i>Tessaria</i>	IC ₅₀ : 14–63 ppm	[6]
Rhabdoviridae (VSV)	Polyphenols: flavonoids: tannin, lignans (peltatin, podophyllotoxin and derivatives), diphyllin, justicidin and derivatives	IC ₅₀ : 1–20 µM	[6]
Paramyxoviridae (RSV)	Flavonoids: flavans and derivatives, aescufloside and other phenolic PSMs	IC ₅₀ : 1–20 µM	[6]

2.2. Mode of Action

Considering the potential targets to attack a viral particle with a drug, we can distinguish between proteins (membrane proteins, capsid proteins), the envelope membrane and the nucleic acids (Figure 1). In addition, there may be specific targets such as integrase, proteases (needed to trim the viral proteins),

RNA-dependent RNA polymerase (RdRp), reverse transcriptases (in the case of retroviruses), proteins of the membrane envelope or the ACE2 receptor on host cells [6–12,14,15].

Medicinal chemistry usually searches for specific inhibitors of enzymes, receptors and other proteins, or nucleic acids and associated processes. For example, analogues of DNA bases (nucleoside analogues) can inhibit the successful viral replication and translation. These compounds are synthetic and hardly found in nature. They are presently being used to treat patients with COVID-19 [15]. In contrast, most of the PSMs with antiviral properties are less-specific inhibitors, which does not rule out their potential utility.

2.2.1. Lipophilic Terpenoids (Essential Oils)

Among the antiviral PSMs, lipophilic terpenoids, as found in the essential oils of many plants [13], are interesting candidates (Table 2). These lipophilic compounds most likely nonspecifically intercalate into the lipid double layer of the viral envelope. Consequently, the fluidity of the membrane is changed and, at a higher concentration, the membrane is even lysed [6]. The same effect can be achieved with lipophilic solvents such as chloroform, which have been used to inactivate viruses in blood products. This interaction can only occur when the viral particle is intact, that is, before it enters a host cell. Once inside a cell, these lipophilic compounds no longer work [6]. As can be seen from Table 2, essential oils from many aromatic plants exhibit antiviral activity in vitro [6–12].

2.2.2. Phenolics and Polyphenols

Phenolic compounds and polyphenols are PSMs with aromatic rings that contain one or several hydroxyl groups. The name is derived from phenol, a simple aromatic phenyl ring with a single hydroxyl group. The phenols have an important chemical property, in that their hydroxyl group can dissociate under physiological conditions. It forms a phenolate ion with a negative charge (and other resonance structures). Polyphenols such as flavonoids, rosmarinic acid and tannins carry several such phenolic OH groups. These OH groups can form hydrogen and ion bonds with the outer groups of proteins, such as the positively charged amino groups. If a tannin and a protein are incubated together, the polyphenols form several hydrogen and ion bonds, which will influence the 3D structure of a protein or inhibit its activity [18]. Consequently, tannins are known as very potent protein inactivators, and are also antiviral. This activity is also seen when phenols or tannins are incubated with viruses (Tables 2 and 3): polyphenols bind to viral proteins in the envelope, which often prevents the docking of a virus to its host cells. Thus, many polyphenols are antiviral as long as virus particles are intact and have not been taken up by a host cell [6]. Most polyphenols are polar molecules, and their absorption into cells is low.

2.2.3. DNA and RNA–DNA Alkylation and DNA Intercalation

The genetic material of a virus is an important target, be it DNA or RNA (Table 1). Several PSMs are known to attack nucleic acids [13]. We distinguish between DNA-alkylating substances and DNA intercalators.

Typical DNA-alkylating PSMs include pyrrolizidine alkaloids, aristolochic acid, cycasin, macrozamin, furanocoumarins and PSMs with aldehyde or epoxide functional groups [13,18]. These compounds lead to mutations and cell death and can even cause cancer. Therefore, alkylating PSMs or plant extracts are not used in phytotherapy, even if they may be active against viruses.

Intercalating PSMs are usually lipophilic and planar aromatic multi-ring structures that can insert between the stacked DNA base pairs of the DNA helix or paired regions of RNAs. Depending on the concentration and affinity, such DNA intercalators stabilize the DNA double helix in such a way that replication is reduced or even impossible. Consequently, a cell will die (usually via apoptosis) [18,19]. At lower concentrations, intercalators can induce deletions, strand breaks and frame-shift mutations.

Among the intercalating PSMs, alkaloids of the isoquinoline, quinoline and β -carboline type provide several powerful antiviral compounds [18–22]. For example, sanguinarine, which occurs in

Sanguinaria canadensis, *Macleaya cordata*, *Bocconia frutescens*, *Eschscholzia californica*, and *Chelidonium majus*, is a very strong DNA intercalator with pronounced cytotoxic, antibacterial and antiviral properties. Additionally, the protoberberine alkaloid berberine and related derivatives, which occur in many species of the Berberidaceae and Papaveraceae, are known intercalators with antibacterial and antiviral properties (Table 3).

Table 3. Selected alkaloids, which intercalate nucleic acids and inhibit viral replication [19–22].

PSM	Type	Occurrence	Activity	Anti-Viral Activity	Ref.
Sanguinarine, chelerythrine, chelidonine	Isoquinoline alkaloids	Papaveraceae	Very strong DNA intercalator	HSV, HIV, HIV, influenza	[23,24]
Berberine, berbamine, berberrubine, coptisine, dicentrine, jatrorrhizine, palmatine	Isoquinoline alkaloids	Berberidaceae, Papaveraceae	Strong DNA intercalator	SARS-CoV, HSV, CHIKV, hepatitis C	[25–29]
Tetrandrine, fangcholine, cepharanthine	Isoquinoline alkaloids	Menispermaceae	DNA intercalator	SARS-CoV	[30]
Quinine, quinidine, cinchonine, cinchonidine	Quinoline alkaloids	Rubiaceae	DNA intercalation, inhibition of DNA polymerase	HSV, influenza, DENV	[31]
Emetine	Quinoline alkaloids	Rubiaceae	DNA intercalation, inhibition of DNA polymerase, Topoisomerase, Reverse transcriptase, protein synthesis	HIV, HSV, Inhibits pseudorabies Semliki Forest	[27,32,33]
Dictamine, ellipticine, evolitrine, fagarine, skimmianine	Quinoline alkaloids	Rutaceae	DNA intercalation		[13]
Cryptolepine	Quinoline alkaloids	Apocynaceae	DNA intercalation	Antimicrobial	[13]
Harmine, harmaline	β -Carboline alkaloids	Zygophyllaceae	DNA intercalation, inhibition of DNA polymerase, Topoisomerase, Reverse transcriptase	HSV, MCMV, influenza	[33]

Intercalating compounds not only inhibit DNA replication, but also DNA polymerase, reverse transcriptase and potentially RNA polymerases and ribosomal protein biosynthesis. The stronger the intercalation, the higher the inhibition of polymerases and protein synthesis [19–22]. As these processes are important for viral replication, intercalating alkaloids have antiviral properties (Table 3).

Most of these alkaloids are readily absorbed into cells and could influence the replication and transcription of a virus within its host cell. Sanguinarine and berberine show low human toxicity [13,24,34] and might be good candidates against viral infections. They would be active against DNA viruses and RNA viruses if the RNA exists in a double helix or forms partial helical structures.

3. Relevance for Coronavirus SARS-CoV-2 and COVID-19

SARS-CoV-2 is a member of Coronaviridae [14,15]. The viral genome is a single-stranded RNA (+ sense), which can function directly as an mRNA. The mRNA is complexed by binding proteins, forming the nucleocapsid. SARS-CoV-2 is a virus with a membrane envelope, which is derived from the endoplasmic reticulum of the host cell. It carries several proteins—a spike protein which binds to the cellular receptor ACE2, as well as membrane and envelope proteins (Figure 1). Once the virus particle has entered a host cell, the viral genome is released. The mRNA is copied by a viral polymerase, which makes several new copies of the viral mRNA. These mRNA copies are translated at ribosomes

attached to the endoplasmic reticulum so that the translated proteins (spike protein, a membrane and an envelope protein) become embedded into the ER membrane. Golgi vesicles are generated, which are finally released by exocytosis. The nucleocapsid proteins are translated at cytoplasmic ribosomes and bind to mRNA. The nucleocapsid is internalized into the ER/Golgi vesicle [14,15].

When the last SARS epidemic (SARS-CoV-1) was active [15], many research teams screened PSMs and medicinal plants against SARS infection [15,25,35–41]. A selection of active drugs are shown in Table 4. As SARS-CoV-2 is a closely related virus, it would be a good idea to check if the findings from SARS-CoV-1 also apply to SARS-CoV-2.

Table 4. Examples of plant extracts active against SARS [17,23–28].

Virus	Class of PSM	Main Findings	Reference
SARS-CoV-1	Alkaloids tetrandrine, fangchinoline and cepharanthine	Inhibits expression of spike and nucleocapsid protein	[15]
	Alkaloids: lycorine and extract from <i>Lycoris radiata</i>	Extract: IC ₅₀ 2.4 µg/mL Lycorine: IC ₅₀ 15 nM	[35]
	Emodin and other anthraquinones	Inhibition of 3-chymotrypsin-like protease (3CLPro) and adsorption	[15]
	Essential oil: <i>Laurus</i>	IC ₅₀ 120 µg/mL	[40]
	Glycyrrhizin from <i>Glycyrrhiza</i>	Inhibition of virus adsorption and penetration	[15]
	Quercetin and other polyphenols	Inhibition of 3CLPro and penetration	[15]
	Saikosaponins	Inhibit viral attachment and adsorption	[39]
	Tannic acid and 3-isothaflavin-3-gallate	Inhibition of 3CLPro; IC ₅₀ 3–7 µM	[36]
	<i>Cassia tora</i> , <i>Cibotium barometz</i> , <i>Gentiana scabra</i> , <i>Dioscorea batatas</i> , and <i>Taxillus chinensis</i>	IC ₅₀ 5–10 µg/mL	[37]
	<i>Cimicifuga racemosa</i> , <i>Coptis chinensis</i> , <i>Melia azedarach</i> , <i>Phellodendron amurense</i>	IC ₅₀ 2–19 µg/mL	[25]
	<i>Isatis tinctoria</i>	Inhibition of 3CLPro	[15]
	<i>Toona sinensis</i> (Meliaceae)	IC ₅₀ 37–70 µg/mL	[41]
	<i>Torreya nucifera</i> ; amentoflavone	Inhibition of 3CLPro; IC ₅₀ 8.3 µM	[38]
	Water extract of <i>Houttuynia cordata</i>	Inhibition of 3CLPro and RNA polymerase	[15]

Traditional Chinese medicine (TCM) has a long tradition, and TCM formulae have been used to treat viral infections with positive results (examples in [15]). Presently, more than 15 clinical studies with complex TCM drugs against COVID-19 are ongoing in China, of which some are already in clinical phase 4 [15]. The traditional approach has its merits, but we could also try a more rational target-orientated approach by studying isolated PSMs with antiviral properties, especially those which inhibit viral replication (Figure 1).

4. Are Plant Drugs with Intercalating Alkaloids Antiviral and Potentially Useful against SARS-CoV-2 and COVID-19?

As mentioned before, PSMs with DNA-intercalating properties [20–22] might be candidates to treat an active infection or can be lead substances for the development of new drugs. Recently, it was found that the antimalarial drug resiquine (chloroquine) would be useful in therapy (review in [15,31,32]). Resiquine is a synthetic derivative of the PSM quinine, an alkaloid used for many years to treat malaria [13]. As shown many years ago, quinine has a planar ring system that can intercalate DNA [19,20]. Furthermore, we proposed that part of its antimalarial activity is associated with the

intercalation activity. It is possible that the efficacy of resiquine towards SARS-CoV-2 could be partly due to its apparent DNA-intercalating activity.

Extracts from traditional Chinese medicinal plants *Coptis chinensis* and *Phellodendron amurense* with berberine, coptisine, jatrorrhizine and palmatine as main PSMs [13] were especially active in vitro against SARS-CoV-1 (IC₅₀ 2 µg/mL) (Table 4) [25]. It has been demonstrated that berberine could inhibit viral replication of HSV and CHIKV [26,27]. Berberine had positive effects in the treatment of influenza virus in vitro and in vivo [38]. In addition, berberine inhibits hepatitis C virus entry by targeting the viral E2 glycoprotein [29].

The isoquinoline alkaloids tetrandrine, fangchinoline and cepharanthine could inhibit the expression of spike and nucleocapsid proteins in SARS-CoV- OC43 in human lung cells [30]. As these alkaloids also intercalate DNA [20,21], these results support the idea that drugs with DNA intercalators are interesting drug candidates.

Palmatine, another DNA-intercalating isoquinoline alkaloid, inhibits West Nile, Zika and Dengue virus replication [22,42,43]. Chelidonine, an intercalating isoquinoline alkaloid [20] from *Chelidonium majus*, is known for its antiviral activity against HSV, HIV and the influenza virus [13]. In addition, sanguinarine, chelerythrine and chelidonine from *Chelidonium* possess known antiviral activities for the treatment of warts and verruca [13,23]. Sanguinarine from *Sanguinaria canadensis* has a broad range of antimicrobial activities; it exhibits antiviral effects against HIV protease and the herpes simplex virus [24].

As mentioned previously, antimalaria drugs such as chloroquine are presently being used against COVID-19 [15,32]. Additionally, the original antimalarial alkaloid, quinine, shows antiviral activity against HSV, influenza and Dengue virus [31]. Emetine, a drug used against amoebae [13], shows DNA-intercalating activities [20] and inhibits protein biosynthesis [20]. It inhibits reverse transcriptase in HIV [27] and might even work against SARS-CoV-2 [32].

Most of the antiviral results have been obtained from in vitro experiments. Therefore, animal and clinical experiments are necessary to determine the optimal dose, safety and optimal time point for an intervention. As these PSMs may not be available in sufficient amounts for a clinical investigation, the medicinal plants which produce these alkaloids might provide an alternative.

5. Conclusions

Antiviral secondary metabolites can target viral proteins (polyphenols), the lipid envelope (essential oils and other lipophilic PSMs) and viral nucleic acids (intercalating alkaloids). DNA-intercalating drugs inhibit DNA and RNA polymerases and protein biosynthesis, and consequently, viral replication. Whereas essential oils and polyphenols are active against the free virus, the intercalators can also inhibit the viral replication inside the host cell. The intercalating alkaloids sanguinarine, chelidonine, chelerythrine, berberine, coptisine, jatrorrhizine, palmatine, tetrandrine, cepharanthine, quinine, cinchonine, harmine and emetine (Tables 3 and 4) represent interesting candidates for direct clinical studies or as lead compounds for the synthesis of synthetic antiviral drugs. Alternatively, extracts from medicinal plants [13] which produce these alkaloids, such as *Bocconia frutescens*, *Chelidonium majus*, *Cinchona* sp., *Eschscholzia californica*, *Berberis* sp., *Coptis chinensis*, *Jateorhiza palmata*, *Hydrastis canadensis*, *Macleaya cordata*, *Phellodendron amurense*, *Psychotria ipecacuanha*, *Sanguinaria canadensis*, *Stephania tetrandra* and others summarized in [34] may be more easily available than the isolated alkaloids. They might be useful as adjunctive therapeutics in the treatment of viral infections such as SARS-CoV-2 but need to be investigated in more detail.

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