

Phytocomplexes as dual modulators of redox homeostasis and autophagy in host-directed antiviral therapy

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ABSTRACT

Phytocomplexes are widely recognized as a source of multi-component therapeutic agents with synergistic potential. Some natural extracts possess potent antioxidant properties, largely mediated by phytochemicals such as polyphenols and flavonoids, which can neutralize reactive oxygen species (ROS) and modulate oxidative-stress-related signaling pathways critical for viral replication and inflammation. Concurrently, host-directed autophagy represents a finely tuned cellular defense mechanism that can be exploited to degrade viral components, although many viruses have evolved sophisticated strategies to evade or hijack this machinery for their own benefit. This review evaluates the antiviral potential of diverse phytocomplexes at the intersection of antioxidant activity and autophagy modulation. This work specifically addresses phytocomplexes and natural extracts as multi-component systems capable of simultaneously modulating autophagy and oxidative stress. By targeting conserved host factors rather than viral proteins, these dual-acting host-directed antivirals (HDAs) could offer a promising strategy to mitigate viral pathogenesis, reduce the likelihood of drug resistance, and provide broad-spectrum protection against emerging and re-emerging viral threats.

1. Introduction

While traditional drug discovery has historically focused on isolating pure compounds, there is a growing appreciation for the intricate and synergistic nature of phytocomplexes, defined as the entire set of bioactive and non-bioactive constituents present in a plant-derived preparation that may act collectively or synergistically, as a valuable resource [1]. Natural extracts, namely preparations obtained through the extraction of plant material using solvents and specific techniques, and phytocomplexes are recognized for their combined potent antioxidant properties, antibacterial and antiviral activities, as well as for their potential applications in cardiovascular and cancer-related diseases [2–6]. In fact, rather than acting through a single dominant mechanism, these extracts, which represent complex mixtures of a variety of chemically distinct compounds, complex natural extracts may exert additive, complementary, or synergistic effects through the combined action of polyphenols, flavonoids, terpenes, alkaloids, carotenoids, and other secondary metabolites. This feature is particularly attractive in antiviral research, where effective antiviral strategies often also require modulation of inflammatory signaling, oxidative damage, and host defense

pathways. On one hand, these compounds effectively neutralize reactive oxygen species (ROS) and modulate oxidative-stress-related signaling pathways, contributing to the preservation of cellular functions and the modulation of immune responses [7,8]. On the other hand, several phytocomplexes have been reported to interfere with viral life cycles through different mechanisms, including inhibition of viral entry, replication and assembly. Because oxidative stress plays a critical role in inflammation, viral replication, and disease progression, the antioxidant capacity of natural compounds may indirectly contribute to antiviral protection [9]. At the same time, many phytocomplexes exhibit additional biological activities that can be exploited in antiviral strategies as the modulation of the autophagic host machinery. Their pleiotropic effects and their general low toxicity profile have increased interest in their application as antiviral agents, in turn exerted through multiple mechanisms. Autophagy is a regulated cellular process, which allows the degradation and recycling of damaged or unnecessary cellular components, and it also plays a relevant role in host-virus interactions [10]. While autophagy generally promotes cell survival under stress, apoptosis eliminates damaged or unwanted cells. Although distinct, these pathways are interconnected, and maintaining their balance is

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particularly important in the context of viral infections. This host machinery can be exploited as an antiviral strategy given its influences on viral replication, pathogenicity, and immune evasion, representing a promising antiviral target. Pharmacologically modulating autophagy can therefore disrupt these viral strategies and limit infection. Natural products have attracted increasing interest as autophagy modulators due to their structural diversity, broad bioactivity, and relatively low toxicity, while natural extracts and phytocomplexes remain less explored, despite their potential to modulate the same pathways through multiple interactions. These mixtures are derived from plants, fungi, marine organisms, and other natural sources, and offer potential scaffolds for antiviral drug development through host-directed autophagy regulation.

Taken together, the modulation of these two interconnected processes, namely antioxidant activity and autophagy modulation, may hold promise for the development of dual acting potent host-directed antivirals (HDAs, Fig. 1).

Complementing our previous reviews comprehensively analyzing the effect of isolated and characterized natural compounds as modulators of autophagy [11,12], the present work centers on the antioxidant and autophagy-mediated antiviral activity of natural extracts and phytocomplexes as multicomponent systems. By shifting attention from single molecules to chemically complex mixtures, this review highlights the possibility that synergistic or complementary phytochemical interactions may provide broader and more adaptable host-directed antiviral effects. Particular emphasis is placed on their dual capacity to modulate autophagy and redox homeostasis, two interconnected host processes that critically influence viral replication, inflammatory signaling, and cellular injury. Literature was gathered from PubMed, Scopus, and Google Scholar using keywords related to antioxidants, autophagy and viral infection, with no restrictions on publication date, exclusively focusing on complex mixtures and not isolated compounds. Selected extracts were included based on documented effects on autophagy, antiviral activity and antioxidant properties when reported. The review aims to highlight the potential of natural extracts and complex mixtures bearing at the same time autophagy modulation with antiviral, antioxidant and scavenging properties in comparison to isolated compounds; while reporting and analyzing natural extract studies and procedures. The goal is to collect current knowledge, identify gaps, and outline directions for future research.

2. Autophagy in viral infections

Autophagy is a highly regulated and conserved cellular process involved in the maintenance intracellular homeostasis through the degradation and recycling of intracellular components. This complex

and interconnected mechanism can be classified according to the involved pathways, the specific delivery mechanism or the selectivity of the process (Fig. 2). Its deregulation has been related to many different pathological conditions [13], including cancer [14–16], neurodegenerative disorders as Alzheimers disease [17] and cardiovascular diseases [18]. In addition to these roles, autophagy is also deeply involved in host-pathogen interactions and immune responses.

In the context of viral infections, autophagy represents a context-dependent process [10], as it can contribute to host defense by promoting the degradation of viral components, regulating inflammatory signaling and supporting antigen presentation [19]. At the same time, it may provide structural platforms and membrane resources that viruses can exploit to sustain replication and facilitate their release from the infected host cells [10]. Therefore the outcome of autophagy modulation, which can be either protective or detrimental, depends on the specific virus and stage of infection (Fig. 2).

In particular, viral entry, and replication-associated stress can activate autophagy as part of the host immune response, promoting the sequestration and degradation of viral particles, contributing to the innate immunity [19]. However, several viruses have evolved strategies to modulate this pathway to their advantage, inhibiting or bypassing this pathway by targeting its initiation. This is frequently achieved through interference with major regulatory signaling pathways including type I PI3K-AKT-mTOR pathway or type III PI3K-VPS34-Beclin1 pathway, ultimately preventing autophagosome formation and enabling viral survival and replication [10].

Conversely, some viruses activate components of the autophagic machinery at later stages of infection to support their replication and propagation [20]. Virus-induced double-membrane vesicles (DMVs) serve as platforms for viral RNA synthesis and are widely exploited by RNA viruses [21]. Although DMVs share structural similarities with autophagosomes, their precise origin and relationship with canonical autophagy remain incompletely understood. In addition to DMV formation, viruses can manipulate downstream steps of autophagy, by blocking autophagosome-lysosome fusion or exploit other membranous vesicles as lysosomes though there is no correlation to autophagy induction, resulting in an incomplete autophagic flux and accumulation of autophagosomes, which can be repurposed for viral maturation and egress [22]. Rather than considering autophagy simply as an “antiviral” or “proviral” process, it is therefore more appropriate to view it as a dynamic host pathway whose modulation depends on the biological context. From a therapeutic perspective, this implies that both activation and inhibition of autophagy may be beneficial, depending on how the virus interacts with the host machinery.

The autophagic process can be broadly divided into sequential stages, including initiation (1), nucleation (2), elongation (3), autophagosome formation, fusion with lysosomes (4), and degradation of the cargo (5) (Fig. 3). Specifically, these steps are activated and modulated by conserved protein complexes and signaling pathways, and each stage may represent a potential target for pharmacological modulation. In the context of phytocomplexes, the relevance of this pathway lies not only in whether autophagy is induced or inhibited, but also in which stage of the process is affected and how this modulation influences viral replication.

3. Host-directed antivirals

Host-directed therapies (HDT) and more specifically, host-directed antivirals (HDA) are an emerging strategy in the field of anti-infective agents. This concept derives from therapeutic approaches already used in other fields, such as cancer, metabolic and cardiovascular therapies for which HDT are amply used and FDA-approved drugs already exist. This strategy exploits host cellular factors crucial for viral replication, instead of directly targeting viral components [23], allowing for the exploration of novel targets that are only mandatory for viruses and not for host survival. Additionally, HDA can also target the immune responses pathways, either enhancing the host protecting responses

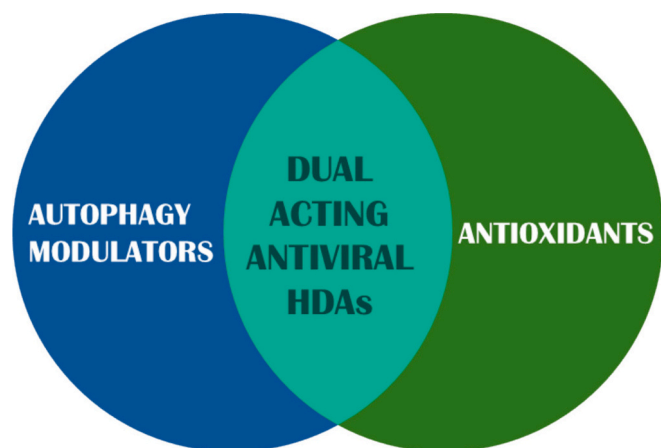


Fig. 1. Dual-acting host-directing antivirals endowed with autophagy modulation and antioxidant properties.

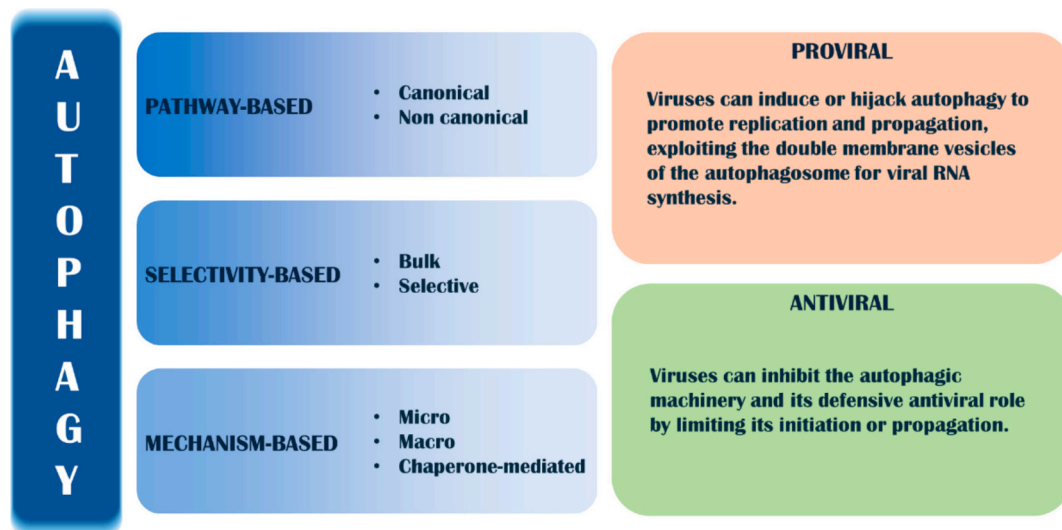


Fig. 2. Dual role of autophagy as promoter or suppressor of antiviral replication, and different and interconnected pathways in which autophagy is activated and exploited.

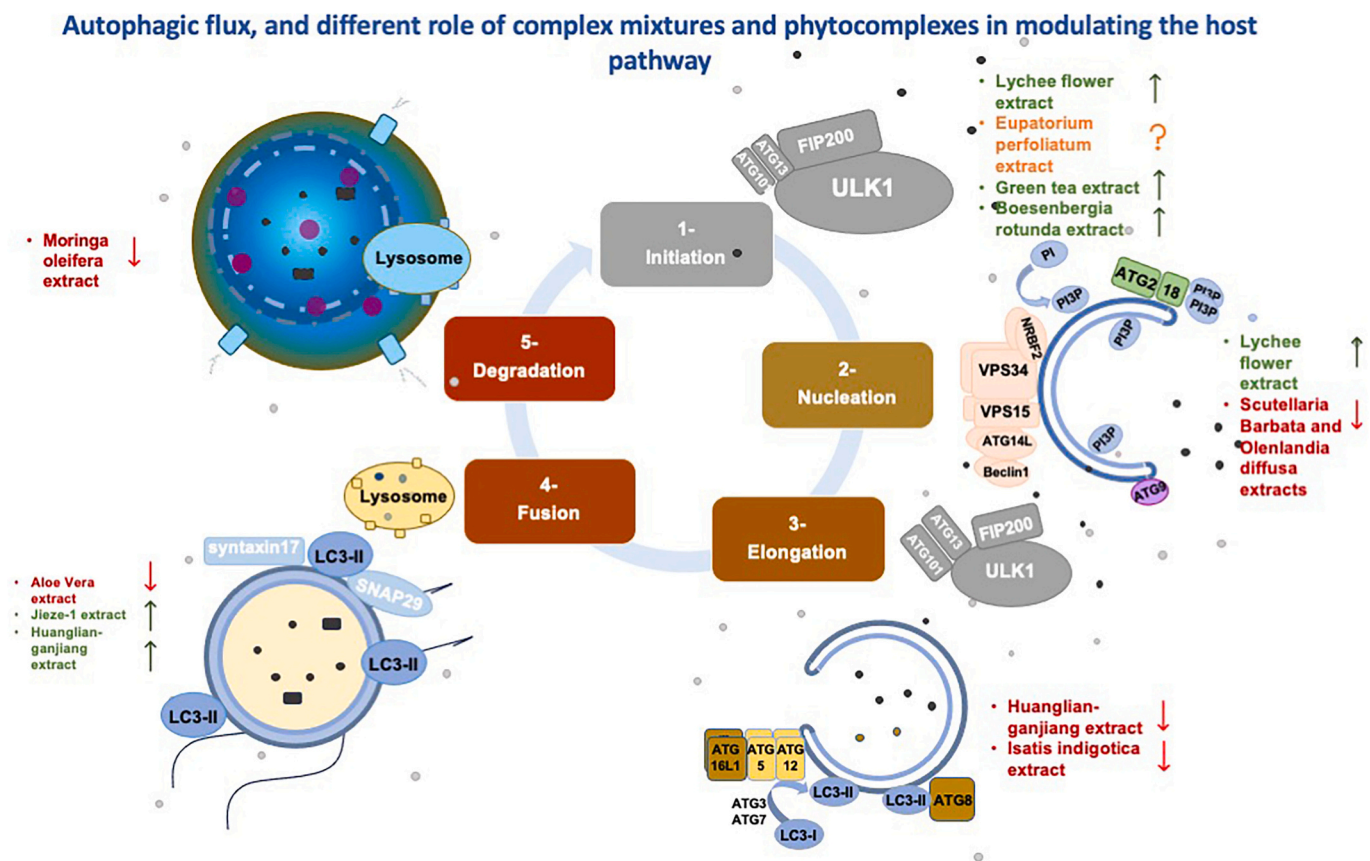


Fig. 3. Autophagy pathway and role of different extracts on the induction (↑), inhibition (↓) or unclarified modulation (?) of the host machinery steps. Specifically, 5 steps have been identified: Step 1- Initiation: autophagy is triggered by cellular stress signals, leading to the activation of the autophagic machinery and the formation of the phagophore. Step 2- Nucleation: the phagophore begins to form through the recruitment of protein complexes and membrane components at specific intracellular sites. Step 3- Elongation and autophagosome formation: the phagophore expands and encloses cytoplasmic cargo, ultimately generating a double-membrane autophagosome. Step 4- Fusion: the mature autophagosome fuses with lysosomes, forming an autolysosome where the cargo is exposed to degradative enzymes. Step 5- degradation and recycling: the sequestered material is degraded and the resulting metabolites are recycled to support cellular homeostasis and survival.

against external pathogens or conversely limiting hyper-inflammation in pathological sites reducing tissue damage and confine microbials niches.

New host-virus interactions and pathways are identified thanks to

technological advances as proteomic studies [24] and can thus be explored for the development of HDAs.

In this context, autophagy regulation, which could either be

inhibited or induced, depending on the virus and its interactions with the autophagic machinery, results to be a promising HDA. This HDA approach may present various advantages, one of the most important being the lower resistance induction potential in comparison to virus-targeting antivirals. In fact, HDAs induce a lower selective pressure, limiting viral resistance [25], which would require the virus to exploit alternative host pathways for replication. Moreover, this approach explores highly conserved host targets, and hosts genetic variability is low when compared to viruses, enabling the development of broad-spectrum antivirals targeting conserved host targets possibly effective also against emerging and re-emerging viruses. Nonetheless, autophagy as HDA may also present some limitations, these include the variability and responsiveness of different viral strains to this strategy, that is connected to the double-edged nature of autophagy in the context of antiviral therapy. Furthermore, autophagy has a critical role in the maintenance of cellular homeostasis, thus altering this mechanism may lead to toxicity or metabolic deregulation. Autophagy is also linked to the innate immune response, cell signaling, and antigen presentation, whose deregulation can result in a compromised host immunity [10,26,27].

4. Antioxidant antivirals

Reactive oxygen species (ROS) are secondary products of physiological cellular metabolism but they can also be produced by mitochondria through interaction between mitochondrial membrane and viral proteins that trigger mitochondrial transmembrane potential (MMP) depolarization and increased ROS production. This latter event ultimately triggers the antiviral innate response via type I interferon pathways [28]. Nonetheless, an increase in ROS levels has been demonstrated to favor viral replication, and in this context, the manipulation of mitochondrial functions is exploited by viruses to proliferate in the host, even though high ROS levels contribute to antiviral immunity and oxidative structural changes and cell death. The ROS production that leads to viral functional advantages can be direct when the ROS induce oxidative changes of viral protein activities, and in parallel it can be indirect with the modulation of host-signaling pathways [8,29]. Studies report increase of oxidative stress and ROS production induced by virus-triggered imbalances in the antioxidant defense mechanisms of cells as for SARS-CoV-2 and Japanese encephalitis virus [30]. Alongside, an excessive ROS production can play a negative role in certain cases, worsening the scenario, as in the case of influenza A virus infections, in which an overwhelming host immune response that initiates the cytokine storm and an over-production of superoxide and ROS in general can lead to fatal prognosis due to acute lung injury [8].

Antioxidants and ROS inhibitors come in play as HDAs that may lead to a decrease in pathogenesis and viral replication [29], complying with the aforementioned advantages of HDAs strategy and additionally furnishing protection against virus-induced cellular and tissue damage due to oxidative damage and modulation of the immune and inflammatory response mitigating cytokine storm and inflammation.

5. Combining autophagy modulation to antioxidant activity of phytocomplexes and natural extracts for dual acting antivirals

Phytocomplexes and natural extracts offer a plethora of biological activities depending on the composition of the mixture. The presence of secondary metabolites as polyphenols may confer antioxidant properties and the presence of other secondary metabolites may exert antimicrobial activity produced by plants for self-protection. As a consequence, these complex phytochemical mixtures may present a dual role as antivirals, even though the interplay between antioxidant activity and autophagy modulation has not been elucidated for the proposed extracts. Nonetheless studies report the pharmacological and therapeutic superiority exerted by herbal drug combinations in comparison to isolated single constituents, in part due to the complex pathophysiology of infections but also to the capability of natural extracts to exert

synergistic multi-target effects [11].

This chapter aims to underscore the potential of exploring phytocomplexes as a reservoir for novel antiviral autophagy modulators endowed with antioxidant activity, a complete summary is reported in Table 1. Acknowledging the inherent complexity of these plant-derived mixtures, we can appreciate the diverse array of compounds collectively contributing to their biological activities. This complexity, while posing challenges, presents numerous opportunities for identifying promising lead compounds and revealing novel mechanisms of action.

5.1. *Lychee flower extract*

Phytochemical Composition and Bioactive Properties - Lychee contains a rich variety of bioactive phytochemicals, including phenolics, flavonoids, triterpenoids, saponins, and terpenes, which are found throughout its fruit, seeds, leaves, pericarp and flowers. These compounds contribute to its numerous pharmacological benefits, such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic, cardioprotective, hepatoprotective, immune-supporting, anticancer, and neuroprotective effects [31]. Lychee flower extracts (LFE) are known for their antioxidant, anti-inflammatory and antimicrobial activity due to the presence of flavonoids, polyphenols and phenolic acids obtained through acetone, ethanol, methanol and hot-water extraction of the lyophilized flowers [32,33]. The composition of extracts and mixtures is determined by HPLC, total polyphenol content and total flavonoid measurements [34,35].

Antioxidant Activity - Yang et al. have reported for the first time the clear components underlying their ROS scavenging activity, identifying (–)-epicatechin and proanthocyanidin A2 as active antioxidant compounds from lychee flower acetone extracts and reporting also significant in vitro antioxidant activity and phenolic content [32]. Liu et al. also reported that LFE contain exceptionally high levels of antioxidant compounds, particularly phenols, flavonoids, and condensed tannins, comparing different solvents for extractions: with acetone extraction yielding significantly higher concentrations than methanol or water extraction. As a result, the acetone extract exhibited the strongest antioxidant activity, achieving nearly 95% DPPH free-radical scavenging and the highest TEAC value, with antioxidant capacity strongly correlated with its phenolic, flavonoid, and tannin content [31].

Autophagy Mediated Antiviral Mechanism - In addition to its antioxidant properties, this extract has been studied also for its antiviral activity against HSV-1. HSV-1 ocular infections can induce a spectrum of diseases, including herpes simplex virus keratitis (HSK). This pathology poses a substantial threat to ocular health, with potential outcomes including stromal scarring, thinning, and neovascularization, leading to irreversible vision impairment [33]. In their investigations, Hsu et al. examined the effects of LFE on HSV-1-infected Statens Serum Institut rabbit corneal (SIRC) epithelial cells. The composition of the ethanolic extract was analyzed. The main active ingredients detected were flavonoids (i.e. epicatechin, rutin, naringin, quercitrin, and neohesperidin), phenolic acids (i.e. gallic acid, gentisic acid, chlorogenic acid, vanillic acid, p-coumaric acid, ferulic acid, sinapic acid, syringic acid, p-anisic acid) and proanthocyanidin A2. The experimental design involved the pre-treatment of SIRC cells with varying concentrations of LFE before exposure to HSV-1 for 24 h. Assessment of cell viability and morphology indicated a notable inhibitory effect of LFE on HSV-1-induced cell proliferation. Mechanistically, the antiviral attributes of LFE were associated with the modulation of mTOR and p70s6k phosphorylation. Furthermore, LFE enhanced the expression of autophagy-related proteins, including Beclin-1 and LC3, while concurrently reducing viral loads [36]. While the therapeutic effect of LFE against HSK was established in this study, the specific contribution of each active ingredient to this antiviral capability remains elusive. Hence, it could serve as a foundational exploration of the chemical profile of LFE, offering a valuable starting point for further investigations into the individual roles and synergistic effects of the phytocomplex components.

Table 1

Summary of phytocomplexes and natural extracts endowed with antioxidant and antiviral activity.

Plant	Type of extract	Identified compounds	Antioxidant activity	Antiviral activity through autophagy modulation	Ref
Lychee flower extract	Acetone, methanol, ethanol and hot water extracts	epicatechin, rutin, naringin, quercitrin, proanthocyanidin A2 and neohesperidin, (flavonoids); gallic acid, gentisic acid, chlorogenic acid, vanillic acid, p-coumaric acid, ferulic acid, sinapic acid, syringic acid, p-anisic acid (phenolic acids)	In vitro antioxidant activity through DPPH radical scavenging activity, copper ion-induced oxidation of LDL inhibition	Antiviral activity against HSV-1, through induction of autophagy on the initiation step (1)	[32,36]
Aloe vera extract	Ethanolic extracts	Quercetin, kaempferol and catechin hydrate (flavonoids)	In vitro antioxidant activity through DPPH free radical-scavenger tests and ROS reduction	Anti-influenza virus activity through autophagy suppression against M2 viral-induced autophagy	[39,40]
JieZe-1 extract	Water decoction and ethanolic extract	Berberine, dictamine (alkaloids), paeoniflorin (terpenoid), neoastilbin, astilbin (flavonoids), paenol (polyphenol)	No specific studies on JieZe-1 extract	Autophagy induction through ATG1/ULK1 complex activation step (1)	[41,42]
Scutellaria barbata & olenlandia diffusa extracts	Ethanol, and ethyl acetate extracts	Scutellarin, luteolin, apigenin and related flavones (flavonoids) ursolic acid (terpenoids)	Antioxidant activity through free-radical scavenger and ROS reduction in vitro assays	Antiviral activity against HBV by inhibiting the nucleation step (2) through inhibition of Beclin1 and LC3B	[45,48]
Eupatorium perfoliatum extract	Ethanol, ethyl acetate, n-butanol, chloroform, and petroleum extracts	Quercetin, eupafolin and rutin (flavonoids) protocatechuic acid and caffeic acid (phenolic acid)	Free radical-scavenger activity	Anti-DENV activity through modulation of autophagy initiation step (1) through mechanisms that still need to be clarified	[50,51]
Green tea extract	Water extract, extraction with ultrasound and deep eutectic solvents	Catechins as epigallocatechin-3-gallate, epicatechin gallate, epicatechin, epigallocatechin, gallic acid, kaempferol, quercetin and myricetin (flavonoids/flavonols)	Oxidative stress modulator and ROS scavenger	Antiviral activity against SARS-CoV-2 through autophagy induction on the initiation phase (1)	[53,55]
Huanglian-ganjiang extract	Non-specified	Berberine (alkaloid), various polyphenols	Wide antioxidant and redox-modulating activity	Activity against H1N1 infections through a dual modulation of the autophagic machinery: reduction of autophagosome production (3) and induction of the fusion of autophagosome and lysosome (4)	[56,57]
Isatis indigotica extract	Water extract	cyandin 3-glucoside, taxifolin, quercetin, astragalin, isovitexin 2"-O-beta-D-glucoside (flavonoids), phenolic compounds, and other secondary metabolites	General antioxidant activity of the mature fruit extracts	Activity against H1N1 infections through inhibition of autophagosome accumulation step (3)	[60,61]
Moringa oleifera extract	Hydroalcoholic extract	Moringa A (glycoside), quercetin, kaempferol (flavonoids), polyphenols, carotenoids, vitamin C and vitamin E	Modulation of endogenous antioxidant activity and ROS scavenging capacity	Antiviral activity against VZV, HIV, HBV and H1N1, specifically anti-H1N1 activity through late stage inhibition of autophagy (step 5 lysosome biogenesis and function in degradation)	[63,64]
Boesenbergia rotunda extract	Ethanol, ethyl acetate and chloroform extracts	Panduratin A (prenylated chalcone), pinostrobin and pinocembrin, various other flavonoids and chalcone derivatives	General antioxidant activity	Antiviral activity through induction of autophagy during initiation step (1)	[65,69]

Future research could focus on elucidating which compound can modulate the autophagic machinery, thereby advancing our understanding of the potential therapeutic applications of natural compounds as antiviral autophagy modulators.

5.2. Aloe vera extract

Phytochemical Composition and Bioactive Properties - *Aloe vera* has been cherished for centuries as "Nature's silent healer". Endowed with anti-inflammatory, antioxidant, antimicrobial, and antiviral properties, it remains a timeless natural remedy with diverse applications such as in burn treatments and constipation. Complementing its well-known cosmetic and nutraceutical properties, it has been under investigation for the treatment of a wide range of diseases [37,38].

Antioxidant Activity - Within the scope of this review, *Aloe vera* extracts (AVEs) exhibited significant antioxidant activity in vitro, as demonstrated by the ability to scavenge free radicals and reduce oxidative agents in multiple assay systems. The extracts showed dose-dependent radical-scavenging activity, particularly in DPPH and ABTS assays, indicating effective neutralization of reactive oxygen species. The antioxidant capacity was found to correlate with the presence of phenolic compounds and flavonoids, suggesting that these constituents play a major role in the observed activity. Overall, the results pinpoint

that AVEs possess moderate to strong antioxidant potential, which may contribute to their protective effects against oxidative stress-related cellular damage [39].

Autophagy Mediated Antiviral Mechanism - AVEs also exhibited noteworthy anti-influenza virus activity, though the precise mechanisms and constituents responsible for the antiviral effect had not been elucidated yet. A pivotal study conducted on MDCK cells, revealed that AVEs treatment significantly reduced the replication of IAV, impacting matrix protein 1 (M1), matrix protein 2 (M2), and hemagglutinin (HA) mRNA synthesis, as well as viral protein expressions. The investigation identified quercetin, catechin hydrate, and kaempferol as active antiviral components in AVEs. Furthermore, AVE was found to inhibit IAV-induced autophagy in MDCK cells. Molecular docking simulations suggested a higher binding affinity of these compounds for the M2 protein compared to known M2 protein inhibitors. Importantly, AVE's antiviral properties were linked to the inhibition of viral-induced autophagy, highlighting its potential against autophagy-exploiting viruses (for example H1N1 or H3N2). The study also demonstrated that autophagy inhibition, achieved with 3-methyladenine, decreased viral yield, supporting the essential role of autophagy in IAV replication. AVE and its constituents, particularly catechin hydrate and quercetin, exhibited significant antiviral effects by suppressing autophagy and inhibiting M2 protein, presenting promising avenues for developing anti-influenza

agents. The research underscores the need for further exploration into the anti-autophagy characteristics of herbal compounds, shedding light on their potential in combating influenza viral infections [40].

5.3. JieZe-1 extract

Phytochemical Composition and Bioactive Properties - JieZe-1 is a herbal prescription derived from Yihuang Tang, a traditional Chinese medicine used to treat several reproductive system diseases, including prostatitis, cervicitis, *Candida albicans* and *Trichomonas vaginalis* infections. It is a mixture of *Phellodendron chinense*, *Ginkgo biloba*, *Solanum nigrum*, *Taraxacum mongolicum*, *Thlaspi arvense*, *Dictamnus dasycarpus*, *Smilax glabra*, *Paeonia suffruticosa*, *Mentha haplocalyx*, and *Borneolum syntheticum*.

Antioxidant Activity - Although direct antioxidant activity of JieZe-1 has not been specifically investigated yet, its constituents, as in many traditional herbal formulations, may contain polyphenolic compounds with potential ROS-modulating effects, which could contribute to HDA activity alongside documented immunomodulatory effects.

Autophagy Mediated Antiviral Mechanism - Aiming to treat genital herpes, a preliminary study was conducted on HSV-2-infected human vaginal epithelial cells to evaluate the antiviral effect of JieZe-1. The study revealed that HSV-2 blocked autophagy in VK2/E6E7 cells by activating the PI3K/Akt/mTOR pathway, thus inhibiting autophagic flux. JieZe-1 demonstrated great promise by promoting autophagy, reducing viral protein expression, and enhancing cell vitality. Experimental data demonstrated that the herbal prescription inhibited the PI3K/Akt/mTOR pathway, fostering autophagy to counteract HSV-2 infection. Moreover, JieZe-1 mitigated the increase in inflammatory cytokines induced by HSV-2 infection [41]. Building upon these findings, a follow-up study performed by the same authors bridged the gap of demonstrating JieZe-1's efficacy in vivo. The experimental design employed a mouse model of HSV-2-induced genital herpes. Administration of JieZe-1 significantly reduced symptom severity, improved weight gain, and mitigated histological damage in HSV-2-infected mice. Validating in vitro data, JieZe-1 attenuated inflammatory responses, characterized by reduced infiltration of inflammatory cells and lower levels of local cytokines. Furthermore, HSV-2 infection-induced cell apoptosis was alleviated by JieZe-1 treatment, with observed restoration of autophagic flux. Inhibition of autophagy correlated with increased apoptosis, while promotion of autophagy reduced apoptosis, indicating the protective role of JieZe-1 through autophagy induction. Additionally, JieZe-1 downregulated the PI3K/Akt/mTOR signaling pathway, providing insights into its mechanism of action in vivo [42]. Further identification of the main bioactives of the phytocomplex could pave the way for the development of novel antiviral autophagy modulators.

5.4. *Scutellaria barbata* & *Oldenlandia diffusa* extracts

Phytochemical Composition and Bioactive Properties - *Scutellaria barbata* (SB) also known as Ban-Zhi-Lian is a perennial herb widely used in traditional Chinese medicine for the treatment of inflammation, tumors, and gynecological disorders. Extracts of SB, long known in traditional Chinese medicine, contain a wide range of phenolic compounds and flavonoids, including scutellarin and related flavones, which are widely recognized for their antioxidant and antimicrobial properties. Similarly, *Oldenlandia* species, formerly known as *Hedyotis*, contain a variety of bioactive compounds, including iridoids, flavonoids, triterpenes, phenolic acids, coumarins, and phytosterols, which contribute to their broad pharmacological potential. Among these constituents, ursolic acid is considered a key active compound due to its anticancer, anti-inflammatory, antimicrobial, and hepatoprotective properties [43]. The phytochemical analysis of the SB root extract was carried out by LC-ESI-MS as well as HPLC-DAD techniques [44].

Antioxidant Activity - Studies reported that extracts and isolated constituents from SB exhibit free radical-scavenging activity and

reducing capacity in vitro, indicating a measurable antioxidant potential, even though the antioxidant activity was not the primary pharmacological activity of this extract [45]. Liu et al. reported the comparison between ethanolic and ethyl acetate extract, specifically, both extract presented a diverse range of bioactive compounds, including phenolics, flavonoids, chlorophylls, carotenoids, polysaccharides, saponins, tannins, alkaloids, terpenoids, and steroids, with the ethanolic extract yielding approximately twice the total functional components of ethyl acetate extraction and demonstrating to be particularly enriched in phenolics and flavonoids, whereas the ethyl acetate extract contained higher levels of chlorophylls and carotenoids. These compounds have been associated with dose-dependent anti-inflammatory activity on RAW 264.7 cells through suppression of NF- κ B signaling and reduced production of pro-inflammatory mediators, including nitric oxide, prostaglandin E₂, IL-1 β , and IL-6 [46].

Autophagy Mediated Antiviral Mechanism - Moreover, antiviral activity of this extract has been reported against chronic HBV infections. These are a major risk factor for hepatocellular carcinoma, accounting for 50–80% of cases worldwide. Within the array of ethnomedicines employed for detoxification and clearing heat, SB and OD emerged as attractive alternatives for the treatment of hepatocellular carcinoma (HCC), as both herbs are endowed with anti-tumor, anti-inflammatory, anti-oxidative, and immunomodulatory therapeutic properties [45,47]. A study investigated the potential therapeutic effects of SB and OD extracts on HBV-related HCC cell lines. The extracts were found to contain several flavonoids, with active ingredients like luteolin and apigenin identified in SB but not in OD. In vitro and in vivo experiments demonstrated that SB and OD extracts significantly inhibited HCC growth, migration, invasion, and HBV activity. Cellular changes observed included nuclear membrane shrinkage, altered nuclear/cytoplasmic ratio, condensed nuclei, crescent-shaped nuclear fragmentation, increased vacuoles, damaged mitochondria, and the presence of autophagosomes, lysosomes, and exosomes. Furthermore, a circRNA-miRNA co-expression network was constructed, revealing alterations in gene expression. Notably, cellular immunofluorescence indicated reduced aggregation of autophagy-associated proteins Beclin1 and LC3B after treatment with SB and OD extracts. Overall, the findings suggest that the extracts of SB and OD may impede HCC cell growth and HBV activity through the circRNA-miRNA-gene expression and autophagy pathways, with the presence of luteolin and apigenin potentially contributing to their efficacy [48]. Further investigations are warranted to elucidate the specific mechanisms underlying the modulation of autophagy. This will contribute to a more comprehensive understanding of the therapeutic potential of SB and OD extracts in combating HBV-related hepatocellular carcinoma and may pave the way for the development of novel host-targeting antiviral agents.

5.5. *Eupatorium perfoliatum* extract

Phytochemical Composition and Bioactive Properties - *Eupatorium perfoliatum* (EP), or boneset, has traditionally been used by Native North American populations as a remedy for fever and as a diaphoretic agent. Its phytochemical profile is dominated by flavonoids, including kaempferol, quercetin, rutin, hyperoside, isoquercitrin, hispidulin, eupafolin, and patuletin, with eupafolin being of particular interest for its anti-inflammatory activity through inhibition of the NF- κ B signaling pathway [49].

Antioxidant Activity - Habtemariam reported the antioxidant activity of the ethanolic extract of EP, demonstrated through DPPH radical-scavenging and ferric reducing power assays. Different solvents were tested for extraction of the components, and the ethyl acetate fraction showed the strongest antioxidant effect, approximately 20 times more potent than the crude extract, and the highest total phenolic content, while reducing power assays confirmed the same activity ranking (ethyl acetate > n-butanol > crude extract > chloroform > light petroleum fraction). Activity-guided fractionation subsequently led to

the identification of key antioxidant constituents, including protocatechuic acid and rutin, which are believed to contribute to the plant's traditional medicinal properties. [50].

Autophagy Mediated Antiviral Mechanism - On the other hand, the molecular mechanism responsible for the antiviral effects of EP extract and its bioactive components, namely quercetin, caffeic acid, and eupafolin, was investigated in a DENV-infected HepG2 cell line. The results indicated that pre-treatment with EP extract exhibited substantial antiviral activity, significantly reducing DENV replication. Quercetin, among the phytochemicals, displayed significant preventive efficacy against DENV infection. Molecular docking analysis suggested that quercetin may act as a competitive inhibitor against T-cell immunoglobulin and mucin domain 1 (TIM-1) transmembrane receptor protein, a critical element in viral invasion. The study also revealed the ability of EP extract to regulate DENV-induced autophagy, potentially through the modulation of Akt and mTORC2 protein expressions. These findings proposed a complex mechanism of action for EP extract, indicating its potential as an effective anti-DENV agent. Additional research to identify other polyphenols contributing to the observed antiviral activity and validation across diverse in vitro and in vivo models are needed. Nonetheless, this study provided valuable insights into the mechanism of action of EP in viral infections [51].

5.6. Green tea extract

Phytochemical Composition and Bioactive Properties – Green tea leaves contain a diverse range of bioactive compounds, including catechins, flavonols, phenolic acids, caffeine, polysaccharides, vitamins, minerals, volatile oils, and thearubigins. The major polyphenols are catechins, in particular epigallocatechin gallate (EGCG), which accounts for approximately 60% of total catechins, as well as flavonols such as kaempferol, quercetin, and myricetin. These compounds are characterized using HPLC and are associated with antioxidant, anti-inflammatory, antibacterial, antiviral, and vascular-protective activities, with green tea generally exhibiting higher antioxidant capacity than darker tea varieties due to its greater polyphenol content [52].

Antioxidant Activity - Green tea catechins exert antioxidant activity through direct scavenging of reactive oxygen species, metal ion chelation, and regulation of redox-sensitive signaling pathways. Importantly, Guo et al. emphasize that tea polyphenols do not function solely as classical antioxidants but rather as redox modulators, influencing endogenous antioxidant defenses and cellular stress responses. Their antioxidant effects are shown to be dose- and context-dependent, with potential pro-oxidant activity under specific conditions, which contributes to adaptive cellular responses rather than simple ROS suppression [53].

Luo et al. compared different extraction methods, comprising traditional ethanol extraction, ultrasonic-mediated extraction, hot-water extraction and a combination of ultrasound and deep eutectic solvent extraction. Extracts obtained with the latter combination presented a higher concentrations of the major catechins, (–)-epigallocatechin, (–)-epicatechin, (–)-epigallocatechin gallate, and (–)-epicatechin gallate, demonstrating superior antioxidant activity which was evaluated using ferric-reducing antioxidant power, DPPH radical-scavenging, and ABTS radical-scavenging assays [54].

Autophagy Mediated Antiviral Mechanism - Moreover, in the context of HDA, a study focused on uncovering the potential of polyphenol catechins for the treatment of COVID-19. The research evaluated their therapeutic effects on SARS-CoV-2 replication, their preventive influence on CD25/CD69/CD94/CD8⁺ cytotoxic T lymphocytes-mediated adaptive immunity, and their protective role against lipopolysaccharide-induced acute lung injury (ALI) in mice. The findings revealed that a formulation including 32.8% epigallocatechin gallate, 15.2% epicatechin gallate, 13.2% epicatechin, 10.8% epigallocatechin, 10.4% gallocatechin, and 4.4% catechin inhibited SARS-CoV-2 replication at sub-micromolecular concentrations. In mice, 4-week

administration of catechins led to a significant increase in CD8⁺ T cell percentage and upregulated CD69⁺/CD25⁺/CD94-NKG2A/CD8⁺ T lymphocytes-mediated adaptive immunity. Additionally, catechins reduced LPS-induced cytokine storm and oxidative stress in ALI by modulating the PI3K/AKT/mTOR signaling pathway to enhance autophagy. Western blot analysis revealed that catechins increased the expression of autophagy-related proteins (Beclin-1, Atg5-Atg12, LC3-II) and inhibited apoptosis markers (cleavage caspase 3, PARP) in the LPS-induced ALI model. Furthermore, catechins suppressed the phosphorylation of PI3K/AKT/mTOR proteins, indicating their involvement in catechins-induced autophagy enhancement during LPS-induced ALI. It was found that pretreatment with 3-methyladenine inhibited the catechins-induced activation of autophagy-related proteins and reversed the suppression of apoptosis signaling enhanced by LPS. Additionally, the levels of phosphorylated PI3K/AKT/mTOR proteins, which are associated with autophagy regulation, were restored after 3-MA administration, suggesting the involvement of the PI3K/AKT/mTOR pathway in the enhancement of autophagy by catechins during LPS-induced ALI. These results imply that catechins exert their protective effects against ALI partially through the induction of autophagy. This effect is attenuated by 3-MA treatment, further emphasizing the significance of autophagy modulation in the observed outcomes. The collected data suggested that catechins effectively reduced cytokine storm and oxidative stress levels by PI3K/AKT/mTOR-signaling-mediated autophagy, ameliorating ALI in vivo and presenting potential applications in the prevention and treatment of SARS-CoV infection [55].

5.7. Huanglian-ganjiang extract

Phytochemical Composition and Bioactive Properties - “Huanglian” or *Coptidis Rhizoma*, *Coptis chinensis*, and “ganjiang” or *Zingiberis Rhizoma*, *Zingiber officinale* Roscoe, is a traditional Chinese remedy often used for treating gastrointestinal and respiratory diseases. The principal bioactive compounds of this extract are berberine and 6-gingerol, respectively. Berberine has demonstrated antiviral activity against influenza and has also shown therapeutic potential in managing hyperglycemia and dyslipidemia, while 6-gingerol exhibits antipyretic, analgesic, anti-inflammatory, antibacterial, and immunomodulatory properties [56].

Antioxidant Activity – This mixture exhibits antioxidant and redox-modulating properties largely attributable to berberine-rich *Coptis chinensis* and polyphenol-rich *Zingiber officinale*, with antioxidant effects contributing to its broader anti-inflammatory and cytoprotective actions [57].

Autophagy Mediated Antiviral Mechanism - The herb pair has recently also been examined for its potential to treat H1N1-induced acute pulmonary inflammation in a mouse model. Huanglian-ganjiang exhibited notable effects, including inhibition of cytokine IL-6 expression and stimulation of IL-2 expression in the serum of influenza virus-infected mice, in a dose-dependent manner. Furthermore, the extract downregulated the gene and protein expression levels of several key targets involved in toll-like and RIG-I-like receptor signaling pathways, namely TLR3, TLR7, MyD88, RIG-I, MAVS, TRAF3, and NF- κ B p65. Additionally, it promoted the fusion of intracellular autophagosomes and lysosomes, thereby improving impaired H1N1-induced autophagosome-lysosome fusion. Moreover, the extract inhibited the proliferation of influenza viruses in autophagosomes by suppressing the production of autophagosomes and reversing impaired autophagosome-lysosome fusion. The expression of the autophagy marker protein LC3-II was also significantly inhibited by the herbal extract, further corroborating its anti-influenza virus effects. Overall, these findings highlighted the potential of this herbal extract to mitigate influenza virus infection by restoring intracellular autophagy processes and modulating cytokine levels [56].

5.8. *Isatis indigotica* extract

Phytochemical Composition and Bioactive Properties – *Isatis indigotica* a flowering plant belonging to the Brassicaceae family, it is widely used in traditional Chinese medicine for its antiviral, antibacterial, anti-inflammatory, detoxifying, and blood-cooling properties, particularly through its roots and leaves. Its major bioactive constituents include indigotin and indirubin, which exhibit hepatoprotective, antimicrobial, and antitumor activities, along with flavonoids, nucleosides, alkaloids, organic acids, lignans, steroids, amino acids, and sulfur-containing compounds that contribute to its broad pharmacological effects [58,59].

Antioxidant Activity – Moreover, *Isatis indigotica* fruits possess a high antioxidant potential. Metabolomic and transcriptomic analyses revealed an accumulation of multiple antioxidant-related metabolites, including phenolic compounds, flavonoids, and other secondary metabolites, whose levels increase during fruit development, representing a rich source of naturally synthesized antioxidants, with antioxidant capacity arising from coordinated metabolic and genetic regulation rather than from isolated compounds alone [60].

Autophagy Mediated Antiviral Mechanism – Furthermore, it has recently been the subject of a study assessing its antiviral properties against H1N1 viral strain. *Isatis indigotica* extract (IIE) exhibited no cytotoxic effects on A549 cells at concentrations up to 40 mg/mL but demonstrated rescue effects on IVA-infected cells. IIE's CC₅₀ on A549 cells was approximately 250 mg/mL, with a selectivity index for H1N1 of 12.5. IIE inhibited IVA propagation by reducing viral mRNA levels in a dose-dependent manner. Notably, IIE interfered with crucial steps in the IVA replication cycle, including viral attachment, internalization, and release. Additionally, IIE significantly reduced the production of key viral proteins, including M1, M2, NP, which are essential for viral replication and assembly. IIE hindered autophagosome accumulation, thus impeding viral replication, and showed a potential cytoprotective effect against IVA infection. Further investigation into the main component, epigoitrin, revealed similar anti-IVA activities as IIE, suggesting its importance in the extract's efficacy [61]. In vivo studies are needed to confirm the full potential of the antiviral effects of *Isatis indigotica* and epigoitrin.

5.9. *Moringa oleifera* extract

Phytochemical Composition and Bioactive Properties – In recent years, moringa has been labeled as a “superfood” due to the great nutritional profile and health benefits it offers. The term usually refers to the powder leaf extract of *Moringa oleifera*, a deciduous tree indigenous to the Indian subcontinent. In ethnomedicine, the plant has been traditionally used to treat wounds, pains and ulcers, but also for inflammation-related diseases. Phytochemical studies have revealed over 90 compounds in the genus *Moringa*, including proteins, amino acids, phenolic acids, flavonoids, glucosinolates, alkaloids, carotenoids, sterols, terpenes, tannins, saponins, fatty acids, glycosides, and polysaccharides [62].

Antioxidant Activity – The leaves extract displays a rich source of antioxidant bioactive compounds, including polyphenols, flavonoids (such as quercetin and kaempferol), phenolic acids, carotenoids, and vitamins C and E. These components contribute to the plant's strong antioxidant capacity, acting through both direct scavenging of ROS and modulation of endogenous antioxidant defenses. The work by Vergara-Jimenez [63] emphasizes that the antioxidant activity of *M. oleifera* plays a key role in reducing oxidative stress-associated damage, thereby contributing to its protective effects against chronic diseases. Rather than functioning solely as a chemical antioxidant, *M. oleifera* is presented as a redox-modulating phytocomplex that supports cellular homeostasis [63].

Autophagy Mediated Antiviral Mechanism – In addition to its antioxidant activity, it also displays a noteworthy antiviral activity against Herpes Zoster virus (VZV), HIV, and HBV. Xiong et al. isolated *Moringa*

A (MA), a symmetric glycoside, which turned out to exert an interesting anti-H1N1 activity. A detailed analysis elucidated the mechanism of action underlying MA's antiviral activity on this influenza virus. MA effectively inhibited the replication of IAVs in RAW264.7 cells, showcasing a virucidal activity. Notably, the compound demonstrated a remarkable ability to protect infected cells from H1N1-induced cytopathic effects. The study observed a significant reduction in the levels of pro-inflammatory cytokines, including TNF- α , IL-6, IL-1 β , and IFN- β , potentially mitigating the cytokine release syndrome associated with severe cases. The compound was found to inhibit the expression and nuclear transfer of transcription factor EB (TFEB), a master regulator of macroautophagy and lysosome function. TFEB inhibition correlated with a significant reduction in autophagic activity in infected cells. The study demonstrated that MA's interference with autophagy led to a substantial decrease in virus production, highlighting this critical aspect of its antiviral action. Additionally, the research explored the temporal aspects of MA's antiviral activity by conducting different treatment experiments. MA exhibited inhibitory effects when added both before and after H1N1 infection, suggesting its effectiveness against various stages of the viral replication cycle. The study also linked TFEB to the regulation of H1N1 virus replication. The upregulation of TFEB expression during H1N1 infection suggested its involvement in virus-triggered autophagy. Silencing TFEB resulted in a significant reduction in virus particle production, highlighting the crucial role of TFEB in H1N1 replication [64]. Overall, these comprehensive experimental results provide valuable insights into the mechanism by which MA exerts its antiviral effects, making it a promising candidate for further development as a preventive and therapeutic agent against influenza virus infections.

5.10. *Boesenbergia rotunda* extract

Phytochemical Composition and Bioactive Properties – *Boesenbergia rotunda* is a medicinal plant widely used in Southeast Asia and traditional Chinese medicine for the treatment of gastrointestinal disorders, where it is valued for promoting Qi circulation, improving appetite, and alleviating pain and digestive discomfort. Phytochemical studies have identified more than 200 metabolites, including flavonoids, monoterpenes, alkaloids, phenols, and diterpenes, which contribute to its diverse pharmacological activities, such as anticancer, anti-inflammatory, antibacterial, antioxidant, hepatoprotective, nephroprotective, and anti-obesity effects [65,66].

Antioxidant Activity – Jitvaropas and coworkers reported the antioxidant activity of the ethanolic extract of *Boesenbergia rotunda*, which demonstrated a moderate antioxidant activity, supporting its potential use in wound healing by reducing microbial burden and oxidative stress. Antioxidant capacity was evaluated using DPPH free-radical scavenging and ferric reducing antioxidant power assays, which showed measurable free-radical scavenging and reducing activities, although weaker than standard antioxidants such as vitamin E and butylated hydroxytoluene [67]. Similarly, Atum et al. performed a comparative extraction with different solvents (ethanol, ethyl acetate and chloroform), which led to the isolation of three major flavonoids, including pinostrobin and pinocembrin, from ethyl acetate and chloroform fractions. Antioxidant activity was evaluated using the DPPH free-radical scavenging assay, and both the ethanolic extract and isolated compounds exhibited strong radical-scavenging effects, with significant antioxidant potential [68].

Autophagy Mediated Antiviral Mechanism – Modern investigations also assessed its inhibitory activity against HIV-1 protease, DENV NS2B/NS3 protease and its therapeutic effect against hand-foot-and-mouth disease [65]. During the COVID-19 public health emergency, intensive research efforts focused on the identification of effective antiviral candidates. Aiming to identify anti-SARS-CoV-2 bioactives, a high-content screening of 122 Thai natural products was carried out. *B. rotunda* extract and its main phytochemical, panduratin A, demonstrated potent anti-SARS-CoV-2 activity. Treatment with *B. rotunda* extract and

panduratin A significantly suppressed SARS-CoV-2 infectivity in Vero E6 cells, displaying an IC_{50} of 3.62 $\mu\text{g/mL}$ (CC_{50} = 28.06 $\mu\text{g/mL}$) and 0.81 μM (CC_{50} = 14.71 μM), respectively. Interestingly, panduratin A showed efficacy both pre- and post-infection and also exhibited effectiveness in human airway epithelial cells. Panduratin A has been found to trigger autophagy, essential for limiting viral replication, although concerns arise regarding its potential dual role in aiding viruses to evade the host's immune response. Its induction of autophagy in mammalian cells involves AMPK activation and mTOR inhibition. Additionally, it can activate AMPK signaling, leading to PPAR α and PPAR δ activation, further promoting autophagy. It is known that MERS-CoV disrupts autophagosome-lysosome fusion, hindering autophagy and aiding viral replication. However, whether panduratin A actually suppressed SARS-CoV-2 via autophagy induction and its specific target pathway remain unclear [69]. Further investigation may support the gathered results, pinpointing *B. rotunda* extract and panduratin A as economically advantageous candidates for COVID-19 treatment.

6. Conclusions and future perspectives

Phytocomplexes represent a vast and strategically significant reservoir for the development of novel dual-acting host-directed antivirals that bridge antioxidant defense and autophagic regulation. The inherent complexity of these natural mixtures allows multi-target effects, addressing the multifaceted pathophysiology of viral infections where oxidative stress often facilitates viral functional advantages and disease progression. Nonetheless, the mechanistic interplay between antioxidant activity and autophagy modulation has not yet been fully elucidated for the phytocomplexes discussed herein. Therefore, while the available evidence supports the coexistence of both activities within these extracts, a comprehensive characterization of their functional interconnection will require dedicated mechanistic studies and remains an important area for future investigation. Additionally, evidence from the study of various extracts demonstrates that pharmacologically modulating the host's autophagic flux can either restore pathogen clearance or revert the viral hijacking of intracellular membranes and the host autophagic machinery. These synergistic effects may arise from the simultaneous modulation of multiple host and viral targets by chemically diverse phytocomponents of the extracts, as well as from pharmacokinetic interactions that influence the absorption, cellular uptake, stability, or bioavailability of individual components. However, the characterization of these interactions is complicated by the intrinsic complexity of phytocomplexes, variability in chemical composition due to different extraction techniques, herbs, roots and flower stocks and origin of substrate, differences in the cellular permeability of individual constituents, and the potential occurrence of off-target effects associated with crude extracts. Moreover, the transition from basic research to clinical application faces significant hurdles, including the need for precise characterization of chemical profiles, the assessment of potential off-target toxicities, and the optimization of pharmacokinetic properties for these complex mixtures. Future medicinal chemistry efforts should focus on identifying lead scaffolds within these phytocomplexes and conducting rigorous in vivo studies to validate their efficacy and safety. Moreover, key challenges as standardization of extracts, reproducibility of bioactivity, and mechanistic deconvolution in complex matrices, while advocating for systems biology and metabolomics approaches to elucidate synergistic interactions should be addressed. Ultimately, leveraging the structural diversity of natural products to target conserved host pathways offers a robust path forward for the development of broad-spectrum therapies capable of safeguarding public health against future pandemics.

CRediT authorship contribution statement

Sara Rossi: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Ilaria Cursaro:** Writing – review &

editing, Writing – original draft, Data curation. **Gabriele Carullo:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mariachiara Pieroni:** Writing – review & editing, Visualization, Data curation. **Stefania Butini:** Writing – review & editing, Data curation. **Sandra Gemma:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Giuseppe Campiani:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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