

Review

Comprehensive Assessment of *Houttuynia cordata* Thunb., an Important Medicinal Plant and Vegetable

Qing Luo^{1,2}, Ping-Hong Meng², Da-Wei Jiang³, Zhong-Ming Han⁴, Zhen-Hui Wang¹, Guo-Fei Tan^{1,2,*}
and Jian Zhang^{1,5,*}

¹ Faculty of Agronomy, Jilin Agricultural University, Changchun 130118, China

² Institute of Horticulture, Guizhou Academy of Agricultural Sciences, Guiyang 550000, China

³ College of Horticulture, Jilin Agricultural University, Changchun 130118, China

⁴ College of Chinese Medicinal Materials, Jilin Agricultural University, Changchun 130118, China

⁵ Department of Biology, University of British Columbia, Okanagan, Kelowna, BC V1V 1V7, Canada

* Correspondence: tagfei@foxmail.com (G.-F.T.); jian.zhang@ubc.ca (J.Z.)

Abstract: *Houttuynia cordata* Thunb., called Yuxingcao in Chinese, is an important medicinal plant and vegetable consumed in the southern regions of China. This review aims to summarize studies on the phyto-physiological chemistry, cytology, molecular biology, and genomics of *H. cordata*. Studies on the physiology and biochemistry of *H. cordata* have grown over the past few decades. Phenotypic and agronomic traits, tissue culture, elemental analysis, photosynthetic studies, bioactive compound identification, and antioxidant research have been reported. Molecular biological studies, such as those of molecular markers, microRNAs, DNA variations, protein variations, and transcriptomes have also advanced. Recent studies have focused on the rDNA and chloroplast genome of this plant. This review could serve as a basis to perform the genetic breeding, genomic advance, and cultivation of this valuable diversified plant resource for medicinal applications and vegetable production.

Keywords: *H. cordata* Thunb.; phyto-physiological chemistry; molecular biology; genome; gene



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1. Introduction

Houttuynia cordata Thunb., also called Yuxingcao in China (Figure 1), is the sole species in the genus *Houttuynia* of the family *Saururaceae*, which consists of the genera of *Saururus* (*S. chinensis* and *S. cernuus*), *Gymnotheca* (*G. involucrate* and *G. chinensis*), *Anemopsis* (*A. californica*), and *Houttuynia* (*H. cordata*); however, the species of *A. californica* and *S. cernuus* are not found in China [1–4]. *H. cordata* is a perennial, polyploid (diploid or tetraploid) flowering herb native to China, Japan, Korea, northeast India, and Southeast Asia [5,6]. The predominant chromosome of *H. cordata* is $X = 9$ ($2n = 18\sim 108$). It is distributed in the central, southeastern, and southwestern regions of China. Some scholars speculated that it originated in the southwest of China. It was then transplanted and formed three groups [4,7,8]. This plant grows well in moist to soggy soil, on shady hillsides, waysides, and ridges of fields with an altitude of 300~2600 m, produces a unique fishy smell, and blooms white flowers in early summer [9–11]. Interestingly, this herb propagates through the formation and separation of underground stems and parthenogenesis rather than sexual reproduction [12].

As a common aromatic, medicinal, and vegetable plant, *H. cordata* is an important herb plant resource to the food, pharmaceutical, and aromatic industries. It has great value in the fields of ethnopharmacology, fermented products, and natural products chemistry [13–15]. It has been traditionally used as a therapeutic plant in folk medicine during the last century, and its phytochemical ingredients (such as essential oils, alkaloids, organic acids, fatty acids, sterols, amino acids, and microelements) are used in some pharmaceutical formulas. It has been applied to treat various diseases because of its pharmacological functions,

such as diuretic, anti-microbial, anti-viral, anti-cancer/anti-tumor, anti-inflammatory, anti-oxidative, anti-diabetic, anti-allergic, and anti-mutagenic effects [16–21].



Figure 1. Morphological characteristics and utilization of *H. cordata*. (A). Wild *H. cordata*; (B). Above ground and underground part of *H. cordata*; (C). Flower and leaves of *H. cordata*; (D). Cultivated *H. cordata*; (E). Harvested *H. cordata*; (F). *H. cordata* above ground part used for medicinal material; (G,H). *H. cordata* roots as vegetable; (I). Fresh roots used for salad.

However, limited information has been obtained on the germplasm resources, from phenotypic diversity to heritable variation in *H. cordata*. Thus, this review aims to summarize studies on the phyto-physiological chemistry, cytology, molecular biology, and genomics of *H. cordata*. Hopefully, this review could provide some useful theoretical and practical information to assist breeding research of *H. cordata*. Further studies are warranted to obtain further information, including the genomics, of *H. Cordata*.

2. Physiology and Biochemistry

2.1. Phenotypic Diversity and Agronomic Traits

Previous studies have described and classified morphologies of the leaves, stems, flowers, and rhizomes of *H. cordata*. The geo-herbalism of *H. cordata* is largely determined by its genetic factors, which have been used to guide the cultivation, breeding, and utilization of wild *H. cordata* populations [22–24]. Guan (2010) analyzed the genetic variation in morphological characteristics of 20 *H. cordata* germplasm populations, and the populations were divided into 3 groups through cluster grouping with 15 measurable traits, showing a

rich variation among these populations [25]. Shun et al. (2014) analyzed and showed that environmental factors exert different effects on the formation and accumulation of active physiochemical compounds in *H. cordata* [26]. Li et al. (2018a) analyzed the phenotypic diversity of leaf traits (9 phenotypic traits and 6 relative traits) in cultivated *H. cordata* populations from Hunan province in China, and showed that the diversity of leaf phenotypic traits is mainly determined by genetic factors, providing a theoretical basis for the breeding of excellent germplasms [27].

2.2. Elemental Analysis

H. cordata is a vegetable rich in proteins, minerals, vitamins, and amino acids, giving *H. cordata* its high nutritional and economic value [28,29]. Many studies analyzed the elemental composition of *H. cordata*. Qin and Yang (2015) measured the contents of 5 trace elements (calcium: Ca, magnesium: Mg, iron: Fe, zinc: Zn, and copper: Cu) through atomic absorption spectrophotometry, and the results showed that the order of element content in the same organ is Mg, Ca, Fe, Zn, and Cu [30]. Mo et al. (2015) compared the contents of 10 macro-elements and micro-elements in the leaves, aerial stems, and underground stems of wild *H. cordata* from different regions, and found that this plant is rich in sulphur (S), phosphorus (P), potassium (K), Ca and Mg [31]. Li et al. (2018b) detected the contents of 14 heavy metals (manganese: Mn, Zn, Cu, cobalt: Co, titanium: Ti, stannum: Sn, antimony: Sb, barium: Ba, chromium: Cr, nickel: Ni, arsenic: As, plumbum: Pb, mercury: Hg and cadmium: Cd) in *H. cordata* via the inductively coupled ICP-MS (inductively coupled plasma mass spectrometry) method, and the results showed that the linear relationship between the concentration of each element ranges from 0.15 to 695 g·L⁻¹ [32]. Fotev et al. (2018) concluded that the micro-elements of *H. cordata* accumulated Mn, Fe, and Cu in the leaves, whereas Fe, Co, Cu, and Zn are detected mainly in the roots [11].

2.3. Photosynthetic Transpiration

The photosynthetic transpiration of plants is directly related to their growth potential and the economic benefits for farmers. Therefore, photosynthesis studies of *H. cordata* are important. Huang et al. (2006) measured the photosynthetic and transpiration characteristics of *H. cordata*, and found that photo flux quantum (PFD), relative humidity (RH), stomatal conductance (Gs), and leaf temperature (TI) significantly correlate with the net-photosynthetic rate (Pn) and transpiration rate (Tr). PFD and Ca (air CO₂ concentration) are the major Pn-affecting factors, and PFD and Ta (air temperature) are the main Tr-affecting factors [33]. Xu et al. (2011b) explored the optimal potassium concentration for the proper growth and physiological response of *H. cordata* and found that 1.28 mM potassium is the optimum concentration to obtain the optimal values of dry weight, shoot height, root length and number, H₂O₂ content, superoxide dismutase activity, and net photosynthetic rate [34]. Lv et al. (2012) tested the effect of different concentrations of NaCl on the photosynthesis of *H. cordata* at different habitats, and concluded that *H. cordata* from Huaihua County, Hunan Province showed improved photosynthesis and adapt to salt stress [35].

2.4. Effects of Bioactive Compounds on Antioxidant Capacities of *H. cordata*

Some studies investigated the nutritional quality and health benefits, and other studies analyzed the bioactive substances and antioxidant capacity of different parts of *H. cordata*. Li et al. (2007) tested the effects of Pb, Zn, and their interactions on the chlorophyll content and antioxidant enzyme systems of *H. cordata* and found that treatment with Pb or Zn alone exerts more beneficial effects on chlorophyll content and antioxidant enzyme systems than their combination. It was also shown that *H. cordata* might have a high tolerance to Pb [36]. Cai et al. (2013) analyzed the total phenol and flavonoid contents and antioxidant activity of leaves from 16 *H. cordata* cultivars, showing that it is divided into two types (I and II type) based on comprehensive agronomic characteristics. The total phenol and flavonoid contents and antioxidant activities of all materials were different due to their genetic backgrounds, in particular, the chromosome number (more than 80) of the material

which had the highest total phenol and flavonoid contents and antioxidant activity [37]. Wang et al. (2015) tested the effects of LED (lightemitting diode) light spectra on the active oxygen metabolism and expression of antioxidant isozymes in *H. cordata* seedlings and found that the antioxidant system of *H. cordata* seedlings is more sensitive to short light wavelength than to long light wavelength [38]. Liu et al. (2016) analyzed the bioactive compounds and antioxidant capacities in *H. cordata*, and the results indicated that (1) the levels of carotenoids, chlorophyll, anthocyanins, vitamin C, pro-anthocyanidins, total phenolics, flavonoids, and antioxidant contents can be arranged in the order of leaves > stems > rhizomes; (2) a significant positive correlation exists between antioxidant capacities and seven bioactive compounds ($p < 0.05$); and (3) the leaves contain more bioactive compounds and anti-oxidant capacity than the stems and rhizomes. Furthermore, a comparison with 8 types of common vegetables revealed that *H. cordata* has great potential for development because this plant, especially its leaves, contains more bioactive substances and higher antioxidant capacity than other vegetables [39].

2.5. Bacteriostatic and Anti-Tumor/Anti-Cancer Effects

Previous studies reported the anti-tumor and anti-microbial properties of *H. cordata* [40–42]. Anti-microbial (including anti-bacterial, and anti-fungal) function is the most basic pharmacological function of *H. cordata*, as has been established through long-term and in-depth studies [43]. *H. cordata* extracts can effectively inhibit microorganisms, such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Aspergillus niger*, *Bacillus polymyxa* and *Saccharomyces cerevisiae* [44–47]. Secondary metabolites from *Streptomyces* sp. K15, an endophyte in *H. cordata*, show anti-microbial activities, particularly against *Botrytis cinerea* [48]. *H. cordata* combined with other drugs (such as levofloxacin, and penicillin) exerts a germicidal action against bacteria (such as *S. aureus*) with biological envelopes [49,50]. The endophytic fungus J3, isolated from *H. cordata* and identified as *Fusarium oxysporum*, demonstrates anti-microbial activities against *S. aureus* and *Enterococcus faecalis* [51]. Another endophytic fungus (*Chaetomium globosum* and *F. oxysporum*) was also identified to exhibit a good broad-spectrum bacteriostatic effect [52,53].

Some studies also focused on the anti-tumor/anti-cancer effects of *H. cordata* [54,55]. *H. cordata* extract inhibits cell growth and induces apoptotic cell death in human primary colorectal cancer cells through a mitochondria-dependent signaling pathway [56]. The extract of *H. cordata* modulates G₀/G₁ phase arrest and Fas/CD95-dependent apoptotic cell death in human lung cancer A549 cells [57]. Meanwhile, extract of *H. cordata* induces A375 programmed cell death in human melanoma cells by p38 phosphorylation associated with HMGB1 reduction and by activating the caspase-dependent pathway [58]. Kim et al. (2017) demonstrated that *H. cordata* promotes the activation of HIF-1A–FOXO3 and MEF2A pathways to induce apoptosis in human HepG2 hepatocellular carcinoma cells, indicating that this plant is a promising candidate for anti-tumor drug development [59]. Lou et al. (2019) showed that *H. cordata* and its bioactive compound 2-undecanone can significantly suppress benzo(a)pyrene-induced lung tumorigenesis by activating the Nrf2-HO-1/NQO-1 signaling pathway significantly [60].

2.6. Physiochemical Compounds

Many researchers authenticated the ingredients and function of the physiochemical compounds, such as polyphenols, and analyzed the relationship between the contents of flavonoids and their biological characteristics in *H. cordata* by using high-performance liquid chromatography (HPLC) [61,62]. Wu et al. (2002a,2002b) analyzed the peroxidase and esterase isozymes variations of the germplasm resources of *H. cordata* from Sichuan Province in China and found 6 types of peroxidase isozyme bands (each band type was composed of from 4 to 6 bands, with the number in the north being higher than that in southern areas) and 10 types of esterase isozyme bands (each band type was composed of from 4 to 8 bands which had no geographic differences) [63,64].

Wu et al. (2009c) analyzed the content variation of flavonoids, including hyperin, quercitrin, and quercetin in *H. cordata* from 22 provinces or geographic origins in China and found that the levels of the three major flavonoids vary remarkably from different provinces, the contents of quercetin is not correlated with the geographic region, and concentrations from the highest to the lowest were in leaves, stems, and rhizomes [65]. Shun et al. (2014) concluded that appropriate shade treatment not only avoids the inhibitory effect of strong light on its growth, but also significantly increases the contents of active components [26]. Li et al. (2015a) examined the contents of major nutrient components, including protein, soluble sugar, fat, volatile oils, and total flavonoids, and the composition and contents of medicinal substances under field conditions and natural light at full intensity, 40% intensity, and 20% intensity in *H. cordata* from sprouting to harvesting. This study showed that sufficient light is necessary when growing *H. cordata* as medicinal and functional food, but appropriate shading or intercropping is necessary when the crop is grown as food [66]. Se (2015) detected the pharmacological volatiles emanating from 3 different parts of *H. cordata* (leaves, aerial stems, and underground stems) from South Korea through fast gas chromatography–surface acoustic wave sensor (GC/SAM) and identified 16 compounds from the leaves (71.0%) and aerial stems (50.1%), including the monoterpenes β -myrcene, cis-ocimene, and decanal in underground stems (74.6%), and 2-undecanone (1.3%) and lauraldehyde (3.5%) in leaves [67]. Zhang et al. (2018) determined the four main volatile components (4-terpenol, α -terpilenol, bornyl acetate, and methyl nonyl ketone) of 47 *H. cordata* germplasm resources. They screened out the high content of the volatile components and provided a theoretical basis for a special type of breeding [68]. Chen et al. (2004) studied the relationship between the essential oil constituents and the chromosome number of *H. cordata* and found a tendency for the number of essential oil spots to increase with the chromosome number [69].

2.7. Secretory Tissues

Few studies focused on the roots, aerial stems, leaves, rhizomes, and other organs (such as secretory tissues), which greatly differ in anatomical structure among different populations of *H. cordata* [28,70]. Lin et al. (2013) showed that many oil cells in the leaves, stems, and rhizomes of *H. cordata* are the storage sites of volatile oil [71]. Some research also showed the structural, componential, and functional characteristics of its secretory tissues in the floral and vegetative parts of *H. cordata* [72].

3. Cytology

3.1. Embryology

Although some researchers have studied the embryology of *Saururaceae* [73–75], studies on the sexual reproduction of *H. cordata* are not comprehensive. In particular, previous studies were insufficient for helping cross-breeding attempts [76]. Nuclear extrusion and abnormal meiosis possibly lead to the high pollen abortion rate (99.6%) of *H. cordata* [25]. Subsequently, Guan et al. (2012) observed the cytomixis and meiotic abnormalities during microsporogenesis in two populations of *H. cordata* with different ploidy levels ($2n = 38\text{--}96$), and found the origin of the intraspecific polyploidy, and suggested that it might lead to a large variation in chromosome numbers in this species [77]. Lin et al. (2011) worked on the histochemistry of anther development in *H. cordata*, and results showed that (1) some starches are distributed in the epidermis and endothelium; (2) plasmolysis in the tapetal cells occurs at the period of microspore mother cells; and (3) lipid accumulation in pollen grains is insufficient during anther development [78]. Li et al. (2010) reported that *H. cordata* pollen grains are abortive for deficiency of lipids in mature pollen grains [79]. Li et al. (2014) determined the pollen viability by I_2 -KI staining and examining the developmental course of male and female gametophytes using paraffin sections, and the results showed that (1) *H. cordata* pollen viability is extremely low (3.18%); and (2) the male gametophyte is normal in the early development stage and disintegrates in the dyad period of the tapetum cell. Then, the cytoplasm of free microspores gradually disappears and shows an empty

flat shape, and the microspore shape changes from sub-orbicular to irregular. Finally, microspore abortion occurs before pollen sac cracking, which might lead to male sterility, and the seed might come from apomixes [80]. Li et al. (2017) reported that they are closely correlated with inflorescence size, anther color, and length at the meiosis stage, suggesting that the uninuclear pollen development rather than the abnormal division of pollen mother cell meiosis is the main reason behind the low pollen counts in *H. cordata* [81].

3.2. Intraspecific Polyploidy

Hsu (1967) studied the chromosomes of many vascular plants, including *H. cordata* from Taiwan, and suggested that the number of chromosomes of *H. cordata* is 24 [82]. Many researchers have studied the phylogenetic development of the *Saururaceae* plant, but their conclusions were contradictory (Table 1).

Table 1. Analysis of the karyotype of *H. cordata* in different countries.

Country	Category	Basic Number of Chromosomes	ChromosomeNumber	Scope	Karyotype	References
China	<i>G. chinensis</i> Decne, <i>G. involucrate</i> Pei	X = 9	2n = 18			[83]
China	<i>H. cordata</i>	X = 9	2n = 36,54,72,81,126	36~126		[84]
China			2n = 22 = 10 m + 10 sm + 2 t		2B	[85]
China	<i>Saururus</i> L., <i>Houttuynia</i> Thunb.	X = 11, X = 12	2n = 22 = 4m + 16 sm + 2st, 2n = 24 = 14 m + 10 sm			[86]
Eastern Asia (Nepal, China, northern Thailand, Taiwan, and Japan)		X = 9,10,12	2n = 72,80,96,112,128			[87]
China	<i>H. cordata</i>	X = 11, X = 12	2n = 20 = 14 m + 6 sm (Hefei, Wuhu) = 10 m + 10 sm (Anqing); 2n = 22 = 14 m + 8sm (Chuzhou, Huoshan) = 18 m + 4sm (Huangshan); 2 n = 24 = 16 m + 8sm (Chaohu) =18 m + 6sm (Tongling) =14 m + 10 sm (Jixi); 2n = 26 = 16 m + 10 sm (Guangde); 2n = 30 = 20 m + 10 sm (Shitai) =20 m + 10 sm (Neijiang); 2n = 32 = 26 m + 6sm (Dujiangyan) =22 m + 10 sm (Luzhou) =18 m + 12 sm + 2 t (Zigong)	20~32	1B,2B	[88]
China		X = 8,9,12	2n = 108,99,94 (the highest frequency),92,38,37,35	36~99		[25]

The position of the centromere is expressed by the ratio of its long arm to its short arm. M: the ratio value is 1.0; m:the ratio value isfrom 1.0 to 1.7; sm: the ratio value is from 1.7 to 3.0; st: the ratio value isfrom 3.0 to 7.0; t: the ratio value is from 7.0 to ∞.

4. Molecular Biology

4.1. Molecular Marker

Many studies explored the genetics and taxonomy of *H. cordata* by using different molecular marker methods such as RAPD (polymerase chain reaction), SRAP (sequence related amplified polymorphism), ISSR (inter simple sequence repeat), and AFLP (amplified fragment length polymorphism), and discussed the relationship among genuineness, genetic, and environmental factors [89–94]. Zhong et al. (2009) analyzed the differentiation coefficients, genetic parameters, and diversity index on the population phenotypic traits of 16 germplasm lines of *H. cordata* from Huaihua city of Hunan Province in China, and the results showed that the differentiation coefficients are rich, and the differentiation degrees are high in the populations [95]. Guan (2010) screened the collection of 34 *H. cordata* populations with SRAP primers and divided them into 3 groups based on the UPGMA (unweighted pair-group with arithmetic means) method, and the results suggested that a correlation exists between the genetic diversity and geographic distribution among the *H. cordata* populations [25]. Li et al. (2010) estimated the genetic diversity of different geographical populations of *H. cordata* from 13 provinces in China using AFLP markers and showed that the coefficient of genetic distance is from 0.0089 to 0.1818 and that 15 populations are grouped into 3 different clusters, suggesting the genetic diversity within different geographical populations of *H. cordata* in China is profound [79]. Zhong et al. (2011) analyzed the genetic characteristics of 16 *H. cordata* populations in Huaihua city of Hunan Province by SRAP markers, and the results divided 15 populations into 5 groups with a genetic distance of 0.5. No significant correlation was found between genetic structure and habitat factors; the gene differentiation coefficient and the gene flow increase with altitude and decrease with increasing latitude and longitude [96]. ISSRs analysis revealed low genetic variations within populations, and high genetic differentiations among populations. The structure of genetic diversity among 226 individuals from 15 populations of *H. cordata* in China suggests that this species might have survived in Southwest China during the glacial age, and subsequently experienced an eastern postglacial expansion [8]. Wang's (2010) conclusions also show that its phenotypic clustering and molecular clustering are similar among different populations [92].

4.2. microRNA

Recent studies have suggested that miRNAs play regulatory roles at the intracellular and intercellular levels, and even in the inter-species manner. He et al. (2019) identified 163 conserved miRNAs and 30 novel miRNAs through high-throughput sequencing of *H. cordata* and found that they are enriched in the endocrine and other factor-regulated Ca reabsorption pathways, the insulin signaling pathway, melanogenesis, and aldosterone-regulated sodium reabsorption pathways, via bioinformatics analysis on the targets of *H. cordata* miRNAs to study the cross-kingdom functions of active compounds in *H. cordata* [97].

4.3. DNA Variation

DNA variation is the basis of the origin and diversity of species. Liu (2014) analyzed the DNA variation of 46 strains of *H. cordata* from the same GAP (good agricultural practices) origin with ISSR and RAPD molecular markers through cluster analysis. The results showed that 9 ISSR primers and 8 RAPD primers have amplification of 134 and 101 bands respectively, which helped to estimate the polymorphisms of the stripe numbers 115 and 72 respectively. Additionally, polymorphic rates were 85.8% and 71.3% and the average genetic similarity (GS) coefficients were 0.6786 and 0.6947, respectively. This result revealed that the gene possessed polymorphisms among *H. cordata* from the same GAP area [62].

4.4. Protein Variation

Some studies have suggested that the stronger frost resistance of the plants located at higher altitudes is associated with their massive accumulation of protein, fat, starch, and related substances [98]. Liu (2014) has shown a wide range of protein types, with molecular weights ranging from 6.5 KD to 97.2 KD from the 53 lines of *H. cordata*, but the protein types warrant further clarification [62].

4.5. Transcriptome

To date, genomic information about *H. cordata* is still limited. Kim et al. (2010) performed the global transcriptome analysis of the *E. coli* O157 in response to the molecular mechanisms of *H. cordata* on its antibiotic effect [99]. Wei et al. (2014a) carried out the high-throughput transcriptomic sequencing of *H. cordata* to generate a large transcriptome sequence dataset, and their major findings are as follows: (1) over 56 million sequencing reads were produced from *H. cordata* mRNA by Illumina paired-end sequencing; (2) subsequent *de novo* assembly yielded 63,954 unigenes, 39,982 (62.52%) and 26,122 (40.84%), of which 30,131 and 15,363 unigenes were assigned to gene ontology categories and clusters of orthologous groups, respectively; (3) 24,434 (38.21%) unigenes were mapped onto 128 pathways and 17,964 (44.93%) unigenes showed homology to *Vitis vinifera* (Vitaceae) genes; and (4) 4800 cDNA (complementary DNA) SSRs were identified as potential molecular markers [100]. Li et al. (2016) analyzed the simple sequence repeats (SSR) loci information in the transcriptome of *H. cordata* contained 63,954 unigenes, and a total of 4800 SSRs were distributed in 4413 unigenes with a distribution frequency of 7.51%. Numerous SSRs with high frequency and various types could provide the basis for studying the genetic diversity and genetic map of *H. cordata* [101].

5. Genome

5.1. Plasmon Diversity (cpDNA and mtDNA)

Some studies examined the chloroplast *trnL-trnF* and *rps16* sequence variation of the alpine species *Primula secundiflora*. These studies revealed the phylogenetic structure of the distributed species in cpDNA (chloroplast DNA) [102]. Wu et al. (2005a) investigated the plasmon diversity of 70 *H. cordata* accessions by using PCR-RFLP and discussed the phylogenetic relationship and phylogeographic information of the genus *Houttuynia*, and the results showed that 59 distinct organelle haplotypes could be identified among 70 accessions, a total of 2 *H. emeiensis* and 57 *H. cordata* of the plasmon variations, the interspecific and intraspecific relationships within the genus of *Houttuynia*, and the average GSs values within *H. emeiensis* and *H. cordata* accessions, which reached 0.986 and 0.950, respectively [103].

5.2. rDNA

Some researchers studied the intraspecific polymorphisms in the exon and group I intron of subunit rDNA (ribosomal DNA) of the obligate plant parasite *Plasmodiophora brassicae* [104]. Zhao (2008) analyzed the nuclear ribosomal DNA based on internal transcribed spacer (ITS) sequences of 23 *H. cordata* germplasm resources from Sichuan province and Chongqing city in China, including 11 cytotypes and 2 chemotypes, in total obtaining 147 ITS sequences, and the PCR product length varied from 670 bp to 684 bp and the length of ITS1 varied from 231 bp to 245 bp, whereas that of ITS2 was uniformly 275 bp for all accessions [105].

5.3. Chloroplast Genome

Although the chloroplast genome contains many noncoding regions, relatively few studies focused on interspecific phylogenetic and intraspecific phylogeographic characteristics [106]. Yu et al. (2019) reported that the complete chloroplast genome sequence of *H. cordata* is 161,090 bp in length, containing a large single copy (LSC) region of 88,180 bp and a small single copy (SSC) region of 19,204 bp, which were separated by a pair of

26,853 bp inverted repeat regions, and *H. cordata* is a sister of *Piper cenocladum* [107]. Zhu et al. (2020) carried out the *de novo* assembling of the complete chloroplast genome of *H. cordata* and showed a typical quadripartite cycle of 160,226 bp, including a pair of inverted repeats (IRa and IRb) is 26,853 bp. It is separated by an SSC region of 18,340 bp and an LSC region of 88,180 bp, including 112 unique genes, 79 protein coding genes, 29 tRNA genes, and 4 rRNA genes. In addition, 81, 13, and 17 two copy genes were located on the LSC, SSC, and IR region, respectively, and the chloroplast genome of *H. cordata* (48 repeat sequences, 86 SSR motifs) had a close relationship with the *Aristolochia* species (38~138 repeat sequences, from 95 to 156 SSR motifs), as revealed by mVISTA analysis [108].

6. Germplasm Genetic Resource

6.1. Genetic Diversity

Intra-species genetic variability assessment was used in formulating genetic improvement and germplasm conservation strategy research. Wu et al. (2005b) tested the genetic diversity of 70 *H. cordata* accessions from Sichuan, Chongqing, Guizhou, and Jiangsu provinces in China by using RAMP, RAPD, and ISSR markers, and they arrived at the following conclusions: (1) a higher degree of genetic diversity exists among the germplasm resources of the genus *Houttuynia* at the molecular level (RAMP markers) [109], (2) the groups based on ISSR GS studies had been correlated with the same chromosome numbers which could have been classified together, while correlated with geographic distribution by RAPD GS [110]. Wei and Wu (2012) assessed the level and distribution of genetic diversity in 226 individuals from 15 populations of *H. cordata* in China by using ISSR markers and revealed low genetic variations within populations, but high genetic differentiations among populations [8]. Gupta and Bharalee (2020) also assessed the genetic diversity of *H. cordata* from four regions of northeast India, which contained 545 genotypes from 18 populations, and found that the genetic differentiation among 18 populations is high ($F_{st} = 0.3894$; $p < 0.001$) with relatively restricted gene flow ($N_m = 0.6564$), which suggested that *ex situ* conservation could be an appropriate measure to adequately capture the total genetic diversity of *H. cordata* populations in northeast India [111].

6.2. GS Values of Cytotypes

Studies of the GS values of cytotypes provided the theoretical basis and the depth of research in another aspect of system diversity of *H. cordata* populations. Wu et al. (2002a) detected the genetic diversity of 92 *H. cordata* germplasm resources and found that the average GSs are from 0.52 to 0.572. Meanwhile, the interspecific GS is 0.517 among these 92 lines' populations. All materials had been divided into 11 types. In addition, the same number of chromosomes tended to cluster together, while the groups classified according to the RAMP GS coefficient were related to the geographic distribution [62]. Wu et al. (2003a) analyzed the genetic diversity of germplasm resources of *H. cordata* by ISSR marker and found that the chromosome number of 36 of *H. cordata* is the most similar in their cellular types. The average value of their GS factors is 0.618. As such, great genetic deference certainly exists at the cellular level in the germplasm resources of *H. cordata*, but the medicinal compositions are determined by its genetic factors [112]. Wu et al. (2005b) showed that the GS between the accessions within *H. emeiensis* and *H. cordata* are 0.660 and 0.575, respectively. Meanwhile, the GS value with the chromosome number of 36 is 0.559 [109]. Zhao (2008) studied the cytotypes of 23 *H. cordata* materials containing A, B, C, D, E, F, G, H, I, J, and K, and the average tracytotypic GS values are 0.0056, 0.0040, 0.0096, 0.0077, 0.0091, 0.0137, 0.0092, 0.0069, 0.0093, 0.0058, and 0.0089 respectively (with the average of 0.0082). Of these, the GS of cytotypes F (chromosome number of 82) is the highest (0.0137), (chromosome number of 72) is the medium (0.0096), and cytotypes B (chromosome number of 54) is the lowest [105].

6.3. Gene Function Characterization

In recent years, cloning and studying the genetic functions of medicinal plants have become research hotspots. Thus, some studies focused on these aspects in *H. cordata* (Table 2). Furthermore, organic *H. cordata* harbors higher abundance and diversity of anti-bacterial resistance genes (ARGs) than that of non-organic origin, but the ARGs are still unknown [113].

Table 2. Cloning and studies of gene function in *H. cordata*.

Name	Open Reading Frame (ORF, bp)	Transmembrane Regions	Signal Peptide	Motif Domain	Molecular Formula	Relative Molecular Weight	Isoelectric Point (PI)	Transcript Abundance	References
<i>CHS1</i>	1188	no	two	CHS	C ₁₉₂₀ H ₃₀₆₇ N ₅₃₁ O ₅₆₆ S ₁₇	43,190.7	6.38	Flowers>stems >rhizomes>leaves	[114]
<i>DXS1</i>	2172	no	no	DXS	C ₃₄₄₃ H ₅₄₅₆ N ₉₅₈ O ₁₀₂₂ S ₃₅	77,745.1	6.57	Flowers>leaves >rhizomes>stems	[115]
<i>DXR</i>	1416	no	no	DXR	C ₂₂₉₈ H ₃₆₆₈ N ₆₂₄ O ₆₇₁ S ₁₈	51,351.2	6.33	Leaves>rhizomes >stems>flowers	[116]
<i>UGT75C1</i>	1461	no	no	PSPG	C ₂₃₇₃ H ₃₇₄₀ N ₆₃₈ O ₇₁₄ S ₁₇	53,176.6	5.22	Leaves>stems >rhizome>flowers	[117]
<i>AACT</i>	1218	no	no	no	C ₁₈₁₂ H ₂₉₅₂ N ₅₁₄ O ₅₆₃ S ₁₉	41,555.6	6.13	Stems>rhizomes >flowers>leaves	[118]
<i>HMGR</i>	1626	two	no	HMGR NADPH	C ₂₅₆₅ H ₄₀₉₃ N ₇₀₁ O ₇₅₈ S ₃₀	57,841.7	7.10	Flowers>leaves >stems>rhizomes	[90,119]

6.4. Vegetative and Sexual Production of *H. cordata*

The seed viability of *H. cordata* is lacking, and vegetative proliferation during winter is poor. Furthermore, *H. cordata* seeds are light-sensitive and small, with a low germination rate [120,121]. Therefore, tissue culture techniques have been used for the rapid propagation and conservation of elite clones of *H. cordata* throughout the years [122,123]. Moreover, studies about the embryo sac, embryo, and the low pollen fertility of *H. cordata* are rarely reported, and the mechanism of male sterility was not studied [124]. Wang (2013) suggested the following: (1) the stigma pollen is incompatible with self-pollination and cross-pollination in the populations, stigma papilla cells produce callose, or the fertility pollen grains germinate regularly but the pollen tube could not grow into the stigma, whereas the tapetum cells degenerate normally providing nutrition for microspore development; (2) the embryo sac development of *H. cordata* belongs to a monospore polygonum type; and (3) during embryonic development, starch gradually accumulates in nucellar cells, resulting in nucellar cells of mature seeds filled with starch grains. Therefore, stem propagation is the main method of reproduction in the practical production culture of *H. cordata* [125].

6.5. Transgenic Engineering

In recent years, molecular biology and genomic studies of *H. cordata* had been reported because of their research and economic value. Attempts to use *H. cordata* for transgenic engineering as a model plant have been carried out. Lai (2008) studied the *Agrobacterium tumefaciens*-mediated cecropin foreign gene transfer in *H. cordata*, which provided a theory for the anti-bacterial peptide expression in Chinese medicinal plants. Anti-microbial peptides are small molecules with broad-spectrum anti-microbial activity. These molecules have become research hotspots of disease resistance breeding in plant genetic engineering. They are expressed in many plants with enhanced disease resistance [126]. Dong et al. (2010a) transformed the anti-microbial fusion gene of peptides cecropinB and rabbit NP-1(CN) fused into *H. cordata*; this study showed that the fusion gene is expressed in the transgenic genome of *H. cordata* and that the transgenic plants show enhanced anti-bacterial ability [127]. Dong et al. (2010b) developed an *Agrobacterium*-mediated method of genetic transformation of *H. cordata* and integrated foreign DNA into the genome of transgenic plants by using PCR and PCR-Southern analyses [128].

7. Conclusions

H. cordata is an important medicinal plant and vegetable. At present, genetic diversity, and GS intra-species and inter-species of *H. cordata* have become increasingly valuable, and comprehensive utilization of germplasm resources remains to be conducted. Data mining and utilization of genome information of *H. cordata* can be applied to fill this gap. These studies on pharmacology, cultivation, and breeding are equally important. In addition, the true value of *H. cordata* secondary metabolites should be considered [129,130]. Obviously, it holds great research value, not only in medicine but also in agricultural biodiversity. In-depth research, however, still needs to be carried out in the molecular, breeding, physiological, genetic, and genomics fields to understand *H. cordata*.

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