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Review article

The therapeutic potential of *Houttuynia cordata*: A current review☆

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HIGHLIGHTS

- *Houttuynia cordata* is widely used as traditional medicine in East Asian countries.
- *H. cordata* extracts ameliorate cancer, inflammation, viral and microbial infection.
- Traditional knowledge linked to research has great potential for new drug discoveries.

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ABSTRACT

The search and development of new drugs for the treatment of numerous illnesses afflicting humans of all ages is an unending endeavour. Moreover, there is constant demand to identify more compounds exhibiting pharmacological properties with improved efficacy and minimal side effects compared to the existing ones. Plants have always served as rich sources of pharmaceuticals, and offer better advantages than synthetic compounds in terms of diversity, production scale and safety. *Houttuynia cordata* is a traditional medicinal plant that is widely distributed in East Asia. Apart from its consumption as a delicacy in many countries, it has a rich history of medicinal use and numerous studies have reported its pharmacological activity against inflammation, cancer, viruses, bacteria, hyperglycaemia, obesity, etc. The various phytoconstituents that have been isolated from this plant include flavonoids, phenolic acids, volatile/essential oils and alkaloids whose therapeutic potentials are yet to be fully harnessed. This review provides an updated summary of the biological activity and therapeutic potential of *H. cordata*, its phytocompounds and derivatives. The amalgamation of traditional plant-derived medicines with modern scientific methods can provide better insights to their mechanism of action and also contribute greatly to the discovery and synthesis of new pharmaceuticals.

1. Introduction

Throughout history, medicinal plants have always been valued sources of bioactive compounds that are used to prevent, treat and cure a host of common illnesses. The vast traditional knowledge of medicinal plants has accounted for 70–95% of treatment prescribed for many diseases especially in Asia, including India (X Wu et al., 2021). Important pharmacologically active compounds such as morphine (an analgesic), artemisinin and chloroquine (anti-malarial drugs), vinca alkaloids (cancer treatment), etc widely used in modern medicine are all plant-derived (Yuan et al., 2016). The search for novel, plant-derived bioactive compounds is boundless and is still a vital source of effective pharmaceutical compounds. One such plant that has gained particular focus, especially in light of the recent COVID-19 pandemic due to its potential anti-viral activity, is *Houttuynia cordata* (*H. cordata*), a perennial plant that belongs to the Family 'Saururaceae' and is native to East Asian countries (Watson and Dallwitz, 1992). It is widely consumed as both herbal medicine and food in countries like China, Korea and Japan. In India, it is found widespread in the North-Eastern states of Assam, Meghalaya, Manipur, Tripura, Mizoram, Arunachal Pradesh and Sikkim (Figure 1), and is considered a delicacy by many. It is also known by many common names such as Chameleon plant, fish wort or heart leaf, and Chinese lizard tail depending on the region (Gupta and Bharalee, 2020). The full taxonomical classification is given in Table 1.

In addition to its culinary use, *H. cordata* has long been used in tradition medicine due to the myriad of reported beneficial effects against ailments such as inflammation, rheumatoid arthritis, viral and bacterial infections, chronic sinusitis and allergies, hyperglycemia, etc

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Figure 1. *Houttuynia cordata* plant.

(Kumar et al., 2014; Shingnaisui et al., 2018). Its reported anti-viral effects have drawn new-found attention especially in the current scenario of the COVID-19 pandemic, since local claims of consuming *H. cordata* in states like Mizoram for the treatment of those infected with SARS-CoV-2 virus has been supported by several scientific studies (Bahadur Gurung et al., 2021). Similar anti-viral effects of the plant were reported by Lau et al. (2008) during the SARS outbreak of 2002–2003.

The efficacy of *H. cordata* and its bioactive compounds in the treatment of various ailments still warrant further detailed studies, and a lot of avenues are still yet to be explored. This review aims to provide an updated assessment of the numerous studies (both *in vivo* and *in vitro*) investigating the pharmacological activities of *H. cordata* and its constituent compounds against different ailments, and also to address the lacunae in the application of the therapeutic potential of *H. cordata* for numerous disorders. A methodical search of electronic literature available online through Pub Med, MEDLINE and Google Scholar databases was performed. Any available human clinical studies and experimental studies using cell cultures and animal models were included.

2. Chemical constituents of *H. cordata*

A large number of phytoconstituents have been identified and isolated from *H. cordata* such as alkaloids, flavonoids, aristolactams, amides, benzenoids, steroids, 5,4-dioxoaporphines, oxoaporphines and different volatile oils, of which alkaloids appear to be the most abundant compounds (Kumar et al., 2014; Ahn et al., 2017). A list of several compounds that have been isolated from *H. cordata* with their biological activity is given in Table 2. It has also been reported that amongst the various constituents, flavonoids and volatile oils seem to exert the highest pharmacological activities (Z Wu et al., 2021). Each identified constituent appears to have its own unique function and biological activity, depending on its chemical characteristics. Although all parts of the plant are edible and used as medicine, some studies have reported differences between constituents isolated from the aerial and underground parts of the plant, and in a study by Ma et al. (2017) in which they isolated 22 alkaloids from the aerial part of the plant, several compounds were found to exhibit PTP1B (a target for Diabetes Mellitus Type II treatment) inhibitory and hepatoprotective activities. Oh (2015) reported that β-Myrcene, *cis*-ocimene and decanal are dominant components of leaves extracts (71.0%) and aerial stems (50.1%) and monoterpenes (74.6%) were dominant in extracts from underground stems. Chou et al. (2009) isolated forty compounds from their study of the whole plant, out of which two compounds, houttuynoside A and houttuynamide A, had not been previously identified. In addition, their study also reported the suppressive activity of another compound norcepharadione B on Herpes Simplex Virus (HSV)-1 replication, and quercitrin and quercetin-3-*O*--beta-D-galactopyranoside were shown to have effective free-radical scavenging activities. Quercitrin in particular has also been investigated for other functions and has been reported to stimulate hair growth, inhibit inflammatory responses, mitigate hyperlipidemia and have apoptotic effects on colon cancer cells (Cincin et al., 2015; Tang et al., 2019; Hur et al., 2020; Kim et al., 2020) A new type of flavonoid, houttuynoids A-E with houttuynin tethered to hyperoside

Table 1. Taxonomic hierarchy of *Houttuynia cordata*.

Kingdom	Plantae
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta
Superdivision	Embryophyta
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Magnoliopsida
Superorder	Magnolianae
Order	Piperales
Family	Saururaceae
Genus	*Houttuynia* Thunb
Species	*Houttuynia cordata* Thunb

Source: Integrated Taxonomic Information System – Report www.itis.gov, CC0 https://doi.org/10.5066/F7KH0KBK.

Table 2. List of some compounds identified from *H. cordata* and their biological activities.

Compound	Reported biological activity	Reference
Houttuynin & Sodium houttuyfonate	Anti-ventricular remodelling	Gao et al. (2014)
	Anti-viral	Pang et al. (2017)
	Anti-pulmonary fibrosis	Zhu et al. (2021)
	Anti-fungal (*Candida albicans*)	Shao et al. (2017)
	Anti-bacterial	Shao et al. (2013)
	Anti-neuroinflammatory	Yao et al. (2021)
	Anti-inflammatory	Zhang et al. (2020)
2- undecanone	Anti-lung tumorigenesis	Lou et al. (2019)
	Anti-inflammatory	Chen et al. (2014)
	Anti-inflammatory (Kidney)	Wu et al. (2021)
Norcepharadione B	Anti-neuronal injury Anti-oxidative stress	Jia et al. (2019)
	Anti-viral	Chou et al. (2009)
Betulinic acid	Anti-parasitic	Vijaya and Yadav (2016)
Houttuynoids A-E	Anti-viral (Herpes simplex virus)	Chen et al. (2012)
Houttuynoid B	Anti-viral (Zika virus)	Basic et al. (2019)
Houttuynoids G-J	Anti-viral	Chen et al. (2013a)
Houttuynoid M	Anti-viral	Li et al. (2017)
Houttuynamide B	Anti-inflammatory	Ahn et al. (2017)
Quercitrin	ROS-scavenging	Chou et al. (2009)
	Hair-growth stimulation	Kim et al. (2020)
	Anti-viral	Chiow et al. (2016)
	Anti-cancer	Jang et al. (2011)
Quercetin	Anti-viral	Chen et al. (2011) Chiow et al. (2016)
	Anti-cancer	Das et al. (2021a)
Caffeic acid	Anti-cancer	Jang et al. (2011)
Myrcene	Anti-microbial Antifungal	Verma et al. (2017)
Chlorogenic acid	Anti-obesity	Wang et al. (2018)
β-sitosterol	Anti-cancer	Das et al. (2021a)

(quercetin-3-*O*-galactoside)were isolated by Chen et al. (2012) also exhibiting anti-HSV activity. Li et al. (2017) also newly identified a related flavonoid, with anti-HSV activity akin to other houttuynoids. Other flavonoids that have been isolated include glycosides, rutin, hyperin and isoquercitrin (Liu et al., 2019), which were demonstrated to have inhibitory effects on both lung injury and influenza virus activity. Five different fatty acids namely linolenic, linoleic, oleic, palmitic and stearic acids along with cepharanone B, phytol and stigmast-4-ene-3, 6-dione had been isolated by Bauer et al. (1996) who also studied their inhibitory effects on prostaglandin synthesis.

Essential oil content isolated by Verma et al. (2017) from the aerial parts included 2-undecanone (19.4–56.3%), myrcene (2.6–44.3%), ethyl decanoate (0.0–10.6%), ethyl dodecanoate (1.1–8.6%), 2-tridecanone (0.5–8.3%), and decanal (1.1–6.9%). From the underground stem region, 2-undecanone (29.5–42.3%), myrcene (14.4–20.8%), sabinene (6.0–11.1%), 2-tridecanone (1.8–10.5%), β-pinene (5.3–10.0%), and ethyl dodecanoate (0.8–7.3%) were the major components isolated. Interestingly, 1-decanal (the predominant metabolite) is the compound responsible for the characteristic 'fishy' odour of the plant (Asakawa et al., 2017). Betulinic acid and ursolic acid are pentacyclic triterpenoids which are another major class of phytochemicals that have been isolated from *H. cordata*, although they have been reported to have mild toxic effects in the users (Mishra et al., 2021). Polysaccharides extracted from *H. cordata* mainly include galacturonic acid, galactose, glucose, and xylose (Cheng et al., 2019). Phenolic acids were also isolated from fermented, powdered *H. cordata* formula namely, gallic acid, protocatechuic acid, *p*-hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-hydroxybenzaldehyde, *p*-coumaric acid, ferulic acid and sinapinic acid (Kumnerdkhonkaen et al., 2018). Ji et al. (2011) also isolated the compounds α-pinene, β-pinene, myrcene along with previously unidentified limonene, terpinen-4-ol, α-terpineol, bornyl acetate and methyl-n-nonylketone using gas chromatography coupled with flame ionization detection method. Further in-depth studies are still necessary to identify the full therapeutic potential and molecular mechanism of action of all these isolates individually and in combination, for better efficacy in treatment of illnesses.

3. Therapeutic activities of *H. cordata*

3.1. Anti-viral activity

Several studies have reported inhibitory effects of *H. cordata* on different types of viral diseases. Interestingly, in light of the current COVID-19 pandemic, Das et al., 2021b have reported inhibitory activity of phytocompounds isolated from *H. cordata* on the SARS-CoV-2 virus. The three main proteins that control the replication process of this virus are Main protease (Mpro), Papain-Like protease (PLpro) and ADP ribose phosphatase (ADRP). For this particular study, about 177 phytocompounds were characterized from *H. cordata* and docking experiments were performed against the corresponding receptors of the three main replication proteins using Epic, LigPrep and Glide module of Schrödinger suite 2020–3. From the experiments, they reported that one of the compounds 6-Hydroxyondansetron (ligand) exhibited a high binding affinity for receptors Mpro (PDB ID 6LU7) with G-score of − 7.274 and PLpro (PDB ID 7JRN) with a slightly lower G-score − 5.672. Quercitrin (A166) demonstrated a strong binding affinity toward ADRP (PDB ID 6W02) with G-score -6.788. Moreover, they also reported that 6-Hydroxyondansetron has the highest potential as a drug to inhibit Mpro and PLpro of SARS-CoV-2 without any toxicity side effects, while quercitrin could serve as a potential inhibitor for ADRP. In another study targeting the SARS-CoV-2 encoded enzyme RNA-dependent RNA polymerase (RdRp) which is critical for viral gene transcription and replication, molecular docking experiments were performed, and it was shown that three *H. cordata*-derived compounds 1,2,3,4,5-pentamethoxy-dibenzo--quinolin-7-one, 7-oxodehydroasimilobine and 1,2-dimethoxy-3-hydroxy-5-oxonoraporphine demonstrated a high affinity for the target enzyme, forming stable protein–ligand complexes throughout the molecular dynamics simulation (Gurung et al., 2021). However, *in vivo* studies are warranted to establish their true anti-viral efficacy.

A previous study by Lau et al. (2008) had reported the anti-viral activity of *H. cordata* extracts against another coronavirus SARS-CoV, which was responsible for an outbreak during late 2002 to mid-2003 in China. Their results showed that aqueous *H. cordata* extracts significantly inhibited SARS-CoV 3C-like protease ($3CL^{pro}$) and RdRp. Further, toxicity tests verified that oral administration of *H. cordata* extracts did not show any toxic effects to laboratory animals even at a dose of 16 g/kg.

The anti-viral properties of *H. cordata* extracts are not just limited to coronaviruses. HSV-1 infection is rather pervasive and contagious, and infection could result in reactivation of other viruses such as human immunodeficiency virus (HIV), Epstein-Barr virus, and human papillomavirus. The flavonoid, houttuynoid A isolated from *H. cordata* was found in a study by Li et al. (2017) to exhibit inhibitory effects on HSV-1 infections both *in vitro* and *in vivo*. The study demonstrated that in a mouse model, the compound could significantly hinder multiplication of HSV-1 and also halt lesion formation. These effects were possible because of the ability of this compound to block viral membrane fusion. Novel houttuynoids A-E isolated from whole plant *H. cordata* extract were found to exhibit effective inhibitory activities against HSV, with respective IC_{50} values of 23.50 ± 1.82, 57.71 ± 8.03, 50.75 ± 11.07, 59.89 ± 6.63, and 42.03 ± 10.22 μM (Chen et al., 2012). Similar reports of anti-HSV-1 activity of other flavonoid compounds were published by Chen et al. (2013a) where they isolated houttuynoids G-J from 50% aq. EtOH extract that were responsible for the anti-HSV effects. The antiviral activity assay showed that these four flavonoids inhibited viral infection with respective IC_{50} values of 38.46, 14.10, 62.00 and 70.76 μM. Houttuynoid M is another compound that was demonstrated to have anti-HSV activity with an IC_{50} values of 17.72 μM in a plaque formation assay (Li et al., 2017).

In another study, it was shown that *H. cordata* water extracts could not only impede the infection of HSV-1, HSV-2, and acyclovir-resistant HSV-1 but also inhibit HSV replication. This process occurred via blocking viral binding and penetration in the beginning of infection, in addition to attenuation of NF-κB activation, an essential mechanism for viral gene expressions. Further, of the compounds isolated, they reported that quercetin and isoquercitrin inhibit NF-κB activation and quercetin could effectively prevent viral entry (Hung et al., 2015). Anti-HSV activity of hot water extract of *H. cordata* via inhibition of NF-κB activation was also reported earlier by Chen et al. (2011), efficiently blocking HSV-2 infection.

Influenza viruses have been responsible for debilitating illnesses and crippling pandemics not just in human populations but also in domestic animals. Out of the three IV-types (A, B, and C), influenza A viruses have mostly been responsible for the most severe epidemics (Monto and Fukuda, 2020). Several studies have also implicated inhibitory effects of *H. cordata* on these virus strains. Quercetin 3-rhamnoside (or Quercitrin), a compound identified in *H. cordata* extract showed significant inhibition of influenza A/WS/33 infection in a cytopathic effect reduction method, and could suppress viral replication at the initial stage of infection via indirect interaction with virus particles. This anti-viral activity was relatively higher compared to that of oseltamivir (Choi et al., 2009). Using a neuraminidase-based bioassay, Han et al. (2016) studied the antiviral activities of selected 26 anti-flu Chinese herbal medicines. Out of these, *H. cordata* was also identified to have strong anti-viral effects, effectively inhibiting neuraminidase enzyme activity (at 250 mg/mL). Influenza A virus (IAV) H1N1 infected mice treated with polysaccharides isolated from *H. cordata* (HCP) showed an increased survival rate, and simultaneously reduced the levels of pulmonary proinflammatory cytokines/chemokines, intestinal goblet cells, and also reinforced the intestinal physical and immune barrier, increased levels of sIgA and tight junction protein (ZO-1) in intestine, thereby significantly ameliorating lung and intestinal injury (Zhu et al., 2018). In an almost comparable

study, HCP was orally administered to H1N1 virus infected mice at a dose of 40 mg/kg/d. The results showed that HCP significantly inhibited the expression of hypoxia inducible factor-1α, reduced mucosubstances in goblet cells, while conversely restoring zonula occludens-1 levels in intestine. Further, change in composition of intestinal microbiota as a result of H1N1 infection was effectively reversed, with significant reduction in populations of pathogenic bacterial genera *Vibrio* and *Bacillus*. It was also suggested that the anti-inflammatory effect was associated with increased production of interleukin -10 (IL-10) and reduction in Toll-like receptors (TLRs) and interleukin-1β (IL-1β) in intestine (Chen et al., 2019). Furthermore, HCP treatment was found to restore the balance of Th17/Treg (regulatory T) cells in gut mucosal-associated lymphoid tissue (GALT) and in the lungs of Influenza-A virus infected mice and also lowered expression levels of chemokine CCL20 in the lungs. HCP administration also resulted in regulating the balance of Th17/Treg carrying CCL20 receptor, $CCR6^{+}$ that is crucial for specific migration of Th17/Treg cells from GALT to lung (Shi et al., 2020). Flavonoid glycosides isolated from *H. cordata* were investigated for their therapeutic effects on influenza A virus (IAV)-induced acute lung injury (ALI) in mice. The glycosides consisting of compounds such as rutin, hyperin, isoquercitrin, and quercitrin significantly improved the survival rate and life span of H1N1-infected mice, lowered lung index and the amount of weight lost overall than the model group. Further, *H. cordata* extract-treated group were found to have more intact lung microstructural morphology, milder inflammatory infiltration, and lower levels of monocyte chemotactic protein 1 (MCP-1), IL-8, tumor necrosis factor-α (TNF-α) and malondialdehyde (MDA) than in the non-treated group (Ling et al., 2020).

Another type of infectious virus, the Zika virus (ZIKV), belonging to the family of Flaviviridae, has emerged as a pathogen of concern in recent times ever since its 2016 outbreak in Brazil, and can cause microcephaly in infants. Yet there are no anti-viral drug or vaccines available against the infection (Plourde and Bloch, 2016). In a recent study by Basic et al. (2019), synthetic tetra-*O*-acetylated houttuynoid TK1023 derived from *H. cordata* was investigated *in vitro* [using African green monkey kidney cells (Vero, Vero E6), human epithelial lung carcinoma cells (A549) and the human hepatocellular cell line Huh7.5] for potential anti-viral effects against Zika virus. The results showed that in the TK1023 treated cells, there was significant decrease in the number of infected cells 24 h and 48 h post infection, when compared to the control, which appeared to be a result of restriction of viral entry into the cell and thus preventing further viral proliferation.

H. cordata polysaccharide (HP; molecular weight of ~43 kDa), purified from *H. cordata* water extract was examined for anti-viral properties against Human noroviruses (HuNoVs) that cause of foodborne viral gastroenteritis. Murine norovirus-1 (MNV-1) was used as a surrogate for HuNoV, and in the plaque forming assays performed, HP treatment at a concentration of 500 μg/mL significantly suppressed the infectivity of MNV-1 to an undetectable level. Analysis with transmission electron microscopic showed deformed and inflated virus particles as a result of HP treatment, which likely inhibited the penetration of viruses in target cells (Cheng et al., 2019). Since there are no mature vaccines and medicines available, Respiratory Syncytial Virus (RSV) is one of the main pathogens causing infant lower respiratory tract infections, and the resulting pneumonia can be fatal. In this regard, a preliminary study by Du et al. (2020) identified candidate compounds of *H. cordata* Thunb and obtained potential targets from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), PubMed, CNKI, PubChem Database, and Swiss Target Prediction database, and after screening a total of 12 potentially active compounds and 47 potential interaction targets, analysis using KEGG enrichment pathway projected that *H. cordata* Thunb exerted its anti-RSV effect by regulating TNF, Rap1, hypoxia-inducible factor (HIF-1), PI3K-Akt, MAPK, and VEGF signaling pathways.

Apart from these, the different constituents of *H. cordata* have been reported to exhibit significant anti-viral activities against other strains of viruses such as mouse hepatitis virus, dengue virus (Chiow et al., 2016), Enterovirus 71 and coxsackievirus A16, causative agents of hand, foot, and mouth disease (Chen et al., 2013b), supporting the potential for development of potent antiviral agents from *H. cordata* phytochemicals.

3.2. Anti-bacterial activity

Antibiotic resistance, caused primarily by the indiscriminate use of antibiotics, is a global problem plaguing the medical field, and the need to identify new and more effective compounds in treating bacterial infections caused by resistant strains is of utmost importance (Davies and Davies, 2010). In this aspect, many plant-derived compounds and metabolites have received increased attention for their potential anti-bacterial activities. Several phytocompounds extracted and derived from *H. cordata* have also been reported to exhibit efficacy against infection by some bacterial strains.

Anti-bacterial effects of *H. cordata* water extracts (HCWE) were studied *in vitro* against *Salmonella typhimurium* (*S. typhimurium*) which showed a dose dependent manner of inhibition, at concentrations from 25 to 100 μg/mL after 8-h incubation. In the *in vivo* study, *S. typhimurium*-infected BALB/c mice treated with HCWE showed prolonged lifespans (25, 50, and 100 μg/mL groups survived until 11, 17, and 23 d, respectively) compared to the untreated group which had 100% mortality rate (Kim et al., 2008).

Sodium houttuyfonate (SH), a constituent of *H. cordata* extract, had been tested for its inhibitory effects on *Pseudomonas aeruginosa (P. aeruginosa),* a bacterium that can cause severe, opportunistic and life-threatening infections in immunocompromised persons, and chronic infections in cystic fibrosis patients (Dolan, 2020). In the study by Wu et al. (2015b) where they performed plate assay, it was found that SH exhibited inhibitory action against swimming and twitching movements in 24 h and swarming in 48 h in a dose-dependent manner, and 1 x minimum inhibitory concentration (MIC) caused bacteria to lose nearly all of their motility. In addition, expression levels of structural gene flgB and pilG were significantly down-regulated by SH, implying that SH inhibition of *P. aeruginosa* motility may be due to the inhibition of flagella and pili bioformation. Synergistic effect of SH with levofloxacin (LFX) against the biofilm formation of *P. aeruginosa* was verified, with MIC values of 0.25 μg/mL and 128 μg/mL, respectively and ½ × MIC SH combined with 2 × MIC LFX was found to effectively suppress biofilm formation with up to 73% inhibition, and a 92% decrease in concentration of alginate, the primary biofilm constituent (Shao et al., 2012). Ability of SH to eliminate *P. aeruginosa* adhesion and formation of biofilms was also corroborated by findings of Cheng et al. (2012). An *in vitro* investigation to determine the effects of SH against biofilm formation and alginate synthesis in a clinical strain of *P. aeruginosa* (AH16) by Wu et al. (2015a) also substantiated these findings, where the results indicated that SH overall could significantly inhibit biofilm formation, and alginate production was suppressed at various stages of biofilm development, most likely due to reduced expression levels of two genes crucial for alginate synthesis, i.e., algD and algR genes. In addition, significant alterations were observed in the cellular and biofilm structures via scanning electron microscope analysis. SH was also shown to prevent biofilm formation in lung-Qi deficiency induced by *P. aeruginosa* in rat airways, reducing cytokine concentrations to prevent inflammation (Wu et al., 2016).

In another study, Shao et al. (2013) demonstrated another inhibition mechanism of SH treatment, where they reported that SH could also significantly shorten the diameter of *P. aeruginosa* swimming motility by 36 % after 24 h incubation, the fold changes of fliC required for swimming motility was 0.36 after 24 h and pyocyanin production decreased by 47% and 56% after 1 and 3-days of treatment respectively. Impediment of biofilm formation by SH in another strain of bacteria *Staphylococcus aureus* (*S. aureus*) was also established, where SH treated cultures showed reduced levels of extracellular DNA (eDNA) of *S. aureus* in a dose-dependent manner, via reduction of cidA expression to inhibit

autolysis. Moreover, microarray results also revealed significant reduction in autolysin *atl*, *sle1*, *cidA* and *lytN* transcripts in the SH-treated strain as compared to the control strain. This decrease is consistent with the induction of the autolytic repressors *lrgAB* and *sarA* and with the downregulation of the positive regulators *agrA* and RNAIII (Liu et al., 2011). Biofilm inhibition in *P. aeruginosa* by SH was also observed in an *in vitro* model, where expression levels of both gene and protein of key biofilm regulator *BdlA* was effectively reduced in a dose dependent manner. In addition, it was also reported that SH could penetrate the biofilm layer and essentially suppress the biofilm life-cycle (Wang et al., 2019). Methicillin-resistant *S. aureus* (MRSA) has posed a new challenge in terms of treatment, highlighting an urgent need for new compounds to battle the strain. Combination of SH along with other antibiotics such as oxacillin or netilmicin showed promising results of MRSA inhibition *in vitro*. SH alone was able to inhibit all test strains with MICs ranging from 16 to 64 μg/mL in susceptibility tests, and in synergistic combinations with oxacillin, cephalothin, meropenem and netilmicin, inhibitory effects were also observed with median fractional inhibitory concentration (FIC) indices of 0.38, 0.38, 0.25 and 0.38 respectively in checkerboard assays (Lu et al., 2013).

Gram positive bacteria *Staphylococcus epidermidis (S. epidermidis)* is a facultative anaerobe which can cause biofilm formation and infections in certain cases (Otto, 2009). Key regulatory genes in quorum sensing of *S. epidermidis* are LuxS and agr and RNA III is the effector molecule of agr system. SH in combination with other antibiotics such as erythromycin displayed synergistic effects, by up-regulating the transcription of luxS and down-regulating the expression of agr/RNA III in certain concentrations, inhibiting mutual aggregation between *S. epidermidis* and biofilm bacteria, and negatively impacting the morphology of biofilm (Guan et al., 2013; Xu et al., 2017). SH has also shown enhanced synergistic effects *in vitro* with EDTA-Na_2 in the suppression of both planktonic and biofilm phenotypes of *P. aeruginosa,* and in *vivo* experiments with *S. aureus* infected mice, SH + EDTA-Na_2 administration improved the lifespan of the animals compared to the untreated group with no detected cytotoxicity (Huang et al., 2015).

Verma et al. (2017) isolated several constituents from *H. cordata* such as essential-oils ranged in concentration from 0.06–0.14% and 0.08–0.16% in the aerial-parts and underground-stem, and then subsequently tested their various antimicrobial activities. They found that the oils exhibited varying magnitudes of effective inhibitory activity against all tested bacteria, which Zone of Inhibition (ZOI) values as *Mycobacterium smegmatis* (15.0mm) > *Streptococcus mutans* (14.0mm) > *S. aureus* (ZOI: 13.0mm) = *Enterococcus faecalis* (13.0mm). The range of MIC was 0.52–1.04 μL/mL, and was lowest for *S. aureus* and *S. mutans* at 0.52 μL/mL. Essential oils derived from *H. cordata*, consisting of monoterpenes, sesquiterpenes and diterpenes were tested for antimicrobial activity on different strains of both Gram positive and Gram-negative bacteria. Interestingly, *H. cordata* essential oils demonstrated effective antimicrobial activity in the range of 128–1024 μg/mL, 512–1024 μg/mL in broth and 1024 μg/mL, 512–1024 μg/mLin agar, respectively, and it was also noted that Gram-negative bacteria showed more resistance to the extracts than Gram-positive bacteria (Řebíčková et al., 2020). The mechanism by which *H. cordata* derived compounds such as Sodium new houttuyfonate (SNH) exhibited bactericidal activity was proposed by Yang et al. (2016) using iTRAQ-based quantitative proteomics in which they analysed SNH treatment-induced protein alterations in *Streptococcus pneumoniae*. Their study validated that SNH was lethal to *S. pneumoniae* in a dose-dependent manner, with increased level of H_2O_2, which elucidated the anti-bacterial mechanism of not only SNH but also of other anti-microbial compounds.

3.3. Anti-parasitic activity

There is still a considerable lack of studies related to the anti-parasitic activity of *H. cordata* extracts in both humans and animal models, although available reports have suggested effective inhibitory activities. As reported by Yadav and Temjenmongla (2011) the leaves of *H. cordata* have long been used as medicine to treat intestinal infection by the Naga tribes in North-east India. In this regard, the anti-parasitic activity of *H. cordata* was investigated in albino rats infected with *Hymenolepis diminuta*, a zoonotic cestode. Anticestodal efficacy of *H. cordata* extract was found to be dose dependent, where 800 mg/kg of extract administered significantly reduced ($P < 0.001$) the eggs per gram (EPG) of faeces counts of infected animals by 57.09% and worm load by 75.00%, after the treatment period. Additionally, anthelmintic testing of *H. cordata* extract was performed *in vitro* against *H. diminuta* and efficacy was compared to the drug praziquantel as reference. *H. cordata* derived compounds biochanin A, ursolic acid, betulinic acid and beta-sitosterol were then screened for inhibitory activities, and physical motility was used as a parameter to measure anthelmintic activity. The results showed that all three compounds except beta-sitosterol showed strong anthelmintic effects in a dose dependent manner. Out of these, betulinic acid (1 mg/mL) displayed the best anthelmintic effect, causing the mortality of test parasites at 3.4 ± 0.66 h (Vijaya and Yadav, 2016). As such, there is still a lot of avenues to be explored regarding the anti-parasitic efficacy of *H. cordata* extracts and derivatives, for the treatment of helminthic diseases.

3.4. Anti-inflammatory activity

Inflammation can be defined as a wide-ranging physiological response to external factors such as human pathogens, dust particles and viruses, and can be categorized into two types-acute and chronic, contingent to numerous inflammatory processes and cellular mechanisms (Arulselvan et al., 2016). Targeting inflammatory responses is a crucial aspect in the treatment of many diseases, and there has been increased focus on therapeutic compounds that are derived from plants. SH and 2-undecanone were derived from *H. cordata* and investigated for their anti-inflammatory properties and mechanism of action in both *in vitro* and *in vivo* models. While both compounds showed high anti-inflammatory efficacies, both *in vitro* and *in vivo*, SH had relatively higher anti-inflammatory effects compared to 2-undecanone at the same dosage. However, they both exhibited similar modes of action, via reduction in concentrations of TNF-α, IL-1β and the expression of TLR4, and enhanced secretion of IL-10 in lipopolysaccharide (LPS)-stimulated RAW264.7 cells. In the *in vivo* study, xylene-induced mouse-ear edema was also significantly reduced by both compounds (Chen et al., 2014).

Inflammation can be induced by *S. typhimurium* infection in intestines causing diarrhoea and other complications. Houttuynin derivative SH could effectively ameliorate inflammation in the intestine of *S. typhimurium* infected BALB/c mice and also improve intestinal barrier. Inflammatory cytokines such as TNF-α, IL-1β, IL-6 and inflammation-related enzymes such as iNOS and COX-2 were significantly reduced in the SH treated group, and inhibition of p-IκBα and p-p65 expression in intestinal tissues was also seen via Western blot, implying the anti-inflammatory property of SH works via regulation the NF-κB signaling pathway (Zhang et al., 2020). Similar anti-inflammatory effects of *H. cordata* derived flavonoids were also seen in ALI caused by H1N1 virus in mice. The treated groups showed reduction in damage levels of lung microstructural morphology, inflammatory infiltration, and decrease in monocyte chemotactic protein 1 (MCP-1), IL-8, TNF-α and MDA expression levels, along with inhibition of TLRs and NF-κB p65(p) in lung tissues compared to the model group (Ling et al., 2020). In a study by Wonoram et al. (2020), anti-inflammatory potential of fermented *H. cordata* extract were investigated both *in vitro* and *in vivo* in RAW264.7 cells and carrageenan-induced paw edema Wistar rats respectively. Results from the *in vitro* study showed concentration-dependent reduction of NO levels and suppression of LPS-stimulated expression of PGE2, iNOS, IL-1β, TNF-α and IL-6 level in the group treated with extracts (aqueous and methanolic) of *H. cordata*. For the *in vivo* study, paw edema reduction was seen from two doses (3.08 and 6.16 mL/kg) after 2 h carrageenan stimulation akin to anti-edematous effect of diclofenac.

Interstitial cystitis/bladder pain syndrome (IC/BPS), accompanied by bladder inflammation and elevated number of activating mast cells in bladder tissues, is another condition that could benefit from treatment with *H. cordata* extracts. In an *in vivo* study, adult female rats induced with cyclophosphamide (75 mg/kg, intraperitoneal injection, once every 3 days for 10 days) served as IC/BPS models, of which one group was treated with *H. cordata* extract. Urinary frequency, nociceptive behaviors, cystometry, bladder weight, histological changes, and cytokine (IL-6, IL-8, TNF-α) concentration were selected as parameters for measurement of anti-inflammatory effects, and it was found that the group treated with *H. cordata* extract had reduced number of mast cells, decreased concentration of cytokines, in addition to longer intercontraction interval, bigger bladder capacity and higher nociceptive threshold. The study demonstrated the inhibitive efficacy of *H. cordata* on inflammation via inhibition of mast cell proliferation and regulation of proinflammatory cytokine levels (Li et al., 2020).

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is highly heterogenous, affecting the diarthrodial joint and can result in irreparable joint damage and significant disability in the afflicted (Lee and Weinblatt, 2001). The anti-inflammatory properties of SH as an alternative or supplement to conventional RA treatment was investigated *in vitro*. Primary cells of synovial tissue were collected from RA patients, cultured and subjected to SH treatment. Interestingly, post treatment, synovial proliferation in SH treatment groups were markedly lower than the control group ($P < 0.05$) in a dose dependent manner, with 200 μg/mL SH showing the highest inhibitory effects (Li et al., 2014).

Acute myocardial infarction (MI) with subsequent ischaemia and cardiac inflammation can result in devastating heart failure. In a rat model of post-myocardial infarction, SH treatment was shown to improve heart rate and left ventricular heart function, decreased expression of brain natriuretic peptide and improved the histopathological changes caused by MI. Fibrosis and inflammation were inhibited by suppressing the expression levels of inflammatory cytokines such as TNF-α, IL-1β, TGF-β as well as collagen I and collagen III. SH also activated AMP-activated protein kinase (AMPK) and suppressed NF-κB p65, thereby resulting in alleviated overall cardiac inflammatory and fibrotic responses post MI (Zheng et al., 2018).

Anti-inflammatory effects were studied in various inflammatory conditions of the lungs such as chronic obstructive pulmonary disease (COPD) and Ventilator-induced lung injury (VILI). In the COPD inflammatory rat model, SH treatment ameliorated tissue abnormalities of COPD-induced lung morphology, neutrophil infiltration and airway obstruction as well as reduction in proinflammatory cytokines, TNF-α and IL-1β, suggesting similar pathways of anti-inflammatory effects via suppression of TLR4/NF-κB pathways (Wu et al., 2017). In male mice VILI model, SH treatment effectively alleviated inflammation by reducing lung injury and apoptosis, inflammatory cytokines, reactive oxygen species, malonaldehyde, and p-JNK/JNK expression in lung tissues, suggesting SH anti-inflammatory mechanism via inhibition of ROS-mediated JNK pathway (Liu et al., 2021b). Another promising application of the anti-inflammatory property of *H. cordata* and its derivatives is in Alzheimer's Disease, a progressive, neurodegenerative condition for which neuroinflammation is an underlying risk factor, and deposition of amyloid-β (Aβ) plaques are a key feature (Minter et al., 2016). In amyloid-β peptide $(Aβ)_{1-42}$-induced AD mice, SH treatment attenuated spatial learning and memory deficiency, and also significantly improved neuronal loss and shrinkage compared to control. Levels of inflammatory cytokine concentrations of IL-6, IL-1β, IL-18, and TNF-α were significantly reduced ($P < 0.01$) compared with the $Aβ_{1-42}$ group, in addition to decreased expression levels of Bcl-2, Bax, and caspase-3 in $Aβ_{1-42}$-induced group, indicating an overall amelioration of neuroinflammation and oxidative stress (Zhao et al., 2021).

Apart from inflammatory diseases in humans, *H. cordata* extracts have also been investigated for inhibitory effects in diseases plaguing the farming industry. Mastitis is an inflammatory condition of cattle mammary glands caused by pathogens, and can result in reduction of milk yield. Anti-inflammatory efficacy of SH was examined *in vitro* using LPS-stimulated primary bovine mammary epithelial cells (bMEC) in which results demonstrated that SH could significantly suppress the expression levels of LPS-stimulated TNF-α, IL-1β and IL-6 and also inhibited LPS-induced TLR4 expression and NF-κB activation (Wang et al., 2017). Similar anti-inflammatory activity was demonstrated in LPS-induced bovine endometrial epithelial cell (bEEC) inflammation by Zhu et al. (2015) via suppression of TNF-α, IL-1β, IL-6 and IL-8 in addition to IκBα degradation, NF-κB p65 phosphorylation, and suppressed phosphorylation of MAPKs, p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK). A later study corroborated these similar findings in LPS-induced mastitis in mice (Liu et al., 2019). Another derivative of *H. cordata*, Norcepharadione B (NB) was shown to have significant efficacy against neuronal injury induced by H_2O_2 in HT22 mouse hippocampal cell lines. The study involved the treatment of HT22 cells with H_2O_2 to induce neuronal toxicity and then treatment with varying doses of NB. Results showed that NB treatment (>50 μmol/L) significantly enhanced cell viability and also inhibited neurotoxicity, reduction in cell volume and apoptosis via increased expression level of Bcl-2 and reduced Bax levels. In addition, protection against oxidative stress was also reported via significant MDA reduction and SOD and GSH increase (Jia et al., 2019).

3.5. Anti-diabetic activity

Type-2 diabetes has become a global epidemic, and the condition is profoundly associated with chronic insulin resistance and hyperglycaemia which in turn can lead to cardiovascular diseases. Overweight or obesity as a result of sedentary lifestyles and compromised diet quality are highly associated with the risk of developing diabetes (Laakso and Kuusisto, 2014). Treatment of this condition necessitates a multi-pronged approach including lifestyle changes, physical activity and nutrition to control obesity, in addition to medication. Although conventional treatment drugs such as metformin are prescribed, they are often contraindicated in many patients which warrants a need for therapeutic alternatives (Pfeiffer and Klein, 2014). Efficacy of *H. cordata* extracts in the treatment of diabetes and combatting insulin resistance and hyperglycemia has been proposed by several studies. In a study by Wang and Bao (2012) on a rat model of diabetes mellitus induced with streptozotocin (STZ) and high glucose-lipid animal feed, it was found that houttuynin, a constituent compound of *H. cordata* extracts could significantly ameliorate diabetes symptoms post treatment by increasing adiponectin (a crucial factor for insulin sensitivity) levels and conversely reducing levels of connective tissue growth factor. The effects of houttuynin were comparable to that of insulin sensitizing drug, Rosiglitazone. Additionally, alleviated kidney injury in diabetic rats post treatment may also be due to reduction in expression levels of Connective tissue growth factor (CGTF). Hsu et al. (2016) demonstrated that treatment of diabetic mice with aqueous extracts of *H. cordata* was able to lower plasma glucose and blood urea nitrogen levels, and also restored creatinine clearance rate. In addition, diabetes-induced renal Aldose reductase activity was decreased along with various markers of inflammation in heart and kidney (IL-6, TNF-α) and gene expression levels of $p47^{phox}$, NF-κB p65 and p-p38 were reduced, which could potentially attenuate cardiac and renal injury in diabetic conditions. Potential use of *H. cordata* extract as a complementary treatment with metformin was also suggested as a result of synergistic effects between these two compounds (Wang et al., 2017). This study showed that *H. cordata* extract administered with metformin strongly enhanced insulin sensitivity when compared to metformin treatment alone, decreased IL-6 and TNF-α expression levels, improved glucose tolerance and decreased fecal and serum endotoxin levels of gut microbiota. Similar outcomes were also presented in a study by Sakuludomkan et al. (2021) where they verified that oral administration of fermented *H. cordata* significantly decreased blood glucose levels and improved glucose tolerance capacity in streptozotocin-induced diabetic rats. Reduced levels of oxidative stress markers in serum and

inflammatory-related mediators in pancreas tissues were also reported. A study by Kumar et al. (2014) had shown that mice fed ad libitum with *H. cordata* extract daily for 21 days at 200 and 400 mg/kg dose level displayed significant ($P < 0.05$) improvements in fasting plasma glucose and insulin levels in streptozotocin-induced diabetic rats. Further, it was also found to attenuate deviations in normal biochemical parameters such as total lipid profile, blood urea, creatinine, protein, and antioxidant enzymes in liver, pancreas, and adipose tissues. have Protective, anti-obesity effects of aqueous extracts of *H. cordata* were verified in mice fed with high saturated fat diet after a treatment period of 8-weeks, which supported anti-oxidative and anti-inflammatory activities via retainment of glutathione content and glutathione peroxidase activity, and also decreasing inflammatory factors such as TNF-α, IL-1β and IL-6 (Lin et al., 2013). An *in vitro* study with ethanol extracts, particularly aqueous fraction of *H. cordata* was found to increase levels of glucose uptake significantly and was even found to be more effective when compared to insulin (Kumar et al., 2016) suggesting its role in improving insulin sensitivity. Anti-obesity properties or hypolipidemic effects were seen in *H. cordata* treated human HepG2 hepatocytes, which resulted in inhibition of high glucose-induced lipid accumulation in these cells, and attenuation of fatty acid synthase, sterol regulatory element-binding protein-1 and glycerol 3-phosphate acyltransferases expression levels (Kang and Koppula, 2014).

3.6. Anti-cancer activity

The different types of cancers afflicting people of all ages entail various approaches of treatment, and although radiotherapy and chemotherapy are still the primary treatments for malignant tumours, they are not without side effects and complications. Recently, there have been proposals suggesting the use of non-conventional form of therapies such as traditional Chinese medicine as adjunct treatments to conventional ones, as they have been shown to alleviate side effects and improve efficacy of drugs (Qi et al., 2015). In this aspect, extracts and derivatives of *H. cordata* have also shown promising results in terms of anti-tumour activities. The anti-proliferative activity of *H. cordata* has been studied in various cell lines such as HeLa, HT29, HCT116, MCF7 and Jurkat cells, using MTT assay and flow cytometric analysis, with the primary mechanisms of action being induction of apoptosis and cell cycle arrest in these cells (Kumnerdkhonkaen et al., 2018). Interestingly, it was also reported the *H. cordata* extracts were comparatively less toxic for non-cancer Vero cells, suggesting better cancer-cell targeted treatments derived from this plant. One of the earliest reports of *H. cordata* efficacy for cancer treatment was on HT-29 human colon adenocarcinoma cells (Tang et al., 2009). In this study, cultured HT-29 cells were treated with different concentration of *H. cordata* extract, and DAPI staining and comet assay results demonstrated that 450 μg/mL treatment concentration for a period of 48 and 72 h caused DNA damage and apoptosis in the cells. Cytochrome c, Apaf-1, pro-caspase-9 and AIF release from mitochondria was observed, associated with decrease of the mitochondria membrane potential and subsequently a significant decrease in the ratio of Bax/Bcl-2 and activation of caspase-9 and caspase-3, suggesting mitochondria-targeted effect of *H. cordata* extract. Similar mitochondria-dependent action of *H. cordata* treatment was also reported by Lai et al. (2010), where treatment of human primary colorectal cancer cells with 250 μg/mL *H. cordata* extracts for 24 h caused chromatin condensation, in addition to increased ROS, cytochrome c, Apaf-1, and caspase-3 and -9 production.

Another potential target of *H. cordata* treatment is Human HepG2 hepatocellular carcinoma cells, where it was shown that apoptosis was triggered by *H. cordata* extracts via induction of pro-apoptotic transcription factors HIF-1A, Forkhead box (FOX)O3, and MEF2A within 24 h. Further, *H. cordata* treatment induced MEF2A expression increased levels of caspase-3 and caspase-7, disrupt Bax, Bcl-2, and Bcl-xL expression levels and could also hinder growth of HepG2 xenografts in nude mice (Kim et al., *2017*).

Lou et al. (2019) studied the effects of *H. cordata* extracts on lung cancer, which is one of the most common and aggressive forms of cancer worldwide. The *in vivo* study involved benzo(a)pyrene (B [a]P)-initiated lung tumorigenesis in mice, which were then treated with 25 and 50 g/kg *H. cordata* extracts and 100 and 200 mg/kg 2-undecanone (a bioactive derivative compound of *H. cordata*) for 38 weeks. Post treatment, the mice showed significantly reduced mean tumour numbers for both concentrations, with tumor inhibition rates at $34.12 \pm 21.42\%$ ($p < 0.05$) and $51.35 \pm 21.96\%$ ($p < 0.01$), respectively. Treatment with 2-undecanone also showed similar tumour inhibiting effects. Simultaneous *in vitro* studies in BEAS-2B cells showed that both *H. cordata* extracts and 2-undecanone could improve cell viability, reduce DNA damage, inflammation and ROS levels. The study concluded that the cancer-preventative effects of *H. cordata* and its derivative operated via activation of the Nrf2-HO-1/NQO-1 signalling pathway.

Anti-cancer activities were also seen in human gastric cancer SGC-7901 cells, via induction of apoptosis and reducing cancer cell viability (Liu et al., 2021a) and cervical cancer cell proliferation was shown to be inhibited, while simultaneously promoting apoptosis via activation of PI3K/Akt signalling pathways in HeLa cells after treatment with copper nanocomplex using *H. cordata* plant extract (Chen et al., 2021).

A recent *in silico* approach to identify phytochemicals from *H. cordata* studied the effects of such chemicals on Human epidermal growth factor receptor2 (HER2) and Vascular endothelial growth factor receptor2 (VEGFR2) whose overexpression cause breast and stomach cancers respectively. Molecular docking studies were used to screen about 100 *H cordata*-derived biologically active phytochemicals and docked against the ligand-binding pockets of HER2 and VEGFR2 kinase domains. Among the screened compounds, it was found that β-sitosterol and Quercetin showed maximum binding affinity for HER2 and VEGFR2 receptors, and proposed as the most suitable candidates for drug development for the treatment of breast and stomach cancers (Das et al., 2021a). However, validation of these studies *in vivo* and at the clinical levels are still necessary.

4. Conclusion

H. cordata is a versatile plant with its extracts and derivatives having diverse potential in the treatment of various ailments afflicting humans globally. Apart from its consumption as a common side-dish, it has a rich history of use for its various medicinal properties such as in Chinese traditional medicine, and it is no surprise that modern science has now started tapping into its myriad therapeutic potentials. Pharmacological properties of its extracts, phytocompounds and derivatives have been reported and verified by numerous studies such as anti-inflammatory, anti-viral, anti-bacterial, anti-cancer and anti-diabetic effects. Apart from these, several studies have also proposed the anti-fungal activity against *Candida albicans* (Shao et al., 2017) and anti-obesity effects (Wang et al., 2018). Till date, current available medical interventions against these diseases are more often than not associated with side effects, low efficacy and contraindications, and require multi-pronged approaches in delivering effective treatments. In addition, adjunct therapy, such as herbal medicines, provided with conventional ones have been shown to increase efficacy of such treatments and minimize their undesirable side effects (Kligler et al., 2016). As such, further detailed research into the therapeutic potential of *H. cordata*-derived compounds may help identify and develop safe, accessible therapeutic options that may serve as standalone treatments, or could be complementary to existing treatments with possibly fewer side effects.

Given the effectiveness of *H. cordata* extracts in treating insulin sensitivity and hyperglycaemia, other potential avenues of application include infertility, endocrinological imbalances and reproductive dysregulation such as polycystic ovarian syndrome (PCOS). Although there is a dearth of information on the use of *H. cordata* to improve fertility, there are still a few limited reports on the use of this plant in this aspect, which

necessitates more comprehensive research (Rathi et al., 2013). Further, there is also a need to identify the full phytoconstituents and determine their specific functions, and also necessitate structural modifications of these compounds in order to minimize their toxicity and increase efficacy for clinical use. Taken together, the pharmacological potential of *H. cordata* and its bioactive components is undeniable, and further in-depth research is still essential to provide more data into its therapeutic activity, to eliminate potential risks, to understand its synergistic action with other drugs, and to comprehend its potential as an adjunct therapy to existing forms of treatment.

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