INTRODUCTION

As a well-known traditional medicine, *Halenia elliptica* (H. elliptica) D. Don, known as “Jiadiranguo” (Tibetan medicine name) is one of the most important herbal medicine in TTM that is from the genus *Halenia* (family: Gentianaceae). The whole herb can be used as a medicine to treat hepatobiliary diseases and xeransis, and possesses many biological and pharmacological activities including heat clearing, bile benefiting, liver soothing, digestion promoting, blood nursing, detoxification activities, and so on. In modern research, *H. elliptica* can be used to treat acute or chronic hepatitis, especially hepatitis B. In addition, the chemical compounds of the herb have potent anthepatitis B virus (anti-HBV) activity *in vitro*. As an important TTM, further studies on *H. elliptica* can lead to the development of new drugs and therapeutics for various diseases, and more attention should be paid on the aspects of how to utilize it better.

Key words: Chemistry, ethnopharmacology, *Halenia elliptica*, pharmacology

ABSTRACT

Traditional Tibetan medicine (TTM) is an old traditional medical system, which is an effective and natural method of improving physical and mental health, and has been widely spread in the western part of China for centuries. *Halenia elliptica* (H. elliptica) D. Don, known as “Jiadiranguo” (Tibetan medicine name) is one of the most important herbal medicine in TTM that is from the genus *Halenia* (family: Gentianaceae). The whole herb can be used as a medicine to treat hepatobiliary diseases and xeransis, and possesses many biological and pharmacological activities including heat clearing, bile benefiting, liver soothing, digestion promoting, blood nursing, detoxification activities, and so on. In modern research, *H. elliptica* can be used to treat acute or chronic hepatitis, especially hepatitis B. In addition, the chemical compounds of the herb have potent anthepatitis B virus (anti-HBV) activity *in vitro*. As an important TTM, further studies on *H. elliptica* can lead to the development of new drugs and therapeutics for various diseases, and more attention should be paid on the aspects of how to utilize it better.

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INTRODUCTION

As a well-known traditional medicine, *Halenia elliptica* (H. elliptica) D. Don (family: Gentianaceae) is customarily used to treat hepatitis and cholecystitis, which is widely distributed across the Qinghai-Tibetan Plateau and the western part of China. It has been officially recorded in “Tibetan medicine standards” since 1995 and more than 100 prescriptions containing *H. elliptica* have been used to treat all kinds of diseases in Tibet and Qinghai.[1] Modern pharmacological studies have shown that *H. elliptica* and its active constituents have a wide range of pharmacological properties including hepatoprotective, anticancer, cardiovascular, and antidiabetic activities, most of which seriously matched with its traditional uses. Meanwhile, it was also served as tea for the people in the Qinghai-Tibetan Plateau.[2]

In this review, the advances in ethnopharmacological, phytochemical, biological, and pharmacological activities; and the toxicology of *H. elliptica* will be revealed, and the increasing data supports further exploration of *H. elliptica* and its active constituents.

Botany and ethnopharmacology

Botany

According to the description of the flora of China, *H. elliptica* is about 15-90 cm tall. The stems are erect, subquadrangular, striate, simple, or branched. The petiole of the basal leaves are flattened and 1-3 cm in length. The stem leaves are sessile or have a short petiolate; the leaf blades are oblong, elliptic, ovate-lanceolate, or ovate with a dimension of 1.5-7 cm × 0.5-3.5 cm. The number of leaf veins is five. The calyx lobes are elliptic to ovate in shape and the apex is acuminate. The corolla is campanulate, varies from blue to purple in color, , 1-2.5 cm in length, basal spurs are 5-14 mm, lobes elliptic to ovate, apex obtuse and apiculate [Figure 1]. According to the size of the basal spurs, two varieties of species were separated from *H. elliptica*, namely, *H. elliptica* var. *elliptica* and *H. elliptica* var. *grandiflora*. However, due to their similar appearance they are called by the same name, “Jiadiranguo” in traditional Tibetan medicine (TTM).
including luteolin-O-β-D-glucopyranoside, swertiamarin and sweroside. Three new xanthones and xanthone glycosides, as well as flavonoids, secoiridoid glycosides, and triterpenoid alkaloids. Some of them display many bioactivities in vivo or in vitro; and the different chemical compositions of *H. elliptica* serve its different pharmacological activities.

**Xanthones and xanthone glycosides**

The main chemical components of *H. elliptica* are xanthones and xanthone glycosides. Sun isolated five kinds of free liposoluble xanthones of *H. elliptica* D. Don plants such as 1,7-dihydroxy-2,3,4,5-tetramethoxyxanthone (I), 1,5-dihydroxy-2,3,7-trimethoxyxanthone (II), 1,2-dihydroxy-3,4,5-trimethoxyxanthone (III), 1,5-dihydroxy-2,3-dimethoxyxanthone (IV), 1,7-dihydroxy-2,3-dimethoxyxanthone (V) were obtained.

Three new xanthone dual glucosides, 1-O-[β-D-xylopyranosyl-(1-6)-β-D-glucopyranosyl]-2,3,5,7-tetramethoxyxanthone (VI), 1-O-[β-D-xylopyranosyl-(1-6)-β-D-glucopyranosyl]-2,3,5,7-tetramethoxyxanthone (VII), and 1-O-[β-D-xylopyranosyl-(1-6)-β-D-glucopyranosyl]-2,3,4,5-tetramethoxyxanthone (VIII) were obtained from a water extract of *H. elliptica* D. Don herbs. Shi got access to two xanthones, 1-hydroxy-2,3,7-trimethoxyxanthone and 1-hydroxy-2,3,4,7-tetramethoxyxanthone. For the first time, Zhang isolated 1-hydroxy-3,7,8-trimethoxyxanthone (XIII) and 1,7-dihydroxy-3,8-dimethoxyxanthone (XIV) from *H. elliptica* D. Don plants. Gao got 1,7-dihydroxy-2,3,5-trimethoxyxanthone (XV) from the ethanol extract of *H. elliptica* D. Don plants and another new xanthone, 1,5-dihydroxy-2,3,4-trimethoxyxanthone, was isolated in 2011 (XVI). The structures of xanthones and xanthone glycosides listed above are shown in Figure 2.

**Phytochemistry Research**

More than 30 compounds have been isolated and identified from the whole plant of *H. elliptica*, which abounds with xanthones and xanthone glycosides, chromones as well as flavonoids, secoiridoid glycosides, and triterpenoid alkaloids. Some of them display many bioactivities in vivo or in vitro; and the different chemical compositions of *H. elliptica* serve its different pharmacological activities.

**Pharmacological effects**

**Protective effects against liver injury**

Hepatoprotective activity, as another important property of *H. elliptica*, has been comprehensively studied. The hepatoprotective
Figure 2: Xanadones and xanadone glycosides structures from *H. elliptica*
Bonds between the C-hydroxyl group and the carbonyl group in the structure, which prevents the dissociation of the hydrogen ion. A stronger antioxidation of C-hydroxyl-substituted compound demonstrated that C-hydroxyl group is an important part of the activity, so the antioxidant role of 1,7-dihydroxy-2,3,4,5-tetramethoxynanthone is especially powerful; it is stronger than the classic antioxidant vitamin E. The presence of active hydrogen in the structure of xanthones is an important factor of the hepatoprotective action of *H. elliptica.*

**Nonspecific immunomodulatory effects**

Zhang has researched the immunopharmacology of *H. elliptica* dry extract to clarify their effect on phagocytic function of the mononuclear macrophage on the basis of their influence on charcoal clearance rate in mice. The results showed that the dry extract could enhance the mononuclear macrophage phagocytic function. But the dry extract had no effect on the hemolytic activity of serum hemolysin and splenocyte in normal mice. In the kidney-yang deficiency model, the dry extract can improve the humoral immunity of the hydrocortisone-induced mice.

**Antioxidant properties**

The antioxidant properties of different extracts of *H. elliptica* were investigated by several established *in vitro* and *in vivo* models. The methanol extract of *H. elliptica* revealed strong antioxidant activity *in vitro*. The CCl₄-induced liver toxicity experiment showed that rats treated with the methanol extract of *H. elliptica* (100 mg/kg and 200 mg/kg) and silymarin (50 mg/kg) as the standard treatment, had lower levels of alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin than those of the CCl₄ group (*P* < 0.01). The results of the methanol extract at 100 mg/kg were comparable to those of silymarin at 50 mg/kg (*P* > 0.05). The methanol extract did not show any mortality at doses up to 2000 g/kg body weight. These results seem to support the traditional use of *H. elliptica* in pathologies involving hepatotoxicity, and the possible mechanism of this activity may be due to the strong free radical-scavenging and the antioxidant activities of the methanol extract.

**Vasodilation effect**

Xanthones from *H. elliptica* are considered to be vasoactive substances, which exhibit either endothelium-dependent or endothelium-independent mechanisms in rat coronary artery. Six xanthones including 1-Hydroxy-2,3,5-trimethoxynanthone (1), 1-hydroxy-2,3,4,7-tetramethoxynanthone (2), 1-hydroxy-2,3,4,5-tetramethoxynanthone (3), 1,7-dihydroxy-2,3,4,5-tetramethoxynanthone (4), 1,5-dihydroxy-2,3-dimethoxynanthone (5), and 1,7-dihydroxy-2,3-dimethoxynanthone (6) caused vasodilation in the coronary artery precontracted with 1 µm 5-hydroxytryptamine. Removal of endothelium of the coronary artery led to decreases in the vasorelaxant effects of 1 and 6 but not of 2, 3, 4, and 5. The mechanism of the vasorelaxant effects of these xanthones may be relevant to the structure-activity differences in the level and the position of the substituent groups with the primary xanthon structure.

**Antihepatitis B virus (anti-HBV) activity**

Chromone derivatives isolated from *H. elliptica* have been tested for their potentials toward inhibiting the secretion of HBV antigens...
in the human HBV-transfected liver cell line HepG2. Lamivudine was used as a positive control, which can suppress HbsAg secretion by 20.1% and HBcAg secretion by 19.7%, at 100 μg/mL (436 μm). The results demonstrated that 2-methylchromones compounds exhibited strong anti-HBV activities, inhibiting HBsAg secretion by 36.8% at a noncytotoxic concentration of 50 μg/mL (284 μm) for 8-hydroxy-2-methyl-4H-1-benzo[4-one and by 70.9% at a noncytotoxic concentration of 100 μg/mL (526 μm) for 8-methoxy-2-methyl-4H-1-benzo[4-one. While halenic acid and halenia chromone were slightly active or totally inactive at low concentrations. Further investigations are necessary to explore the values of 2-methylchromones as anti-HBV agents.

Other effects

*H. elliptica* also showed an inhibition effect on contraction of frog heart *in vitro* and *in vivo*. The chloroform extract of the whole plant has antiamoeba effect.[10]

**Metabolic pathways of xanthone**

Feng has studied the *in vitro* metabolic pathways of 1-hydroxyl-2,3,5-trimethoxyxanthone, the main constituent purified from *H. elliptica*, identified three metabolites (M1-M3), which demonstrated that demethylation and hydroxylation were the major phase I metabolic reactions for 1-hydroxyl-2,3,5-trimethoxyxanthone in human liver microsomes; and illustrated that CYP3A4 and CYP2C8 were the primary CYP450 isoforms responsible for its metabolism, and CYP1A2, CYP2A6, CYP2B6, CYP2C9, and CYP2C19 were also involved, especially in the formation of M3.[13] 1-hydroxyl-2,3,5-trimethoxyxanthone revealed moderate inhibitory effects on CYP1A2 (IC50 = 1.06 μm) and CYP2C9 (IC50 = 3.89 μm), minimal inhibition on CYP3A4 (IC50 = 11.94 μM), and no inhibition on CYP2D6 (dextromethorphan) and probe substrates CYP2E1 (chlorozoxazone).[11] In *in vitro* metabolic transformations of five xanthones of *H. elliptica* have been evaluated by metabolic transformation in rat liver microsomes *in vitro*. The results showed that the metabolic transformation occurred mainly at 2-, 4-, 5-, and 7-carbonic positions on their structures. The metabolites could be considered as the new vasoactive substances.[12]

**Toxicology**

The results of acute toxicity test show that LD50 of *H. elliptica* decoction intraperitoneally injected in mice is 27.4 g/kg, and no death is observed in mice after intragastric administration at dose of 100 g/kg. The subacute oral toxicity of *H. elliptica* was investigated in rats. Comparison between the normal control group and the treated group two months after oral administration revealed that the latter were more active with increased food consumption and had more lustrous fur. There were no significant differences in body weight, hemogram, hepatic function, activity of glutamic pyruvic transaminase (GPT), and histological observations of the heart, the liver, and the kidney between the two groups. The results indicated that the medicine was safe in the given dose range.[13]

**Future perspectives**

*H. elliptica* is one of the most representative Tibetan medicine, which have been recorded in many traditional ancient books. In recent years, phytochemical and pharmacological studies of *H. elliptica* have attracted considerable interest. Large amount of extracts and active constituents have been isolated and proved to have hepatoprotective, antiviral, and antioxidant properties, and enhance the immune response effects, etc. However, many challenges such as poor quality control and failed development of *H. elliptica* still exist. In the future, it is necessary to carry out further study on the structure-activity relationships and action mechanisms of major xanthones. Research should pay attention to the anti-HBV and other antivirucus activities of *H. elliptica in vitro/in vivo*. Further studies on *H. elliptica* can lead to the development of new drugs.

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