Pharmacological Effects of *Houttuynia cordata* Thunb (*H. cordata*)

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Contributor: Shahzad Rafiq, Haihong Hao, Muhammad Ijaz, Ahmed Raza

Houttuynia cordata Thunb (*H. cordata*) is a rhizomatous, herbaceous, and perennial plant widely distributed in Asia. It has multiple chemical constituents, such as alkaloids, essential oils, phenolic acids, and flavonoids used against various health problems. The essential oils and flavonoids are the main components of *H. cordata* that play an essential role in disease treatment and traditional health care. Moreover, the leaves and stems of *H. cordata* have a long medicinal history in China. In addition, *H. cordata* is used against several health issues, such as cold, cough, fever, pneumonia, mumps, and tumors, due to its anti-inflammatory, anti-bacterial, anti-viral, anti-oxidant, and anti-tumor effects.

Keywords: Houttuynia cordata Thunb ; anti-inflammatory ; anti-viral ; anti-bacterial ; immunomodulatory ; anti-tumor

1. Chemical Components of *H. cordata*

H. cordata has a variety of chemical constituents with characteristic medicinal properties and belonging to different chemical groups, such as alkaloids, essential oils, and flavonoids [1]. The alkaloids consist of aristolactam A, 3,4-dimethoxy-N-methyl aristolactam, lysicamine, noraritolodione, norcepharadione B, 3,5-didecanoyl-pyridine, 7-chloro-6-demethyl-cepharadione B, cis-N-(4-Hydroxystyryl) benzamide and trans-N-(4-Hydroxystyryl) benzamide, 2-nonyl-5-decanoylpyridine, 3,5-Didecanoyl-4-nonyl-1,4-dihydropyridine, cepharadione B, splendidine, piperolactam A, 3-decanoyl-4-nonyl-5-dodecanoyl-1,4-dihydropyridine, aristolactam B, 3,5-didodecanoyl-4-nonyl-1,4-dihydropyridine, 7-chloro-6-demethylcepharadione B, 3-nonylpyrazole, N-methyl-5-methoxy-pyrrolidin-2-one, phenanthrolactam compounds [2][3]. The flavonoid compounds included quercetin, rutin, hyperin, afzelin, quercitrin, isoquercitrin, kaempferol, quercetin hexoside, avicularin, apigenin, isorhamnetin, phloridzin, quercetin-3-*O*-*β*-D-galactoside-7-*O*-*β*-D-glucoside, and polyphenols include chlorogenic acid, vanillic acid, protocatechuic acid, catechin, *p*-hydroxy-benzoic acid methyl ester, chlorogenic acid methyl ester, cryptochlorogenic acid, neochlorogenic acid, procyanidin B, quinic acid, caffeic acid, *cis*-methyl ferulate, *trans*-methyl ferulate, methyl vanillate, vanillin, houttuynamide A, and houttuynoside A [4][5][6]. The main components of the essential oil are houttuynin, decanal, trans-caryophyllene, decanoic acid, camphene, β-pinene, lauraldehyde, α-pinene, limonene, nonanol and linalool bornyl acetate, methyl n-nonyl ketones, beta myrcene, monoterpene, 4-terpineol, caryophyllene oxide, phenylpropene derivatives, sesquiterpenes, and oxidized diterpenes [7].

H. cordata has many components, and alkaloids are abundant ingredients [8]. Essential oil and flavonoids are known to be major components that exert pharmacological activities. Moreover, decanoyl acetaldehyde in *H. cordata* has a fishy smell called Yu-Xing-Cao, and is a herb in traditional Chinese medicine [2]. It has anti-bacterial effects and is easily transformed to 2-undecanone at higher temperatures [9]. Steam distillation extracts of *H. cordata* contain some important oils, which consist of oxidized diterpenes, monoterpenes, sesquiterpenes, and oxidized diterpenes [10]. Others present in *H. cordata* include bornyl acetate (0.4–8.61%), ketones (2.10–40.36%), and β-myrcene (2.58–18.47%) [7]. Eleven ingredients have been isolated from leaves of *H. cordata,* and seven have been isolated from the roots and are not present in the leaves [11]. It is also reported that *H. cordata* from various areas has various anti-bacterial effects [12]. Flavonoids in *H. cordata*, such as quercetin, quercitrin, and hyperoside, are mostly combined with rhamnose in glycosides [6]. A new form of hyperoside and houttuynia has been isolated from flavonoid compounds in *H. cordata* [13]. Other new components are houttuynamide A and houttuynoside A [5]. Caffeic acid derivatives, quinic acid derivatives, chlorogenic acid, neochlorogenic acid, and cryptochlorogenic acid are considered the essential components of *H. cordata* [4]. Alkaloids such as phenanthrolactam, piperolactam, and aristololactam are key components of *H. cordata* and play an essential role in pharmacological effects [3].

2. Anti-Inflammatory Effects and Immunomodulatory Activity of *H. cordata*

Inflammation is a protective response of the body against offending agents such as viruses, bacteria, toxic chemicals, and damaged cells. There are two forms of inflammation. One is acute inflammation and the other is chronic inflammation [14]. All extracts have good anti-inflammatory activity. It has been found that the anti-inflammatory effects of water extract are better than those of ethnolic extract. Fresh *H. cordata* extracts showed better pharmacological activity than dry *H. cordata* extract [15].

Cells involved in body immunity are basophils, eosinophils, mast cells, lymphocytes, and neutrophils. They play vital immune functions. Antibodies, tumor necrosis factors, interferons, and interleukin also play an essential role in body immunity. Abnormal immune functions result in microcirculation, anaphylactic shock, and central nervous system disorders [16]. The polyphenols present in *H. cordata* show anti-allergic effects. Due to *H. cordata* extracts, decreased activity of iIgE and FcεRI expression on basophilic cells was observed. Moreover, mRNA activity associated with γ-chains and FcεRI was decreased, and histamine secretions were inhibited [17]. It was observed that *H. cordata* extract decreased cutaneous anaphylaxis in vivo in mice. The level of cAMP present in mast cells is enhanced by using *H. cordata,* which shows that *H. cordata* can speed up the recovery from allergic reactions. HCP-2 polysaccharides extracted from *H. cordata* regulate the expression of T cells with a dosage of 0.1–25 μg/mL. It increases tumor necrosis factor-α (TNF-α), immune molecule interleukin-1β, and macrophage inhibitory protein-1α and -1β, which increases body immunity. It has been recorded that *H. cordata* reduces Th2-mediated immune disorders. Ethanol extract of *H. cordata* decreases the migration of T cells, which ultimately strengthens immune response [18]. *H. cordata* extract helps in the regulation of immune mediators. After 18 h of treating vaginal epithelial cells with *H. cordata*, levels of leukocyte protease inhibitor mRNA and human β-defensin 2 were increased. Moreover, an increase in IL-2 and IL-6 and a decrease in CCL5 were observed. These findings show an increase in the overall immune response. *H. cordata* has the same effects on oral immune mediators by expressing human β-defensin 2, IL-8, CCL20, and secretory leukocyte protease inhibitor. In this manner, *H. cordata* regulates oral immune response [19].

3. Effect of *H. cordata* on Different Organs

Lung inflammation is one of the most important signs during lung infection. *H. cordata* has an anti-inflammatory property that plays a significant role in treating lung inflammation. Quercetin obtained from HC, when administered orally at a dose rate of 100 mg/mL in an LPS-induced model, significantly decreased the production of NO and inflammatory mediators such as cytokines [20]. Researchers compared the effect of different dosage levels of flavonoid glucoside extract of *H. cordata* at 50, 100, and 200 mg/kg compared with ribavirin 100 mg/kg with the use of acute injury of lung tissues by the H1N1 virus. At 14 days, they found a lower lung index and less weight loss [21]. The oxidative lung damage caused pulmonary fibrosis. In rats, when pulmonary fibrosis was induced by bleomycin, *H. cordata* aqueous extracts showed a better and stronger anti-oxidant property than vitamin E by decreasing concentration of hydroxyproline, superoxide dismutase, and malondialdehyde [22].

The intestinal barrier is a structure that allows uptake of essential nutrients, while restricting pathogenic molecules and bacteria. The microflora present in the intestine also play a vital role in protecting the intestine [23]. The constituents of *H. cordata* are polysaccharides, and sodium houttuyfonate is instrumental in reducing or regulating the production of mucus from the goblet cells and wart formation of Secretory IgA (antibodies in the secretions and excretions). Moreover, the protein ZO-1, which forms a gap junction between the intestinal cells, is up-regulated or enhanced to compact intestinal, mechanical, and immunological barriers [24]. Intestinal inflammation induced by *Salmonella typhimurium* is dampened by sodium houttuyfonate in the form of up-regulating tight junction proteins between the mucosal cells of the intestine and the signaling pathway that leads to interleukin production [25]. These studies showed that *H. cordata* has a therapeutic effect on the GIT system.

H. cordata protects the intestine various barriers (mucosal barriers, chemical, mechanical, biological, and immune barriers) are present in the intestine. Moreover, intestinal flora also play an essential role in protecting the intestines. Recently, it has been found that sodium houttuyfonate and polysaccharides extracted from *H. cordata* decrease the expression of sIgA, intestinal goblet cells, and tight junction protein present in the intestines. Sodium houttuyfonate is also involved in reducing inflammation caused by *Salmonella typhimurium*. Regulation of bacteria, such as Vibrio and Bacillus, also includes polysaccharides made up of galactose, glucose, rhamnose, and arabinose at a 40 mg/kg dosage. These findings show that sodium houttuyfonate and polysaccharides of *H. cordata* have protective activity by inhibiting NF-κB and regulating intestinal flora in the intestines [26].

Many natural extracts from plants have effective results in preventing and treating various liver ailments. For instance, the chemical components of extracts such as terpenoids, glycosides, coumarins, and alkaloids prevent liver fibrosis. Cholestasis is a common problem inhibited by compounds such as quercetin and rutin. Liver cells are very sensitive to oxidative stress. *H. cordata* ethyl acetate extract reduces liver damage through its anti-oxidant activity. Ethyl acetate of *H. cordata* extract at a dose rate of 1000 mg/kg causes an increase in superoxide dismutase, glutathione, and catalase enzymes, and a decrease in malondialdehyde and serum transaminase resulting in liver protection. The mixture of ethanol and water extract of *H. cordata* at a dosage of 300 mg/kg/day for seven days reduces oxidative factors in the liver [27].

Oxidative damage, inflammation, and infections caused by various pathogenic organisms are the major factors involved in kidney problems. It was observed that 1 to 2% of *H. cordata* water extract reduced the level of serum creatinine and blood urea nitrogen and oxidative factors in the kidney. Moreover, 2% extract of *H. cordata* causes inhibition of membrane-anchored receptor made up of end products (RAGE) and glycation, which activate mitogen-activated protein kinase. They induce intracellular reactive oxygen species generation and are involved in renal protection. Sodium houttuyfonate present in *H. cordata* causes a decrease in expression of MCP-1 and nuclear NF-κB at a dosage of 60–120 mg/kg. It protects against renal glomerulonephritis and kidney oxidative stress [28].

Anti-oxidants such as catechin and procyanidin B present in *H. cordata* intervene in remodeling of the heart. The use of 2% *H. cordata* water extract was found to down-regulate cardiac activity related to oxygen, interleukin-6, inflammatory factors, and protein carbonyl. Moreover, 1 and 2% of *H. cordata* water extract block expression of NF-κB p65, p47phox, and p-p38 in the mouse heart. Sodium houttuyfonate shows activity against myocardial hypertrophy induced by isoprenaline with a dosage of 90 and 180 mg/kg up to 1 week. Cyclic adenosine, left ventricular weight index, heart weight index, and angiotensin 2 were also decreased using sodium houttuyfonate. Moreover, the cross-sectional area of cardiomyocytes and expression of hydroxyproline was also reduced [29]. Sodium houttuyfonate with 50 and 100 mg/kg dosages causes down-regulation of renin-angiotensin-aldosterone, which involves controlling blood pressure. Sodium houttuyfonate is also associated with NF-κB pathway inhibition and adenosine monophosphate-activated protein kinase at the same dosage. It also reduces heart fibrosis and myocardial inflammatory factors. *H. cordata* reduces the release of inflammatory mediators of the heart and oxidative damage to the heart. Sodium houttuyfonate present in *H. cordata* also affects the sympathetic nervous system and the renin-angiotensin system by reversing hypertrophy and remodeling of myocardium. Sodium houttuyfonate treatment elevated the activation of adenosine monophosphate-activated protein kinase (AMPK) on post-infarct heart and post-hypoxia H9C2. AMPK did not suppress NF-κB signaling directly; its inhibition of NF-κB was realized indirectly via its downstream mediators, e.g., Sirtuin-1 (SIRT1), Forkhead box O (F oxO) family, and peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α). Therefore, AMPK activation and suppression of NF-κB and inflammatory cytokines was critically involved in the anti-remodeling effect of SH post-myocardial infarction. [30].

4. Anti-Tumor Activity of *H. cordata*

In a study of mice with lung tumors induced by benzo-pyrene, it was found that the active components of *H. cordata*, such as 2-undecanone, had an anti-tumor effect that may be due to Nrf2-HO-1/NQO-1 pathway activation, which reduces inflammation of lung cells and damage of DNA. In addition, no signs of systemic toxicity were recorded [31]. Moreover, the polysaccharides present in *H. cordata* exhibited anti-tumor potential. The polysaccharide HCA4S1 inhibited proliferation of tumor cells by cancer cell cycle/A549 lung tumor arrest and apoptosis. Similarly, after HCA4S1 treatment, the activities of cyclin B1 and cleaved caspase3 in cells dramatically reduced [32]. The extracts of *H. cordata* with the concentration of 0 to 80 µg/mL caused a decrease in lipid accumulation in HepG2 cells when HepG2 cells were merged with a high level of glucose [33]. The ethanolic extract of *H. cordata* had anti-cancer effects against the colon cancer cell line HT-29. Cancer cell apoptosis was induced when treated with 450 µg/mL extract, which also resulted in lower mitochondrial membrane potential and increased reactive oxygen [34]. *H. cordata* also has activity against breast cancer. The development and progression of tumors are significantly influenced by the overexpression of the HER2/neu (receptors on breast cells) receptor. With an IC50 of 5.52 µg/mL, Houttuyninum suppressed HER2 phosphorylation in a dose-dependent manner in MDA-MB-453 cells without altering the expression of the HER2/neu protein. Additionally, HER2/neu-mediated signal transduction pathway downstream molecules ERK1/2 and AKT were blocked by houttuyninum from becoming activated [35]. At the concentration of 100 to 500 µg/mL, the ethanolic extract of *H. cordata* promotes apoptosis in breast cancer cells [36]. These studies showed that *H. cordata* has anti-tumor activity (**Figure 1**).

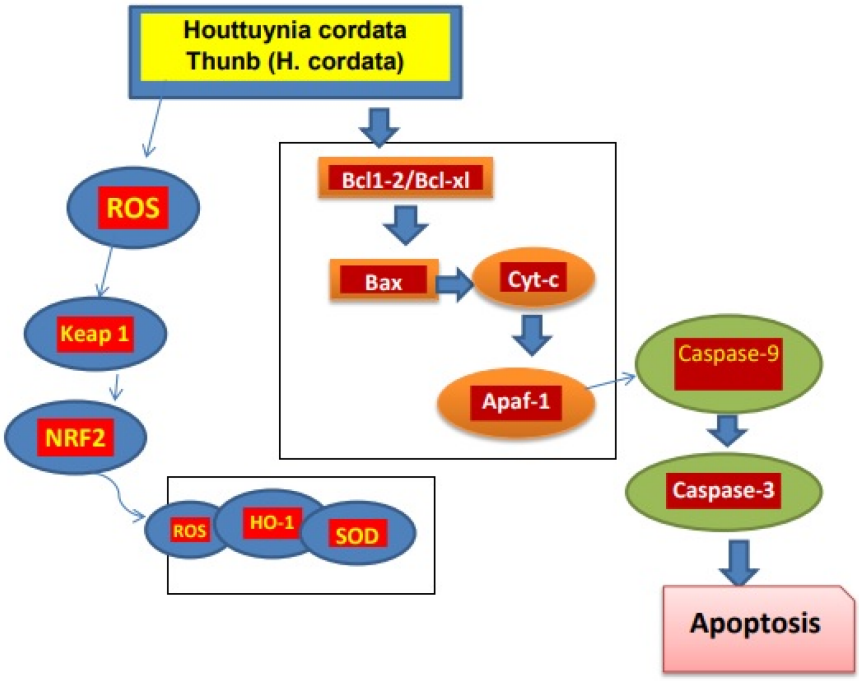

Figure 1. Mechanism of *H. cordata* acts as an anti-tumor agent. *H. cordata* suppresses cancerous cells by blocking NRF2/Bcl1, Bcl-xl signaling pathway and leading to apoptosis of cancerous cells [11].

5. Effect of *H. cordata* on Viruses

The research on plants for the treatment of AIDS has made significant progress over the last ten years. Many plants and their products, such as *H. cordata,* have been found to have anti-HIV properties [37]. In vitro, the steam distillate and three main components from *H. cordata* manifested virucidal effects against HSIV-1 and influenza. The pretreatment with the distillate for 2 and 6 h, respectively, resulted in the inactivation of 20% and 40% of HIV-1 at two-fold dilution [38]. *H. cordata* aqueous extract has immunomodulatory and anti-SARS properties. *H. cordata* causes an increase in the spread of mouse splenic lymphocytes. According to flow cytometry, *H. cordata* enhanced the fraction of CD4+ and CD8+ T cells. Furthermore, it increased the interleukin 2 and interleukin 10 releases by mouse splenic cells. Regarding anti-viral activity, *H. cordata* inhibited the 3C-like protease of the SARSCOV and RNA-dependent RNA polymerase [39]

6. Anti-Bacterial Effect of *H. cordata*

Staphylococcus aureus is a food-borne, gram-positive bacterium that can cause infection of the skin, nasal cavity, GIT, and other human parts. MRSA was synergistically inhibited by sodium houttuyfonate and EDTA-Na_2. Mice infected with MRSA were given sodium houttuyfonate combined with EDTA-Na_2. After 28 days of MRSA infection, the survival rate of mice with sodium houttuyfonate treatment combined with EDTA-Na_2 was 75 percent. It was significantly higher than the 43.75 and 50 percent survival rates of mice treated independently with EDTA-Na_2 and sodium houttuyfonate, respectively [40]. At doses of 500 and 50 mg/mL, the aqueous *H. cordata* extracts demonstrated anti-bacterial effects against isolates of MDR *E. coli*, with the maximum and minimum zone diameters of inhibition of 29 and 13 mm, respectively. These findings suggest that *H. cordata* water extract (HCWE) has anti-microbial action against MDR *E. coli* in vitro [41]

Pseudomonas aeruginosa is a Gram-negative bacterium that infects deep wounds of the body and causes systemic illness. It was reported that sodium houttuyfonate had anti-bacterial activity against pseudomonas aeruginosa. The biosynthesis of alginate, a key ingredient for PA biofilm development, was suppressed, and is linked to sodium houttuyfonate's down-regulation of algD and algR genes. Simultaneously, electron microscope observations showed that the bacteria's shape changed after treatment, and the amount of alginate present in bacterial biofilm decreased [42].

Water extracts of *H. cordata* were found to have anti-bacterial effects against salmonellosis. It was observed that, after 8 h, the anti-bacterial activity of *H. cordata* increased with concentrations of 25 to 100 mg/mL. Bacterial absorption and morphologic alterations of body cells showed that there was no significant difference in the replication of bacteria. *H. cordata* showed a decrease in the pathogenicity of salmonella bacterium. The death rate of bacteria at the 7th day in the untreated group was 100%, and with a dose rate of 25, 50, and 100 µg/mL of *H. cordata,* the extract group lived up to 11, 17, and 23 days, respectively. It was recorded that *H. cordata* water extract is effective and safe in treating salmonella bacteria infections and various replicating pathogens [43].

7. Toxicity of *H. cordata*

H. cordata is an edible plant. Therefore, the toxic level of this plant is mostly ignored. However, it has been reported in some studies that aristolactams and aristolochic acid present in *H. cordata* can cause cancer [22].

Increased levels of aristolochic acid in liver cells also cause toxicity of proximal tubule epithelial cells present in the kidney. Aristolochic acid is also toxic in vivo because of its mutagenicity. A study revealed that 95% ethanol extracts from *H. cordata* show potential toxicity to zebrafish. A single dose of 2000 mg/kg of *H. cordata* with oral use had no harmful effects in mice during 14 days of treatment. However, oral administration of *H. cordata* with a dosage of 500–1000 mg/kg/day for 28 consecutive days led to some rats' death. The histopathological examination showed inflammatory cell infiltration and vacuum degeneration of liver tissue, and focal necrosis of epithelial cells in kidneys. However, *H. cordata* has shown a very weak potential for toxicity. There is no evidence that *H. cordata* causes long-term toxicity. Nonetheless, *H. cordata* leaves and rhizomes are consumed in South China as an agricultural vegetable [44].

Research was conducted in 2018 to evaluate the toxicological effect of fermented Houttuynia cordata juice (FHJ) in a rodent model. FHJ was prepared by fermentation of *Houttuynia cordata* for 30 days and its active ingredients were evaluated. Due to lactic acid production, it has a lower pH of 3.63. Rats were fed with FHJ for 60 days and toxicological effects were evaluated using different biochemical, hematological, and histological tests. These revealed that there was no significant biochemical, histological, or hematological change in rats when compared with the control group. Therefore, it was postulated that FHJ did not have any toxicological effect in rats; hence, experiments should be conducted with humans in safety and toxicological studies. [45].

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