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A comprehensive review on traditional uses, chemical compositions, pharmacology properties and toxicology of \textit{Tetrastigma hemsleyanum}

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\begin{abstract}
Ethnopharmacological relevance: \textit{Tetrastigma hemsleyanum} Diels et Gilg (\textit{T. hemsleyanum}), a rare herbal plant distributed in subtropical areas of mainland China, has become a focus of scientific attention in recent years because of its high traditional value, including uses for treatment of children with fever, pneumonia, asthma, rheumatism, hepatitis, menstrual disorders, scrofula, and pharynx pain. 

Aim: This systematic review aims to provide an insightful understanding of traditional uses, chemical composition, pharmacological effect and clinical application of \textit{T. hemsleyanum}, and lay a foundation for the further study and for the utilization of \textit{T. hemsleyanum} resource.

Materials and methods: A domestic and overseas literature search in known databases was conducted for published articles using the relevant keywords.

Results: One hundred and forty-two chemical constituents identified from \textit{T. hemsleyanum} have been reported, including flavonoids, phenolic acids, polysaccharide, organic acids, fatty acids, terpenoids, steroids, amino acid and others. Among these components, flavonoids and polysaccharides were the representative active ingredients of \textit{T. hemsleyanum}, which have been widely investigated. Modern pharmacological studies have shown that these components exhibited various pharmacological activities, such as anti-inflammatory, antioxidant, antivirus, antitumor, antipyretic, anti-hepatic injury, immunomodulatory, antibacterial etc. Moreover, different toxicological studies indicated that the clinical dosage of \textit{T. hemsleyanum} was safe and reliable.

Conclusions: Modern pharmacological studies have well supported and clarified some traditional uses, and \textit{T. hemsleyanum} has a good prospect for the development of new drugs due to these outstanding properties. However, the present findings did not provide an in-depth evaluation of bioactivity of the extracts, the composition of its active extracts was not clear. Moreover, they were insufficient to satisfactorily explain some mechanisms of action. Data regarding many aspects of \textit{T. hemsleyanum}, such as links between the traditional uses and bioactivities, pharmacokinetics, quality control standard and the clinical value of active compositions is still limited which need more attention.
\end{abstract}

1. Introduction

\textit{Tetrastigma hemsleyanum} Diels et Gilg (\textit{T. hemsleyanum}), mostly known as “San ye qing”, is a kind of folk plant. Because of its slow growth, it usually takes 3–5 years to meet the requirements of commercial medicinal materials, so it is a precious perennial medicinal resource. It mainly grows in the eastern, central, southern and southwestern provinces of China, such as Zhejiang, Jiangsu Guangxi, Fujian and Yunnan provinces (Peng and Wang, 2018). \textit{T. hemsleyanum} is known worldwide as sources of phytotherapeutics, which have been used for the treatment of conditions related to inflammatory and immune response, and been recorded based on clinical trials or the use of animal models (Xu, 2006). As an edible plant, the leaves of \textit{T. hemsleyanum} consumed as a functional tea or dietary supplement for its health benefits, such as improving the immune system of the body (Sun et al., 2013), while the aerial parts of \textit{T. hemsleyanum} developed as potential new traditional chinese medicine (TCM) preparations (Guo et al., 2019).
The root tubers of *T. hemsleyanum* are extensively used either alone or in combination with other herbal medicines in TCM clinics for the treatment of children with fever, convulsion, pneumonia, asthma, rheumatism, hepatitis, menstrual disorders, scrofula, and pharynx pain (Sun et al., 2015; Chen and Guo, 2012). Therefore, it was called as “natural plant antibiotic” according to its wide spectrum of prominent bactericidal and anti-inflammatory activities. In February 2018, *T. hemsleyanum* was awarded as the new “eight famous kinds of TCM in Zhejiang province”, meant that it has become a key object of industrialization development of Zhejiang’s dominant large varieties of medicinal materials.

In 2019, COVID-19 broke out and has caused more than 4600 deaths in China, and infection cases have been reported in more than 200 countries. Hu Shi Xuan Fei mixture (Approval number of Zhejiang medicine, Z20200026000), which is mainly composed of *T. hemsleyanum*, has been approved by Zhejiang Provincial Drug Administration for clinical treatment of COVID-19. Furthermore, the modern pharmacological studies had shown that *T. hemsleyanum* also had effects of anti-inflammatory (Ji et al., 2019), antioxidant (Hossain et al., 2011), antiviral (Ding et al., 2019), antitumor (Lin et al., 2014), antipyretic (Yang and Wang, 2014), anti-hepatic injury (Ma et al., 2012), immunomodulatory (Xu et al., 2008), anti-bacterial (Chen et al., 2019), hypoglycemic (Ru et al., 2018a, b) etc. Numerous reports have demonstrated that the biological activities of *T. hemsleyanum* are attributed to its many chemical components (Fu et al., 2019). Wang has reported isolated alkaloids from the aerial parts of *T. hemsleyanum* (Wang et al., 2018). Ru extracted a novel polysaccharide TDGP-3 from *T. hemsleyanum* with a molecular weight of $3.31 \times 10^5$ Da by enzymolysis-ultrasonic assisted extraction method (Ru et al., 2019a, b). Large amounts of flavonoids were found in leaves, aerial parts and root tubers of *T. hemsleyanum* (Xu et al., 2014a, b; Deng et al., 2018; Yu et al., 2016). In addition, *T. hemsleyanum* also contains a variety of functional components, such as organic acids (Hu et al., 2013), phenolic acids (Liu, 2000), minerals (Fan et al., 2017), amino acids (Fu et al., 2015) etc.

In recent years, wild resources of *T. hemsleyanum* have been over-exploited and now are on the verge of extinction due to its multiple medicinal values coupled with the strict requirements of the growing environments. In 2011, it was listed in the preferentially protected crop germplasm resources of Zhejiang province. Based on our team’s preliminary research (Peng et al., 2013, 2015, 2016, 2019; Peng et al., 2016a, b; Li et al., 2019), we comprehensively summarized and analyzed the domestic and overseas research progress on traditional uses, the bioactive components of *T. hemsleyanum*, pharmacological activities, toxicology with the aim of providing guidance for in-depth research and reference for its development and utilization.

### 2. Materials and methods

The available information about the traditional uses, phytochemicals and pharmacological properties of *T. hemsleyanum* was searched via Web of Science, Google Scholar, PubMed, Science Direct, China National Knowledge Infrastructure (CNKI), and Springer search using Chinese or English as the retrieval languages. The keywords used include *T. hemsleyanum*, root tubers of *T. hemsleyanum*, Radix Tetrastigma,
traditional uses, phytochemistry, bioactive components, pharmacological activities, toxicology, and other related words. All references were from experimental studies and published prior to April 2020 were reviewed. All chemical structures were drawn using ChemDraw Pro 7.0 software.

3. Botanical characteristics

*T. hemsleyanum* is a perennial grass climbing vine with longitudinal ribs, glabrous or sparsely pilose. It is usually grown in a cool and humid environment, and the main soil type is yellow soil or yellow brown soil with rich humus. The optimum pH is between 4.29 and 7.65. The root tubers are thick, spindle shaped or elliptical, and single or several are connected into a string of beads, generally 1.5–3 cm long and 0.7–1.5 cm in diameter (Fig. 1). The epidermis of the root tubers is tan, and most of them are smooth, a few of them have folds and lenticle like protuberances, some of them have depressions, in which there are residual tan roots, hard and brittle, with a flat and rough section. The stem of *T. hemsleyanum* is thin and weak with longitudinal rhombus, rooting on the lower node. Palmate compound leaves alternate, leaflets are lanceolate, oblong or ovate lanceolate. The leaflets are 3–10 cm long and 1.5–3 cm wide, with a tapered tip and a wedge-shaped or round base. The flowers of *T. hemsleyanum* are small, yellow green and ovate. The flowering stage of *T. hemsleyanum* ranges from April to June, and the fruit phase is normally from August to November. When the flower withered, it will form a small green round fruit with the size of millet. When it is mature, the fruit will turn from green to red, the berries are spherical and soft spherical.

4. Traditional uses

*T. hemsleyanum*, belonging to the family Vitaceae, was firstly recorded in Ben Cao Gang Mu (Ming Dynasty, A.D. 1590). The aliases of Sanyeqing include Shi Hou Zi, Shi Bao Zi, Shi Lao Shu, Lan Shan Hu, Lei Dan Zi, Po Shi Zhu, Tu Jing Wan, Sou Jia Feng, San Ye Dui, golden wire hanging gourd, golden bell, golden wire hanging potato, etc. The root tubers or whole grass of *T. hemsleyanum* traditionally and ethnically used as a medicine for a long time, it has been recorded in multiple ancient books of TCM, such as Zhi Wu Ming Shi Tu Kao (Qing Dynasty, Wu, 2014), Jiangxi herbal medicine, Common folk herbal medicine in Zhejiang. All of these ancient works described the effects of *T. hemsleyanum* were heat-clearing, toxicity-removing, dyspnea-relieving, promoting blood circulation and pain relief, thus, it can be applied to cure febrile convulsion, pneumonia, bronchitis, pharyngitis, sore throat, acute and chronic hepatitis, rheumatic arthralgia, viral meningitis, bruise, eczema, insect and snake bite, poor joint flexure and extension, irregular menstruation of women (National compilation team of Chinese herbal medicine, 1975). In the TCM culture, the properties of *T. hemsleyanum* was described as bitter and acrid in taste, cool in nature which recorded in dictionaries of traditional Chinese medicine and Zhong Hua Ben Cao (Shanghai Science and Technology Press, 1999). The channel tropism was lung, heart, liver and kidney meridians.

Decothing with water or mashing for external application are the traditional possess methods of *T. hemsleyanum*. Considering its extensive traditional effects, many prescriptions containing *T. hemsleyanum* have been passed down from generation to generation, and have been well supported and clarified by modern pharmacological studies. Excitingly, it has reported that Jinlian disinfection drink containing san ye qing combined with interferon can treat Covid-19 (He et al., 2020). Jinqi Tablet, made up of san ye qing, astragalus and ginsenoside, was used to treat 120 cases of malignant tumor, 52 cases were completely relieved, 42 cases were partially relieved, the total effective rate was 78.33% (Wei et al., 2007). Moreover, Zhonggan mixture, including san ye qing, could improve the quality of life and prolong the survival time of patients with stage III primary liver cancer (Jiang and Gong, 2005). In addition, it has been used in the treatment of common gynecological diseases such as blood avalanche and leucorrhea (Gao, 2004), and it also has a good effect on measles complicated with pneumonia, anal fissure, chronic bronchitis and mosquito bites (Ji, 2010).

5. Chemical compounds of *T. hemsleyanum*

The chemical constituents of *T. hemsleyanum* have been widely investigated (Sun, 2018; Sun et al., 2018; Zeng et al., 2017; Xu et al., 2014a,b; Fu et al., 2015; Fan et al., 2016; Chen, 2014; Ding et al., 2015a,
fifty-one flavonoids and their glycosides have been extracted and identified from *T. hemsleyanum* until now. The information about compound name, molecular weight, compound formula, detection method, analysis sample is summarized in Table 1.

### 5.1. Flavonoids and their glycosides

Modern phytochemical studies have indicated that flavonoids are the representative and predominated class of constituents isolated from *T. hemsleyanum* (Lin et al., 2016; Zhang et al., 2016) (Table 2). To date, fifty-one flavonoids and their glycosides have been extracted and identified from *T. hemsleyanum*. In this series compounds, quercetin (1), orientin (8), vitexin (13), isorhamnetin (20), apigenin (23) and kaempferol (36) are the main types of skeleton, some of their analogues can be identified from hydroxy moiety on C3′ and C4′ on the B ring of flavonoid aglycone. At present, many modern analytical techniques have been used for qualitative and quantitative analysis of flavonoids. Among them, ultra high performance liquid chromatography tandem triple quadrupole time of flight mass spectrometry (UPLC-ESI-Q-TOF-MS) has become a powerful tool for identifying the complicated compounds due to its higher mass accuracy and resolution. Our team used UPLC-ESI-Q-TOF-MS to identify 31 chemical constituents from the aerial part of *T. hemsleyanum*, including 22 flavonoids, such as isoorientin (10), quercetin (1), kaempferol (36), vitexin (13), isovitexin (17), kaempferol-3-glucoside (37), etc (Sun et al., 2018). According to the report (Liu et al., 2015), total flavonoids of *T. hemsleyanum* could protect the aged mice from acute lung injury through inhibiting the phosphorylation of mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) in lung tissue. Moreover, the flavonoids of *T. hemsleyanum* had the activity of anti-lung cancer (Wei et al., 2019). Luteolin (30), a flavonoid found in *T. hemsleyanum*, acted as an anticancer agent against various types of human malignancies such as lung, breast, glioblastoma, prostate, colon, and pancreatic cancers (Mohammad et al., 2019). It is certain that *T. hemsleyanum* flavonoids give a new vision for researchers to explore clinical anticancer drugs.

### 5.2. Polysaccharide

Saccharide is another important active ingredient extracted from *T. hemsleyanum* (Shao et al., 2011). Polysaccharide has great potential in clinical anticancer drugs. In the study, 20 polysaccharides have been used for qualitative and quantitative analysis of flavonoids. At present, many modern analytical techniques have been used for qualitative and quantitative analysis of flavonoids. From the aerial part of *T. hemsleyanum*, including 22 flavonoids, such as isoorientin (10), quercetin (1), kaempferol (36), vitexin (13), isovitexin (17), kaempferol-3-glucoside (37), etc (Sun et al., 2018). According to the report (Liu et al., 2015), total flavonoids of *T. hemsleyanum* could protect the aged mice from acute lung injury through inhibiting the phosphorylation of mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) in lung tissue. Moreover, the flavonoids of *T. hemsleyanum* had the activity of anti-lung cancer (Wei et al., 2019). Luteolin (30), a flavonoid found in *T. hemsleyanum*, acted as an anticancer agent against various types of human malignancies such as lung, breast, glioblastoma, prostate, colon, and pancreatic cancers (Mohammad et al., 2019). It is certain that *T. hemsleyanum* flavonoids give a new vision for researchers to explore clinical anticancer drugs.

### 5.3. Phenolic acids

Phenolic acids refer to aromatic carboxylic acids with multiple phenolic groups substituted on one benzene ring. As a secondary metabolite, phenolic acids are widely found in many natural plants and have anti-inflammatory, antioxidant and lipid lowering effects. Twenty-three phenolic acids (No.52–84, Table 1) have been reported in the aerial parts of *T. hemsleyanum*, such as caffeic acid (54), chlorogenic acid (67), 1-O-galloyl-β-D-glucose (75), protocatechol glucoside (76), epigallocatechin (77), 1-cafeoylquinic acid (56), 3-cafeoylquinic acid (57), 4-cafeoylquinic acid (58), 5-cafeoylquinic acid (59), 1-p-coumarylquinic acid (66), 4-p-coumarylquinic acid (61) and 5-p-coumarylquinic acid (62). There were twenty-one phenolic acids in the root tuber of *T. hemsleyanum*, some of which were the same as aerial parts.

### 5.4. Alkaloids

Alkaloids are a group of basic organic compounds containing nitrogen that exist in nature. Alkaloids are stored in small quantities in *T. hemsleyanum*, and the bioactivity investigations of those alkaloids are still rather rare. Wang (Fu et al., 2019) extracted the aerial parts of *T. hemsleyanum* with 90% ethanol, and then isolated ten alkaloids for the first time, including seven indole alkaloids, an amide, a maleimide, and extracted the polysaccharides from roots of *T. hemsleyanum*, RPT-1, RPT-2 and RPT-3 were successively found by protein precipitation and purification. Moreover, further study indicated RPT-3-1 was high purity polysaccharide with a molecular weight of 1244.2 kDa, and it is mainly composed of 4 kinds of monosaccharides: arabinose, galacturonic acid, galactose, and fructose, the proportion is 8.39%, 7.18%, 20.70%, and 63.70%, respectively. Ru et al., 2018,a,b) extracted a polysaccharide THP from *T. hemsleyanum*, with the average molecular weight estimated as 93.307 kDa. The results of study on the composition of polysaccharide showed that it was mainly composed of rhamnose, arabinose, mannose, glucose, galactose with the molar ratio of 0.07:0.14:0.21:0.31. In 2019, Ru et al., 2019,a,b) successfully extracted polysaccharide THDP-3 from *T. hemsleyanum* with molecular weight of 77.98 kDa, which consists of rhamnose, arabinose, mannose, glucose and galactose with molar ratio of 1.0: 1.3: 2.5: 2.3: 3.1. Moreover, TDGP-3 mainly consists of --4)α-D-GalAp-(1→, --4)β-D-Galp-(1→ and --4)α-D-GlcP-(1→, residues as backbones and β-D-Manp-(1→, --3,6β-D-Manp-1→ and α-D-Araf-(1→ residues as branches.

### Table 1

| Prescriptions name | Main composition | Traditional use | Usage | References |
|--------------------|-----------------|----------------|-------|------------|
| Qihteng Fengshi Jiu | T. hemsleyanum, Paraburum chianamusa | Treatment of joint pain, wind cold dampness arthropathy | Oral administration, 15-25 ml, once, 3 times a day | Ministrial standard |
| Qufengshi Yaojiu   | T. hemsleyanum, Deeringia amarathoides (Lam.) Merr., Blumea aromatica (Wall.) DC. | Treatment of articulargia syndrome, rheumatitis, rheumatoid arthritis, scapulohumeral periartritis | Oral administration, 25 ml, once, 3 times a day | Ministrial standard |
| Huatuo             | T. hemsleyanum, Deeringia amarathoides (Lam.) Merr., Blumea aromatica (Wall.) DC. | Treatment of articulargia syndrome, rheumatitis, rheumatoid arthritis, scapulohumeral periartritis, joint pain, muscular constricture | Oral administration, 2 capsules, once, 3 times a day | Ministrial standard |
| Sanyeqing Gypsum   | T. hemsleyanum, Gypsum, Loniceria japonica Thunb, Houtouyaia cordata Thunb, Ophiopogon japonicus (Linn. L.) Ker-Gawl | Treatment of infantile hyperpyretic convulsion | One dose a day, decoc according to the guide and take it 4-6 times after mixing | Xu (2006) |
| Decocction         | T. hemsleyanum, Gypsum, Loniceria japonica Thunb, Houtouyaia cordata Thunb, Ophiopogon japonicus (Linn. L.) Ker-Gawl | Treatment of blood avalanche, leucorhexia | Oral administration, 30 ml, once, 3 times a day | Gao (2004) |
| Sanyeqing Power    | T. hemsleyanum, Gypsum, Loniceria japonica Thunb, Houtouyaia cordata Thunb, Ophiopogon japonicus (Linn. L.) Ker-Gawl | Treatment of liver cancer | Oral administration, 30 ml, once, 3 times a day | Jiang and Gong (2005) |
| Zhonggan mixture   | T. hemsleyanum, Lonicera japonica Thunb, Ophiopogon japonicus (Linn. L.) Ker-Gawl | Treatment of malignant tumor | Oral administration, 2 capsules, once, 3 times a day | Wei et al. (2007) |
| Jinqi Tablet       | T. hemsleyanum, gineseoside, Astragalus propinquus Schischkin | Treatment of Covid-19 | Oral administration, 125 ml, once, 2 times a day | Zhejiang Provincial Drug Administration |
Table 2
Chemical constituents isolated from the different parts of *T. hemsleyanum*.

| Name                          | Detection Mode | Analysis parts of sample | Reference                  |
|-------------------------------|----------------|--------------------------|----------------------------|
| quercetin                     | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun (2018)                 |
| quercetin                     | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun et al. (2018), Zeng et al. (2017) |
| quercetin-3-O-glucoside       | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun (2018)                 |
| quercetin-3-O-rutinoside      | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Sun et al. (2018)          |
| quercetin-3-galactoside       | UPLC-ESI-QTOF-MS/MS | root tuber              | Sun (2018)                 |
| quercetin-3-oxylygoside-glucoside | UPLC-ESI-QTOF-MS/MS | root tuber              | Zeng et al. (2017)         |
| quercetin-3-oxylygoside-7-O-rhamnoside | UPLC-ESI-QTOF-MS/MS | root tuber              | Zeng et al. (2017)         |
| orientin                      | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| orientin-2′-O-rhamnoside      | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| isoorientin                   | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun et al. (2018)          |
| isoorientin-2′-O-rhamnoside   | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| vitexin                       | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018), Sun et al. (2018) |
| vitexin-2′-O-glucoside         | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018), Sun et al. (2018) |
| vitexin-2′-O-arabinoside       | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018), Zeng et al. (2017) |
| isovitexin                    | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018), Sun et al. (2018) |
| isovitexin-2′-O-rhamnoside     | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| epicatechin                   | UPLC-ESI-QTOF-MS/MS | root tuber               | Sun (2018)                 |
| kaempferide                   | UPLC-ESI-QTOF-MS/MS | root tuber               | Sun (2018)                 |
| kaempferol-3-glucoside        | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Sun (2018), Sun et al. (2018) |
| kaempferol-3-rutinoside       | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Sun (2018), Sun et al. (2018) |
| kaempferol-3-sambubioside     | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Sun (2018), Sun et al. (2018) |
| kaempferol-3-o-neohesperidin  | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun et al. (2018), Zeng et al. (2017) |
| kaempferol-3-O-rhamnoside     | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun (2018), Zeng et al. (2017) |
| kaempferol-3-O-glucoside-3′-O-rhamnoside | UPLC-ESI-QTOF-MS/MS | root tuber              | Sun (2018)                 |
| kaempferol-3-0-carfuran-7-O-rhamnosyl glucoside | UPLC-ESI-QTOF-MS/MS | root tuber              | Zeng et al. (2017)         |
| daidzein                      | UPLC-ESI-QTOF-MS/MS | root tuber               | Sun (2018)                 |
| biochanin A                   | UPLC-ESI-QTOF-MS/MS | root tuber               | Sun (2018)                 |
| procyanidin dimmer            | UPLC-ESI-QTOF-MS/MS | root tuber               | Sun (2018)                 |
| procyanidin B1                | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun et al. (2018), Xu et al. (2014b) |
| procyanidin B2                | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun et al. (2018), Xu et al. (2014b) |
| procyanidin trimmer           | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun et al. (2018), Zeng et al. (2017) |

**Phenolic acids and derivatives**

| Name                          | Detection Mode | Analysis parts of sample | Reference                  |
|-------------------------------|----------------|--------------------------|----------------------------|
| gallic acid                   | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun (2018), Xu et al. (2014b) |
| protocatechuic acid           | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun (2018)                 |
| caffeic acid                  | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018), Sun et al. (2018) |
| dihydroxybenzoic acid hexoside | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 3,4-dihydroxybenzoic acid hexoside | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 1-caffeoylquinic acid         | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 3-caffeoylquinic acid         | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 4-caffeoylquinic acid         | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 5-caffeoylquinic acid         | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 1-p-coumaroylquinic acid      | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 4-p-coumaroylquinic acid      | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| 5-p-coumaroylquinic acid      | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun et al. (2018), Zeng et al. (2017) |
| p-hydroxybenzaldehyde        | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| p-coumaric acid              | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| ferulic acid hexoside         | UPLC-ESI-QTOF-MS/MS | aerial part              | Sun (2018)                 |
| salicylic acid               | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber  | Sun (2018), Fu et al. (2015) |
| chlorogenic acid             | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Sun (2018), Sun et al. (2018) |
| neochlorogenic acid           | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Xu et al. (2014b), Fan et al. (2016) |
| cryptochlorogenic acid        | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part  | Xu et al. (2014b), Fan et al. (2016) |
| protocatechuadehyde           | UPLC-ESI-QTOF-MS/MS | root tuber              | Sun (2018)                 |
| Name | Detection Mode | Analysis parts of sample | Reference |
|------|----------------|--------------------------|-----------|
| salacin-2-benzoate (71) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| tribhydroxyniminoquinic acid isomer (72) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| protocatechuric acid hexoxide (73) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| apionyglucosyl 4-hydroxybenzoeate (74) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| 1-O-galloyl-D-glucose (75) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun et al. (2018), Zeng et al. (2017) |
| protocatechol glucoside (76) | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber | Sun et al. (2018), Zeng et al. (2017) |
| epigallocatechin (77) | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber | Sun et al. (2018), Xu et al. (2014b) |
| vanillic acid-1-O-furan celerly glucosyl ester (78) | UPLC-ESI-QTOF-MS/MS | root tuber | Zeng et al. (2017) |
| protocatechuric acid-1-O-furan celerly glucosyl ester (79) | UPLC-ESI-QTOF-MS/MS | root tuber | Zeng et al. (2017) |
| methoxynphenol-1-O-furan glycosyl-O-glucoside (80) | UPLC-ESI-QTOF-MS/MS | root tuber | Zeng et al. (2017) |
| 2-methoxy-4-methylbenzen-1-o-furacresyl glucoside (81) | UPLC-ESI-QTOF-MS/MS | root tuber | Xu et al. (2014b) |
| oxysresveratrol (82) | UPLC-ESI-QTOF-MS/MS | root tuber | Xu et al. (2014b) |
| dicafeoylquinic acid (83) | UPLC-ESI-QTOF-MS/MS | root tuber | Xu et al. (2014b) |
| 4-hydroxycinnamic acid (84) | UPLC-ESI-QTOF-MS/MS | root tuber | Chen (2014) |
| **Alkaloids** | | | |
| indole (85) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| indole-3-carboxylic acid (86) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| indole-3-propanoic acid (87) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| 5-hydroxy-indole-3-carbonaldehyde (88) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| 5-hydroxynindole-3-carboxylic acid (89) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| 6-hydroxy-3, 4-dihydro-1-oxo-β-carbone (90) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| hippocamidine (91) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| 4-hydroxycinnaminate (92) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| pyrrole-3-propanoic acid (93) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| S-(−)-trololine (94) | NMR, UV, MS | aerial parts | Fu et al. (2019) |
| **Fatty acids** | | | |
| tribhydrox octadeadienoic acid (95) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| tribhydrox octadeccenoic acid (96) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| dihydrox octadeccenoic acid (97) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| 9-hydroxy-10,12-octadeadienoic acid (98) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| 9-hydroxy octadeceatrienoic acid (99) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| hydroxy-octadeccenoic acid (100) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| hydroxy-octadeceatrienoic acid (101) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| Dihydroxy-octadeceatrienoic acid (102) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| Dihydroxyoctane-trismin ethyl ether (103) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| Tribhydrox octadeceadienoic acid isomer (104) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| hydroxono-octadeceatrienoic acid (105) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| octadecenoic acid di-Me-ester (106) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| stearic acid (107) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| linoleic acid (108) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| linoleic acid (109) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| palmitic acid (110) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| oleic acid (111) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| stearic acid (107) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| **Organic acids and derivatives** | | | |
| malic acid (112) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| quinic acid (113) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| citric acid (114) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018), Sun et al. (2018) |
| aconitic acid (115) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| oxalic acid (116) | UPLC-ESI-QTOF-MS/MS | root tuber, aerial part | Sun (2018) |
| galactonic acid (117) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| gallic acid (118) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| succinic acid (119) | UPLC-ESI-QTOF-MS/MS | aerial part, root tuber | Sun (2018), Sun et al. (2018) |
| fumaric acid (120) | UPLC-ESI-QTOF-MS/MS | aerial part | Sun (2018) |
| propanoic acid (121) | GC-MS | root tuber | Sun et al. (2018) |
| **Terpenoids and steroids** | | | |
| β-sitosterol (122) | TCL | root tuber | Chen, 2014 |
| daucosterol (123) | H-NMR, C-NMR, MS | root tuber | Ding et al. (2015) |
| campsterol (124) | GC-MS | root tuber | Sun et al. (2018) |
| Stigmasterol (125) | GC-MS | root tuber | Sun et al. (2018) |
| 6-O-benzoyl daucosterol (126) | IR, H-NMR, EI-MS | root tuber | Guo (2018) |
| ergosterol (127) | IR, H-NMR, MS, aerial part | root tuber | Ru et al. (2019) |
| taxerone (128) | IR, H-NMR, MS, aerial part | root tuber | Ru et al. (2019) |
| Taxerol (129) | IR, H-NMR, MS, aerial part | root tuber | Ru et al. (2019) |
| α-amyrine (130) | IR, EI-MS | root tuber | Ru et al. (2019) |
| pteroside Z (131) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| ganoderic acid H (132) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| 3-epipapyriferic acid (133) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |
| oleic acid (134) | H-NMR, C-NMR, MS | root tuber | Ding et al. (2015) |
| **Saponins** | | | |
| Ginsenoside Rh3 (135) | UPLC-ESI-QTOF-MS/MS | root tuber | Sun (2018) |

(continued on next page)
a carboline. By comparing with the spectral data of known compounds, the alkaloids were respectively identified as indole (85), indole-3-carboxylic acid (86), indole-3-propanoic acid (87), 5-hydroxy-1-oxo-β-carboline (90), hippophamide (91), 4-hydroxycinnamidine (92), pyrrole-3-propanoic acid (93) and S-(−)-trolline (94). The chemical structures were shown in Fig. 2.

5.5. Organic acids and derivatives

The biologically essential organic acids have been isolated and characterized from *T. hemsleyanum* as well. Ten organic acids and seventeen fatty acids were identified from the aerial parts and root tuber of *T. hemsleyanum*, most of which were found in the aerial parts, except stearic acid (97), propanoic acid (121) and dihydroxy octadecenoic acid (102). All the organic acids and fatty acids are listed in No.112-121 and No.95-111 of Table 1, respectively.

5.6. Terpenoids and steroids

Terpenoids and steroids are other kinds of secondary metabolites of *T. hemsleyanum*, thirteen of these compounds have been isolated and identified (NO.122–134, Table 1). Liu (Yang et al., 1998; Liu et al., 2000) isolated and identified α-amyrine (130), β-sitosterol (122), ergosterol (127), taraxerone (128), taraxerol (129) from the aerial part of *T. hemsleyanum*. In addition, daucosterol (123), campesterol (124), stigmasterol (125), 6-O-benzoyl-daucosterol (126), pteroside Z (131), ganoderic acid H (132), 3-epipapyriferic acid (133) and oleanic acid (134) were successively separated from the tuber roots of *T. hemsleyanum* (Liu and Yang, 1999).

5.7. Inorganic elements

The mineral elements of TCM are indispensable supplements to the bioactive components, which are closely related to the efficacy, toxicity and side effects of TCM. Wu (Wu et al., 2018) demonstrated that *T. hemsleyanum* contains twenty-seven different mineral elements, namely Li, Be, Na, Mg, Al, K, Ca, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Rb, Ag, Cd, Cs, Ba, Hg, Ti, Pb, U. Moreover, Ca, Cu, Ni, Ba, Al, K have higher loading values, which are the characteristic elements of *T. hemsleyanum*. Wang (Wang et al., 2017) has indicated that the contents of Fe, Mn, Zn and Cu in three populations of *T. hemsleyanum* cultivated in different environments were 323.1–346.6, 36.3–38.1, 23.0–25.1, 3.8–4.1 mg kg−1, respectively.

5.8. Other compounds

In addition to the seven kinds of compounds mentioned above, amino acids derivatives in *T. hemsleyanum* are also reported, such as phenylalanine, pyroglutamic acid, glutamic acid hexose, tryptophan, L-glutamic acid.

6. Pharmacology

The ethnomedical uses of *T. hemsleyanum* have stimulated various pharmacological studies on it. The extracts and isolated compounds from *T. hemsleyanum* showed a variety of bioactivities, such as antiviral, antibacterial anti-oxidant, antipyretic, analgesic, hepatoprotective, immunoregulatory, and antitumor activity. The detailed pharmacological activities of *T. hemsleyanum* were presented in Table 3 and summarized as follows.

6.1. Antiviral activity

According to Yang’s literatures (Yang et al., 1989), the nitrogenous alkali-containing extract (A), ketone-containing extract (F), crude extract (S1), and crude extract (S2) of *T. hemsleyanum* had different antiviral effect on mice and chicken embryo fibroblast (CEF) infected with Hemagglutinating virus of Japan (HVJ), influenza virus PR6, vesicular stomatitis virus (VSV). Specifically, S2 strongly inhibited the proliferation of influenza virus PR6 with at the concentration of 0.5 mg/mL and 0.5 mg/mL S1 has obvious antiviral effect on HVJ. At the concentrations of 10 mg/mL and 1 mg/mL, both F and S1 displayed a strong suppressive effect on the plaque formation of VSV. In vivo, A, F, S1, S2 have different degrees of antiviral activity. When the concentration of A was 0.1 g/kg, the protective rate was up to 50%, and that of S1 (0.2 g/kg) was 20%. However, the author did not give the sample preparation method. Ding et al. (2019) had demonstrated compounds quercetin-3-O-rutinoside (4), kaempferol (36), kaempferol-3-glucoside (37), quercitrin (2), quercetin (1), kaempferol-3-O-rutinoside (38), procyanidin dimmer (48), and epicatechin (34), which were isolated from *T. hemsleyanum*, were positively related to the inhibition of *T. hemsleyanum* against H1N1 influenza virus. The ethyl acetate extracts of *T. hemsleyanum* have been shown to obviously restrain the secretion of HbsAg and HbeAg released by HBV, with the IC50 values of 1.3–48.6 mg/L. However, the specific mechanism of action needs to be further confirmed (Yang and Wu, 2009). Wang had proved that the n-butanol and ethyl acetate extraction of *T. hemsleyanum* had antiviral activity against RSV and were superior to ribavirin with the EC50 values of 0.008 mg/L (Wang et al., 2019). Moreover, the *T. hemsleyanum* extracts had different degrees of inhibition to different HIV-1 strains. The EC50 values were between 3.54 μg/mL and 78.56 μg/mL and the therapeutic index values were between 2.03 and 43.18. The EC50 values of *T. hemsleyanum* extract for blocking the fusion of HIV-1 chronic infected cells and normal lymphocytes C8166 cells was 14.79 μg/mL and the EC50 for inhibiting the recombinant HIV-1 reverse transcriptase was 170.15 μg/mL (Dong and Li, 2016). Although these studies have demonstrated that *T. hemsleyanum* could be used in the treatment of different viruses, the mechanism has been barely reported.

6.2. Antibacterial activity

*T. hemsleyanum* was used in the treatment of throat swelling and pain, sore and toxin, pneumonia and fever, and these diseases were mostly relevant to the invasion of microorganisms. Xiong (2015) used *S. aureus* LMA1213 and *B. subtilis* LMA0106, *E. coli* LMA 1226, *S. typhi*
LMA0217, *K. pneumonia* LMA0725, *M. racemosus* LMA3221, *P. citrinum* LMA7126, *A. flavus* LMA0816, *A. niger* LMA3601, *R. nigricans* LMA2429 as tested species, and evaluated the inhibitory diameter, minimum inhibitory concentration (MIC) of *T. hemsleyanum* ethanol extracts using oxford cup method and broth micro-dilution method. The results indicated that *T. hemsleyanum* showed the strongest activity against *S. aureus* and *B. cereus*, MIC value both were 62.5 μg/mL. Ethyl acetate extract of *T. hemsleyanum* ethanol extract (EAF) exhibited the strongest inhibitory activity on *E. coli*, *S. typhi* and *K. pneumonia*. MIC value ranges from 125 μg/mL to 250 μg/mL. Meanwhile, chloroform extract of *T. hemsleyanum* ethanol extract (CFF) exhibited remarkable activity against *P. citrinum*, *A. flavus*, *A. niger* and *R. nigricans*. MIC value ranges from 31.3 μg/mL to 125 μg/mL. Chen (Chen et al., 2019) had clarified the antibacterial mechanism of *T. hemsleyanum*’s polysaccharide was that it could inhibit the proliferation of *E. coli* by interfering with glycolysis and gluconeogenesis.

6.3. Antioxidant activity

Antioxidant activity is a prominent value for the further development of natural products. According to the study (Sun et al., 2013), 80% methanol extract of *T. hemsleyanum* leaves exhibited the highest DPPH radical scavenging activity, with the value of 3.32 mmol of Trolox/g DW, and a similar result was also found in the ABTS radical scavenging activity experiment (1.38 mmol of Trolox/g DW). In the ferric reducing activity assay, 80% methanol extract of *T. hemsleyanum* leaves had the highest value (1.85 mmol of FeSO$_4$/g DW). Moreover, the results of relationship between phenolic content and antioxidant activity suggested that the phenolics of *T. hemsleyanum* leaves extracts were the main contributors to the antioxidant activities. In Fu’s research (Fu et al., 2015), it had been found that the antioxidant activities of quercetin (1), epigallocatechin (77), procyanidin B1 (49), procyanidin B2 (50), protocatechualdehyde (70) and quercetin-3-O-glucoside (3) in *T. hemsleyanum* were better than those of vitamin C, and the antioxidant capacity was correlated with the amount of total flavonoids and total polyphenols. It was also confirmed by literature (Xu et al., 2015; Ye and

Fig. 2. Selected structures of chemical constituents isolated from *T. hemsleyanum*.
Liu, 2015), which suggested that total flavonoids and total phenols might be the material basis of antioxidant activity. Sun (Sun et al., 2017) established an oxidative stress rat model by D-galactose, total antioxidant capacity, superoxide dismutase (SOD), glutathione (GSH) peroxidase activities of rats were increased after treatment of T. hemsleyanum. Meanwhile, the content of GSH was increased and malondialdehyde (MDA) content was decreased in plasma and tissues of these rats. Interestingly, Chu (Chu et al., 2019, 2020) isolated a purified polysaccharide from T. hemsleyanum, the results of pharmacological experiment showed that it could ameliorate oxidative damage in RAW264.7 cells via Nrf2-Keap1 and Sirt1-FoxO1 pathways. Based on the above findings, the antioxidant activity of T. hemsleyanum has the characteristics of multi-components, multi-targets and multi-pathways.

6.4. Anti-inflammatory activity

In the folk, T. hemsleyanum is widely used in the treatment of infantile hyperpyretic convulsion, which was also confirmed by Brewer’s yeast or 2,4-dinitrophenol induced hyperthermia test of rats (Huang et al., 2005). More specifically, the temperature of rats treated with T. hemsleyanum extracts remarkably fell and 5-hydroxytryptamine (5-HT), norepinephrine (NE), dopamine (DA) in hypothalamus also significantly decreased (Yang and Wang, 2014). Besides, a purified polysaccharide from aerial parts of T. hemsleyanum with average molecular weight of 66.2 kDa could markedly suppress the levels of pros taglandin E2 (PGE2) in serum of mice (Zhu et al., 2020). The analgesic activity of T. hemsleyanum was investigated by acetic acid or oxytocin induced writhing response in mice and hot plate test, and the results manifested that T. hemsleyanum could reduce the number of abdominal writhing and increase the pain threshold in hot plate test in a dose-dependent manner (Wang, 2017). T. hemsleyanum could reduce the tension of isolated mouse uterus and the writhing times of oxytocin-induced mice model (Lv et al., 2011). The results further showed the aerial parts of T. hemsleyanum also had analgesic activity taken these finding into consideration as follow: increased the rate of pain threshold prolongation with the maximum extension of analgesic ratio of 65.58%, inhibited acetic acid-induced writhing pain in mice, prolonged the latency of mice’s writhing and alleviated the writhing responses with the maximum inhibition ratio of 51.80% (Liao et al., 2017). However, the bioactive compounds and the mechanism of action have not been reported in any literature.

6.5. Anti-inflammatory activity

Inflammation has been reported to produce negative effect on various diseases. Consistent with traditional uses, T. hemsleyanum exerted anti-inflammatory activity, the regulation mechanism was closely related to the target molecules including NF-κB and MAPK (Liu et al., 2015). A purified polysaccharide with the average molecular weights of 478.33 kDa from T. hemsleyanum could attenuate inflammation stimulated with lipopolysaccharide (LPS) through suppressing the phosphorylation of MAPKs, down-regulating the expression of COX-2 and iNOS in RAW264.7 cells. Moreover, the purified polysaccharide also improved the growing development and athletic ability of Caenorhabditis elegans (C.elegans), ameliorated the ability of scavenging ROS, O2−, recovered GSH against LPS-induced inflammation in C. elegans (Chu et al., 2019, 2020). Liu (Liu et al., 2016) discovered that T. hemsleyanum reduced the production of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin 6 (IL-6), interleukin 12 subunit p40 (IL-12p40), soluble TNF receptors 1 (sTNF-R1) and increased anti-inflammatory cytokine interleukin 10 (IL-10) expression in LPS-induced RAW264.7 cells, which were consistent with the other studies (Wang, 2016; Huang, 2017). Meanwhile, T. hemsleyanum dose-dependently inhibited the production of inducible NO synthase (iNOS) and NO, attenuated the up-regulated expression of Toll-like receptor 4 (TLR4), myeloid differentiation factor-2 (MD-2), myeloid differentiation protein 88 (MyD88) and TLR4/MD-2 complex induced by LPS. Along with the change of TLR4/MD-2, the phosphorylation and activity of c-Jun N-terminal kinase (JNK) and NF-κB were changed at the same time. These data revealed T. hemsleyanum might contribute to the alleviation of LPS-induced inflammatory reaction in RAW264.7 cells via TLR4/MD-2 mediated NF-κB and JNK pathway. Besides, our previous research proved that total flavonoids from T. hemsleyanum (1, 2 and 4 g/kg) and a positive control drug bifendate (200 mg/kg) could ameliorate inflammatory response in autoimmune hepatitis mice by mediating Treg/Th17 immune homeostasis (Li et al., 2019).

6.6. Hepatoprotective activity

Previous findings have demonstrated that T. hemsleyanum has protective effects on various types of liver injury. Water decoction of T. hemsleyanum (1.6 g/mL and 0.16 g/mL) relieved liver injury caused by carbon tetrachloride (CCL4) through decreasing the contents of glutamic-pyruvic transaminase (GPT), glutamic-oxalacetic transaminase (GOT), alkaline phosphatase (ALP) and MDA, while increasing the activity of SOD (Wu et al., 2006). Moreover, water extract and total amino acids of T. hemsleyanum could obviously reduce the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), liver index and the content of MDA in liver, increase the activity of SOD in live, and the protective effect of T. hemsleyanum on liver injury was better than that of biphynyl diester. Furthermore, the pathologic changes of hepatic tissue demonstrated that they could reduce the degree of necrosis, degeneration of inflammatory cell, and infiltration of hepatocytes (Zhong et al., 2006a,b; Huang and Mao, 2007). Besides, T. hemsleyanum extract had a protective effect on liver injury induced by α-isothiocyanate in mice, which was relevant to the reduction of inflammatory factors, promotion of the total bilirubin metabolism and alleviation of the lipid peroxidation (Li et al., 2018). As for chronic liver injury, Zhang (Zhang and Ni, 2008) observed that the extract of T. hemsleyanum reduced the levels of ALT, AST, hyaluronan (HA), laminin (LN), and total bilirubin (T-Bil), suppressed the content of total protein (TP) and albumin, improved the ratio of albumin/globulin and the survival rate of chronic hepatic damage rat administrated with CCl4 (Fig. 3). With regard to the mice with immune liver injury induced by Calmette-Guerin bacillus vaccine and LPS, T. hemsleyanum (20, 30, 40 g/kg) could also regulate the change of above factors at different levels (Yang, 2008). Unfortunately, the bioactive components of T. hemsleyanum against liver injury have not been reported so far.

6.7. Immunoregulatory activity

It is believed that the ability of body to cope with diseases depends not only on the adaptive immune response of T and B lymphocytes to specific antigens, but also on the natural immune response. Once the immune system is out of order, the pathological changes of organ tissues will ensue. Xu (Xu et al., 2006) had reported that the ethyl-acetate fraction of T. hemsleyanum enhanced the proliferation of T and B lymphocyte and antibody activity at the dose of 1.82 mg/mL, 5.48 mg/mL, and 9.12 mg/mL, affected delayed-type hypersensitivity and mononuclear-macrophage phagocytosis, and increased the production of serum interferon-gamma (IFN-γ) and serum TNF-α at the dose of 9.12 mg/mL, which was in accordance with Ding’s findings (Ding et al., 2008). The extract of T. hemsleyanum (1.2, 2.4, 4.8 g/kg) could antagonize the decrease of serum immunoglobulin A (IgA) content and secretory immunoglobulin A (S-IgA) content in ileum mucus, spleen lymphocyte proliferation, natural killer cell activity, the increase of MDA content in intestinal mucus and serum IL-6 level in scalded rats (Zhang et al., 2006a,b). In addition, it has been reported that T. hemsleyanum could also increase the levels of IL-1, IL-4 and the index of immune organs (Fig. 4) (Chen and Li, 2015). Due to the complex constituents of the extract, the immunomodulatory mechanism of T. hemsleyanum need to be further studied.
Table 3  Pharmacological effects of T. hemsleyanum.

| Crude drug/compounds                  | Model method                                      | Dose range/concentration | Results                                                                 | references          |
|---------------------------------------|--------------------------------------------------|--------------------------|-------------------------------------------------------------------------|---------------------|
| **Antiviral Activity**                |                                                  |                          |                                                                         |                     |
| A, F, S₁, S₂                          | Mice and CFF infected with HIV-1, influenza virus PR8, VSV | 0.1–25 g/kg (i.g. for 114 days in vivo, 0.125–1 mg/mL in vitro) 12.5–100 μg/mL | Cell proliferation, plaque formation, animal mortality | Yang et al. (1989) |
| quercetin (1), quercitrin (2), epicatechin (34), kaempferol (36), kaempferol-3-glucoside (37), kaempferol-3-rutinoside (38), procyanidin dimer (48) Ethyl acetate extracts of T. hemsleyanum | HepG² cells                              |                                        |                                                                                     |                     |
| BAF, EAF                             | MA104 cells                                      | TC₅₀ and EC₅₀ of BAF: 2 × 10⁻³ and 2 × 10⁻¹, respectively, TC₅₀ and EC₅₀ of EAF: 2 × 10⁻³ and 2 × 10⁻¹; respectively | IC₅₀ 1.3–48.6 mg/L, CC₅₀ 385.0 ± 56.9 mg/L | Yang and Wu (2009) |
| PEF                                  | HIV-1-infected cells                             | CC₅₀: 92.54 μg/mL         | E₅₀ 3.54–78.56 μg/mL, TC₂₀ 2.03–43.18                                   | Dong and Li (2016) |
| **Antibacterial Activity**           |                                                  |                          |                                                                         |                     |
| EAF, CFF                             | E. coli, S. typhi, K. pneumonia, P. carinii, A. flavus, A. niger, R. nigricans | MIC of EAF: 125–250 μg/mL, MIC of CFF: 31.3–125 μg/mL | Inhibitory diameter zone >10 mm | Xiong (2015) |
| T. hemsleyanum ‘s polysaccharide     |                                                  |                          |                                                                         |                     |
| **Antioxidant Activity**             |                                                  |                          |                                                                         |                     |
| Total phenolic acid of T. hemsleyanum| DPPH assay, ABTS Assay, FRAP Assay              | 8.28–38.47 mg/g          | DPPH, 3.32 mmol of Trolox/g DW; ABTS, 1.38 mmol of Trolox/g DW; FRAP, 1.85 mmol of FeSO₄/g DW | Sun et al. (2013) |
| Quercetin (1), quercetin-3-O-glucoside (3), protocatechuic acid (70), epigallocatechin (77) Methanol extracts of T. hemsleyanum leaf | DPPH assay                             | IC₅₀ 12.4–15.99 μmol/L | Their antioxidant activities were better than that of vitamin C | Fu et al. (2015) |
| SD rats intraperitoneally injected with D-glucose solution |                                          | 200–1000 mg/kg | SOD, GSH, GSH, T-AOC | Sun et al. (2017) |
| A polysaccharide from T. hemsleyanum | ICR mice received a high-fat diet for 35 consecutive days | 100–300 mg/kg | SOD, GSH, Px, CAT, MDGA | Chu et al. (2019) |
| Ethanol extract of T. hemsleyanum     | DPPH assay, FRAP Assay, Prieto method            | 20–1000 μg/mL            | The antioxidant capacity was associated with the contents of total flavonoids and total phenolics | Xu et al. (2015) |
| Total flavonoids of T. hemsleyanum root tuber | DPPH assay, ABTS Assay, FRAP Assay              |                            | DPPH, 27.4 μmol of Trolox/g DW; ABTS, 35.1 μmol of Trolox/g DW; FRAP, 43.3 μmol of Trolox/g DW | Ye and Liu (2015) |
| Total flavonoids and phenolic acid of T. hemsleyanum leaf | DPPH assay                             | 6.25–100 mg/kg           | The antioxidant capacity was associated with the contents of total phenolics | Hostain et al. (2011) |
| **Antipyrétic and Analgesic Activity** |                                                  |                          |                                                                         |                     |
| Ethanol extract of T. hemsleyanum     | Rats induced with Brewer’s yeast or 2, 4-dinitrophenol | 1.2–4.8 g/kg           | Body temperature, the duration was up to 180 min 5-HT, NE, DA            | Huang et al. (2005) |
| Aqueous extract of T. hemsleyanum     | Wiser rats induced with Brewer’s yeast          | 2–6 g/kg                | Body temperature           | Yang and Wang (2014) |
| A polysaccharide from T. hemsleyanum | Kunming mice induced with Brewer’s yeast       | 200, 400 mg/kg          | The pain threshold, times of twisting body | Zha et al. (2020) |
| Ethanol extract of T. hemsleyanum     | Mice induced with acetic acid and hot plate test | 1.2–4.8 g/kg           | The pain threshold, times of twisting body, the pain threshold | Huang et al. (2005) |
| Ethanol extract of T. hemsleyanum     | Mice induced with acetic acid                   | 2.5 g/kg                | Times of twisting body, the tension of smooth muscle | Wang (2017) |
| Aqueous extract of T. hemsleyanum     | Mice induced with diethylstilbestrol and oxytocin | 1.25–5.0 g/kg         | Times of twisting body, the pain threshold | Lv et al. (2011) |
| Ethanol extract of T. hemsleyanum     | Kunming mice induced with acetic acid and hot plate test | 30–120 mg/kg           | The pain threshold, times of twisting body, the maximum of analgesic ratio was 65.58% | Liao et al. (2017) |
| **Anti-inflammatory Activity**       |                                                  |                          |                                                                         |                     |
| Ethanol extract of T. hemsleyanum     | Xylene-induced ear edema in mice                | 2.5 g/kg                | Degree of swelling, the inhibition rates | Wang (2017) |
| Ethanol extract of T. hemsleyanum     | Xylene-induced ear edema in mice, carrageenan-induced paw edema of acute inflammation in rats | 30–120 mg/kg (i.g. for 3 days or 7 days) | The inhibition rates | Liao et al. (2017) |
| Ethanol extract of T. hemsleyanum     | 1.2–4.8 g/kg (i.g. for 4 days)                  | (continued on next page) |                                                                         |                     |
tumorigenesis. CyclinD1 is a key regulatory protein in G1 phase, and the enhancing immune function.

marker, and both of them highly expressed in a variety of tumor.

oxygen c-myc is a nuclear protein regulatory gene, Lgr5 is a stem cell marker, and both of them highly expressed in a variety of tumor.

2019, 2020). It has the characteristics of multi-target, multi-pathway, new drugs for the treatment of tumor. Although the mechanism has not

Table 3 (continued)

| Crude drug/compounds | Model method | Dose range/concentration | Results | references |
|----------------------|--------------|--------------------------|---------|------------|
| A purified polysaccharide from T. hemsleyanum | RAW264.7 cells induced by LPS | 12.5-50 μg/mL | Degree of swelling↑, the inhibition rates↑ | T. Ji et al. (2021) |
| Total flavonoids of T. hemsleyanum | RAW264.7 cells induced by LPS | 40-80 μg/g (i.g. for 3 days) | TNF-α↑, IL-10↑, IL-6↑, IL-12p40↑, sTNF-R1↑, IL-10↑ | Li et al. (2019) |
| Total flavonoids of T. hemsleyanum | RAW264.7 cells induced by LPS | 10-160 μg/mL | TNF-α↑, IL-10↑, IL-6↑, IL-12p40↑, sTNF-R1↑, IL-10↑, INOS↑, NFκB↑, phosphorylation of JNK↑ | Li et al. (2016) |
| Aqueous extract of T. hemsleyanum | COPD model rats were induced by exposure to cigarette smoke and endotracheal instillation of LPS | 1.0 g/kg (i.g. for 28 days) | IL-23↑, IL-17↑ | Wang (2016) |
| Polysaccharide from T. hemsleyanum | RAW264.7 cells induced by LPS | 25-100 μg/mL | TNF-α↑, IL-6↑ | Huang (2017) |
| Total flavonoids of T. hemsleyanum | Balb/c mice induced by Con A | 1.4 g/kg (i.g. for 28 days) | IL-17↑, IL-6↑, TGF-β1↑, IL-10↑, Foxp3↑, RORγt↑ | Ji et al. (2019) |

Hepatoprotective Activity

| Crude drug/compounds | Model method | Dose range/concentration | Results | references |
|----------------------|--------------|--------------------------|---------|------------|
| Aqueous extract of T. hemsleyanum | SD rats induced by CCl4 | 1.6 g/kg, 16 g/kg (i.g. for 6 days) | ALT↑, AST↑, MDA↑, SOD↑, GPT↑ | Wu et al. (2006) |
| Aqueous extract of T. hemsleyanum | Kunming mice induced by CCl4 | 0.6-2.4 g/kg (i.g. for 7 days) | ALT↑, AST↑, liver index↑, MDA↑, SOD↑ | Zhong et al. (2006) |
| Total amino acids from T. hemsleyanum | Kunming mice induced by CCl4 | 250, 500 mg/kg (i.g. for 7 days) | ALT↑, AST↑, liver index↑, MDA↑, SOD↑ | Huang and Mao (2007) |
| Ethanol extract of T. hemsleyanum | Kunming mice induced by α-synuclein | 1.0-4.0 g/kg (i.g. for 10 days) | ALT↑, AST↑, MDA↑, SOD↑, TNF-α↑ | Li et al. (2018) |
| Aqueous extract of T. hemsleyanum | SD rats induced by CCl4 | 1.0-4.0 g/kg (i.g. for 8 weeks) | ALT↑, AST↑, HA↑, LNI↑, T-BiLi↑, TP↑ | Zhang and Ni (2008) |
| Aqueous extract of T. hemsleyanum | Kunming mice induced by calmette-Guérin bacillus vaccine and LPS | 20-40 g/kg (i.g. for 10 days) | MDA↑, SOD↑, ALT↑, AST↑, LDH↑ | Yang (2008) |
| Polysaccharide from T. hemsleyanum | ICR mice induced by CCl4 | 0.125, 0.2 mg/g (i.g. for 7 days) | ALT↑, AST↑, MDA↑, SOD↑ | Ma et al. (2012) |

Immunoregulatory Activity

| Crude drug/compounds | Model method | Dose range/concentration | Results | references |
|----------------------|--------------|--------------------------|---------|------------|
| Ethyl acetate extract of T. hemsleyanum | ICR mice induced by Con A | 2.5-25 g/kg (i.g. for 15 days) | IFN-γ↑, TNF-α↑ | Ding et al. (2008) |
| Aqueous extract of T. hemsleyanum | Back of SD rats were immersed in 100 °C water for 12s | 1.2-4.8 g/kg (i.g. for 7 days) | IgG↑, S-IgG↑, MDA↓, IL-6↓ | Zhong et al. (2006) |
| T. hemsleyanum powder | Sanhuang Broiler mixed feeding with 0.5%, 1% and 2% of T. hemsleyanum powder diet for 20 days | IL-1↑, IL-4↑, the index of immune organs↑, TNF-α↑, TNF-β↑ | | Chen and Li (2015) |
| Ethyl acetate extract of T. hemsleyanum | ICR mice induced by Con A | 9.1-91.2 mg/kg (i.g. for 15 or 30 days) | IFN-γ↑, TNF-α↑, the proliferation of T and B↑ | Xu et al. (2008) |

6.8. Antitumor activity

In recent years, T. hemsleyanum has been widely used in the prevention and treatment of lung cancer, stomach cancer, colorectal cancer, liver cancer, breast cancer, cervical cancer, thyroid cancer, esophageal cancer, pancreatic cancer, lymphoid cancer and brain tumor (Chu et al., 2019, 2020). It has the characteristics of multi-target, multi-pathway, synergistic effect, non-toxicity, which is valuable for the development of new drugs for the treatment of tumor. Although the mechanism has not been fully elucidated, its antitumor effect may be achieved by inhibiting tumor cell proliferation and migration, inducing cell apoptosis, enhancing immune function.

6.8.1. Inhibiting tumor cell proliferation and migration

The abnormal regulation of cell cycle is an important reason for tumorigenesis. CyclinD1 is a key regulatory protein in G1 phase, and the disorder of G1 phase would lead to the occurrence of tumor. Proto oncogene c-myc is a nuclear protein regulatory gene, Lgr5 is a stem cell marker, and both of them highly expressed in a variety of tumor. Epithelial-mesenchymal transition (EMT) is characterized by a loss of epithelial proteins including E-cadherin, and increased expression of vimentin. EMT is closely connected with the migration and invasion of malignant tumors which accompanied by change activity of matrix metalloproteinase (MMPs) and tissue inhibitor of matrix-metalloproteinase (TIMPs). According to the studies (Xia et al., 2018; Zhang et al., 2017, a,b; Ni et al., 2009; Zhong and Wei, 2014; Zhong et al., 2016; Zhong et al., 2017; Yu et al., 2016; Yu, 2016; Wang et al., 2017; Wang et al., 2014; Jiang and Xu, 2015; Xu et al., 2011; Xu et al., 2010; Yan et al., 2013, a,b; Yan et al., 2013, a,b), the active components of T. hemsleyanum on the one hand could suppress the expression of Lgr5, CyclinD1 and c-myc, block the cell cycle in G0/G1 phase, reduce the transformation of tumor cells from G1 phase to S phase and then intercept the cell cycle in S and G2/M phase, so that the mitosis process of tumor cells would be blocked and cell proliferation be inhibited (Fig. 5). On the other hand, they could decrease the expression of E-cadherin, vimentin, MMP-2 and MMP-9, increase the expression of TIMP-2, suppress the activity of the Wnt/β-catenin pathway and Notch pathway, so that tumor migration and invasion would be inhibited.
6.8.2. Inducing apoptosis of tumor cells

Apoptosis is a cell suicide phenomenon that occurs in a specific time and space. It is closely regulated through a variety of cell signaling pathways, such as mitochondrial apoptotic pathway and death receptor apoptotic pathway. Bcl-2 protease family is the key protein in mitochondrial apoptosis pathway, which can be divided into two categories: pro-apoptotic proteins such as Bax and anti-apoptotic proteins such as bcl-2 (Fig. 6). Cytochrome c (Cyt-c) and apoptosis inducing factor were released under the action of apoptotic signal. The combination of Cyt-c and apoptosis activator, such as caspase-8, caspase-9 and caspase-10 could activate the downstream apoptosis executor enzymes, such as caspase-3 and caspase-6, and that finally lead apoptosis. Besides, ROS can produce many kinds of free radicals, which cause cell stress reaction and trigger cell apoptosis. However, many types of antioxidant enzymes can scavenge excessive ROS, such as SOD, catalase (CAT) and glutathione peroxidase (GSH-Px). As shown in Table 4, T. hemsleyanum could reduce mitochondrial membrane potential, increase intracellular Ca²⁺ concentration, down-regulate the expression of Bcl-2 protein, promote the expression of Bax and Cyt-C protein in tumor cells, and thus activate mitochondrial apoptosis induction pathway. On the other hand, it could activate the expression of caspase protease family, thus induce apoptosis (Peng et al., 2016a,b; Sun et al., 2018; Chen et al., 2018; Xiong et al., 2015; Peng, 2016; Liu and Xia, 2010; Li and Wei, 2012; Ding et al., 2017; Lin et al., 2016; Li and Peng, 2014; Wang and Peng, 2015; Zeng et al., 2012; Zeng et al., 2013; Zhong et al., 2014; Zhang et al., 2017a,b; Zeng et al., 2010; Wu et al., 2016). Furthermore, T. hemsleyanum could
reduce the activity of SOD, CAT and GSH-Px, increase the level of MDA, and enhance the oxidative stress response of tumor cells, thus accelerate the occurrence of apoptosis (Xiong, 2015).

6.8.3. Enhancing immune function

It has been well documented that the promotion of body immunity played a pivotal role in cancer development and treatment (Neil et al., 2008; Hinrichs and Rosenberg, 2014). Regulatory T cells (Tregs) have significant functions in the regulation of immune responses (Fig. 7). Tregs can express CD4, CD25 and Foxp3, which are associated with solid tumors. The inhibiting effect of Tregs on other CD4T cells and cytotoxic CD4T cells depends on intercellular communication and the secretion of inhibitory cytokines such as transforming growth factor beta (TGF-β). TGF-β induces the expression of cyclooxygenase 2 (COX2), and the overexpression of COX2 secretes high levels of PGE2. PGE2 significantly up-regulates the expression of the Treg cell-specific transcription factor forkhead/winged helix transcription factor gene (Foxp3) in CD4+ and CD25+ T cells. Thus, the induction, maintenance and function of the Tregs are closely related to COX2-PGE2 pathway. Numerous studies have shown that *T. hemsleyanum* could decrease the expression of PGE2,

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Fig. 5. *T. hemsleyanum* blocked the mitosis process of tumor cells and inhibited the cell proliferation, invasion and metastasis.

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Fig. 6. The enhancement of mitochondrial membrane permeability, the destruction of mitochondrial integrity and the stimulation of ROS cause apoptosis of tumor cells.
### Table 4
Mechanism of *T. hemsleyanum* in the treatment of tumor.

| Crude drug/Compound | Methods used | Dose range/concentration | Results | Reference |
|---------------------|--------------|--------------------------|---------|-----------|
| **Inhibiting proliferation of tumor cell** | | | | |
| Quercetin-3-O-glucoside (3) | NBT-II cells | 1–25 μg/mL | HGF/SF-Met signaling, migration, invasion | Xia et al. (2018) |
| *T. hemsleyanum* Flavones | EC9706 cells | 0.5–20 g/L | The inhibition rate of cell growth, adhesion rate, migration rate, invasion cell number, Notch1 mRNA ↓ | Zhang et al. (2017) |
| *T. hemsleyanum* Flavones | mice inoculated H22 cells | 15–90 mg/kg (i.g. for 12 days) | Cell growth ↑, TIMP-2 ↑ | Ni et al. (2009) |
| *T. hemsleyanum* Flavones | A549 cells | 0.5–10 g/L | Cell growth, apoptosis, p-p38, p-ERK | Zhong et al. (2014) |
| *T. hemsleyanum* Flavones | A549 cells | 0.5–10 g/L | Cell proliferation, cell migration, MMP-2, MMP-9, TIMP-2 ↑ | Zhong et al. (2016) |
| *T. hemsleyanum* Flavones | A549 cells | 1–10 mg/mL | Cell proliferation, DUB activity, ub-p38, USP14, UCHL5, POH1 | Zhong et al. (2017) |
| **Inducing apoptosis of tumor cells** | | | | |
| Ethylacetate extract of *T. hemsleyanum* | HepG2 cells | 0–200 μg/mL | Ca2⁺↑, cytochrome c↓, caspase-3↑, caspase-9↑ | Peng et al. (2016) |
| Methanol extract of *T. hemsleyanum* leaves | Kun-Ming mice inoculated H22 cells | 50–200 μg/mL (i.g. for 16 days) | Cell growth ↓, Bcl-2↑, Bax↑, VEGF↓, cle-caspase-9↑, cle-caspase-9↑ | Sun et al. (2018) |
| Ethylacetate extract of *T. hemsleyanum* root tuber | HepG2 and SMMC7721 cells | 50–200 μg/mL | Cell proliferation ↓, Bcl-2↓, caspase-3↑, Bax↑ | Chen et al. (2018) |
| Ethylacetate extract of *T. hemsleyanum* | HaLa cells | 10–40 μg/mL | Cell growth ↓, caspase-3↑, caspase-8↑ | Xiong et al. (2015) |
| Ethylacetate extract of *T. hemsleyanum* | HepG2 cells | 50–200 μg/mL | The proportion of Bcl-2/Bax↓, p53↑, the outflow of Ca2⁺↑, Cytochrome C↓, caspase-9↓, PARP↓, pro-caspase-3↓ | Peng (2016) |
| Ethylacetate extract of *T. hemsleyanum* | HT-29 cells | 0.1–10 μg/L | Cyto C↑, Bax↓, Cytochrome C↑ | Liu and Xia (2010) |
| Ethylacetate extract of *T. hemsleyanum* | C57BL/6 J mice inoculated Lewis lung cancer cells | 0.1–0.3 g/kg (i.g. for 14 days) | Apoptosis rate↑, Bcl-2↑, Bax↓, caspase-3↑ | Li and Wei (2012) |
| Ethylacetate extract of *T. hemsleyanum* | Panc-1 cells | 50–200 μg/mL | Bax↑, P53↑, Bcl-2↑ | Ding et al. (2017) |
| Ethylacetate extract of *T. hemsleyanum* | Balb/c mice inoculated HT-29 cells | 0.1–0.3 g/kg (i.g. for 14 days) | Tumor weight↑, caspase-3↑ | Lin et al. (2016) |
| Ethylacetate extract of *T. hemsleyanum* | HaLa cells | 1–16 μg/L | The inhibition rate of cell growth↑ | Li and Peng (2014) |
| Ethylacetate extract of *T. hemsleyanum* | HCCC-9810 cells | 25–200 μg/mL | Cell proliferation↓, caspase-3↑ | Wang and Peng (2014) |
| Ethylacetate extract of *T. hemsleyanum* | A549 cells | 1–100 μg/L | Rate of apoptosis↑ | Zeng et al. (2012) |
| Ethylacetate extract of *T. hemsleyanum* | A549 cells | 1–100 μg/L | Caspase-3↑ | Zeng et al. (2013) |
| Ethylacetate extract of *T. hemsleyanum* | H1299 cells | 0.5–10 μg/mL | pro-caspase-3↓, cle-PARP, pro-caspase-9↓, PARP↓, cle-caspase-9↑, cle-caspase-9↑ | Zheng et al. (2014) |
| *T. hemsleyanum* Flavones | SPCA-A1 cells | 0.5–10 g/L | Cell proliferation↓, cleaved-caspase-3↑ | Zhang et al. (2017) |
| *T. hemsleyanum* Flavones | SMMC7721 cells | 2–10 μg/mL | Cell proliferation↑, Rate of apoptosis↑ | Zhang et al. (2010) |
| *T. hemsleyanum* Flavones | SW620 cells | 0.25–1 mg/mL | Cell proliferation↓, cle-caspase-3↑, cle-caspase-9↑, Bax↑, Bcl-2↑ | Wu et al. (2016) |
| Petroleum Ether Fraction of *T. hemsleyanum* | Hela cells | 10–40 μg/mL | Caspase-3↑, caspase-8↑, caspase-9↑, CAT↓, SOD↓, GSH-pX↓, MDA↑ | Xia et al. (2015) |
| **Enhancing immune function** | | | | |
| Total flavonoids of *T. hemsleyanum* | C57BL/6 mice inoculated Lewis lung carcinoma cells | 5–15 mg/kg (p.o. for 14 days) | Tumor growth↓, regulatory T-cell development↑, TGF-β↑ | Feng et al. (2014) |
| *T. hemsleyanum* Flavones | C57BL/6 mice inoculated Lewis lung carcinoma cells | 7.5–30 mg/kg (i.g. for 14 days) | Tumor volume↑, TGF-β↑, PGE2, COX2↑ | Feng et al. (2014) |
| *T. hemsleyanum* Flavones | | | | |

(continued on next page)
COX2 and TGF-β, down-regulate the proportion of CD4+ and CD25+, Foxp3+ T and Tregs, consequently improve the immunosuppressive state of tumor patients or animals, enhance the immune function of the body and achieve the anti-tumor effect (Feng et al., 2014a,b,c; Feng et al., 2014; Zhang and Feng, 2017a,b; Hu et al., 2018; Zhang and Feng, 2017, 2017; Li et al., 2012; Guo et al., 2019; Feng et al., 2014).

### Toxicology

More and more attention has been paid to the toxicological study of *T. hemsleyanum*. Jiang made a toxicological evaluation on the decoction of *T. hemsleyanum* root tuber according to the dosage for folk clinical use was 15 g/person/day, and results indicated that the oral LD50 of rats and mice was more than 100 g/kg and 40 g/kg, respectively (Jiang and Guo, 2005). Furthermore, after feeding with *T. hemsleyanum* root tuber at 6.25, 12.5 and 25.0 g/kg daily for 30 days, there was free of mortality and toxicity, which demonstrated that the long-term use of *T. hemsleyanum* root tuber was safe and non-toxic (Jiang and Xu, 2005). The acute toxicity test of crude extracts of *T. hemsleyanum* aerial parts showed that the maximum tolerated dose given by intragastric administration in mice could reach as high as 80.4 g/kg/d, which was equivalent to 321.6% of the daily dose of 60 kg of human body weight. During the 14 day observation period, no toxic reaction, no animal death and no other abnormal changes about blood and biochemical indexes, organ coefficient and organ pathology were found (Chen et al., 2017). Besides, it also had been proved that the oral toxicity of *T. hemsleyanum* aerial

### Table 4 (continued)

| Crude drug/Compound | Methods used | Dose range/concentration | Results | Reference |
|---------------------|--------------|--------------------------|---------|-----------|
| *T. hemsleyanum* Flavones | C57BL/6 mice inoculated lewis lung carcinoma cells | 3.125–12.5 mg/kg (i. g. for 14 days) | Arg-1↓, iNOS↓, MDSCs(GR-1+ CD11b+), proportion of CD8+ T cells↑, CD4+ T cells↑, ratio of CD4+/CD8+ T↑ | Zhang and Feng (2017) |
| *T. hemsleyanum* Flavones | Lewis lung cancer cells | 5–20 mg/kg (i.g. for 14 days) | COX2↓, iNOS↓, proportion of T cells↑, CD4+ T cells↑, CD4+ CD8+ T↑ | Hu et al. (2018) |
| Ethylacetate extract of *T. hemsleyanum* | C57BL/6 mice inoculated Lewis lung cancer cells | 7.5–30 mg/kg (i.g. for 23 days) | The proportion of Treg cells↑, CD152↑ | Zhang and Feng (2017) |
| Polysaccharide of *T. hemsleyanum* aerial part | C57BL/6 mice inoculated Lewis lung cancer cells | 5–25 g/kg (i.g. for 14 days) | Tumor weight↑, spleen index↑, thymus index↑, IFN-γ↑, TNF-α↑ | Li et al. (2012) |
| *T. hemsleyanum* and its formula with ginseng or curcuma wenyujin | BALB/c mice inoculated with 4T1 cells | 50–250 mg/kg (i.g. for 14 days) | Tumor volume↓, liver index↓, COX-2↓, PGE2↓ | Guo et al. (2019) |
| *T. hemsleyanum* Flavones | 615 mice inoculated MFC cells | 2.25–2.70 g/kg (i.g. for 22 days) | Tumor volume↑, Treg ratio↓, COX-2↓ | Feng et al. (2014) |

Fig. 7. The role of Treg cells, PGE2, COX2 and TGF-β in tumor cell immunity.
parts formula granules was small, the maximum tolerable dose of gavage was more than 30.4 g/kg/d, and it was safe and reliable in clinical dosage (Xie et al., 2019).

8. Conclusion and future perspectives

*T. hemsleyanum* is an excellent medicinal plant containing bioactive constituents, which have been linked to its traditional application, such as anti-febrile convulsion, anti-pneumonia, anti-hepatitis, anti-upper respiratory infection, anti-asthma, anti-traumatic injury, and antitumor. Available pharmacological studies on compounds and crude extracts indicated broad biological effects of *T. hemsleyanum*, providing basic evidences for traditional uses. Although the present review comprehensively summarized the knowledge on the botany, traditionally and ethnobotanical uses, phytochemistry, pharmacology and toxicity of the *T. hemsleyanum*, there are some gaps still require scientific evaluation and exploration.

First, a large number of studies focused on the verification of traditional pharmacological activities by now, while the phytochemical analysis of the assessed extract was lack, and the functional components were unknown. As is known to all, TCM generally contains extremely complicated phytochemical components, and different medicinal parts contain different kinds of chemical components. Different phytochemical profiles of herbs may result in different potencies in biological assessments, and the synergistic effect of different components may also affect their pharmacological activities. Therefore, phytochemical analyses are indispensable to determine the correlation between components and pharmacological activities with the aim of discovering promising precursors for the clinical drug development. Additionally, the lack of sample preparation method, or inaccurate use different part of TCM could result in low reproducibility of the reported pharmacological effects. Moreover, the identification of *T. hemsleyanum* has not been described in some studies and no voucher number has also been reported, so that the taxonomic validity of the voucher specimen cannot be validated. Some studies did not mention the identification methods and the detailed information (including location, collection date, developmental stage, plant or plant parts, collector, etc) of the *T. hemsleyanum*.

Second, some current findings have been assessed with some problems concerning their pharmacological methods and experimental designs. Some methods used in pharmacological activities of *T. hemsleyanum* do not have an appropriate design due to the lack of a positive control group, which makes the results less reliable. Additionally, few of the in vitro studies mentioned the passage number and population doubling time (PDL) of the cell line used. Regarding the tests on animal models, few study described complete data regarding compliance with regulations on the ethical treatment of experimental animals, including the institutional committee or organization that approved the design of the experiments. Furthermore, some pharmacological studies above-mentioned assessed the pharmacological activities only using a simple cell line or animal model without further investigating the underlying mechanisms of action. Moreover, the characteristic mode of “multi-component, multi-target, integrated adjustment” of TCMs urgently needs further pharmacological research to fully clarify.

Third, the reliability of *T. hemsleyanum* for treating poor joint flexure and extension, irregular menstruation of women, rheumatic arthralgia, viral meningitis, bruise and eczema has been confirmed by long-term clinical practice, but current findings are not enough to verify and elucidate these traditional uses from the perspective of modern pharmacology. Moreover, data on many aspects of *T. hemsleyanum*, such as acute and chronic toxicity, pharmacokinetics, quality control standard and the clinical value of active compositions is still limited which call for further study in order to establish safety and toxicological limits and provide guidance for clinical applications.

In conclusion, the information of *T. hemsleyanum* on the traditional usages, origin, chemical constituents, pharmacological activities, and toxicology has been comprehensively shown to make people more aware of *T. hemsleyanum* and promote its further investigation for the development of new herbal medicine and health products.

Author contributions

Ji T. performed experiments, analyzed data, and prepared the manuscript. Ji W. W. and Wang J. participated in analysis of data and preparation of the manuscript. Chen H. J. participated in pharmacological studies and data analysis. Cheng K. J., Qiu D. and Yang W. J. provided the samples and did help in the manuscript preparation. Furthermore, as the guarantor of this work, Peng X. designed and supervised the overall study and prepared the manuscript. They had full access to all available data and took responsibility for the integrity and the accuracy of the data in this study.

Declaration of competing interest

The authors declare no conflict of interest pertaining to this manuscript.

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