

Potential Health Benefit of *Houttuynia Cordata* on Inflammation, Cancer and Diabetes

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Abstract. In Asian areas, *Houttuynia cordata* thunb (HCT) has traditionally been utilized as medication. Recent research reveals the bioactive ingredients in HCT and tests its efficacy to counter several diseases using the HCT extract. In this article, we focus on HCT's potency in treating inflammation, cancer, and diabetes. Collectively, the data suggests HCT can effectively reduce inflammation, promote apoptosis in cancer cells, smoothen symptoms of diabetes and increase glucose tolerance. These findings are essential for the future development of drugs targets at those disease. More research is needed to further unveil the mechanisms behind HCT pharmaceutical efficacy.

Keywords: *Houttuynia Cordata*, Anti-inflammation, Anti-cancer, Anti-diabetic.

1. Introduction

With a fishy-smelling, *Houttuynia cordata* thunb (HCT) can grows to be 15–50 cm tall in several years. The lower part of the stem is prostrate, rooted, and the upper part is upright [1]. It grows mostly in moist habitats in Asia [1]. There are two preparation methods, fresh *houttuynia cordata* to remove impurities. Dried *houttuynia cordata* removes impurities, washes quickly, cuts into sections and dries. In China, India and other regions, as a daily cooking ingredient and medicine, *houttuynia cordata* has a lot of medicinal effects. In the medical books of ancient Chinese history, it is recorded that the doctor used the whole plant of *houttuynia cordata* into medicine for the treatment of cough, diarrhea, vomiting, thick phlegm and other symptoms. At the same time, in the northeastern region of India, the young shoots, leaves, juice, stems, and whole plants of *Houttuynia cordata* can be used as medicines for the treatment and prevention of different diseases [1]. The various chemical components contained in *Houttuynia cordata* are also an important part of its pharmacological activity. The ingredients in alkaloids, volatile oils and flavonoids have a positive effect in both anti-inflammatory and anti-cancer aspects [2]. This article analyzes the antibacterial and anticancer effects of *Houttuynia cordata* and provides some insights into the therapeutic mechanisms and methods of *Houttuynia cordata* for different diseases.

2. *Houttuynia Cordata* and Anti-Inflammation

When the body is subjected to external stimuli, inflammation is the body's natural defense reaction to damage or sickness (such as injury, infection, virus, etc.). This reaction is generally classified as acute or chronic inflammation. Acute inflammation can help the immune system respond to damage to the body and disappear on its own. Chronic inflammation may lead to excessive production of inflammatory factors such as reaction vector NO, related pro-inflammatory factors and chemokines, induced chronic inflammatory diseases due to long response time and reaction location throughout the body tissue [3]. Currently common treatments for related inflammation are aspirin, diclofenac, and ibuprofen [4]. However, these drugs can also bring about associated adverse reactions and effects.

HTC is widely spread as a herbal medicine and food in China, Korea, Japan, India and Southeast Asia [1]. In the relevant literature that has been published so far, there are many articles about houttuynia cordata as an anti-inflammatory food and drug. As a plant that treats inflammation, most of its efficacy comes from substances on the extract [1].

The inflammatory response are controlled by pro-inflammatory cytokines, NO, and prostaglandin E₂, etc., produced in inflammatory cells such as macrophages [5]. Among these, induced iNOS produces NO, whereas COX-2 produces PGE [6]. Similar to NSAIDs, Houttuynia cordata thumb (HCT) impacts protein and gene expression by decreasing COX-2 enzyme processes, as demonstrated in Figure 1.

All of the houttuynia cordata extracts, including aqueous extracts, ethanol extracts, supercritical extracts, volatiles, essential oils, polysaccharides and bioactive molecules have all produced different anti-inflammatory effects on different inflammations [5]. In general, inflammatory factors related to inflammatory diseases include the TNF- α , various types of interleukins and NO that induces iNOS synthesis [5]. During LPS induction, via lowering NO and TNF- α production, aqueous extract of Houttuynia cordata can lower the elevation of TNF- α , IL-6, and IL-10 in acetaminophen induction [6].

The extract of the upper part of the houttuynia meadow contains flavonoids and ethanol extracts [3]. Among them, the flavonoids isolated from the extract inhibited NO produce in LPS-induced MH-S cells through concentration dependence, thereby inhibiting inflammation [3]. Experiments have shown that when flavonoids are administered orally at 100 mg/kg, their activity is similar to the effect of NASID anti-inflammatory drugs [3]. Through the NF- κ B signaling system, ethanol extract lowers inflammation by lowering the generation of pro-inflammatory cytokines [7]. The capacity of houttuynia cordata essential oil to reduce the generation of PGE₂ by LPS-induced macrophages is reliant on its ability to decrease COX-2 enzyme activity. [4].

HCT supercritical extract is extracted from the aerial part in a supercritical environment for up to two hours [8]. The NO and PGE₂ release are suppressed via the TNF/NO and COX/PGE₂ pathways, respectively, a mediator of inflammation, by extracts extracted under these conditions [8]. HSE directly produces inhibitory activity against PGE₂, resulting in direct inhibition of COX II or inactivation of this inflammatory cell [8]. The above process illustrates that houttuynia supercritical extract (HSE) clarifies the anti-inflammatory effect of HSE in inflammatory mediators by inhibiting two pathways of inflammation [8].

In summary, houttuynia cordata extracts diminish or limit the generation of numerous pro-inflammatory mediators by blocking the signaling pathways activated by pro-inflammatory cytokines, indicating that houttuynia extract inhibits the inflammatory response.

Houttuynia cordata Thunb (Saururaceae; HC) mediates inhibition of COX-2 enzyme activity and can affect related gene and protein expression. HC works by a mechanism of action similar to that of NSAIDs.

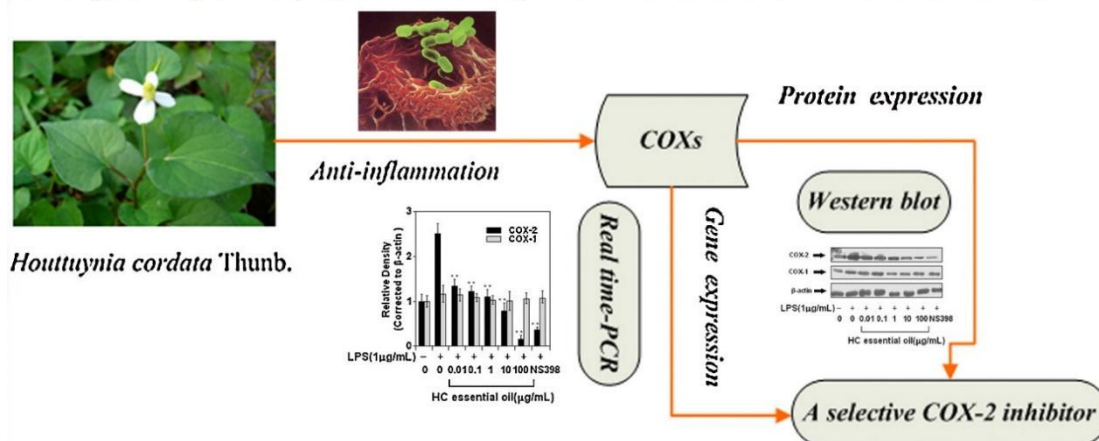


Figure 1. The mechanism of action of HCT [6]

3. Houttuynia Cordata and Acute Pneumonia

A novel kind of severe viral acute respiratory syndrome called Covid-19 has been discovered. Since the virus is transmitted mainly through the air, the virus spread rapidly around the world, gradually evolving into a pandemic [9]. As of April 2021, the outbreak has killed 6.24 million people worldwide, with 515 million cases [10]. The main route of transmission of the coronavirus is airborne, and the most common symptom after infection is respiratory infection, but it can also affect the digestive tract and lead to systemic infection [9]. Since covid-19 is a novel coronavirus, there has been no effective drug treatment against the virus until now [9]. Therefore, when medical workers are confronted with treatment of the virus, they can only treat it symptomatically, which means that when a patient develops any symptoms, both effective treatment for that symptom is carried out.

According to studies, HCT extract possesses anti-inflammatory and antiviral properties. [9]. In experimental models of H1N1 acute lung injury mice, ethanol extracts and polysaccharides from Houttuynia cordata toll-like receptor activation and viral neuraminidase activity were both suppressed. [9]. At the same time, studies have proved that there are six anti-covid-19 active components in Houttuynia cordata [11]. By targeting core proteins, quercetin and kaempferol provide the ability to treat covid-19-related cytokine storms [11]. At the same time, the molecule quercetin 3- β -D-glucoside isolated from Houttuynia cordata showed antiviral activity by inhibiting MERS-CoV 3Cpro activity [12].

In summary, polysaccharides, ethanol extracts and several active molecules of Houttuynia cordata have preventive and therapeutic effects on covid-19. But a large amount of experimental data is still needed to support Houttuynia cordata extract as a therapy for coronavirus disease.

4. Houttuynia Cordata and Anti-Cancer Activity

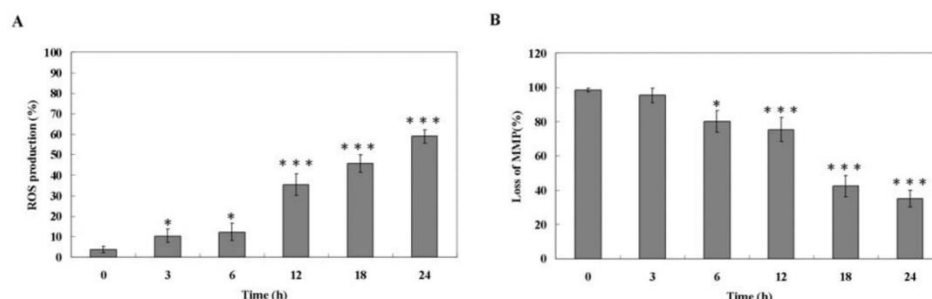
Apoptosis is defined as the process of programmed cell death, which can be triggered by both internal and external cues. HCT could acts as an external cue that activates apoptosis in cancer cells.

ROS is one of the signals that could trigger apoptosis [13]. When the cells cannot prevent ROS from reacting with cell constituents by producing enzymes or antioxidant, it will induce apoptosis. The extent of apoptosis can be assessed with the cell viability assay. With the addition of HCT, the vitality of HT-29 cells was observed to be decreased [13]. The extent of inhibition is determined by the concentration of HCT and the exposure time to HCT [13]. By treating HT-29 cells with HCT, it has been shown that HCT could induce mitochondria stress, the rise in ROS concentration and decrease in mitochondrial membrane potential reflect this. (Figure 2) [13]. This evidence reveals the possibility of ROS being part of the signaling pathway in HCT-induced apoptosis.

Researchers have found that HCT initiates apoptosis in HT-29 cells through a mitochondrial pathway and Caspase-3 and -9 are involved in the HCT-induced apoptosis [13]. In the presence of HCT, apoptosis occurs within HT-29 cells as a defense mechanism to prevent the proliferation of the cancer cells. The general mechanism of HCT-induced apoptosis aligns with the mechanism lies in chemotherapy-either drug or irradiation. However, chemotherapy not only targets cancer cells but also healthy cells, which could do damage to the patients during the treatment.

According to IARC, there has been 2 206 771 new cases of lung cancer in 2020, which ranks the second among all types of cancer [14]. Meanwhile, lung cancer also possesses high mortality rate-1 796 144 cases of death has been reported in 2020, ranking the first among others [14]. Although lung cancer is fatal with high morbidity, the treatment has been limited to chemotherapy and radiotherapy. Human lung cancer A549 cells constitute a cell line and this has been widely used for research in lung cancer [15]. HCT consists of a type of polysaccharide called HCA4S1, which is effective in controlling the activity of the lung cancer cells. By treating A549 cells with HCA4S1, researchers have found that the majority of the A549 cells were arrested in the S phase [15]. Meanwhile, HCA4S1 increases apoptosis via the caspase-3 and cyclin B1 pathways, according to bioactivity tests [15]. This biological mechanism together indicates the effectiveness of HCA4S1 in inhibiting the proliferation of lung cancer cells. Thus, the polysaccharide within Houttuynia cordata has the potential in

becoming the new treatment for lung cancer. In terms of colon cancer, HCT has the potential to inhibit the activity of cancer cells. Thus, HCT is a potential treatment to cancer which is promising because of its less-damaging manner towards patients and more research need to be conducted to evaluate the potency of HCT towards cancer.



(A) loss of mitochondrial membrane potential (B). HT-29 cells were treated with 450 $\mu\text{g/ml}$ of HCT then detected for the changes of ROS production and loss of MMP. The zero concentration was defined as control. The percentage of cells that were detected for ROS and MMP by DCFH-DA, DiOC6 dye and the stained cells were determined by flow cytometry, as described in Materials and methods. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 2. Analysis of ROS production in HT-29 cells after treating with HCT using flow cytometry [13]

5. Houttuynia Cordata and Anti-Diabetic Activity

Among the three types of diabetes, type II diabetes has the most patients in America with a percentage of about 90-95% of all population [16]. The risk factors of type II diabetes include but not limited to family heritage, obesity, increased in age and physical inactivity. A prominent characterization of type II diabetes is the high blood glucose level (hyperglycemia). This is related to the insulin-resistance caused by the dysfunction of β -cells in insulin secretion.

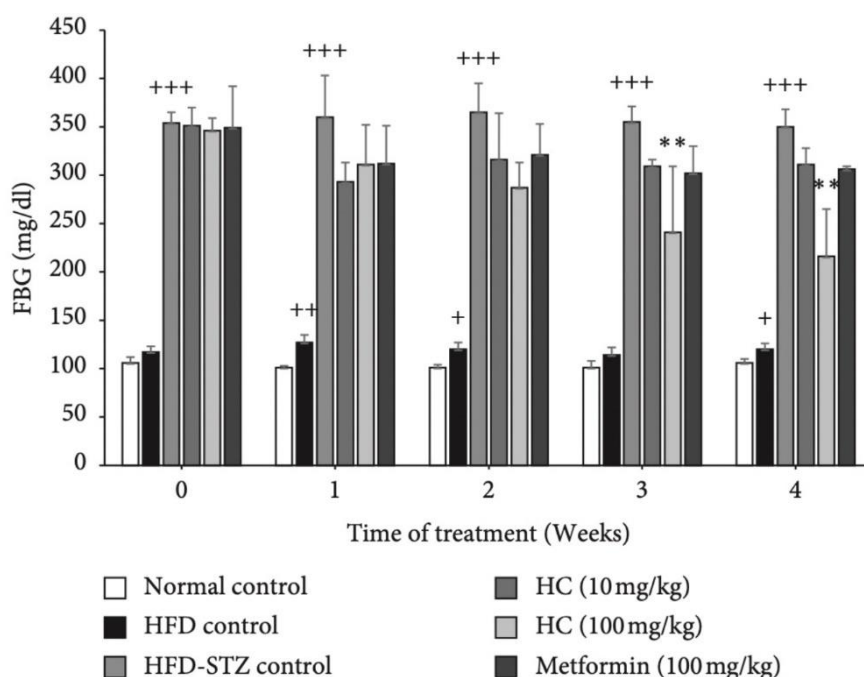
There are currently two types of drugs in treating type II diabetes are anti-diabetic agents and hypoglycemic drugs. Common hypoglycemic drugs include Biguanides (Metformin), Thiazolidinediones (rosiglitazone), and Meglitinides (repaglinide). However, there are various side effects of these drugs and research in developing new treatments is under great demand.

Previous studies have shown that various flavonoids have therapeutic effects on type 2 diabetes, and flavonoids are parts of the main bioactive compounds in HCT, the four main types of flavonoids in HCT are rutin, hyperoside, quercitrin and quercetin [17]. Biological functions of quercetin include glucose homeostasis, insulin sensitization, and secretion [18]. In China, quercetin consumption is inversely related to the prevalence of type 2 diabetes, showing quercetin's anti-diabetic properties [18]. Rutin enhances glucose absorption and suppresses gluconeogenesis within tissues, activates insulin synthesis from β -cells, and protects the islets of Langerhans from degenerative changes [18].

Researchers have investigated the anti-diabetic activity in HCT on rats [19]. After serving the rats with high fat diet (HFD), there are mild insulin resistance been detected [19]. When the rats are further injected with streptozotocin (STZ), there are symptoms of diabetes occurring [19].

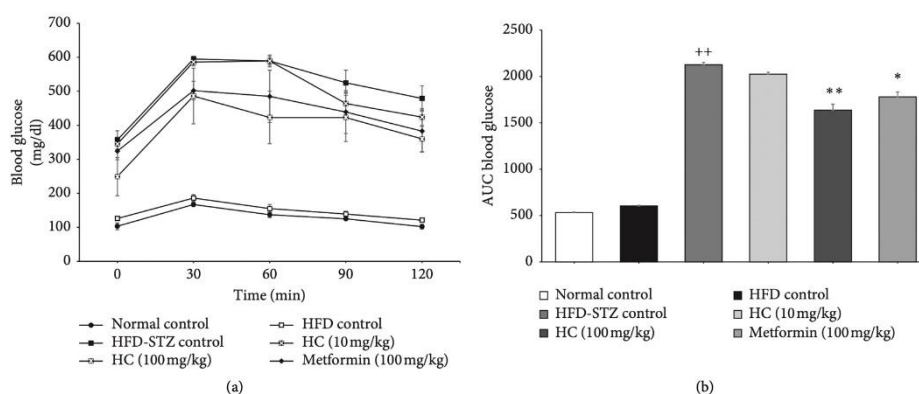
The rats given 100 mg/kg HCT had considerably lower fasting blood glucose levels than the control group (Figure 3) [19]. HCT is capable of smoothing the symptoms of diabetes as evidenced in the increased food intake, water consumption and pancreas weight in HCT-treated group rats [19].

Furthermore, there are evidences showing HCT can help to improve glucose tolerance (Figure 4) [19]. However, it was shown that the decrease in fasting blood glucose in the rats is caused by the increase in insulin level instead of the increase in insulin sensitivity [19]. 100mg/kg HCT can significantly lower total triglycerides in the bloodstream compared to metformin [19].



fasting blood glucose level of each group. + $p < 0.05$, ++ $p < 0.01$, and +++ $p < 0.001$ versus normal control group. ** $p < 0.0001$ versus HFD-STZ control group. Results are presented as means $\pm$ SD ($n = 6$ each group).

Figure 3. The effects of HCT on the bodyweight and FBG levels of rats [19]



(a) Oral glucose tolerance test curves of rats determined during the last weeks of the experiment; (b) area under the curve. ++ $p < 0.001$ versus normal control group. * $p < 0.001$ and ** $p < 0.001$ versus HFD-STZ control group. Results are presented as means $\pm$ SD ($n = 6$ each group).

Figure 4. Effect of HCT on rats' glucose tolerance [19]

6. Houttuynia Cordata and Toxicity

Recent reports indicate the weak potential toxicity in HCT because of its aristolactam constituent [2]. Since there is correlation between liver cancer and aristolactams, some are concerned with the safety of consuming HCT [2]. However, the toxicity of HCT in long-term consumption as edible plants or medical use has not been reported yet. Future research is needed to establish the potential toxicity within HCT.

Besides the natural toxicity exhibited by HCT, there are also recent report suggesting there could be different levels of mercury (total mercury and methylmercury) accumulation in different collection sites [20].

People in different regions in China differ in their preference of the parts of HCT and there are evidence that the consumption of aboveground parts of HCT is at greater risk of total mercury contamination while the consumption of underground part of HCT is at greater risk of methylmercury contamination [20].

7. Conclusions

Despite the rapid development of health care research and development technology in today's society, cancer remains an illness with a high death rate. Lung cancer, in particular, is the first and second most prevalent of all different types of cancers. Since treatments for cancers, such as lung cancer, are limited, it is important to discover new treatments and drugs. But chemotherapy and radiation remain the most effective treatment modalities until new treatments are developed. Among them, chemotherapy is mainly through the powerful chemicals in the drug directly kill the rapidly growing cells in the body. Therefore, chemotherapy kills normal cells at the same time as cancer cells. This is very harmful to the human body. Diabetes is one of the world's most common chronic illnesses, with limited therapies available. Current prevalent medication treatments have several adverse effects.

Therefore, *Houttuynia cordata*, as a medicinal plant that has existed for a long time in nature, its various types of extracts have anti-inflammatory, antiviral and antidiabetic effects, which are supported by different research. *Houttuynia cordata* can replace the mechanism of preventing cancer cell proliferation in chemotherapy, and its bioactive molecules, such as quercetin and rutin, have a positive effect on the treatment of type 2 diabetes. At the same time, almost all *Houttuynia cordata* extracts or active molecules have inhibitory or blocking effects on inflammation through different pathways. Therefore, *Houttuynia cordata* should have a significant curative effect on new coronary pneumonia caused by coronavirus. However, this theory only exists in mouse experiments, and a large number of case data are still needed to support it. These are a summary of the potential anti-inflammatory, anticancer and antiviral efficacy of *Houttuynia cordata* and its extracts. However, due to the increasingly serious environmental pollution, as herbs growing in the soil, it is difficult not to be affected by air, soil and groundwater pollution. The toxicity produced by its contamination is also a problem that researchers need to pay attention to when preparing *Houttuynia cordata* related drugs.

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