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Nutraceutical prospects of *Houttuynia cordata* against the infectious viruses

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ABSTRACT

The novel enveloped β -coronavirus SARS-CoV-2 (COVID-19) has offered a surprising health challenge all over the world. It develops severe pneumonia leading to acute respiratory distress syndrome (ARDS). Like SARS-COV-2, other encapsulated viruses like HIV, HSV, and influenza have also offered a similar challenge in the past. In this regard, many antiviral drugs are being explored with varying degrees of success to combat the associated pathological conditions. Therefore, upon scientific validation & development, these antiviral phytochemicals can attain a futuristic nutraceutical prospect in managing different encapsulated viruses. *Houttuynia cordata* (HC) is widely reported for activities such as antioxidant, anti-inflammatory, and antiviral properties. The major antiviral bioactive components of HC include essential oils (methyl n-nonyl ketone, lauryl aldehyde, capryl aldehyde), flavonoids (quercetin, rutin, hyperin, quercitrin, isoquercitrin), and alkaloids (norcepharadione B) & polysaccharides. HC can further be explored as a potential nutraceutical agent in the therapy of encapsulated viruses like HIV, HSV, and influenza. The review listed various conventional and green technologies that are being employed to extract potent phytochemicals with diverse activities from the HC. It was indicated that HC also inhibited molecular targets like 3C-like protease (3CLPRO) and RNA-dependent RNA polymerase (RdRp) of COVID-19 by blocking viral RNA synthesis and replication. Antioxidant and hepatoprotective effects of HC have been evident in impeding complications from marketed drugs during antiviral therapies. The use of HC as a nutraceutical is localized within some parts of Southeast Asia. Further technological advances can establish it as a nutraceutical-based functional food against pathogenic enveloped viruses like COVID 19.

1. Introduction

Nutraceuticals offer a wide range of therapeutic properties against various microbial infections. The current viral pandemics have made us re-evaluate our immunity and consider the importance of medicinal food products. Nutraceutical products generally include dietary supplements (enriched with micro-nutrients, vitamins, co-enzyme Q, etc.), functional foods (such as, yogurts, cereals, etc.), and are scientifically processed and validated products (Chauhan et al., 2014) Stephen DeFelice (1979) termed the word “Nutraceuticals” by amalgamating “nutrition” and “pharmaceutical” and hence act as both functional foods with both disease prevention and management properties. These are “food-like substances” that can be easily incorporated into the patient’s dietary habits, making them more consumer compatible. Therefore, the

nutraceutical market is emerging as a new-generation functional foods (Durazzo et al., 2020). Time and again, humankind has faced horrific attacks of viral infection primarily caused by encapsulated viruses like HIV (Human immunodeficiency virus), Influenza, Herpes simplex virus (HSV), Swine flu, and Coronavirus (SARS-COV2). The associated pathological condition becomes fatal in a concise duration of viral invasion in the body. The capsule proteins of these viruses help easy entry into the cells and facilitate faster replication surpassing the body’s natural immune protection (Chou & Fasman, 2009). Among the existing array of synthetic drugs, none of them have restricted the spread of the infection. Herbal molecules offer stronger immune surveillance and eliminate the dangerous complications with existing synthetic antiviral agents. The application of Phyto-nutraceuticals is gaining popularity in the management of fatal bacterial and viral infections. Phytochemicals have also

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been reported to show reduced drug resistance and increased sensitivity to drugs (Ayaz et al., 2019).

Polyphenol-rich herbs, especially coffee and green tea with potent antioxidant properties, have been extensively used as functional foods in viral infections. Bioactive peptides, naturally present in food proteins have also been documented to elicit physiological responses associated with immunological aspects of the human system (Alkhatib et al., 2020). Fruits like citrus, apples, red grapes, cherries and leafy vegetables, and quercetin-based formulations have shown good antioxidant and antiviral properties. For instance, flavonol quercetin was found to possess dose-dependent antiviral activity against HSV-1, poliovirus type 1, parainfluenza virus type 3 (PF3), and respiratory syncytial virus (RSV) (Wu et al., 2016). Chalcones and chalcone derivatives obtained from the bark of *Milletia leucantha* are potent flavonoids recorded for their antiviral property against HSV (Phrutivorapongkul et al., 2003). Calanolide A, which was first discovered in Malaysia, isolated from *Calophyllum lanigerum*, is hypothesized to have potential anti-HIV activity as a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) (Wu et al., 2020). An anthraquinone substance, Emodin from the genus *Rheum* and *Polygonum* found in rhubarb and knot weed can be classified as an excellent antiviral with activity against SARS-CoV (Ho et al., 2007). Many other herbal molecules are also being investigated for their therapeutic potential against a range of viral infections.

Houttuynia cordata (HC) is also one such medicinal plant, consumed as a functional food in parts of south-east Asia. It is a flowering and perennial herb with a stoloniferous rhizome native to the mountainous region of China, Japan, Korea, and Southeast Asia, occurring at an altitude of up to 300–2600 m along the Himalayas. The *Houttuynia cordata* Thunb., is commonly referred to as chameleon, chinese lizard, fish wort/mint, heart leaf is native of the South East Asian region and belongs to the *Saururaceae* family (Chen et al., 1993). In north-eastern (NE) India, it has various indigenous names such as Ja-myrdia in Khasi; and Pnar-Jarmendo in Assam; Mumbre, Muchandariin in Arunachal Pradesh; while in Nepal, it is called Gandhi Jhar (Rathi et al., 2013).

There are two distinct types differing in flavor: the Chinese variety, native to China, India and Vietnam, has a strong coriander-like aroma and resembles Vietnamese coriander (*Eryngium foetidum*); the Japanese variety has a lemony and ginger-like aroma and is distributed (Ravindran et al., 2012) in an area from Nepal to the Korea region, extending to Japan. (Tutupalli & Chaubal, 1975). The eastward region of China, mainly towards Taiwan and the southwest region towards Tibet and Yunnan, and the northern region towards Shaanxi and Gansu, is marked as few available regions of the herb (Yang et al., 2015). HC is also widespread in India's North-eastern (NE) region, especially in the Brahmaputra valley of Assam (Bhattacharyya & Sarma, 2010). In Japan, HC leaves are prepared as a beverage and called "Dokudami cha," which translates into "*Houttuynia cordata* tea" (Chaturvedi et al., 2011). Throughout Asia, food has long been considered as a medicine and Chinese medicinal herbs have long been used to create dishes that are believed to be an effective way of treating a wide range of illnesses and ailments. In addition, a number of Chinese Buddhist temples serve dishes, with '*Houttuynia cordata* called as 'kanten jelly'. The ingredients of it include dried 'Kanten' jelly salt, soybean sauce, and egg. The Vietnamese use it as a leaf vegetable to garnish dishes. The fishy taste and aroma of the herb have caused people to enjoy it as a mint or basil in many parts of the world. In several southwestern provinces of China like Guizhou, Sichuan, and Yunnah, the roots of this plant are consumed as a root vegetable. The leaves of the plant are loved and relished in pakoras and salads in places like Manipur. Japanese use leaves and entire plant for making beverages, and deodorant. Korean people apply the entire plant in food recipes such as kimchi, soy sauce, knife cut noodles, syrup, and carbonated drinks. In Thailand, young leaves of it used as vegetable (Leardkamolkarn et al., 2012). In northeast India, people make a paste of these leaves and consume it in the form of a 'Chutney' and relish in pakoras and salads. Throughout Asia food has long been considered as a

medicine and Chinese medicinal herbs have long been used to create dishes that are believed to be an effective way of treating a wide range of illnesses and ailments. Considering the ethnobotanical and functional food value of HC, we intend to fill in the literature gap in the current review by highlighting the scientifically validated ethnomedicinal uses and focus the discussion on the various antiviral mechanisms by which it destroys encapsulated viruses. The article also outlines the recent updates on the pharmacological properties of HC in association with the viral infections. We have discussed various technologies which aid in the isolation/extraction of the anti-viral bioactive components of HC which may aid in the establishment of HC as a nutraceutical for the prophylaxis and management of COVID-19.

1.1. Ethnomedicinal uses of *Houttuynia cordata*

Houttuynia cordata traditionally has been utilized in many Asian countries for its edible and medicinal purposes. In China, this plant has also been recorded in oriental medicine (Traditional Chinese Medicine) since ancient times for its therapeutic effects. In 1998, HC was included in the list of medicines and food by the Ministry of Health, people's republic of china (P.R.C) (Zheng et al., 1998). The folk uses of the herb in China are listed below.

The herb removes free radicals (toxins) from the body and thus is beneficial against bacterial infection (caused by bacteria such as *Trichophyton*, *Staphylococci*, *Gonococci*, *Tubercle bacilli*, etc.), allergies and asthma. This herb can combat oxidative stress-associated diseases such as cancer, coronary heart disease, diabetes (Kusirisin et al., 2009) and infections (Chopra, 1956). The entire plant is utilized for its cooling, resolvent, and emmenagogue properties along the Indo-China region. Leaves were found helpful in treating measles, dysentery, and gonorrhoea (Rathi et al., 2013). Assamese people make a paste of these leaves and consume it in the form of a chutney which helps to cure blood deficiency, cholera, and dysentery and purifies the blood (Hynniewta & Kumar, 2008). Fresh decoctions from the leaves and stems are prepared during the growing season to manage conditions like fever, coughs, dysentery, and enteritis. The leaf juice is also used as an antidotal astringent. The North Cachar hills tribes of Assam control dysentery by eating the leaves and stems of the plant (Medhi & Borthakur, 2012). The leaves have been known to show anthelmintic properties and hence consumed in North Bengal and Sikkim. The Manipuri people call the plant "Maiba" and employ this herb to cure stomach ulcer, dysentery, and muscular sprain (Devi Khumbongmayum et al., 2005) and also tuberculosis, anemia, and gastritis (Yonzon et al., 2012). The root juice is applied to the skin to treat wounds, snake bites, anal prolapsed, abscesses, bone growth stimulation (Chopra, 1956), urinary & digestive troubles, swelling, and detoxification (Rathi et al., 2013). It has been proven effective for immune stimulation and as an anticancer agent (Nuengchamnonng et al., 2009a).

HC and its extract usage can elicit potent antioxidant and anti-inflammatory activities and robust antiviral properties and therefore used in managing encapsulated viruses like HIV, HSV, and Influenza virus (Chiang et al., 2003). During the SARS outbreak in 2003, HC gained acknowledgment for use in treating infected people in China. It is a medicinal plant with a proven anti-inflammatory effect and has been found to be useful in combating severe acute respiratory syndrome (SARS) The major flavor-contributing components are myrcene and 2-undecanoate (Ravindran et al., 2012).

1.2. Phytochemical constituents of *Houttuynia cordata*

Houttuynia cordata is a medicinal herb used extensively in traditional Chinese medicine for its diverse therapeutic activities. HC was reported to contain many mineral nutrients essential to the human body and other active components. Six critical amino acids and essential trace elements such as zinc, iron, copper, and manganese are reported in HC extract, which serves crucial biological functions The main active

constituents of HC include Essential oils, flavonoids, alkaloids, water-soluble polysaccharides (Yang & Jiang, 2009). Essential oils have shown promise as antiviral agents against several pathogenic viruses. The prominent essential oils include methyl n-nonyl ketone, decanoyl acetaldehyde, and lauric aldehyde. The botanical polysaccharides act by mechanisms which can modulate innate immunity and, more specifically, enhanced an activated macrophage function. This leads to immunomodulation, anti-tumor activity, anti-inflammatory, wound-healing and other therapeutic effects (Schepetkin & Quinn, 2006; Zhang et al., 2020) identified the components of water-soluble polysaccharides composed of glucose, fructose, arabinose, galactose, xylose, rhamnose and an unknown pentaglucose. Some of the reported polysaccharides include HCA4S1, HCP-2, HP etc. Similarly, flavonoids class of polyphenols include quercetin, rutin, quercitrin, isoquercitrin, Hyperoside, Houttuynoid A & B etc., (Li et al., 2017a). Similarly the phenolic acid class of polyphenols include Linolenic acid, linoleic acid, oleic acid, palmitic acid, stearic acid, neochlorogenic acid and chlorogenic acid (Nuengchamnong et al., 2009b). Conventional methods for extracting active compounds from HC are soxhlation, steam distillation, and maceration (Liang et al., 2005). Steam distillation was reported to yield a range of essential oils like decanoyl acetaldehyde, myrcene, lauric aldehyde, α -pinene, β -limonene, methyl nonyl ketone (Diao et al., 2014). The essential oils are responsible for the critical therapeutic activities of HC extract. The application of volatile oil as anti-mutagenic, anti-bacterial, antiviral, and insecticidal has been reported in several independent studies (Chiang et al., 2003; Hayashi et al., 1995). The principal essential oil lauric aldehyde is correlated with the potent antiviral properties of the herb.

Steam distillates of HC were reported to show efficacy against Herpes simplex virus (HSV), Human immunodeficiency virus (HIV), and influenza virus (Liang et al., 2005; Lu, Liang, et al., 2006). Post extraction, the essential oils are dissolved in Tween 80 solution-based formulations were used as injectables against inflammation. Some of the volatile oils during the hydro distillation of HC are degraded by oxidation, polymerization or condensation reactions and were reported to cause adverse drug reactions like hemolysis and allergic reactions (Godbole et al., 2019). Flavonoids are another class of bioactive molecules present in HC extract, including quercetin, quercitrin, isoquercitrin, afzelin, hyperin, reutrin, and rutin. The leaves of the HC contain a higher percentage of flavonoids than the roots of the herb. Ultrasound assisted

extraction has also been used as an alternative method to extract chengenolic compounds like flavonoids from HC (Prommajak et al., 2014). The UAE reduces the time taken for extraction as well as increases the yield of the biomolecules. Ultrasonic energy produces cavitation bubbles in the solvent, which cause microjet impacts and shockwave-induced damage to the plant cell wall, thereby releasing cellular components into the solvent. UAE could also be operated at moderate temperature which is beneficial in the case of thermolabile herbal biomolecules. Organic acids in HC extract are oleic acid, linolenic acid, linoleic acid, palmitic acid, and stearic acid. A blockade of HC extract's prostaglandin formation is noted owing to the fatty acids and their cyclooxygenase inhibiting potential (Bauer et al., 1996). A complete list of the major bioactive components of HC is listed in Fig. 1.

2. Pharmacological properties of *Houttuynia cordata* in relevance to infectious viruses

2.1. Antiviral properties

HC has been known to show promising antiviral activities against many catastrophic "enveloped viruses" like human immunodeficiency virus-1 (HIV-1), herpes simplex virus-1 (HSV-1), influenza virus and Corona virus. HC was proposed to treat life-threatening pneumonia caused by SARS-CoV. HC's primary bioactive antiviral components include volatile oils, polysaccharides and polyphenolic compounds like flavonoids and phenolic acids. Scientific evidence has suggested various antiviral mechanisms attributed to its chemical constituents. For instance, essential oils in HC extract impede the viral envelope's normal function, destroying the virus (Hayashi et al., 1995).

HC water extract containing the polysaccharides possesses immunomodulatory activities, which induce the proliferation of lymphocytes in experimental animals. Simultaneously an increase in Interleukins (IL-2 & IL-10) was observed with the administration of HC in murine models. Many novel targets have been recognized which is crucial for RNA synthesis and replication, such as papain-like protease (PLPRO or nsp3), 3-Chymotrypsin-like protease (3CLPRO or nsp5), RNA-dependent RNA polymerase (RdRp or Nsp12), and helicase protein (nsp13) are the primary targets for developing RNA synthesis and replication inhibitors.

Houttuynoid A, a flavonoid isolated from HC, was examined for its potent anti-HSV-1 activity in an in vitro study. The compound also

Bioactive constituents of <i>Houttuynia cordata</i>				
Flavonoids	Essential oils	Alkaloids	Polysaccharides	Polyphenols
<ul style="list-style-type: none"> • Quercetin • Quercitrin • Isoquercitrin • Afzelin • Hyperoside • Hyperin • Houttuynoid-A • Houttuynoid-B • Quercetin 3 rhamnoside 	<ul style="list-style-type: none"> • Methyl n-nonyl ketone • B-Myrcene • Bornyl acetate • Laurylaldehyde • Capraldehyde • Ethyl caprate • Ethyl dodeconoate 	<ul style="list-style-type: none"> • Norcepharadione • Perlolyrine • Splendidine • Aristolactam-B • Aristolactam-A • Piperolactam-A • Cephadione-B • Houttuynoside A • Houttuynoside B 	<ul style="list-style-type: none"> • Pectic polysaccharide-HCA4S1 • Pectic polysaccharide-HCP-2 • CHCP 	<ul style="list-style-type: none"> • Syringic acid • Vanillic acid • Hydroxybenzoic acid • Ferulic acids • Chlorogenic acid • Linoleic acid • Linolenic acid

Fig. 1. Major bioactive components of *Houttuynia cordata*.

proved effective against HSV-2 and varicella-zoster virus (VZV) (Li et al., 2017a). Hot water extract of HC is correlated with antiviral activity against HSV-1 through inhibition of NF- κ B signaling. Flavonoids quercitrin and isoquercitrin are accountable for inhibiting HSV-1 mediated infection (Chen et al., 2020). Ethanol extract of HC corresponds to the antiviral properties against murine coronavirus and dengue virus in vitro (Chiow et al., 2016). The herbal extract is effective against human noroviruses, the most common pathogen accountable for food-borne viral gastroenteritis (Cheng et al., 2019). HC herb has a wide range of medical applications. Recent pharmacological studies indicated that the plant owed its anti-inflammatory (Chiang et al., 2003), anti-bacterial, and antiviral activities to the essential oil components present in it (Hayashi et al., 1995), (Lu, Liang, et al., 2006). Besides antineoplastic, antioxidant, anti-mutagenic activities, free radical scavenging property of the plant was also recognized to be contributed by the flavonoid components (Chen et al., 2003; Choi et al., 2002; Hoang et al., 2003). Other than the benefits mentioned above, it also has an anti-leukemic effect (Kwon et al., 2003) and an antianaphylaxis effect (Li et al., 2005) along with the ability to promote immunological functions. Its virucidal effects and anti-leukemic activity on the human immunodeficiency virus (HIV) were recorded (Hayashi et al., 1995). Literature data analysis revealed HC's various mechanisms (Fig. 2) against some of the major encapsulated viruses.

2.1.1. Human immunodeficiency virus (HIV)

HIV is a sexually transmitted pathogen that causes acquired immunodeficiency syndrome in humans, belonging to the genus Lentivirus and family Retroviridae (Simon et al., 2006). It can be classified into Type 1 and 2 (HIV-1, HIV-2) based on genetic characteristics and viral antigens' differences. Many plant products, including HC, is effective against HIV infection (Singh et al., 2005). *In vivo* findings indicated the essential oils (decanoyl acetaldehyde, myrcene, lauric aldehyde, α -pinene, β -limonene, methyl n-nonyl ketone) present in HC against HIV-1. Three components of the steam distillate from the plant, methyl n-nonyl ketone, lauryl and capryl aldehyde, showed dose-dependent virucidal activity against HIV-1. Although in vitro cytotoxicity was not observed in experimental subjects, these volatile oils interfere with the virus envelope function. Pretreating with a 2-fold dilution of the distillate for 2 h and 6 h showed approximately 20% and 40% inactivation of HIV-1, respectively. Lauryl aldehyde was established to be the most potent molecule. HC steam distillate was effective against other encapsulated viruses such as herpes simplex virus type 1 (HSV-1) and influenza virus, but inactive against non-encapsulated viruses such as poliovirus and coxsackie (Hayashi et al., 1995). An accessory gene product of HIV-1 called Viral-associated protein (Vpr) was discovered to induce abnormality in the host cell cycle leading to an increase in HIV replication. Quercetin, a flavonoid found in HC extract, was reported to inhibit Vpr functioning, and this novel strategy was introduced to combat HIV-1 infection (Shimura et al., 1999).

2.1.2. Influenza virus

It is an RNA virus that can be simply classified into three types: A, B, and C, based on their levels of protein consumption. Influenza A is the most virulent human pathogen, but the Influenza B virus isn't typically found in humans, while Influenza C viruses are known to cause mild illness in humans (Neumann et al., 2009). Based on the type surface proteins available, hemagglutinin (H) and neuraminidase (N), the influenza A virus is again divided into H1N1 virus, H3N2 virus, H7N7 virus, H1N2 virus, H9N2 virus, and H7N2 virus. Usually, the influenza virus is responsible for seasonal flu infections and can shape into epidemics and pandemics. The H1N1 strain of influenza A virus was identified in April 2009, and it caused a pandemic flu, generally referred to as Swine flu.

HC extracts were found to exert its cytopathogenic effect by inhibiting the replication of influenza virus A, B, and mumps viruses, at the lowest antiviral concentration of 4.5, 2.25, and 14 μ g/mL, respectively.

Antiviral assays demonstrated that quercetin 3-rhamnoside (Q3R) from HC possessed strong inhibitory effects on the influenza A/WSN/33 virus. At the concentration of 100 μ g/mL, it displayed 86% of antiviral activity, while at a concentration of 10 μ g/mL, it showed 66% of action against the same virus. It was established to reduce the formation of an apparent cytopathic effect and inhibit viral replication by direct interaction with virus particles during the initial stage of infection (Choi et al., 2002). Polysaccharides extracted from *H. cordata* (HCP) relieved pneumonia in rats by inhibiting inflammation caused by overactivation of complement system (Lu et al., 2018). Although HCP had no antiviral activity in vitro, oral administration of HCP improved the gut and lung injuries induced by influenza virus via affecting the gut-lung axis (Shi et al., 2020). The efficacy and the mechanisms of these two components were overlapping in anti-inflammation. Different antiviral mechanisms of HC against enveloped viruses are schematically represented in Fig. 2.

2.1.3. Swine-flu virus

Recent findings also provided evidence of the utilization of *H. cordata* for Swine flu treatment. Polysaccharides of HC were reported to alleviate H1N1 virus-induced acute lung injury and intestinal dysfunction in a mouse model (Cheng et al., 2019; Choi et al., 2002). Ethanol extract of HC was found to contain flavonoids in the majority. In contrast, flavonoid glycosides made up 78.5% of the content. The flavonoid glycosides were identified as rutin, hyperin, isoquercitrin, and quercitrin with the aid of high-pressure liquid chromatography. BALB/c mice and RAW 264.7 cell models were infected with H1N1 and treated with flavonoids from HC at a dose of 50, 100, or 200 mg/kg. HC's antiviral and anti-inflammatory effects helped alleviate H1N1-induced acute lung injury in mice (Ling et al., 2020). Innate immune responses are initiated by pattern recognition receptors like Toll-Like Receptor 7 (TLR7), which senses viral RNA of the influenza virus (Iwasaki & Pillai, 2014). The flavonoids also inhibit TLR and viral neuraminidase activity (Ling et al., 2020).

2.1.4. Herpes simplex virus type 1 (HSV-1)

The Alpha herpes viridae subfamily comprises linear dsDNA with a spiky envelope (Rechenchoski et al., 2018). Steam distillates from fresh plants of HC containing lauryl aldehyde, capryl aldehyde, and methyl n-nonyl ketone, were assayed for anti-HSV activity. The former two compounds exhibited moderate cytotoxicity, while the latter did not affect them. An *in-vitro* cytotoxicity assay was performed to evaluate the antiviral activity. Basal cell carcinoma (BCC-1/KMC) cell lines were infected with the virus and cultured with an HC hot water extract. At a concentration of 250 μ g/mL the hot water extract of the herb was found to significantly inhibit the replication of HSV type 1 (HSV-1) by 0.2% ($p < 0.05$) and of HSV type 2 (HSV-2) by 32.9% ($p < 0.005$). HC was suggested to be more useful against HSV-2 since it has lower ED50 against HSV-2 and more effective against HSV-2 when compared with HSV-1 (Chiang et al., 2003). Another in vitro study revealed that nor-cepharadione B (a 4-5 dioxoaporphin) isolated from the n-hexane fraction of HC, at a concentration of 100 μ M, was found to suppress replication of HSV-1 by 46.38% (Chou & Fasman, 2009). Flavonoids quercitrin or isoquercitrin present in hot water extracts of HC was found to inhibit HSV-2 infection by inhibiting NF- κ B activation at a concentration of 10 μ M (Chen et al., 2011).

2.1.5. Corona viruses

The corona virus family is widely distributed in nature and may infect humans or vertebrates. Among them acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing the current world pandemic (Adhikari et al., 2021). Oral administration of HC water extract exhibited inhibition of SARS-CoV 3C-like protease (3CLPRO) and RNA-dependent RNA polymerase (RdRp) in an *in-vitro* study. HC extract mechanism on SARS may be biphasic mode. Initially, the HC extract may activate the cell-mediated immunity to prevent viral infection. HC extract may inhibit the viral replication process by interfering with the

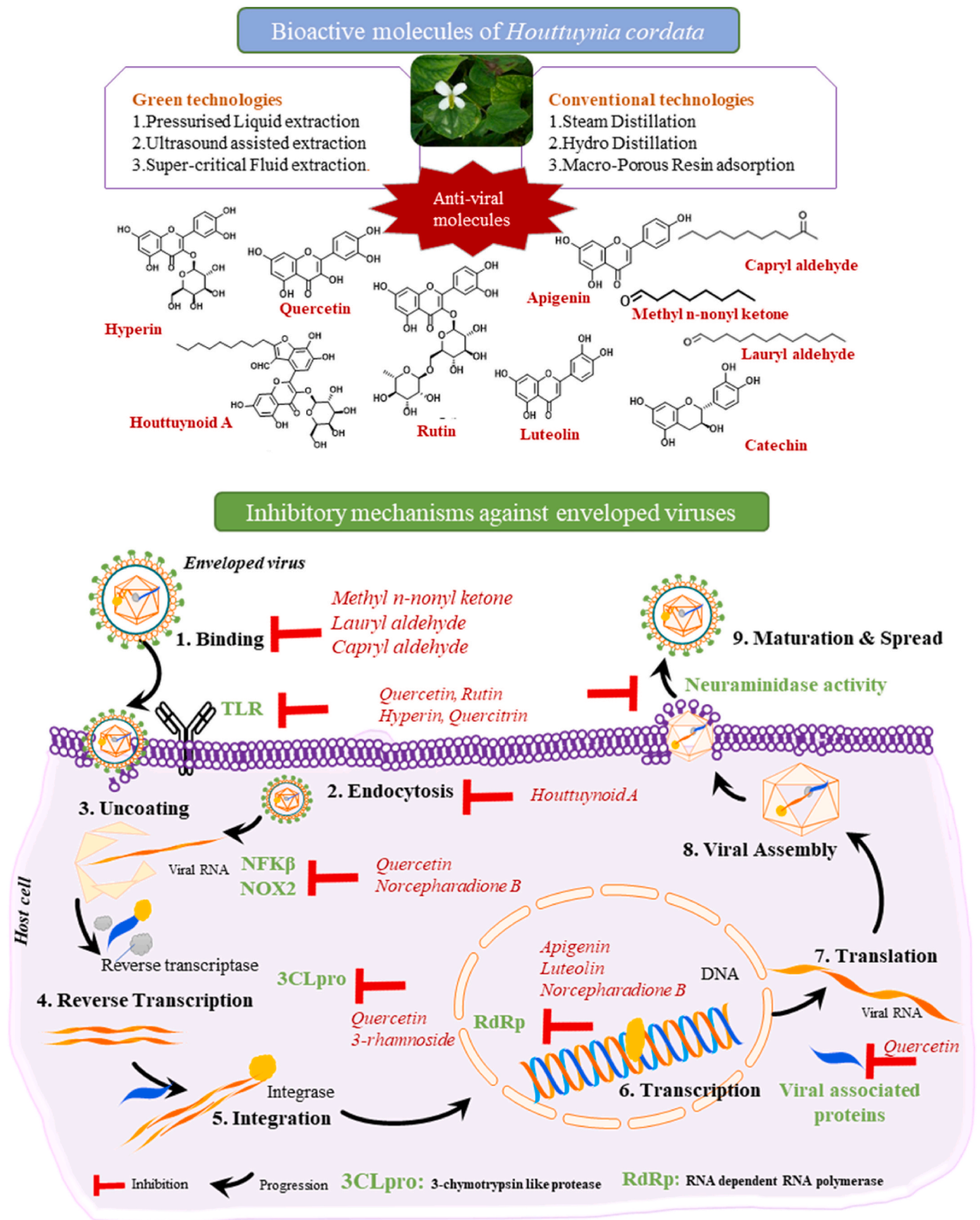


Fig. 2. Major class of compounds of *H.cordata* and their reported antiviral mechanism.

pivotal enzymes and trigger negative feedback control in immune system (Lau et al., 2008). Main protease (Mpro), ADP ribose phosphatase (ADRP) and papain-like protease (PLpro) and are the three main replication proteins of SARS-CoV-2. The docking studies with the compounds from HC indicated a strong binding affinity the results showed the potential therapeutic activity (Das et al., 2022). However, the data obtained was from the docking data, which needs to be confirmed with the experimental evidence.

2.1.6. Miscellaneous viruses

Pseudorabies virus (suid herpesvirus 1) belongs to the subfamily Alpha herpesvirinae, family Herpesviridae and causes encephalitis mostly in pigs. Vero cells (a monkey kidney cell line) and swine testis cells model infected with pseudorabies herpesvirus were used to study the in vitro effect of *H.cordata* injection. The HC injection displayed an antiviral effect against the virus at an optimal dosage while it alone initiated cell apoptosis (Ren et al., 2011). Among other traditional herbs, HC was also reported to have antiviral activity against epidemic hemorrhagic fever virus (EHFV) infection (MO et al., 1993). The antiviral screening was conducted for extracts from various traditional herbs against three genotypes of EV71. HC extract was reported to have Anti-Enterovirus-71 activity, especially against genotype A, by inhibiting the virus-induced cytopathic effects in infected Vero cells. The herb extract was said to have IC50 of 125.92 ± 27.84 $\mu\text{g}/\text{mL}$ against EV71. A plaque reduction assay concluded that the herb extract significantly inhibited plaque formation. The extract was suggested to influence EV71-infected Vero cells' apoptotic processes, inhibiting viral protein expression, viral RNA synthesis, and virus-induced caspase-3 activations. Pretreatment was more effective than treating the cells after the infection (Lin et al., 2009). Porcine epidemic diarrhea virus (PEDV) causes severe enteropathogenic diarrhea in swine. A flavonoid, quercetin 7-rhamnoside (Q7R), present in HC, was effective against this virus. Q7R was reported to have 50% inhibitory concentration (IC50) of 0.014 $\mu\text{g}/\text{mL}$, 50% cytotoxicity concentration (CC50) of 100 $\mu\text{g}/\text{mL}$ and therapeutic index of 7142. Structural analogs of Q7R, such as quercetin, apigenin, luteolin, and catechin, were also reported to have moderate anti-PEDV activity. Q7R was also found to be effective against transmissible gastroenteritis virus (TGEV) and porcine respiratory coronavirus (PRCV). Q7R was also found effective against the rotavirus and rhinovirus (Mendelson et al., 2020). Thus, Q7R could be a potential lead compound for anti-PEDV drug development (Choi et al., 2002) (Song et al., 2011).

One of the studies claimed that HC aqueous extract (polysaccharides) exhibits antiviral activity against dengue virus serotype 2 (DEN-2), strain 16681. HC (10–100 mg/mL) displayed a significant reduction in intracellular production of DEN-2 RNA, thus decreasing the dengue protein expression in HepG2 cells after both the pre and post-incubation process. The effective dose (EC50) was revealed to be 0.8 mg/mL in the direct blocking mode. *H. cordata* extract at a low concentration of 10–40 mg/mL exhibited a protective effect against infected monkey kidney cell line (LLC-MK2) cells (Leardkamolkarn et al., 2012). The components of HC extract with potent antiviral properties found in the literature are listed in Table 1.

3. Pharmacological role of *Houttuynia cordata* in mitigating viral pneumonia intervening conditions

3.1. Anti-inflammatory role during viral infection

HC extract has evident anti-inflammatory and antioxidant activities along the antiviral activities. The additional effects of the nutraceutical help mitigate the complications that arise from respiratory syndromes and adverse reactions of synthetic drugs used in the therapy of COVID-19. Interestingly, respiratory viral syndromes may lead to increased expression of pro-inflammatory biomarkers and mitochondrial dysfunction. During a viral infection, the triggered host defense response

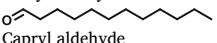
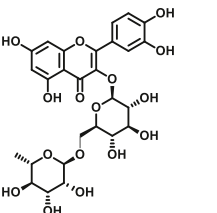
mainly involves increased reactive oxygen species (ROS) due to dysregulation of mitochondrial biogenesis and mitophagy (Jaitovich & Jourdeuil, 2017) (Akaike et al., 1998). The virus is encountered by the immune cells via pathogen-associated molecular patterns (PAMPs). Also, overexpression of type I interferon (IFN) is correlated with suppression of viral replication in the early stages. Therefore, delayed/reduced antiviral IFN response instigates uncontrolled viral replication. The viral over-replication triggers an influx of the neutrophils and monocytes/macrophages. Hyper-inflammatory conditions are created by excess production of pro-inflammatory chemokines/cytokines such as IP-10, MCP-1, MIP-1A, and TNF α . Th1/Th17 gets activated, and B cells/plasma cells produce COVID-19-specific antibodies, further exacerbating the inflammatory responses. The entire immune response results in “cytokine storms” in the infected people (Prompetchara et al., 2020). Pro-inflammatory cytokine IL-2 is upregulated and leads to the induction of NO production (Hibbs et al., 1992; Li et al., 2020; Samlowski et al., 2011). At the same time, pro-inflammatory cytokines IL-6 and TNF α provoke superoxide production in neutrophils (Kharazmi et al., 1989).

The anti-inflammatory effect of HC injection (HCI) was evaluated using the carrageenan-induced rat pleurisy model and xylene-induced mice ear edema model. Carrageenan induced an acute inflammatory activity that caused leukocyte infiltration and protein-rich fluid accumulation in the rat's pleural cavity. HCI attenuated the inflammatory responses at a dose of 0.54 ml/100 g or more. However, its anti-inflammatory effect is less robust than compared to dexamethasone. In the xylene-induced mice ear edema model HCI was found useful too, having an inhibition percentage of 50% (Lu, Liang, et al., 2006). A similar experiment was conducted for oral administration of HC supercritical extracts on the carrageenan-air pounce model. At a 200 mg/kg dose, the extract showed recommendable suppressing the exudation and albumin leakage. It was also found to be more efficient in reducing both TNF- α /NO and cyclooxygenase 2/PGE2 pathways when compared with standard drugs such as dexamethasone (2 mg/kg, i.p.) and indomethacin (2 mg/kg, i.p.) (Shin et al., 2010; Wan et al., 2016). The flavonoid, afzelin, isolated from a methanolic fraction of HC exerted a profound reduction in expression of AMPK and production of pro-inflammatory cytokines (TNF- α and IL-6) in D-galactosamine/LPS induced mice model when given in intra-peritoneally (200 mg/kg) dose (Lee et al., 2017). A detailed list of the anti-inflammatory reports of *H. cordata* is presented in Table 2.

3.2. Hepatoprotective properties

Angiotensin-converting enzyme 2 (ACE2) has been established as the component for surface attachment for the COVID-19, through which viral internalization takes place (Gurwitz, 2020). Although no studies showed concluding data to prove ACE2 in the liver, few recent studies have indicated its presence in cholangiocytes in the bile duct (Darnindro et al., 2020; Hamming et al., 2004). Previously in SARS coronavirus abnormal liver function was reported in some patients (Cui et al., 2004). The retrospective analysis suggested significant relation between other respiratory viral infections and abnormal liver function in infected hosts (Adams & Hubscher, 2006). Acute phase laboratory investigations also revealed elevated levels of lactate dehydrogenase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), which lead to disruption of normal liver function in COVID-19 patients (Zhou et al., 2020). Increased AST levels in COVID-19 cases are more frequent than in patients with mild symptoms of liver injury (Chen et al., 2020; Guan et al., 2020; Liu, Cao, et al., 2020; Zhang et al., 2020). Diabetic patients suffer from various metabolic syndromes and are at risk of developing non-alcoholic fatty liver disease (NAFLD). Consequently, NAFLD has been reported to sensitize the liver toward hepatotoxicants like antipyretics and analgesics used in symptomatic relief of COVID-19 patients (Michaut et al., 2014). The available drugs in COVID-19 management produce harmful side effects, which include fatal heart conditions and hepatotoxicity. Drug-induced liver

Table 1
Antiviral phytochemicals reported from *Houttuynia cordata*.

S. No	Phytochemical compound/s	Mechanism of action	Target encapsulated viruses	Reference
01.	Methyl n-nonyl ketone 	Blocking of viral binding and penetration	HIV, HSV	Hayashi et al. (1995)
02.	Lauryl aldehyde 	Blocking of viral binding and penetration	HIV, HSV	Hayashi et al. (1995)
03.	Capryl aldehyde 	Blocking of viral binding and penetration	HIV, HSV	Hayashi et al. (1995)
04.	Quercetin 	Inhibit the expression of TLR and viral neuraminidase activity	Influenza, PEDV	Ling et al. (2020)
05.	Rutin 	Inhibit the expression of TLR and viral neuraminidase activity	Influenza	Ling et al. (2020)
06.	Hyperin 	Inhibit the expression of TLR and viral neuraminidase activity	Influenza	Ling et al. (2020)
07.	Quercitrin 	Inhibit the expression of TLR and viral neuraminidase activity	Influenza	Ling et al. (2020)
08.	Isoquercitrin 	Inhibit the expression of TLR and viral neuraminidase activity	Influenza	Ling et al. (2020)
10.	Apigenin 	Inhibitory activity against viral proliferation	Porcine epidemic diarrhea virus (PEDV)	Kwon et al. (2011)
11.	Luteolin 	Inhibitory activity against viral proliferation	PEDV	Kwon et al. (2011)
12.	Catechin 	Inhibitory activity against viral proliferation	PEDV	Kwon et al. (2011)
13.	Norcepharadione B 	Antityrosinase and antioxidant activity	HSV	(Chen et al., 2011)

(continued on next page)

Table 1 (continued)

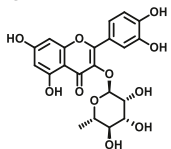
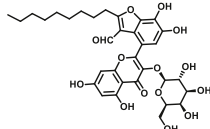
S. No	Phytochemical compound/s	Mechanism of action	Target encapsulated viruses	Reference
14.	Quercetin 3-rhamnoside (Q3R) 	Inhibit viral replication	Influenza	Choi et al. (2009)
15.	Houttuynoid A 	Blocking of viral membrane fusion	HSV, Varicella zoster virus	Li et al. (2017a)

Table 2

Anti-inflammatory reports available on the *H. Cordata*.

S. No.	Plant material used	Disease model	Outcome of the study	Reference
1	HC injection (essential oil)	Carageenan induced pleu model	leukocyte infiltration and protein-rich fluid accumulation	Lu, Liang, et al. (2006)
2	HCl injection	xylene induced mice ear edema model	Decreased leukocyte	Lu, Liang, et al. (2006)
3	HC supercritical extracts (essential oil methyl nonyl ketone, β -myrcene, β -pinene, α -pinene, α -terpineol and n-decanoic acid)	Carageenan air pouce model	Decrease exudation and albumin leakage	Shin et al. (2010)
4	Aqueous extract of HC	Acetaminophen induced liver injury in Balb-c mice	Increase in TNF, IL-6, IL-10	Chen et al. (2014)
5	Ethanol extract of HC	Oxaliplatin induced neuropathic SD rats	Decreased level of IL-6, MIP-1 α	Abassi et al. (2020)
6	Afzelin (Methanolic extract)	D-Galactosamine LPS induced mice model (i.p.)	Decreased level of AMPK and cytokines (TNF, IL-6, IL-10)	Li et al. (2017a)

impairment (1–3 week dosing) has been reported using azithromycin. (Martinez et al., 2015; Zhang et al., 2020). Azithromycin is being employed along with hydroxychloroquine as a potential therapy against COVID-19. Thus, along with antiviral agents hepato-protective drugs are needed to lessen the collateral defects by the available drugs in COVID-19. Interestingly, the HC extracts or its components has been identified to protect liver function. Isolated phenylethanoid glycosides from HC (Plantainoside D, Plantamajoside, Scroside E, Forsythiaside F, Acteoside) at a concentration of 10M were found to exhibit moderate hepatoprotective action counteracting the D-galactosamine-induced WB-F344 cell damage. Bioactive alkaloids isolated from the plant (3-hydroxy-1,2-dimethoxy-5-methyl-5H-dibenzoindol-4-one, 1,2,3,4,5-pentamethoxy-dibenzoquinolin-7-one, 3-methoxy-6-methyl-6H-benzodioxole benzoquinoline-4, 5-dione, piperolactam C, liriodenine, cepharadione A also displayed moderate hepatoprotective action towards D-galactosamine-induced WB-F344 cells damage (Ma et al., 2017).

In a study, CCl₄-induced oxidative stress in mice liver shows elevated serum levels of AST, ALT, alkaline phosphatase, total bilirubin, and hepatic MDA in mice along with increases in GSH, SOD, and CAT. The

phenolic composition of HC ethyl acetate extract was employed to check its protective effects in the liver against CCl₄-induced acute hepatic damage. This ethyl acetate extract showed practical antioxidant effects. This ethyl acetate fraction at three doses (250, 500, and 1000 mg/kg.bw) in vitro exhibited predominant ferric-reducing antioxidant power (FRAP) and scavenging activity against the DPPH radical. The serum biochemical parameters were reduced if pretreated with EAF (1000 mg/kg.bw) before CCl₄ administration. This ethyl acetate fraction under HPLC analysis revealed the predominant presence of the polyphenolic compounds that are quercitrin (quercetin 3-O-L-rhamnoside, 111.7 μ g/mg), quercetin (flavonol, 43.8 μ g/mg), and hyperoside (quercetin-3-O-galactoside, 29.1 μ g/mg). On correlating these studies with liver histopathology, the ethyl acetate extract was established to have hepatoprotective action due to the predominant antioxidant activity of phenolic components (Tian et al., 2012). A similar study was further conducted that established that at a concentration of 15.5 and 410 μ g/ml the extract scavenges 50% of alkyl and hydroxyl radicals, respectively (Kang & Koppula, 2014). Although further research is required to prove the hepatoprotective function of HC extract in COVID-19 therapy, the nutraceutical can be used concurrently with other antiviral drugs to suppress hepatotoxicity in the infected hosts. A detailed list of reports on *H. cordata* for its potential hepatoprotective role is presented in the Table 4.

3.3. Antibacterial properties

Since most of the viral infectious pneumonia are accompanied with the bacterial infections, the ideal anti-viral molecules are expected to possess potential anti-bacterial properties also. Therefore, the anti-bacterial reports were also reviewed. HC was found to possess potent anti-microbial abilities paving its applications in the health-care and food packaging industries. HC is commonly used in the treatment of cough, leucorrhoea and urethritis. The hydro distillation based essential oils are also marketed as Yuxingcao. The anti-microbial effect of the HC essential oils potential anti-bacterial effect. The broth and agar dilution methods were used against the *Staphylococcus aureus* and *Sarcina ureae*. The results indicated that the essential oil components clearly their antibacterial activities (Lu, Wu, et al., 2006). The essential oils of HC were effective against *Salmonella* enteritidis and *Salmonella* Paratyphi β (Xu et al., 2022). Another study indicated that the Essential oil components obtained by hydro distillation method exhibited a robust anti-microbial effect against both the Gram-negative and Gram-positive bacteria like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Serratia marcescense* and *Bacillus subtilis*. This indicate the prospective role of the HC in the natural medicine or natural food preservation (Rebíčková et al., 2020). The ethanolic extract of HC was reported to possess certain antibacterial, antibiofilm properties against *S. aureus*. Overall the study results indicated that the HC may be clinically applied in preventing oral/nasal infectious diseases (Sekita et al.,

2016). The antibacterial property of the HC was also validated in the food packaging. Essential oils of HC obtained by the multi-solvent consecutive extraction technique and ethanol extraction with a pre-heating method were tested against the *Bacillus subtilis*. The extract obtained by the single ethanol extraction with a pre-heating method was more satisfactory from the operational and economic aspects for the inhibitory activity on the growth and breeding of *Bacillus subtilis*, indicating its use as eco-friendly antibacterial agent for food packaging (Kong et al., 2022).

3.4. Antioxidant properties

Numerous studies have reported robust antioxidant activities of HC, both *in-vitro* and *in-vivo*. Traditionally HC is used in various diseases like acute respiratory syndrome, inflammation, muscular strain, gastric ulcers, etc. Thorough investigations revealed the role of oxidative stress and related damage in the pathogenesis of the disease conditions. Constituents of HC target various cell signaling pathways and may result in suppressive or reversal oxidative stress-mediated damage. Free radicals are the primary source of oxidative stress in the cell, and mitochondria predominantly account for the imbalance between free radicals and natural antioxidants. Essentially mitochondrial dynamics regulate oxidative stress by maintaining an equilibrium between mitophagy and mitochondrial biogenesis. Afzelin, isolated from *H. cordata* herb, controls mitochondrial dysfunction through Rev-Erb- α /phospho-AMPK/SIRT1 signaling. Afzelin also regulates the expression of mitophagy associated with PINK1 and perkin proteins (Shingnaisui et al., 2018). This active biomolecule is useful in LPS induced hepatic injury owing to its inhibitory action on mitochondrial dysfunction (Lee et al., 2013). An *in vitro* study with methanolic extract of HC suggested an inhibitory activity against palmitate-induced oxidative damage in human aortic endothelial cells by regulating nitric oxide (NO) (Yang et al., 2015). Water extract of HC positively affected bleomycin-induced pulmonary fibrosis in rodents.

Potent inhibition of lipid peroxidation ($IC_{50} = 1.02$ mg/ml), slightly weaker than vitamin E and free radical scavenging properties, were also noted in rats (Ng et al., 2007). Isolated compounds like active polyphenols, quercetin also purport antioxidant properties and possess protective roles against H₂O₂-induced oxidative damage to DNA in human lymphocytes when employed in low concentration (Lin et al., 2013). Quercetin, quercitrin, and hyperoside in ethyl acetate extract of HC (1000 mg/kg) exhibited a reduction in GSH level. The decline in SOD and CAT activity in CCl₄ induced oxidative stress in mouse liver (Quan et al., 2018). Another *in vivo* study showed that HC extract (200 and 400 mg/kg) blocks the streptozotocin-induced oxidative stress and maintains continuous mitochondrial function in the pancreatic β -cells (Kumar, Prasad, & Hemalatha, 2014). In a study, Kang et al. examined HC's antioxidant properties and protective effect on rats' gentamicin-induced oxidative stress. Treatment of rats with methanolic extract of HC exhibited an increased level of GSH, SOD, and catalase activity in gentamicin-induced nephrotoxicity (Kang et al., 2013).

In LPS induced mouse macrophages-like cell line, RAW 264.7 cells, aqueous extract from HC hindered NO production in a dose-dependent manner while TNF- α production was hindered (minimally up to 30%) at 0.06 and 0.12 mg/ml (Park et al., 2005). Ethanolic extract of HC impeded the expression of inflammatory biomarkers, such as IL-6 and NO in LPS-treated alveolar macrophages (MH-S) and lung epithelial cells (A549) (Lee et al., 2015). Mast cells are multifunctional immune cells, and histamine is its main secretory product. Histamine provokes the activation of pro-inflammatory cytokines, such as IL-6 and IL-8 (Krystel-Whittemore et al., 2016). Apart from this, the mast cells are involved in the IgE-mediated allergic reactions through the Fc epsilon RI receptor. HC water extract reduced IgE binding activity and m RNA expression of the α - and γ -chains of Fc ϵ RI receptor in human KU812F cells. The extract also reduced Fc epsilon RI mediated histamine release (Shim et al., 2009). The extract showed a significant anti-inflammatory role by

suppressing DNPBSA-induced release of beta-hexosaminidase, histamine, ROS, TNF- α and IL-6 in IgE-mediated allergic response in rat mast RBL-2H3 cells. It also hindered the DNP-BSA-induced phosphorylation of various kinases such as Syk, Lyn, LAT, Gab2, PLC γ 2, Akt, and MAP (Han et al., 2009).

Volatile oils from HC were found to suppress LPS stimulated production of NO and TNF- α in the mouse resident peritoneal macrophages in a concentration-dependent manner. Along with the iNOS activity inhibition ($IC_{50} = 562.3$ mg/mL), the oil treatment was also influential in regulating the translational and transcriptional levels of iNOS and TNF- α in the LPS primed macrophages (Li et al., 2013). The HC polysaccharides displayed preventive action against complement activation and macrophage migration thus hindering NO and pro-inflammatory cytokines (TNF- α , IL6, and IL-1 β) production (Xu et al., 2015). Antiviral therapy is helpful in the early stage of COVID-19 since the virus in the first week is far less than in the second week (Lescure et al., 2020). In the second and third stage, the period of hospitalization, there is a commencement of respiratory difficulties and multiple organ failures. During these conditions, cytokine storms and the free radical storm should become the primary target. Yet, there is no acknowledgment of the role of free radical damage in COVID-19 in the current official guidelines (Wu et al., 2020). Based on the above studies on HC extract and isolated components from the herb, HC can be proposed as an excellent therapeutic alternative against the cytokine storm caused by COVID-19. A detailed list of reports on *H. cordata* for its antioxidant role is presented in the Table 3.

4. The contemporary global market of nutraceuticals

Nutraceuticals are products that provide essential nutrients to the body and prevent diseases. These are employed to avoid the disease as well as complementary medicine in various chronic diseases. Recent years have seen significant progress toward the usage of nutraceuticals due to their safety and natural healing mechanism (Braithwaite et al., 2014). A report by transparency market research in September 2015 also indicated the growth phase based on their study. The global nutraceutical market is expected to reach US\$278.96 billion by the end of 2021 at a CAGR rate of 7.3% (Market-Global, 2015).

Table 3
Hepatoprotective reports available on the *H. Cordata*.

S. No.	Plant material/ compound used	Disease Model	Outcome	Reference
1	Bioactive alkaloids (3-hydroxy-1,2-dimethoxy-5-methyl-5H-dibenzoindol-4-one, 1,2,3,4,5-pentamethoxy-dibenzo-quinolin-7-one, 3-methoxy-6-methyl-6H-benzodioxole benzoquinoline-4,5-dione, piperolactam C, lirioidenine, cepharadione A	D-galactosamine-induced WB-F344 cells damage	Hepatoprotective action (inhibits cell damage)	Ma et al. (2017)
2	HC ethyl acetate extract (quercitrin, rhamnose, quercetin, hyperoside and galactoside)	CCl ₄ -induced acute hepatic	Increased antioxidants activity	Tian et al. (2012)
3	Afzelin (Methanolic extract)	D-Galactosamine LPS induced mice model (i. p.)	Decreased level of AMPK and cytokines (TNF α , IL-6, IL-10)	Lee et al. (2017)

Table 4
Antioxidant Properties reports available on the *H. Cordata*.

S. No.	Plant material/compound used	Disease Model	Outcome	Reference
1	Afzelin	LPS induced hepatic injury	Inhibits mitochondrial dysfunction	Lee et al. (2017)
2	Methanolic extract (Chlorogenic acid, rutin, and quercitrin)	Palmitate-induced oxidative damage in human aortic endothelial cells	Increased NO production	Yang et al. (2015)
3	Water extract of HC (whole extract)	bleomycin-induced pulmonary fibrosis in rodents	Reduced IgE binding activity and Down-regulation of expression FcεRI	Shim et al. (2009)
4	Quercetin	H ₂ O ₂ -induced oxidative damage	Increased antioxidative property	Lin et al. (2013)
5	Quercetin	streptozotocin-induced oxidative stress	Maintains mitochondrial function	Kumar, Prasad, Krishnamurthy, and Hemalatha (2014)
6	β-myrcene and 2- undecanone	Gentamicin induced oxidative stress	Increased level of GSH, SOD, and catalase activity	(Kang et al., 2013)
7	HC extract	In LPS induced mouse macrophages	Hindered production of NO, TNFα and IL-6	Park et al. (2005)
8	Water extract of HC (whole plant extract)	Bleomycin-induced pulmonary fibrosis in rodents	Increased free radical scavenging property	Ng et al. (2007)
9	Methanolic extract (Bioactive components as chlorogenic acid, rutin, and quercitrin)	Palmitate induced oxidative damage	Regulates production of Nitric Oxide (NO)	Yang et al. (2015)
10	Quercetin	H ₂ O ₂ -induced oxidative damage	Increase antioxidant and decrease ROS generation	Lin et al. (2013)
11	Afzelin	LPS induced hepatic toxicity	Inhibits mitochondrial dysfunction	Lee et al. (2017)
12	Quercetin, quercitrin, and hyperoside in ethyl acetate extract	Chloroform induced oxidative stress in mice	elevation in serum levels of AST, ALT, alkaline phosphatase, total bilirubin, and hepatic MDA in mice along with increases in GSH, SOD, and CAT	Tian et al. (2012)
13	Bioactive alkaloids (3-hydroxy-1,2-dimethoxy-5-methyl-5H-dibenzoindol-4-one, 1,2,3,4,5-pentamethoxy-dibenzo-quinolin-7-one, 3-methoxy-6-methyl-6H-benzodioxole benzoquinoline-4,5-dione, piperolactam C, lirioidenine, cepharadione A	D-galactosamine-induced WB-F344 cells damage	Hepatoprotective action	Ma et al. (2017)

Curcuma longa and Solanum Nigrum being hepato-protective, have been exploited as nutraceutical sources (Sikander et al., 2020). Synergistic responses of combined nutraceuticals are also being studied, such as curcumin combined with quercetin and nobiletin metabolite, which shows enhanced anticancer effects (DiMarco-Crook et al., 2020; Sharma et al., 2019). Fulvic acid found in humus has been marketed as an anti-inflammatory beverage effective against influenza and HIV (Ganapathy, 2009; Zhernov et al., 2021). Nutraceuticals such as Chyawanprash containing amla, ashwagandha, and pippali, being favored for their immunity enhancement activity in the Indian market, were under increased demand during the recent pandemic (Sharma et al., 2019) Calcitriol, D-3 is a widely prescribed calcium supplement for women (Rangarajan et al., 2018). Establishing the Food Safety and Standard Act in 2006 and Food Safety and Standards Authority (FSSAI) has boosted the standard of the Indian nutraceutical market (Chauhan et al., 2014).

5. Future aspects of *Houttuynia cordata* as a potential nutraceutical

HC can be employed as a potent nutraceutical for its versatile role in different disease management. The consumable plant opens up various potential approaches to convert it into a readily available therapeutic supplement to treat COVID-19. Ethnomedical properties of the plant are already being commercialized in countries like South Korea in the form of tea powder (Dokudami/Yuxingcao) and tincture, while in Thailand as capsules. The therapeutic claims are being made without proper experimental validation. Thus, attempts were made to evaluate the claims, which in turn presented promising results.

The dietary supplement HC fermentation product (HCFP), Dokudami, from the Prolac (Thailand) was tested for its anti-inflammatory action as claimed. It was reported to contain mainly the aerial part of the plant. HCFP and its methanolic extracts were found to inhibit NO production in RAW264.7 cells along with concentration-dependent

suppression of PGE₂, iNOS, IL-1β, TNF-α, and IL-6 levels when stimulated with LPS. The suppression was less pronounced in the case of the COX-2 level. A dose of 3.08 and 6.16 mL/kg HCFP administered after 2hrs carrageenan injections displayed a reduction in paw edema comparable to diclofenac (150 mg/kg), suggesting a second phase anti-edematous effect. The dose of 6.16 mL/kg HCFP displayed paw edema reduction after 1hr of carrageenan administration, thus indicating the first phase anti-edematous effect. Quantitative HPLC analysis of the commercialized product revealed that anti-inflammatory phenolic compounds present in it are syringic, vanillic, *p*-hydroxybenzoic, and ferulic acids (Woranam et al., 2020). The antiviral activity of flavonoids present in HC spurred the interest of researchers. Fermentation increased plant flavonoids (such as rutin, quercitrin, and quercetin) expression (Philip et al., 2009), thus enhancing the antioxidant activity. 6 Bacillus strains were isolated from fermented HC and identified employing 16S rDNA sequencing method. The strains were reported to be *B. amyloliquefaciens* subsp. *plantarum* FZB42T, *B. licheniformis* ATCC 14580T, *B. aerius* 24 KT, *B. methylotrophicus* CBMB205T, *B. safensis* FO-036bT, and *B. sonorensis* NRRL B-23154T (Kwon & Ha, 2012). The main target of the study was to establish fermented HC as a potential probiotic. Although a majority of the Bacillus species are classified as “generally regarded as safe” (GRAS) (Patel et al., 2010), recruiting viable spores of Bacillus in form of probiotic supplements raises safety concerns. There are reports regarding many Bacillus species employed as plant protection products, seed-coating agents, animal feed supplements, and probiotics to cause food poisoning (Gaggia et al., 2010). Thus, if the challenges regarding safety are tackled, HC can be efficiently used as a probiotic.

Hydro-distillation extraction of HC essential oil (HEO) from fresh *H. cordata* followed by dissolution in Tween 80 solution is the general method to prepare the HCl (Ren et al., 2011). Houttuynin (3-oxododecanal, Hou) was reported to be the main active compound found among volatile compounds (A), but it was found to be present in very small

amount in the injection form (Qing-Song & Sai-Jin, 2015). Due to high heat during hydro distillation extraction, Hou loses its stability and is degraded (Xu et al., 2009). Solvent extraction at room temperature was reported to be highly efficient in extracting Hou-riched HEO. Pure HEO containing a high concentration of Hou (43.4%) was obtained after solvent extraction and was purified using macroporous resin (D101). It was further encapsulated into microemulsion by high-pressure homogenization, which enhanced its safety and in vitro antiviral activity (Pang et al., 2017). Microemulsions are considered excellent potential carriers for bioactive molecules as they provide enhanced bioavailability and thermodynamic stability (Garti et al., 2012; Spornath & Aserin, 2006). Microemulsion from the essential oils extracted from HC can be potentially employed as a nutraceutical agent for COVID-19 treatment.

Many other potential approaches can be considered to translate the use of HC as essential nutraceuticals. In tackling the challenges with HC delivery, novel formulation design plays a crucial role. Dosage formulations like solutions, lozenges, pastilles can be exploited in place of available products. Solution formulations improve the physicochemical properties of nutraceutical therapy, improving their solubility, permeation, stability, and efficacy. Various conventional dosage forms like tablets, capsules, and solutions deliver the nutraceuticals during the initial phase. With the advancement of novel technologies, developing various drug delivery systems is possible to overcome the associated difficulties. Novel drug delivery systems can be used to deliver the nutraceuticals as these may solve the issues like poor solubility, low permeability with the help of particle size reduction, improved wetting, use of amphiphilic molecules etc. In nanocarriers, these further increase the molecule's stability by encapsulation of active constituents in the matrix. However, these techniques require a high concentration of surfactants as in self-emulsifying drug delivery and microemulsions. Technologies like liposomes and nanoparticles require highly pure excipients and complex unit operations, increasing the cost of the final product. Hence newer concepts or newer drug delivery systems that are easy to produce on a large scale, patient-friendly (easy to administer to pediatric and geriatrics) and help improve the bioavailability of compounds are needed in the current scenario. Few technologies are depicted in the following section can be used to enhance the efficacy of selected nutraceuticals.

Lozenges are one of the versatile formulations which are utilized to overcome drug delivery challenges. The advantages of these delivery systems are convenient administration, multiple active loading, higher drug loading, patient-friendly due to smooth feel and pleasant taste, and cost-effectiveness. Another advantage with the lozenges is that they can be easily given to the pediatric and geriatric population with difficulties swallowing effect and taste. Pastilles or soft lozenges are meant to be kept at the cheek, and slowly we need to engulf the juice; between the cheek and used to deliver the nutraceuticals either for local action or systemic action where chewing in between the buccal cavity leads to entry of actives directly into systemic circulation via buccal route. As medication directly enters systemic circulation via buccal absorption is helpful to enhance the bioavailability of the incorporated nutraceuticals. Few examples of marketed pastilles include Curkey, Denmkur, containing curcumin. Rescue pastilles with five flower formulas (Barkat et al., 2020). Oro dispersible granules produce dosage with consistent content uniformity. These are easy to carry and manufacture without the need for high compression force. Extremely patient-friendly, especially in the case of pediatric and geriatric patients avoiding swallowing difficulty. It also improves the handling, transportation, and stability issues associated with liquid dosage forms. These are filled into sachets and can be placed on the tongue during administration.

6. Discussion

HC is an important herb used in traditional medicines for its range of beneficial effects such as antiviral, antimutagenic, anti-inflammatory, antihyperglycemic, and antioxidant activities. It is consumed as a

beverage, "dokudami cha" which is mainly found in China and the Northeast region of India. Major bioactive constituents of HC include essential oils, flavonoids, polysaccharides, and alkaloids. The essential oils present in HC extract methyl n-nonyl ketone lauryl aldehyde, the capryl aldehyde is reported with potent antiviral properties.

Previously HC is employed in other viral infections such as HIV-1, HSV, and SARS. Apparent genetic similarity between other encapsulated viruses like HIV and influenza can be observed with the novel SARS-CoV. The viral envelope protein (mainly glycoprotein) helps in the fusion between viral and host cellular membranes. This membrane fusion process allows the capsid and viral genome to enter the host cell, thus infecting it. In the coronaviridae family, coronavirus spike proteins (S proteins) are cleaved into 2 functional subunits known as S1 and S2 by which the virus gets internalized into the host cell (Gallagher & Buchmeier, 2001; Liu, Liu, & Liu, 2020). Human immunodeficiency virus type 1 (HIV-1) has two non-valently associated subunits of envelope glycoprotein indicated as gp120 and gp41, which facilitates the membrane fusion process between viral and host cellular membranes (Chan et al., 1997). Sequence analysis of the two viral proteins (HIV-1 gp41 and SARS-CoV S2 proteins) revealed similar sequence motifs contributing to their active conformation. The study revealed a common N-terminal leucine/isoleucine zipper-like sequence (Gallagher & Buchmeier, 2001), along with a common C-terminal heptad repeat in the upstream of an aromatic residue-rich region adjacent to the transmembrane segment (Kligler & Ievanon, 2003). Comparing the 3D model of the S2 subunit from SARS-CoV with the core model of gp41 from HIV-1 revealed that they share the same two α helices, which indicates that both might follow an analogous analog membrane fusion mechanism (Zhang & Yap, 2004). Enfuvirtide is a synthetic peptide similar to the C-terminal heptad repeat of HIV-1 gp41, FDA approves an anti-AIDS agent: Enfuvirtide, along with C34 (another anti-HIV-1 peptide) inhibits the conformational change of the gp41 required for its activation by binding to a leucine/isoleucine zipper-like sequence present in gp41. Thus by the above study, peptides corresponding to the C-terminal heptad repeat of the S2 protein may act as SARS-CoV entry inhibitors (Kligler & Ievanon, 2003).

Furthermore, the similarity between both coronaviruses and the influenza A virus can be recognized. The transmission passage for Coronaviruses and Influenza A viruses is through direct contact and airborne droplets (Algahtani et al., 2016). Both types of viruses are enveloped viruses with single strand negative-sense RNA viruses, reported to have similar significant clinical symptoms and pathological changes in the patients after infection. The significant difference in both the viruses' life cycle is that Influenza A viruses need to replicate the genome in the nucleus. The virions are released from the cellular membrane by budding processes (Jiang et al., 2020). Considering the genetic and structural similarities between other encapsulated virus, HIV, HSV and Influenza virus and novel coronavirus (COVID-19), agents that interfere with the viral envelope proteins can be employed to maintain the infection. Novel coronavirus, officially COVID-19, is an enveloped, single-stranded RNA virus that causes respiratory distress, pneumonia, and in some cases, lead to respiratory coma and death (Goh et al., 2020). Combating the novel viruses hold a difficult challenge because of their higher rate of mutation and poor proofreading ability that generate ever-emerging, more virulent strains. ACE-2 has been established as the binding moiety through which viral internalization occurs (Yang et al., 2015). Therefore ACE-2 inhibitors and some other putative antiviral drugs are currently being used in the management of COVID-19 (Mulangu et al., 2019; Vaduganathan et al., 2020). No medication has been yet approved officially due to fatal complications that arise from dysregulated use of the marketed drugs. Globally, researchers are searching for better and safer medicinal agents to mitigate the rapid spread of infection. Numerous phytochemicals and nutraceuticals are considered to be employed in COVID-19 therapy as a safer alternative to presently available synthetic drugs.

Essential oils in HC extracts have been reported to block the

membrane fusion and viral internalization to the host cell (Li et al., 2017b). Therefore, HC extracts can be beneficial in the suppression of viral endocytosis. In the SARS-CoV, the main protease, 3CLpro, is in-charge for facilitating the releasing the key replicative enzymes like RNA-dependent RNA polymerase (RdRp) and helicase from the poly-protein precursors. The RdRp is responsible for both positive and negative strand RNA synthesis and replicase complex that is expected to contain additional viral and cellular proteins (Thiel et al., 2003). Therefore, the role of RdRp is crucial in many viral infections including human immunodeficiency virus type 1 (HIV1), human hepatitis B virus (HBV), HCV and herpes virus, and aid as an attractive target for the development of effective anti-viral drugs (Lau et al., 2008). HC extracts also exhibited direct inhibition of 3-Chymotrypsin-like protease (3CLPRO) and RNA-dependent RNA polymerase (RdRp). By directly interfering with the above-mentioned similar molecular targets the HC components may reduce the viral load in COVID-19 infected patients.

With the virtue of HC's anti-inflammatory and antioxidant properties, flavonoids in the plant can reduce the overexpression of pro-inflammatory cytokines and reactive oxygen species. As a result, HC can maintain the upregulated immune system and oxidative damages in the host tissues. The latter half of the infection's underlying pathological condition is called a cytokine storm because of elevated immunological responses in the host. HC extracts can be pivotal in improving associated conditions such as cytokine storms in critically infected people. Azithromycin is currently being used along with HCQ in COVID-19 therapy. Hepatotoxicity is reported with the use of Azithromycin in COVID-19 infected people treated with the drug. By its hepatoprotective and antioxidant effects, HC extract can be used as a nutraceutical agent to suppress the liver toxicity associated with Azithromycin use.

7. Conclusion

Now and then, encapsulated viruses have been offering a challenge to humanity. Despite the advancement in medical technologies, the novel Coronavirus infection is rapidly spreading worldwide. Also, to date, there is no approved therapy or treatment for the management of COVID-19. The available antiviral drugs can not completely mitigate the viral load and, conversely, arise with their harmful complications. Medicinal plants were considered relatively safe agents with potential therapeutic benefits against various ailments. *Houttuynia cordata* is one such nutraceutical agent with potent antiviral, anti-inflammatory, and antioxidant activities. Its action is well documented to treat various encapsulated viruses like SARS, HIV, HSV, Dengue fever, and Influenza virus. Herein, we have reviewed the HC's therapeutic effects as a possible nutraceutical agent in the management of COVID-19 in correlation with the therapeutic benefits in other similar viruses. Therefore, further research on the reported bioactive molecules from the HC against COVID-19 therapy can be beneficial in tackling the current pandemic emergency.

Authorship contributions

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Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

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

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References

- kang, C., lee, H., hah, D.-Y., heo, J. H., kim, C. H., kim, E., & kim, J. S. (2013). Protective effects of *Houttuynia cordata* Thunb. on gentamicin-induced oxidative stress and nephrotoxicity in rats. *Toxicological Research*, 29, 61–67.
- Abassi, Z. A., Skorecki, K., Heyman, S. N., Kinaneh, S., & Armaly, Z. (2020). Covid-19 infection and mortality: A physiologist's perspective enlightening clinical features and plausible interventional strategies. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, 318, L1020–L1022.
- Adams, D. H., & Hubscher, S. G. (2006). Systemic viral infections and collateral damage in the liver. *American Journal Of Pathology*, 168, 1057–1059.
- Adhikari, B., Marasini, B. P., Rayamajhee, B., Bhattarai, B. R., Lamichhane, G., Khadayat, K., Adhikari, A., Khanal, S., & Parajuli, N. J. P. R. (2021). In *Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review* (Vol. 35, pp. 1298–1312).
- Akaike, T., Suga, M., & Maeda, H. (1998). Free radicals in viral pathogenesis: Molecular mechanisms involving superoxide and NO. *PSEBIM*, 217, 64–73.
- Algahtani, H., Subahi, A., & Shirah, B. (2016). Neurological complications of Middle East respiratory syndrome coronavirus: A report of two cases and review of the literature. *Case reports in neurological medicine*, 2016.
- Alkhatib, I. I., Garlisi, C., Pagliaro, M., Al-Ali, K., & Palmisano, G. (2020). Metal-organic frameworks for photocatalytic CO₂ reduction under visible radiation: A review of strategies and applications. *Catalysis Today*, 340, 209–224.
- Ayaz, M., Ullah, F., Sadiq, A., Ullah, F., Ovais, M., Ahmed, J., & Devkota, H. P. (2019). Synergistic interactions of phytochemicals with antimicrobial agents: Potential strategy to counteract drug resistance. *Chemico-Biological Interactions*, 308, 294–303.
- Barkat, M. A., Das, S. S., Potttoo, F. H., Beg, S., & Rahman, Z. (2020). Lipid-based nanosystem as intelligent carriers for versatile drug delivery applications. *Current Pharmaceutical Design*, 26, 1167–1180.
- Bauer, R., Pröbstle, A., Lotter, H., Wagner-Redecker, W., & Matthiesen, U. (1996). Cyclooxygenase inhibitory constituents from *Houttuynia cordata*. *Phytomedicine*, 2, 305–308.
- Bhattacharyya, N., & Sarma, S. (2010). Assessment of availability, ecological feature, and habitat preference of the medicinal herb *Houttuynia cordata* Thunb in the Brahmaputra Valley of Assam, India. *Environmental Monitoring and Assessment*, 160, 277–287.
- Braithwaite, M. C., Tyagi, C., Tomar, L. K., Kumar, P., Choonara, Y. E., & Pillay, V. (2014). Nutraceutical-based therapeutics and formulation strategies augmenting their efficiency to complement modern medicine: An overview. *Journal of Functional Foods*, 6, 82–99.
- Chan, D. C., Fass, D., Berger, J. M., & Kim, P. S. (1997). Core structure of gp41 from the HIV envelope glycoprotein. *Cell*, 89, 263–273.
- Chaturvedi, N., Sharma, P., Shukla, K., Singh, R., & Yadav, S. (2011). Cereals nutraceuticals, health ennoblement and diseases obviation: A comprehensive review. *Journal of Applied Pharmaceutical Science*, 06–12.
- Chauhan, V. P., Boucher, Y., Ferrone, C. R., Roberge, S., Martin, J. D., Stylianopoulos, T., Bardeesy, N., Depinho, R. A., Padera, T. P., & Munn, L. L. (2014). Compression of pancreatic tumor blood vessels by hyaluronan is caused by solid stress and not interstitial fluid pressure. *Cancer Cell*, 26, 14–15.
- Cheng, D., Sun, L., Zou, S., Chen, J., Mao, H., Zhang, Y., Liao, N., & Zhang, R. (2019). Antiviral effects of *Houttuynia cordata* polysaccharide extract on Murine Norovirus-1 (MNV-1)—a human norovirus surrogate. *Molecules*, 24, 1835.
- Chen, C.-J., Hong, D.-Y., & Keng, H. (1993). *Orders and families of seed plants of China*. World Scientific.
- Chen, Y.-Y., Liu, T.-F., Chen, C.-M., Chao, P.-Y., & Chang, T.-J. (2003). A study of the antioxidative and antimutagenic effects of *Houttuynia cordata* Thunb. using an oxidized frying oil-fed model. *Journal of Nutritional Science and Vitaminology*, 49, 327–333.
- Chen, X., Wang, Z., Yang, Z., Wang, J., Xu, Y., Tan, R.-X., & Li, E. (2011). *Houttuynia cordata* blocks HSV infection through inhibition of NF- κ B activation. *Antiviral Research*, 92, 341–345.
- Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., Wang, T., Zhang, X., Chen, H., & Yu, H. (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *Journal of Clinical Investigation*, 130, 2620–2629.
- Chen, W.-T., Yang, C.-L., & Yin, M.-C. (2014). Protective effects from *Houttuynia cordata* aqueous extract against acetaminophen-induced liver injury. *Biomedicine*, 4, 1–5.
- Chiang, L.-C., Chang, J.-S., Chen, C.-C., Ng, L.-T., & Lin, C.-C. (2003). Anti-Herpes simplex virus activity of *Bidens pilosa* and *Houttuynia cordata*. *The American Journal of Chinese Medicine*, 31, 355–362.
- Chio, K., Phoon, M., Putti, T., Tan, B. K., & Chow, V. T. (2016). Evaluation of antiviral activities of *Houttuynia cordata* Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. *Asian Pacific Journal of Tropical Medicine*, 9, 1–7.
- Choi, C. W., Kim, S. C., Hwang, S. S., Choi, B. K., Ahn, H. J., Lee, M. Y., Park, S. H., & Kim, S. K. (2002). Antioxidant activity and free radical scavenging capacity between

- Korean medicinal plants and flavonoids by assay-guided comparison. *Plant Science*, 163, 1161–1168.
- Choi, H. J., Song, J. H., Park, K. S., & Kwon, D. H. (2009). Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication. *European Journal of Pharmaceutical Sciences*, 37, 329–333.
- Chopra, R. N. (1956). *Glossary of Indian medicinal plants*.
- Chou, P., & Fasman, G. D. (2009). Amino acid sequence. *Advances in Enzymology and Related Areas of Molecular Biology*, 47, 45.
- Cui, H.-J., Tong, X.-L., Li, P., Hao, Y.-X., Chen, X.-G., Li, A.-G., Zhang, Z.-Y., Duan, J., Zhen, M., & Zhang, B. (2004). Serum hepatic enzyme manifestations in patients with severe acute respiratory syndrome: Retrospective analysis. *World Journal of Gastroenterology: WJG*, 10, 1652.
- Darnindro, N., Mokoagow, M. I., Manurung, A., Nasarudin, J., Wardoyo, E. Y., Sari, A. P., Djojo, A. Y., Iskandar, M., Aji, G., & Mardiyah, R. (2020). Association of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with mortality in patients with coronavirus disease 2019 (COVID-19) in Fatmawati general hospital: A preliminary data. *The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy*, 21, 89–94.
- Das, S. K., Mahanta, S., Tanti, B., Tag, H., & Hui, P. K. J. M. D. (2022). Identification of phytochemicals from *Houttuynia cordata* Thunb. as potential inhibitors for SARS-CoV-2 replication proteins through GC–MS/LC–MS characterization. *Molecular Docking and Molecular Dynamics Simulation*, 26, 365–388.
- Devi Khumbongmayum, A., Khan, M., & Tripathi, R. J. B. (2005). Sacred groves of Manipur, northeast India: Biodiversity value, status and strategies for their conservation. *Conservation*, 14, 1541–1582.
- Diao, W.-R., Zhang, L.-L., Feng, S.-S., & Xu, J.-G. (2014). Chemical composition, antibacterial activity, and mechanism of action of the essential oil from *Amomum kravanh*. *Journal of Food Protection*, 77, 1740–1746.
- Dimarco-Crook, C., Rakariyatham, K., Li, Z., Du, Z., Zheng, J., Wu, X., & Xiao, H. (2020). Synergistic anticancer effects of curcumin and 3', 4'-didemethylnobiletin in combination on colon cancer cells. *Journal of Food Science*, 85, 1292–1301.
- Durazzo, A., Lucarini, M., & Santini, A. (2020). *Nutraceuticals in human health*. MDPI.
- Gaggia, F., Mattarelli, P., & Biavati, B. (2010). Probiotics and prebiotics in animal feeding for safe food production. *International Journal of Food Microbiology*, 141, S15–S28.
- Gallagher, T. M., & Buchmeier, M. J. (2001). Coronavirus spike proteins in viral entry and pathogenesis. *Virology*, 279, 371–374.
- Ganapathy, R. (2009). *In vitro analysis of the anti-influenza virus activity of pomegranate products and fulvic acid* (Vol. 527). Masters Theses.
- Garti, N., Libster, D., & Aserin, A. (2012). Lipid polymorphism in lyotropic liquid crystals for triggered release of bioactives. *Food & Function*, 3, 700–713.
- Godbole, E., Tyagi, S., Kulkarni, P., Singla, S., Mali, S., & Helge, S. (2019). Efficacy of liquorice and propolis extract used as cavity cleaning agents against streptococcus mutans in deciduous molars using confocal microscopy: An in vitro study. *International Journal of Clinical Pediatric Dentistry*, 12, 194.
- Goh, K. J., Choong, M. C., Cheong, E. H., Kalimuddin, S., Wen, S. D., Phua, G. C., Chan, K. S., & Mohideen, S. H. (2020). Rapid progression to acute respiratory distress syndrome: Review of current understanding of critical illness from coronavirus disease 2019 (COVID-19) infection. *Annals Academy of Medicine Singapore*, 49, 108–118.
- Guan, W.-J., Ni, Z.-Y., Hu, Y., Liang, W.-H., Ou, C.-Q., He, J.-X., Liu, L., Shan, H., Lei, C.-L., & Hui, D. S. (2020). *Clinical characteristics of 2019 novel coronavirus infection in China*. MedRxiv.
- Gurwitz, D. (2020). Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Development Research*, 81, 537–540.
- Hamming, I., Timens, W., Bultthuis, M., Lely, A., Navis, G. V., & Van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, 203, 631–637.
- Han, E. H., Park, J. H., Kim, J. Y., & Jeong, H. G. (2009). *Houttuynia cordata* water extract suppresses anaphylactic reaction and IgE-mediated allergic response by inhibiting multiple steps of FcεRI signaling in mast cells. *Food and Chemical Toxicology*, 47, 1659–1666.
- Hayashi, K., Kamiya, M., & Hayashi, T. (1995). Virucidal effects of the steam distillate from *Houttuynia cordata* and its components on HSV-1, influenza virus, and HIV. *Planta Medica*, 61, 237–241.
- Hibbs, J., Westenfelder, C., Taintor, R., Vavrin, Z., Kablitz, C., Baranowski, R., Ward, J., Menlove, R., Mcmurry, M., & Kushner, J. (1992). Evidence for cytokine-inducible nitric oxide synthesis from L-arginine in patients receiving interleukin-2 therapy. *Journal of Clinical Investigation*, 89, 867–877.
- Hoang, T., Ha, V., Tran, Q., & Ha, V. (2003). Anti-neoplastic activity of flavonoid components extracted from leaves of *H. cordata* Thunb. *Vietnam. Tap Chi Duoc Hoc*, 51, 9–10.
- Ho, T.-Y., Wu, S.-L., Chen, J.-C., Li, C.-C., & Hsiang, C.-Y. (2007). Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Research*, 74, 92–101.
- Hynniewta, S., & Kumar, Y. (2008). *Herbal remedies among the Khasi traditional healers and village folks in Meghalaya*.
- Iwasaki, A., & Pillai, P. S. (2014). Innate immunity to influenza virus infection. *Nature Reviews Immunology*, 14, 315–328.
- Jaitovich, A., & Jourdeuil, D. (2017). A brief overview of nitric oxide and reactive oxygen species signaling in hypoxia-induced pulmonary hypertension. *Pulmonary Vasculature Redox Signaling in Health and Disease*, 71–81.
- Jiang, C., Yao, X., Zhao, Y., Wu, J., Huang, P., Pan, C., Liu, S., & Pan, C. (2020). Comparative review of respiratory diseases caused by coronaviruses and influenza A viruses during epidemic season. *Microbes and Infection*, 22, 236–244.
- Kang, H., & Koppula, S. (2014). Hepatoprotective effect of *Houttuynia cordata* thunb extract against carbon tetrachloride-induced hepatic damage in mice. *Indian Journal of Pharmaceutical Sciences*, 76, 267.
- Kharazmi, A., Nielsen, H., Rechner, C., & Bendtzen, K. (1989). Interleukin 6 primes human neutrophil and monocyte oxidative burst response. *Immunology Letters*, 21, 177–184.
- Kliger, Y., & Ievanon, E. Y. (2003). Cloaked similarity between HIV-1 and SARS-CoV suggests an anti-SARS strategy. *BMC Microbiology*, 3, 1–7.
- Kong, P., Abe, J. P., Nakagawa-Izumi, A., Kajiyama, M., & Enomae, T. J. R. A. (2022). Preparation of an eco-friendly antibacterial agent for food packaging containing *Houttuynia cordata* Thunb. *Extract*, 12, 16141–16152.
- Krystel-Whittemore, M., Dileepan, K. N., & Wood, J. G. (2016). Mast cell: A multi-functional master cell. *Frontiers in Immunology*, 620.
- Kumar, M., Prasad, S. K., & Hemalatha, S. (2014). A current update on the phytopharmacological aspects of *Houttuynia cordata* Thunb. *Pharmacognosy Reviews*, 8, 22.
- Kumar, M., Prasad, S. K., Krishnamurthy, S., & Hemalatha, S. (2014b). Antihyperglycemic activity of *Houttuynia cordata* Thunb. in streptozotocin-induced diabetic rats. *Advances in Pharmacological Sciences*, 2014.
- Kusirisin, W., Srichairatanakool, S., Lertrakarnnon, P., Lailerd, N., Suttajit, M., Jaikang, C., & Chaiyasut, C. (2009). Antioxidative activity, polyphenolic content and anti-glycation effect of some Thai medicinal plants traditionally used in diabetic patients. *Medicinal Chemistry*, 5, 139–147.
- Kwon, D. H., Choi, W. J., Lee, C. H., Kim, J. H., & Kim, M. B. (2011). *Flavonoid compound having an antiviral activity*. Google Patents.
- Kwon, R. H., & Ha, B. J. (2012). Increased flavonoid compounds from fermented *Houttuynia cordata* using isolated six of *Bacillus* from traditionally fermented *Houttuynia cordata*. *Toxicological Research*, 28, 117–122.
- Kwon, K.-B., Kim, E.-K., Shin, B.-C., Seo, E.-A., Yang, J.-Y., & Ryu, D.-G. (2003). Herba *houttuyniae* extract induces apoptotic death of human promyelocytic leukemia cells via caspase activation accompanied by dissipation of mitochondrial membrane potential and cytochrome c release. *Experimental & Molecular Medicine*, 35, 91–97.
- Lau, K.-M., Lee, K.-M., Koon, C.-M., Cheung, C. S.-F., Lau, C.-P., Ho, H.-M., Lee, M. Y.-H., Au, S. W.-N., Cheng, C. H.-K., & Bik-San Lau, C. (2008). Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *Journal of Ethnopharmacology*, 118, 79–85.
- Learadkamolkarn, V., Sirigulpanit, W., Phurimsak, C., Kumkate, S., Himakoun, L., & Sripanidkulchai, B. (2012). The inhibitory actions of *Houttuynia cordata* aqueous extract on dengue virus and dengue-infected cells. *Journal of Food Biochemistry*, 36, 86–92.
- Lee, J. H., Ahn, J., Kim, J. W., Lee, S. G., & Kim, H. P. (2015). Flavonoids from the aerial parts of *Houttuynia cordata* attenuate lung inflammation in mice. *Archives of Pharmacal Research*, 38, 1304–1311.
- Lee, S. B., Kang, J. W., Kim, S. J., Ahn, J., Kim, J., & Lee, S. M. (2017). Afzelin ameliorates D-galactosamine and lipopolysaccharide-induced fulminant hepatic failure by modulating mitochondrial quality control and dynamics. *British Journal of Pharmacology*, 174, 195–209.
- Lee, H. J., Seo, H. S., Kim, G. J., Jeon, C. Y., Park, J. H., Jang, B. H., Park, S. J., Shin, Y. C., & Ko, S. G. (2013). *Houttuynia cordata* Thunb inhibits the production of pro-inflammatory cytokines through inhibition of the NFκB signaling pathway in HMC-1 human mast cells. *Molecular Medicine Reports*, 8, 731–736.
- Lescure, F.-X., Bouadma, L., Nguyen, D., Parisey, M., Wicky, P.-H., Behillil, S., Gaymard, A., Bouscambert-Duchamp, M., Donati, F., & Le Hingrat, Q. (2020). Clinical and virological data of the first cases of COVID-19 in Europe: A case series. *The Lancet Infectious Diseases*, 20, 697–706.
- Liang, M., Qi, M., Zhang, C., Zhou, S., Fu, R., & Huang, J. (2005). Gas chromatography-mass spectrometry analysis of volatile compounds from *Houttuynia cordata* Thunb after extraction by solid-phase microextraction, flash evaporation and steam distillation. *Analytica Chimica Acta*, 531, 97–104.
- Li, G. Z., Chai, O. H., Lee, M. S., Han, E.-H., Kim, H. T., & Song, C. H. (2005). Inhibitory effects of *Houttuynia cordata* water extracts on anaphylactic reaction and mast cell activation. *Biological and Pharmaceutical Bulletin*, 28, 1864–1868.
- Li, W., Fan, T., Zhang, Y., Fan, T., Zhou, P., Niu, X., & He, L. (2013). *Houttuynia cordata* Thunb. volatile oil exhibited anti-inflammatory effects in vivo and inhibited nitric oxide and tumor necrosis factor-α production in LPS-stimulated mouse peritoneal macrophages in vitro. *Phytotherapy Research*, 27, 1629–1639.
- Li, Y., Hu, Y., Yu, J., & Ma, T. (2020). Retrospective analysis of laboratory testing in 54 patients with severe-or critical-type 2019 novel coronavirus pneumonia. *Laboratory Investigation*, 100, 794–800.
- Li, T., Liu, L., Wu, H., Chen, S., Zhu, Q., Gao, H., Yu, X., Wang, Y., Su, W., & Yao, X. (2017a). Anti-herpes simplex virus type 1 activity of *Houttuynia cordata*, a flavonoid from *Houttuynia cordata* Thunb. *Antiviral Research*, 144, 273–280.
- Li, T., Liu, L., Wu, H., Chen, S., Zhu, Q., Gao, H., Yu, X., Wang, Y., Su, W., & Yao, X. J. A. R. (2017b). In *Anti-herpes simplex virus type 1 activity of Houttuynia cordata*, a flavonoid from *Houttuynia cordata* Thunb (Vol. 144, pp. 273–280).
- Ling, L.-J., Lu, Y., Zhang, Y.-Y., Zhu, H.-Y., Tu, P., Li, H., & Chen, D.-F. (2020). Flavonoids from *Houttuynia cordata* attenuate H1N1-induced acute lung injury in mice via inhibition of influenza virus and Toll-like receptor signalling. *Phytomedicine*, 67, Article 153150.
- Lin, T.-Y., Liu, Y.-C., Jheng, J.-R., Tsai, H.-P., Jan, J.-T., Wong, W.-R., & Horng, J.-T. (2009). Anti-herpesvirus 71 activity screening of Chinese herbs with anti-infection and inflammation activities. *The American Journal of Chinese Medicine*, 37, 143–158.
- Lin, K.-H., Yang, Y.-Y., Yang, C.-M., Huang, M.-Y., Lo, H.-F., Liu, K.-C., Lin, H.-S., & Chao, P.-Y. (2013). Antioxidant activity of herbaceous plant extracts protect against hydrogenperoxide-induced DNA damage in human lymphocytes. *BMC Research Notes*, 6, 1–10.

- Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery*, 6, 1–4.
- Liu, S., Liu, Y., & Liu, Y. (2020). Somatic symptoms and concern regarding COVID-19 among Chinese college and primary school students: A cross-sectional survey. *Psychiatry Research*, 289, Article 113070.
- Lu, Y., Jiang, Y., Ling, L., Zhang, Y., Li, H., & Chen, D. (2018). Beneficial effects of *Houttuynia cordata* polysaccharides on “two-hit” acute lung injury and endotoxin fever in rats associated with anti-complementary activities. *Acta Pharmaceutica Sinica B*, 8, 218–227.
- Lu, H., Liang, Y., Yi, L., & Wu, X. (2006). Anti-inflammatory effect of *Houttuynia cordata* injection. *Journal of Ethnopharmacology*, 104, 245–249.
- Lu, H., Wu, X., Liang, Y., Zhang, J. J. C., & Bulletin, P. (2006). In *Variation in chemical composition and antibacterial activities of essential oils from two species of Houttuynia T HUNB* (Vol. 54, pp. 936–940).
- Market-Global, O. T. F. D. (2015). *Forecast, market share, size, growth and industry analysis 2014-2020*. Transparency Market Research, 2014.
- Martinez, M. A., Vuppalanchi, R., Fontana, R. J., Stolz, A., Kleiner, D. E., Hayashi, P. H., Gu, J., Hoofnagle, J. H., & Chalasani, N. (2015). Clinical and histologic features of azithromycin-induced liver injury. *Clinical Gastroenterology and Hepatology*, 13, 369–376. e3.
- Ma, Q., Wei, R., Wang, Z., Liu, W., Sang, Z., Li, Y., & Huang, H. (2017). Bioactive alkaloids from the aerial parts of *Houttuynia cordata*. *Journal of Ethnopharmacology*, 195, 166–172.
- Medhi, P., & Borthakur, S. (2012). In *Phytoresources from North Cachar hills of Assam-III: Edible plants sold at Hafflong market*.
- Mendelson, D., Keane, M., Bagaric, M., & Graydon, C. (2020). Legal implications of personal protective equipment use when treating patients for COVID-19 (SARS-CoV-2). *Journal of Law and Medicine*, 27, 856–864.
- Michaut, A., Moreau, S., Robin, M. A., & Fromenty, B. (2014). Acetaminophen-induced liver injury in obesity and nonalcoholic fatty liver disease. *Liver International*, 34, e171–e179.
- Mo, H., Ke, C., Zheng, J., & Zhong, N. (1993). Anti-viral effects of Lianhua Qingwen capsule against influenza A virus in vitro. *Traditional Chinese Drug Research & Clinical Pharmacology*.
- Mulangu, S., Dodd, L. E., Davey, R. T., JR., Tshiani Mbaya, O., Proschan, M., Mukadi, D., Lusakibanza Manzo, M., Nzolo, D., Tshomba Oloma, A., & Ibanda, A. (2019). A randomized, controlled trial of Ebola virus disease therapeutics. *New England Journal of Medicine*, 381, 2293–2303.
- Neumann, G., Noda, T., & Kawakita, Y. (2009). Emergence and pandemic potential of swine-origin H1N1 influenza virus. *Nature*, 459, 931–939.
- Ng, L.-T., Yen, F.-L., Liao, C.-W., & Lin, C.-C. (2007). Protective effect of *Houttuynia cordata* extract on bleomycin-induced pulmonary fibrosis in rats. *The American Journal of Chinese Medicine*, 35, 465–475.
- Nuengchamnong, N., Krittasilp, K., & Ingkaninan, K. (2009a). Rapid screening and identification of antioxidants in aqueous extracts of *Houttuynia cordata* using LC-ESI-MS coupled with DPPH assay. *Food Chemistry*, 117, 750–756.
- Nuengchamnong, N., Krittasilp, K., & Ingkaninan, K. J. F. C. (2009b). Rapid screening and identification of antioxidants in aqueous extracts of *Houttuynia cordata* using LC-ESI-MS coupled with DPPH assay. *Food Chemistry*, 117, 750–756.
- Pang, J., Dong, W., Li, Y., Xia, X., Liu, Z., Hao, H., Jiang, L., & Liu, Y. (2017). Purification of *Houttuynia cordata* Thunb. essential oil using macroporous resin followed by microemulsion encapsulation to improve its safety and antiviral activity. *Molecules*, 22, 293.
- Park, E., Kum, S., Wang, C., Park, S. Y., Kim, B. S., & Schuller-Levis, G. (2005). Anti-inflammatory activity of herbal medicines: Inhibition of nitric oxide production and tumor necrosis factor- α secretion in an activated macrophage-like cell line. *The American Journal of Chinese Medicine*, 33, 415–424.
- Patel, A. K., Ahire, J. J., Pawar, S. P., Chaudhari, B. L., Shouche, Y. S., & Chincholkar, S. B. (2010). Evaluation of probiotic characteristics of siderophoregenic *Bacillus* spp. isolated from dairy waste. *Applied Biochemistry and Biotechnology*, 160, 140–155.
- Philip, K., Sinniah, S. K., & Muniandy, S. (2009). Antimicrobial peptides in aqueous and ethanolic extracts from microbial, plant and fermented sources. *Biotechnology*, 8, 248–253.
- Phrutivorapongkul, A., Lipipun, V., Ruangrunsi, N., Kirtikara, K., Nishikawa, K., Maruyama, S., Watanabe, T., & Ishikawa, T. (2003). Studies on the chemical constituents of stem bark of *Milletia leucantha*: Isolation of new chalcones with cytotoxic, anti-herpes simplex virus and anti-inflammatory activities. *Chemical & Pharmaceutical Bulletin*, 51, 187–190.
- Prommajak, T., Surawang, S., & Rattanapanone, N. (2014). Ultrasonic-assisted extraction of phenolic and antioxidative compounds from lizard tail (*Houttuynia cordata* Thunb.). *Songklanakarin Journal of Science and Technology*, 36.
- Promptchara, E., Ketloy, C., & Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pacific Journal of Allergy & Immunology*, 38, 1–9.
- Qing-Song, X., & Sai-Jin, W. (2015). Highly efficient extraction of decanoyl acetaldehyde from *Houttuynia cordata* by a cryogenic grinding technique. *Chemistry of Natural Compounds*, 51, 359–360.
- Quan, M., Li, Q., Zhao, P., & Tian, C. (2018). Chemical composition and hepatoprotective effect of free phenolic extract from barley during malting process. *Scientific Reports*, 8, 1–9.
- Rangarajan, R., Mondal, S., Thankachan, P., Chakrabarti, R., & Kurpad, A. V. (2018). Assessing bone mineral changes in response to vitamin D supplementation using natural variability in stable isotopes of calcium in urine. *Scientific Reports*, 8, 1–8.
- Rathi, R., Roy, S., Misra, A., & Singh, S. (2013). In *Ethnobotanical notes on Houttuynia cordata Thunb. in North-Eastern region of India*.
- Ravindran, P., Pillai, G., & Divakaran, M. (2012). Other herbs and spices: Mango ginger to wasabi. In *Handbook of herbs and spices*. Elsevier.
- Řebříčková, K., Bajer, T., Šilha, D., Houdková, M., Ventura, K., & Bajerová, P. J. M. (2020). In *Chemical composition and determination of the antibacterial activity of essential oils in liquid and vapor phases extracted from two different southeast Asian herbs—Houttuynia cordata (saururaceae) and Persicaria odorata (polygonaceae)* (Vol. 25, p. 2432).
- Rechenchoski, D., Galhardi, L., Cunha, A., Ricardo, N., Nozawa, C., & Linhares, R. (2018). Antiviral potential of mangiferin against poliovirus. *International Journal of Pharmacological Research*, 8, 34–39.
- Ren, X., Sui, X., & Yin, J. (2011). The effect of *Houttuynia cordata* injection on pseudorabies herpesvirus (PrV) infection in vitro. *Pharmaceutical Biology*, 49, 161–166.
- Samlowski, W. E., Kondapaneni, M., Tharkar, S., McGregor, J. R., Laubach, V. E., & Salvemini, D. (2011). Endothelial nitric oxide synthase is a key mediator of interleukin-2-induced hypotension and vascular leak syndrome. *Journal of Immunotherapy*, 34, 419–427.
- Schepetkin, I. A., & Quinn, M. T. (2006). Botanical polysaccharides: Macrophage immunomodulation and therapeutic potential. *International Immunopharmacology*, 6, 317–333.
- Sekita, Y., Murakami, K., Yumoto, H., Amoh, T., Fujiwara, N., Ogata, S., Matsuo, T., Miyake, Y., & Kashiwada, Y. (2016). *Preventive effects of Houttuynia cordata extract for oral infectious diseases*. BioMed Research International, Article 2581876, 2016.
- Sharma, R., Martins, N., Kuca, K., Chaudhary, A., Kabra, A., Rao, M. M., & Prajapati, P. K. (2019). Chyawanprash: A traditional Indian bioactive health supplement. *Biomolecules*, 9, 161.
- Shim, S.-Y., Seo, Y.-K., & Park, J.-R. (2009). Down-regulation of Fc ϵ R1 expression by *Houttuynia cordata* thunb extract in human basophilic KU812F cells. *Journal of Medicinal Food*, 12, 383–388.
- Shimura, M., Zhou, Y., Asada, Y., Yoshikawa, T., Hatake, K., Takaku, F., & Ishizaka, Y. (1999). Inhibition of Vpr-induced cell cycle abnormality by quercetin: A novel strategy for searching compounds targeting Vpr. *Biochemical and Biophysical Research Communications*, 261, 308–316.
- Shingnaisui, K., Dey, T., Manna, P., & Kalita, J. (2018). Therapeutic potentials of *Houttuynia cordata* thunb. Against inflammation and oxidative stress: A review. *Journal of Ethnopharmacology*, 220, 35–43.
- Shin, S., Joo, S. S., Jeon, J. H., Park, D., Jang, M.-J., Kim, T.-O., Kim, H.-K., Hwang, B. Y., Kim, K.-Y., & Kim, Y.-B. (2010). Anti-inflammatory effects of a *Houttuynia cordata* supercritical extract. *Journal of Veterinary Science*, 11, 273–275.
- Shi, C.-C., Zhu, H.-Y., Li, H., Zeng, D.-L., Shi, X.-L., Zhang, Y.-Y., Lu, Y., Ling, L.-J., Wang, C.-Y., & Chen, D.-F. (2020). Regulating the balance of Th17/Treg cells in gut-lung axis contributed to the therapeutic effect of *Houttuynia cordata* polysaccharides on H1N1-induced acute lung injury. *International Journal of Biological Macromolecules*, 158, 52–66.
- Sikander, M., Malik, S., Rodriguez, A., Yallapu, M. M., Narula, A. S., Satapathy, S. K., Dhevan, V., Chauhan, S. C., & Jaggi, M. (2020). Role of nutraceuticals in COVID-19 mediated liver dysfunction. *Molecules*, 25, 5905.
- Simon, V., Ho, D. D., & Karim, Q. A. (2006). HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *The Lancet*, 368, 489–504.
- Singh, I. P., Bharate, S. B., & Bhutani, K. (2005). Anti-HIV natural products. *Current Science*, 269–290.
- Song, J. H., Shim, J. K., & Choi, H. J. (2011). Quercetin 7-rhamnoside reduces porcine epidemic diarrhea virus replication via independent pathway of viral induced reactive oxygen species. *Virology Journal*, 8, 1–6.
- Spernhart, A., & Aserin, A. (2006). Microemulsions as carriers for drugs and nutraceuticals. *Advances in Colloid and Interface Science*, 128, 47–64.
- J. J. O. G. V. Thiel, V., Ivanov, K. A., Putics, A., Hertzog, T., Schelle, B., Bayer, S., Weißbrich, B., Snijder, E. J., Rabenau, H., & Doerr, H. W. (2003). In *Mechanisms and enzymes involved in SARS coronavirus genome expression* (Vol. 84, pp. 2305–2315).
- Tian, L., Shi, X., Yu, L., Zhu, J., Ma, R., & Yang, X. (2012). Chemical composition and hepatoprotective effects of polyphenol-rich extract from *Houttuynia cordata* tea. *Journal of Agricultural and Food Chemistry*, 60, 4641–4648.
- Tutupalli, L. V., & Chaubal, M. G. (1975). Saururaceae. V. Composition of essential oil from foliage of *Houttuynia cordata* and chemo systematics of Saururaceae. *Lloydia*, 38, 92–96.
- Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J. J., Pfeffer, M. A., & Solomon, S. D. (2020). Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *New England Journal of Medicine*, 382, 1653–1659.
- Wan, C.-F., Zheng, L.-L., Liu, Y., & Yu, X. (2016). *Houttuynia cordata* Thunb reverses oxalipatin-induced neuropathic pain in rat by regulating Th17/Treg balance. *American Journal of Tourism Research*, 8, 1609.
- Woranam, K., Senawong, G., Utaiwat, S., Yunchalard, S., Sattayasai, J., & Senawong, T. (2020). Anti-inflammatory activity of the dietary supplement *Houttuynia cordata* fermentation product in RAW264. 7 cells and Wistar rats. *PLoS One*, 15, Article e0230645.
- Wu, S.-H., Chen, X.-Q., Kong, X., Yin, P.-L., Dong, L., Liao, P.-Y., & Wu, J.-M. (2016). Characteristics of respiratory syncytial virus-induced bronchiolitis co-infection with *Mycoplasma pneumoniae* and add-on therapy with montelukast. *World Journal of Pediatrics*, 12, 88–95.
- Wu, H. F., Morris-Natschke, S. L., Xu, X. D., Yang, M. H., Cheng, Y. Y., Yu, S. S., & Lee, K. H. (2020). Recent advances in natural anti-HIV triterpenoids and analogs. *Medicinal Research Reviews*, 40, 2339–2385.

- Xu, R., Jiang, L.-M., He, J.-M., & Liu, Y.-L. (2009). The condensation mechanism of sodium new houttuynonate and determination of the chemical structure of condensation products. *Yao xue xue bao= Acta Pharmaceutica Sinica*, *44*, 609–614.
- J. J. O. F. P. & PRESERVATION Xu, Z., Wu, J., Dai, S., Jiang, Y., & Zhang, L. (2022). Antimicrobial activity of combined essential oils of *Origanum vulgare* L. and *Houttuynia cordata* T. against *Salmonella enteritidis* and *Salmonella Paratyphi* β , *46*, Article e16472.
- Xu, Y.-Y., Zhang, Y.-Y., Ou, Y.-Y., Lu, X.-X., Pan, L.-Y., Li, H., Lu, Y., & Chen, D.-F. (2015). Houttuynia cordata Thunb. polysaccharides ameliorates lipopolysaccharide-induced acute lung injury in mice. *Journal of Ethnopharmacology*, *173*, 81–90.
- Yang, L., & Jiang, J.-G. (2009). Bioactive components and functional properties of Houttuynia cordata and its applications. *Pharmaceutical Biology*, *47*, 1154–1161.
- Yang, X., Jiang, Y., Yang, J., He, J., Sun, J., Chen, F., Zhang, M., & Yang, B. (2015). Prenylated flavonoids, promising nutraceuticals with impressive biological activities. *Trends in Food Science & Technology*, *44*, 93–104.
- Yonzon, R., Lama, D., Bhujel, R., & Rai, S. (2012). Orchid species diversity of Darjeeling Himalaya of India. *International Journal of Pharmacy & Life Sciences*, *3*.
- Zhang, C., Shi, L., & Wang, F.-S. (2020). Liver injury in COVID-19: Management and challenges. *The lancet Gastroenterology & hepatology*, *5*, 428–430.
- Zhang, X. W., & Yap, Y. L. (2004). Structural similarity between HIV-1 gp41 and SARS-CoV S2 proteins suggests an analogous membrane fusion mechanism. *Journal of Molecular Structure: THEOCHEM*, *677*, 73–76.
- Zheng, H., Dong, Z., & She, J. (1998). *Modern study of traditional Chinese medicine* (Vol. 3). Xue Yuan Press Beijing China, 2057.
- Zhernov, Y. V., Konstantinov, A. I., Zhrebker, A., Nikolaev, E., Orlov, A., Savinykh, M. I., Kornilaeva, G. V., Karamov, E. V., & Perminova, I. V. (2021). Antiviral activity of natural humic substances and shilajit materials against HIV-1: Relation to structure. *Environmental Research*, *193*, Article 110312.
- Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., & Gu, X. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *The Lancet*, *395*, 1054–1062.