Chemical constituents and pharmacological activities of *Stellera Chamaejasme*

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Abstract: ***Background:*** *Stellera Chamaejasme* is a perennial weed *and is found across a* wide geographic range. It is found inthe Altai of eastern Russia, northern China and Mongolia southwards and reaches as far as the western Himalayas of the Qinghai-Tibet and Yungui Plateaus. The dried roots of *S. Chamaejasme* are named "Rui-Xiang-Lang-Du" and this herb with toxic properties is widely used in Traditional Chinese Medicine for the treatment of various disorders. It is effective against dispelling phlegm by water and displays toxicity against insect pests. This review provides a comprehensive overview of the chemical composition and the pharmacological properties of S. Chamaejasme thus providing a better insight in its application in the prevention of human disease . M***ethods:*** A comprehensive literature review was undertaken and the main chemical compounds found in *S. Chamaejasme* were identified on the basis of their chemical formula and structure. These included coumarins, lignans, diterpenes plus others, and their pharmacological properties were also summarized in detail.

Results: The main constituents of *S. Chamaejasme* included flavonoids, diterpenoids, coumarins, lignans plus other compounds. The pharmacological properties of these compounds displayed a wide spectrum and include anti-tumors, anti-viral, anti-bacterial, anti-convulsive, anti-epileptic, insecticide, anti-inflammation, regulation of immunity etc. The diterpenoids were widely recognized as the constituent responsible for the anti-tumor effect.

Conclusions: A large number of studies conclude that *S. Chamaejasme* displays a wide spectrum of pharmacological activity with the anti-tumor activity being significant.

Keywords: *Stellera Chamaejasme*, Chinese herbal medicine, Chemical compositions, Analytical method, Pharmacological activities, Toxicity.

1. INTRODUCTION

Stellera Chamaejasme (Thymelaeaceae) is derived from genus *Stellera Linn and* is represented by 48 genera and 650 species, widely distributed in both hemispheres. *Stellera Linn.* is about 10 to 12 genus, is distributed in temperate regions east to west of Asia and there are two species which are found in China, *S. Chamaejasme* and *S. Formosana*, respectively. *S. Chamaejasme* is a perennial weed with a wide geographic range and is found in the Altai of eastern Russia, northern China, and Mongolia southwards and as far as the western Himalayas of the Qinghai-Tibet and Yungui Plateaus [1]. It is mainly distributed in Qinghai, Gansu, Hebei, Inner Mongolia, Tibet, and Xinjiang in China. *S. Chamaejasme* is also known as the graceful jessamine herb (Inner Mongolia), steamed bread spend (Qinghai), chervil and laevigata (Hebei). It is recorded in the *Shennong's Classic of Materia Medcia* as a well-known traditional Chinese herbal medicine. It is bitter, pungent, and poisonous, and can enter the channels of lung, spleen and liver. It displays efficacy against dispeling phlegm by water and is lethal against insect pests. Its dried roots, named "Rui-Xiang-Lang-Du" in traditional Chinese medicine, have been used for the treatment of scrofula and neurodermatitis and it has also been used as a traditional Chinese medicine formula for the clinical treatment of cancer, lymphatic structure, tuberculosis, skin diseases, and other diseases [2].

The chemical compositions of *S. Chamaejasme* is very complex. Previous phytochemical studies have reported that the main compounds of interest isolated have been reported to be flavonoids, coumarins, lignans, diterpenes, sesquiterpenes, phenylpropanol glycosides, volatile oil, etc. Recent pharmacological studies show that *S. Chamaejasme* has anti-viral, anti-bacterial, anti-convulsive, anti-epileptic, insecticide, anti-inflammation, regulation of immunity and various other biological activities. A study found that the flavonoid extract from *S. Chamaejasme* had strong *in vivo* and *in vitro* antitumor effects whilst total lignans had a strong antitumor effect *in vitro*. Coumarin compounds are characteristic of these components, not only does it have strong toxicity, it also has a wide range of pharmacological effects such as anti-HIV, anti-tumor, anti-oxidation, anti-microbial, anti-pressure, anti-radiation etc. The diterpenoid gnidimacrin is widely recognized as the main component of the anti-tumor effect because of its strong anticancer activity [3]. Thus it can concluded from these studies that *S.*

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Chamaejasme is of great medicinal value. This review comprehensively summarizes the chemical components and pharmacological activities of *S. Chamaejasme* and provides future directions for the the development and utilization of the plant for the treatment of diseases.

2. CHEMICAL COMPOSITIONS

Over the past few decades, studies on bioactive phytochemicals isolated from *S. Chamaejasme* have signicantly increased, and an increasing number of bioactive constituents have been discovered and reported. The major active constituents are flavonoids, coumarins, diterpenes, lignans, sesquiterpenes, phenylpropanol glycosides, volatile oils, as well as sterol, acid composition, amino acid, triterpenoid, resin etc.

2.1 Flavonoids

The flavonoids isolated from *S. Chamaejasme* are mainly dihydroflavones and chamaechromone compounds. A study confirmed that the contents of flavonoids in the leaf and root of *S. Chamaejasme* were 2.92% and 1.13%, the content of its leaves were higher than that of the the root [4]. A total number of 46 flavonoids were isolated from *S. Chamaejasme* (Fig. 1).and these were chamaejasmine (**1**) [5], 7-methoxychamaejasmin (**2**) [5], ruixianglangdu B, A (**3** and **22**) [6], chamaejasmine A–E (**4**, **7**–**9**, **13**) [7-9], chamaejasmin D (**14**) [9], chamaeflavone A (**15**) [10], isochamaejasmin (**5**) [11]，neochamaejasmin A–C (**10**, **16**, and **17**) [12, 13], 7-methoxylneochaejasmin A (**11**) [14], sikokianin A–C (**12**, **18**, and **24**) [9, 15]. isoneochamaejasmin A (**19**) [14], euchamaejasmin A–C [16], isochamaejasmin B, C (**20** and **21**) [15, 17], isosikokianin A (**23**) [15] as well as mesomer isochamaejasmin [18].

Niwa separated chamaechromone (**25**) [19] from *S. Chamaejasme* in 1984 followed by isolations of mohsenone (**26**) and isomohsenone (**27)** [20]. The other flavonoids isolated were 3′,14-dimethyl-4′,11-dimethoxy-5,7-dihydroxybenzene dihydroflavone (**28**), (−)-epiafzelechin-7-*O*-*β*-D-glucopyranoside (**29**) [20], stelleranol (**30**) [14], 7-*O*-*β*-D-glucopyranosyl-isochamaejasmin (**6**) [21], (+)-epiafzelechin (**31**) [14], wikstrol A, B (**32** and **33**) [22], apigenin (**34**), quercetin (**35**), rutin (**36**) [15], dihydrokaempferol (**37**) [23], isoquercitrin (**38**) [24], daphnodorin B (**39**), dihydrodaphnodorin B (**40**), genkwanol A (**41**) [25], 4',5,7-trihydroxyflavanone (**42**) [26], 5,4'-dyhydroxyl-7-methoxydihydroflavone (**43**), 3,5,7-trihydroxyflavanone (**44**), 4'-methoxy-7-hydroxyflavone (**45**) ， kaempferol-7-*O*-*β*-D-glucoside (**46**) etc. [27].. The total flavonoid extracts are of great significance in the investigation of the anti-tumor effects *in vivo* and *in vitro*.

2.2 Coumarins

Coumarin compounds are a class of natural active substances with α-pyrone nuclear parent. They are one of the characteristic components of the thymelaeaceae plants with aromatic smell, and are also one of the important active constituents present in higher plants. Coumarin compounds are distributed in the roots and the above-ground parts of *S. Chamaejasme*. The components that have been isolated from the *S. Chamaejasme* were all the umbelliferone derivatives. A total of 19 coumarins were reported from *S. Chamaejasme* (Fig. 2). They were sphondin (**47**), isobergapten (**48**), pimpinellin (**49**), isopimpinellin (**50**) [28], umbelliferone (**51**), daphnetin (**52**), scopoletin (**53**) [29], daphnin (**54**) [8], 5,7-dihydroxycoumarin (**55**) [30], daphnoretin (**56**), chamaejasmoside (**57**) [12], isodaphnoretin (**58**) [31], isodaphnoretin B (**59**) [15], *O*-[*β*-D-xylopyranosyl (1→6)-*β*-D-glucopyranosyl]-7-hydroxycoumarin (**60**) [32], 3-hydroxy-6-methoxy-7,7'-dicoumarinyl ether (**61**) [33], bicoumastechamin (**62**) [34], daphnin (**63**), daphnetin-8-*O*-glucoside (**64**) and rutarensin (**65**) [24]. Coumarins act as a phytohormone in plants and they are the most toxic type of phenolic compounds, and they play an important role in the growth and development of plants and against the invasion of foreign bodies [35].

2.3 Lignans

Lignans are a kind of natural compounds which are formed by the oxidation of phenylpropanoids, and most of them are of furan or tetrahydrofuran structure. The total lignans in *S. Chamaejasme* significantly inhibited the tumor cells *in vitro* [36], and the antitumor activity was higher than that of vincristine. At present there are 30 lignans which have been isolated from *S. Chamaejasme* (Fig. 3). Among them, were lirioresinol B displaying ichthyism activity (**66**), pinoresinol (**67**) [37] and matairesinol (**70**) [37]. Eudesmin displaying anti-HIV activity was also isolated (**71**) [16]. Other lignin compounds were (−)-eudesmin (**68**) [38], syringaresinol di-*O*-*β*-D-glucopyranoside (**69**) [39], bursehernin (**72**) [14], lappaol F (**73**) [40], arctiin (**74**) [40], magnolenin C (**75**) [41], isohinokinin (**76**) [41], demethyl-trachelogenin (**77**), isolariciresinol (**78**), (+)-secoisolariciresinol (**79**) [42], (+)-lariciresinol-4,4'-*O*-bis-*β*-D-glucopyranoside (**80**) [43], (−)-haplomyrfolin (**81**) [44], stelleralignan (**82**) [44], two new neolignans named (−)-(7R,8S,7′E)-4-hydroxy-3,5′-dimethoxy-7,4′-epoxy-8,3′-neolign-7′-ene-9,9′-diol 9′-ethyl ether and (−)-(7R,8S,7′E)-4-hydroxy-3,5,5′-trimethoxy-7,4′-epoxy-8,3′-neolign-7′-ene-9,9′-diol 9′-ethyl ether (**83** and **84**) [45], stellerachama A (**85**) [46], syringaresinol (**86**), (−)-medioresinol (**87**), (−)-pinoresinol (**88**), epipinoresinol (**89**), caruilignan D (**90**), (−)-lariciresinol (**91**), 5′-methoxylariciresinol (**92**), 7′-oxomatairesinol (**93**), (+)-guayarol (**94**), acutissimalignan B (**95**) [47] etc.

2.4 Diterpenes

There were varieties of diterpenes isolated from *S. Chamaejasme* with significant pharmacology activity. To date, 37 diterpenes have been reported from *S. Chamaejasme* (Fig. 4). In 1982, Niwa found four diterpenes with antitumor activity based on ichthyism activity, they were huratoxin (**96**), subtoxin A (**97**), simplexin (**98**), and pimelea factor P2 (**100**) [37]. In 1992, Feng found a strong anti-pain active ingredient named gnidimacrin(**101**) [48] for the first time in the root of the plant. Following this the compounds of stelleramacrin B (**99**) and stelleramacrin A (**102**) [49] were isolated. These compounds represent rare diterpene original acid esters compounds found in nature. The other diterpenoids were neostellerin A–C (**103**–**105**), neostellin (**106**) [16], neostellerin (**107**) [14], a new daphnane-type diterpene (**108**) [32], wikstroelide F (**109**) [50], stelleralides A–C (**110**–**112**) [51], stelleralides D–J (**113**–**119**) [52], pimelotide A (**120**)

[53], wikstroelide A, B (**121** and **122**) [50], wikstrotoxin A (**123**) [54], wikstroelide M and J (**124** and **125**) [50], stellerarin (**126**), 12-*O*-benzoylphorbol 13-octanoate (**127**), stelleracins A–E (**128**–**132**) [10] etc. Many studies have shown that the diterpenoids have strong biological activity especially against cancer and HIV.

2.5 Sesquiterpenes

There were 8 sesquiterpenes which were isolated from *S. Chamaejasme* (Fig. 5), these were 3-oxo-guai-4-ene-11,12-diol (**133**), (+)-(11S)-3-oxo-1,7α*H*-guai-4-en-11,12-diol (**134**), (+)-(11S)-3-oxo-1,7αH-guai-4-en-10α,12-diol (**135**), (+)-3-oxo-1,7α*H*-guai-4(5),11(13)-dien-10α,12-diol (**136**), chamaejasmone A–C (**137**–**139**) [45], chamaejasmone D (**140**) [44].

2.6 Volatile oils

There were 22 species of volatile oils isolated from the root of *S. Chamaejasme*, namely ethyl acetate, caprylic aldehyde, 13-myrcene, neral, 5-methyl decane, 3,7,11-trimethyl-12-carbon-α-trans-6,6-cis-10-enol, etc. [55]. Another 18 constituents were also identified from volatile oils of *S. Chamaejasme* [56], and included 7 kinds of ketone compounds, 3 kinds of alcohols, 2 kinds of alkanes and amides, and one type of esters, aldehydes, acetylene and acids. In addition, the volatile oils of two rare amide-hydrazine diphenylamine and acetanilide were also found in the leaf of *S. Chamaejasme*, and the former had a quality score of 17.26%, so these two compounds are likely to be the source of the distinctive pungent odour of *S. Chamaejasme* leaves [55].

2.7 Other components

Besides containing flavonoids, coumarins, diterpenes, lignans, phenylpropanol glycosides, and volatile oils *S. Chamaejasme*also contain sterol, amino acids, triterpene, sesquiterpene, resin, saponins, tannins, polysaccharides, the toxic macromolecule organic acid and other constituents [57]. The monosaccharide content was 1.37%, the polysaccharide was 43.13%, it contained sucrose, fructose, glucose and flavonoid glycoside [58]. The14 compounds found in *S. Chamaejasme* are summarized in Fig. 6. In 1999 there were 6 phenylpropanol glycosides isolated for the first time [59], and these were coniferinoside (**141**), syringin (**142**), syringinoside (**143**), sinapylalc-1,3-diglucopyranoside (**144**), 4-(-*β*-D-glucopyranosyloxy-1-E-propenyl-2,6-dimethoxyphenyl-6-*O*-*β*-D-glucopyranosyl-*β*-D-glucopyranoside (**145**), and 4-(3-hydroxy-1-Z-propenyl)-2,6- dimethoxyphenyl-6-D-glucopyranosyl-*β*-D-glucopyranoside (**146**). The other compounds isolated from the plant were β-sitosterol (**147**), daucosterol (**148**), stigmasterol-4-alkene-3,6-diketone (**149**), rel-(−)-(3R,3'R,4R,4'R)-6,6'-dimethoxy-[3,3'-bichroman]-4,4'-diol (**150**), methyl 3-(2-hydroxy-4-((7-hydroxy-6-methoxy-2-oxo-2*H*-chromen-3-yl)oxy)phenyl) propanoate (**151**) [42], 1,5-diphenyl-1-pentanone (**152**), 1,5-diphenyl-2-alkene-1-pentanone (**153**) [60], (+)-S-1,5-diphenyl-3-hydroxy-1-pentanone (**154**) etc. [61].

3. ANALYTICAL METHOD

There were four flavonoids isolated from the root of *S. Chamaejasme* by silica column chromatography, which were identified as neochamaejasmin, epiafzelechin, chamaechromone and wikstrol [62]. The root of *S. Chamaejasme* ethanol extract, petroleum ether extract and chloroform extract was used for further separation by using the method of active tracking. *β*-sitosterin was isolated from the petroleum ether extract; three active components were also isolated from chloroform extract and were identified as umbelliferone, daphne pavilion and chamaechromone respectively[63]. Various methods were used to extract flavonoids from *S. Chamaejasme* and the content of flavonoids was determined by spectrophotometer. It has been reported that the ultrasonic extraction method was the best and the content of the flavonoids was the highest in the polyamide resin column chromatography [64]. The extraction of *S. Chamaejasme* by quenching with ultrasonic extraction and solvent extraction method, resulted in the extraction ratio of total flavonoids being high, and the the utilization rate of raw material was obviously higher and the costs were lower when compared to other methods ; this method is suitable for a large number of extractions [65]. Using ultrasonic technology total flavonoids exytacted from *S. Chamaejasme*, were 24.3%. Also the flavonoids of *S. Chamaejasme* displayed significant ability to remove superoxide anion free radical and hydroxyl free radical *in vitro*, its effect was stronger than VC [66].

The content of coumarins of *S. Chamaejasme* was determined by ultrasonic extraction and spectrophotometry, The content of coumarins were significantly different in the nutritive organs, the highest concentration was found in the root, and lowest in the leaves and stems [35]. Reversed-phase high performance liquid chromatography (HPLC) was used to establish the content of 7,8-dihydroxy coumarin in the root, stem, leaf and flower of *S. Chamaejasme and* at the same time diode array detector was used to confirm the purity of the standard and the plant extracts and ultraviolet spectrum identification was also used. This method is simple, accurate and reproducible, and it is suitable for the quality evaluation of drugs and herbs containing this component [67]. . This method is simple, accurate and reproducible, and it is suitable for the evaluation of the quality of drugs and herbs containing this component [67]. The response surface method of extraction pressure was 30MPa, extraction temperature was 53°C and the volume of ethanol was 3 mL/g and under these conditions the total yield of coumarins was 0.36%, which is very close to the theoretical yield. This proves that the optimized extraction process parameters obtained by the response surface method was accurate and reliable and was of practical value [68]. A chromatographic method was used to identify the chemical structure of the components of the monomers. The multiple lignin compounds were isolated from the root of the *S. Chamaejasme*, and four of them were identified as lappaol F, clemastanin B, arctiin and matairesinol [40].

There were four kinds of rexane diterpenes with anticancer activity which were isolated from methanol extract of *S. Chamaejasme*, they were huratoxin, subtoxin A, simplexin,

and pimelea factor P2 respectively [37]. The components of volatile oils separated from the root of *S. Chamaejasme* were analyzed by gas-uality combined method, including ethyl acetate, octal, 13-laurene, neral, 5-methyldecane, etc. [55].

The quantitative analysis and comparison of total saponins and tannins of *S. Chamaejasme* were performed by means of weight method and complexation titration. The content of the total saponins and tannins were 2.75% and 3.62% respectively [69].

4. PHARMACOLOGICAL ACTIVITY

4.1 Anti-tumor activity

4.1.1 Anti-liver cancer activity

The medicated mice serum containing *S. Chamaejasme* could significantly increased anti-cancer activity of adriamycin and cytarabine resistant in human liver cells $Bel_{5-FU2000}$ in a concentration-dependent manner [70]. After comparing the inhibitory effects of different *S. Chamaejasme* extracts on liver cancer cells (SMMC-7721), the results showed that the total flavonoid extract presented the strongest *in vitro* antitumor activity [71]. The efficacy component Zp1111 of *S. Chamaejasme* had a good inhibitory effect on liver cancer cells HepG2, BEL-7402, and SMMC-7721 cultured *in vitro*, with the IC_{50} 37.75, 28.60, 29.22 μg/mL, respectively, while the inhibitory effect was not obvious in normal hepatocellular LO2. Zp1111 induced apoptosis of bel-7402 cells, controlled the distribution of bel-7402 cell cycle *in vitro* culture, reduced the cell proportion of S stage, and had a better inhibitory effect on protein kinase cyclin-dependent kinases (CDK2) [72]. The water extract of *S. Chamaejasme* (SCLA) was observed to prolong survival time of liver cancer H22 tumor-burdened mice in the low dose group, suggesting that SCLA had a significant inhibitory effect on liver cancer [73].

4.1.2 Anti-lung cancer activity

After treatment of lung cancer cell lines by SCLA, immunohistochemical SP method was used to detect gene expression of multi-resistant related protein (MDM_2), lung resistance protein (LRP), heat shock protein 27 (HSP_{27}), and multi-drug resistance (MDR-1). The positive rate and brightness of MDR-1, LRP, and MDM2 of the NCI-h_{446} cells were significantly decreased, while the expression of HSP27 was not significantly different ($P > 0.05$); the positive rate and brightness of MDR-1, LRP, and HSP27 of the NCI-H157 cell were obviously depressed ($P < 0.05$), while the expression of MDM_2 did not change significantly ($P > 0.05$), when compared with the control group. These results indicate that SCLA had obvious inhibitory effects on the expression of some gene proteins in lung cancer cell lines [74]. The flavonoids extract of *S. Chamaejasme* (ESC) displayed inhibitory effect on human lung cancer cell line NCI-H157. It had significant cytotoxicity to NCI-H157 cell, with IC_{50} of approximately 18.50 g/mL^{-1}. ESC caused an obvious increase in total apoptosis rate, and the activity of caspase-3 and -8 as well as the expression of Fas protein was significantly enhanced ($P < 0.05$), it is likely that the inhibitory effect was caused by activation of Fas death receptor pathway [75]. The flavonoid extract from *S. Chamaejasme* was able to inhibit the proliferation of A549 cells, showing a significant time-dose dependence. The total flavonoid extract also induced apoptosis of A549 cell and blocked A549 cell in G1 phase [76]. Chamaejasmine B and neochamaejasmin C were potential anti-proliferative compounds isolated from *S. Chamaejasme*, which had significant anti-tumor efficacy in sensitive human lung cancer A549 cell line. The IC_{50} of chamaejasmenin B and neochamaejasmin C were 1.08 μmol/L and 5.72 μmol/L, respectively, indicating that chamaejasmenin B had a slightly higher cytotoxic effect on A549 cell than neochamaejasmin C. The two compounds induced significant expression of DNA damage marker γ-H2AX and apoptosis. In addition, G0/G1 phase was also remarkably suppressedand the protein level of Myeloid cell leukemia-1 (Mcl-1), a basic regulator of survival, was evidently reduced. After the treatment of chamaejasmine B, the expression of X Linked Inhibitor of Apoptosis Protein (XIAP) in A549 cells was decreased, indicating that Chamaejasmine B might induce double strand breaks (DSBs), activate apoptosis pathway, and produce anti-proliferation effect in A549 cells. Chamaejasmine B and neochamaejasmin C could be used as candidates for effective treatment of cancer [77]. *S. Chamaejasme* extracts ESC and ESC-2 possessed significant inhibitory effects on tumor cells NCI-H157 and NCI-H460 *in vitro*, with the order ESC-2 > ESC. ESC and ESC-2 greatly increased the apoptotic rate and caspase -3, -8 enzyme activities in NCI-H460 cells. ESCs had no significant effects on expression of Fas and Fas-L proteins, but TNF-α/TNFR1 protein expression significantly changed in NCI-H460 cell after treatment with ESC and ESC-2 [78].

4.1.3 Antigastric cancer activity

Diterpenoid compound gnidimacrin of *S. Chamaejasme* had a strong inhibitory effect on human gastric cell Kato-III. The IC_{50} was 0.00075 μg/mL in MTT and 0.002 μg/mL in the colony forming test of Kato-III cell under the action of the gnidimacrin; The IC_{50} was Ⅲ 0.044g/mL in MTT and 0.05μg/mL in the colony forming test of Kato-III cell under the action of the adriamycin. Revealed that gnidimacrin had stronger inhibition of gastric cancer [79]. The multidrug resistance of cell line SGC7901/ADM could be reversed by SCLA. After adding 0.25 mg/mL adriamycin (ADM) (final concentration), the accumulation of ADM was significantly increased in the control group of SGC7901/ADM cells ($P < 0.05$); and the expression of p-gp in the SCLA group was significantly lower than that in the control group ($P < 0.05$), suggesting that SCLA of 0.25 mg/mL could partly reverse the drug resistance of SGC7901/ADM cells to ADM, with the ratio of 2.54 times. The mechanism might be related to downregulation of the p-gp expression of SGC7901/ADM cell membrane, increasing of the intracellular ADM concentration, and activation of the apoptosis signaling pathways of caspase protein family [80].

4.1.4 Anti-bladder cancer activity

The mice were given different doses of SCLA orallly, the serum was collected at different times and was exposed to human T24 bladder cancer cells cultured *in vitro*. The medicated serum collected after 2h of intragastric administration significantly reduced T24 cell proliferation,

but the proliferation inhibition was weaker after collection of 1h and 3h, which might be associated with different SCLA concentrations in the serum due to incomplete absorption [81]. SCLA could inhibit proliferation, promote apoptosis and lower the expression of survivin protein in bladder cancer T24 cells in a concentrations and time-dependent manner [82]. SCLA also inhibited proliferation of biu-87 human bladder cancer cell (biu-87) and promoted apoptosis by restraining the expression of b-celllymphoma/leukemia-2 (bel-2) proteins. Furthermore, with the increase of drug concentration and the extension of time, the inhibitory effect on biu-87 cells was more obvious [83].

4.1.5 Anti-leukemia activity

SCLA had a significant inhibitory effect on the growth and colony formation in P388 cells *in vitro* as SCLA significantly inhibited the growth of tumor cells at the concentration of 2 $mg \cdot mL^{-1}$ [84]. The medicated mice serum of SCLA (5–20 $g \cdot kg^{-1}$) markedly inhibited the proliferation of leukemia K562 cells, induced the morphological changes and DNA changes in K562 cells. The apoptotic rate was positively correlated with the dose of SCLA [85]. SCLA medicated serum evidently reduced cell viability and clone formation rate in mice leukemia L_{1210} cells it also showed stronger proliferative inhibition in tumor cells, this direct inhibition of cancer cell proliferation and DNA synthesis is an important anticancer approach [86]. The ethanol extract of *S. chamaejasme* induced autophagy in chronic leukemia cells K562. After 72h of treatment at concentrations of 0.002–0.5%, the cell growth was inhibited dose dependently from 20 to 70% compared to the control group. 70% of autophagosome formation inhibition was detected after 24h of treatment with 0.2% extract treated cells, while the inhibitory rates were 35% and 18%, respectively, at the extract concentrations of 0.02% and 0.002%, suggesting that the anticancer effect of *S. Chamaejasme* could be related to induction of autophagy in malignant cells [87].

4.1.6 Anti-breast cancer activity

Breast cancer is the second killer of womenand it is worth noting that more than 90 percent of patients with breast cancer were found to have tumor metastasis [88] with a significant mortality of 80% [89]. SCLA displayed a dose-dependent cytotoxic effect on drug resistant cells (Mcrophge Colony Stimulting Fctor/Adriamycin) MCF-7/ADM. SCLA inhibited the MCF-7/ADM cell growth rate up to 95% at the concentration of 0.25 mg/mL and SCLA reversed the resistance of MCF-7/ADM cells to ADM up to 2.53 times ($P < 0.05$). The mechanism was probably related to reduction in the expression of the p-gp in the cell membrane and increase in the drug concentration of ADM in the cells, suggesting that SCLA is of great clinical value in treatment of breast cancer with refractory, recurrent and MDR high expression [90]. Chamaejasmine inhibited the proliferation of breast cancer mda-mb-231 cells by restraining G2/M and inducing cell apoptosis. It reduced the levels of WAF1/p21, kip1/p27, cycloelement A, cycloelement B_1, cell dependent kinase (CDK) 2 and cdc2 in mda-mb-231 cells. The nuclear translocation, phosphorylation of NF-κb, activation of IKKα and IKKβ and degradation of IκBα were also suppressed by Chamaejasmine [91]. The known TGF-beta blockers exert little selectivity on its functions, indiscriminately causing the anti-metastatic and pro-growth effects. Under such circumstances, specifically rebalancing the oncological function of TGF-beta provides a crucial oncotarget against metastasis. Chamaejasmin B (CHB) extracted from *S. Chamaejasme* suppressed the migration and invasion in breast cancer cells *in vitro*. Moreover, by dynamical quantification of breast cancer progression using small-animal imaging system, CHB was proved to be a potent inhibitor of metastasis with minimal toxic side effects. CHB efficiently blocked TGF-beta induced EMT, disrupted the interaction between β3 integrin-TβRII complexes and consequently resulted in the selective inhibition of FAK/Src/p38 pathway. It was not the universal blocker for TGF-beta. In contrast, the cytostatic effect of TGF-beta was significantly activated by CHB treatment, and as such, CHB re-balanced the functional output of "TGF Paradox" in tumor microenvironment. Collectively, owing to targeting TGF-beta Paradox, CHB could be a promising candidate for metastatic intervention [92].

4.1.7 Anti-MDR activity

Multidrug resistance (MDR) is a major barrier to the effectiveness of cancer chemotherapy and finding new anti-MDR drugs is an important way to overcome resistance to cancer drugs [93]. CHB could inhibit the growth of the sensitive and drug-resistant cell lines *in vitro*, while the average resistance factor (RF) of CHB was only 1.26. In addition, CHB showed good anti-MDR activity in xenograft mice KB and KBV200 cancer cells. Subsequent studies have shown that CHB resulted in the blockage of g0/g1 cell cycle and apoptosis in KB and in resistant KBV200 cancer cells. CHB had no influence on the level of Fas/FasL and activation of procaspase 8. However, CHB-induced apoptosis was dependent on the activation of caspase -9 and -3. Moreover, CHB treatment was responsible for the elevation of the Bax/Bcl-2 ratio, attenuation of mitochondrial membrane potential (ΔΨm), and release of cytochrome c and apoptosis-inducing factor from mitochondria into cytoplasm both in KB and KBV200 cells. CHB had good anti-MDR activity *in vitro* and *in vivo*, and the underlying mechanism might be related to activation of mitochondrial apoptosis pathway. Currently there were no effective MDR reversal agents used in clinical treatment, and these findings for MDR treatment provide a new potential [94].

4.2 Antibacterial activity

Human pathogenic bacteria include escherichia coli, staphylococcus aureus, candida albicans trichophyton rubrum, trichophyton gypseum, microsporum gypseum, epidermophyton floccosum and others. The ethyl acetate extract of *S. Chamaejasme* had inhibitory effects on common bacteria and fungi at 33.33 g/L concentrations with bacteriostatic ring diameter up to 12.02 mm in the bacteria group and up to 9.4 mm in the fungus group [95]. The antibacterial active substance was also found in the ethanol extract of *S. Chamaejasme*, the inhibitory effect on sclerotinia sclerotiorum, phytophthora capsici, alternaria solani and strawberry grey mould fungus were better. The antibacterial rates were all over 50%, specifically more than 80% for phytophthora capsici. Plant fungicide of natural origin which are safe to human and livestock, have many advantages, such

as little environmental pollution, tough induction of drug resistance, easy degradation, etc. So looking for the bacteriostatic active substance from plants is one of the hot spots of development new fungicide, thus it is necessary to investigate *S. Chamaejasme* [96] further. The inhibitory effect of the ethyl acetate extract of *S. Chamaejasme* on the growth of magnaporthe oryzae was highly significant. The deformation of mycelium was observed under inverted microscope, and the cytoplasmic agglutination, separation of plasmolysis and organelle degradation were also found under transmission electron microscope. The acetate extract of *S. Chamaejasme* had a strong inhibitory effect on the germination and emergence of the rice blast spores, which could control the incidence of magnaporthe oryzae [97]. The ethanol extract of *S. Chamaejasme* leaf enlarged the diameter of staphylococcus aureus up to 12.8 mm and the diameter of trichomycosis gypsum up to 12.0 mm at 100 mg/mL concentration, which was better than dichloromethane extract. The extract of *S. Chamaejasme* had stronger inhibitory activity against trichomycosis gypsum when compared to staphylococcus aureus. The extract might inhibit or interfere with the synthesis of bacterial cell walls to achieve the bacteriostatic effect [98].

4.3 Anti-HIV activity

The MeOH extract stelleralide A−C from *S. Chamaejasme* were found to be high in anti-HIV activity with EC_{90} values of 0.50, 0.56, and 0.66 nM, respectively. They also demonstrated relatively low cytotoxicity (IC_{50} 5.1, 4.4, and 4.7 μM). Structurally, these three compounds differ only in the C-13 ester substituent [10]. The petroleum ether extract of roots of *S. Chamaejasme* named stelleralides F−H, gnidimacrin, and pimelea factor all exhibited extremely potent anti-HIV activity, with EC_{50} values were 0.93, 0.73, 0.98, 0.06, and 1.1 nM respectively and selectivity index values of more than 10 000. Structurally, the main difference between the most potent compound was in ring A, suggesting that the importance of a cyclopentane ring A for optimal anti-HIV activity [99**]**.

4.4 Antiepileptic and anticonvulsant activity

Epilepsy is a chronic paroxysm group with abnormal electrical activity of nerve cells and patients need lifelong treatment in order to effectively control the condition. Traditional western medicine can't effectively control the seizures, and furthermore patients have to tolerate the toxic side effects of the drugs for long periods of time. The acetone extract of *S. Chamaejasme* (AESC) had anti-convulsive effects on various acute and chronic experimental epilepsy models. AESC could increase the rat cortical convulsion thresholds of electrical stimulation (TLS) after gavage of 384 mg/kg and intraperitoneal injection of 174 mg/kg, and the effect lasted for 7−10 d. In comparison, the effect of magnesium valproate injection duration is only 8h. AESC had a dose-dependent antagonistic effect on mice auditory convulsion (As), maximum electroconvulsive convulsion (MEs), and pentazole convulsions (MET), with ED_{50} of the anti-AS, anti-MES and anti-MET 103.05, 123.83 and 132.01 mg/kg, respectively. AESC was also able to antagonise the marine alginate convulsions of the rats, significantly reducing the wet sample shivering (WDS) ($P < 0.05$), and effectively extending the convulsion latency ($P < 0.05$). AESC was effective in many animal convulsion models, displaying long duration and high antiepileptic spectrum. Its action properties were similar to the magnesium valproate [100]. *S. Chamaejasme* acetone extract had strong antagonistic effect on the rats' maximal electroshork seizure test (MES), tetrazole convulsion experiment (MET) and threshold in a localized seizure (TLS) model, and the treatment index reached up to 14.9 for the acetone extract with reduced toxicity. A promising antiepileptic drug with strong anticonvulsive effect and slight toxicity can possibly be developed from the acetone extract of *S. Chamaejasme* [101].

4.5 Anti-inflammatory activity

S. Chamaejasme ethanol extract (SCE) displayed healing and anti-inflammatory effects on the full-thickness skin defect of the Sprague Dawley (SD) rats. *In vivo*, the wound size was reduced and epithelial cells were also improved after SCE treatment. *In vitro*, SCE could induce the migration of keratinocyte cells by regulating the chain cells, extracellular signal regulation kinase and Akt signaling pathway. SCE also increased the mRNA expression of I and III collagenin Hs68 fibroblasts and inhibited the release of inflammatory mediators NO, prostaglandin E2 (PGE2) and mRNA expression in the original 264.7 macrophages. SCE enhanced the activity of black keratinocytes and promoted the healing of skin wounds in SD rats [24].

4.6 Immunocompetence

S. Chamaejasme polysaccharide (RXLDDT) could improve the inhibitory effect of cyclophosphamide (CTX) on immune function in mice. After continuously intragastric administration of RXLDDT 0.4–2 $g \cdot kg^{-1}$ for 7 days, the mice thymus weight increased significantly. Feet pad delay hypersensitivity reaction stimulated by Sheep Red Blood Cell (SRBC) increased by 52.2%–183.0% and the proliferation of splenic lymphocytes increased by 94.6%–274.1% in Con A-stimulated mice. The phagocytosis of macrophages in mice was also significantly enhanced. RXLDDT could improve the nonspecific immunity, cell-mediated immunity and humoral immune function of mice treated with cyclophosphamide (CTX) [102]. *S. Chamaejasme* aqueous extract and alcohol extract could significantly inhibit the proliferation of T lymphocytes induced by the Con A. The ear swelling of Delayed Type Hypersensitivity (DTH) mice was significantly inhibited by the alcohol extract of *S. Chamaejasme*. Moreover the high concentration of alcohol extract was effective in inhibiting the index of animal thymic gland. The levels of interleukin-2 (IL-2) and interferon-γ (IFN-γ) in the laboratory animal serum were also markedly decreased. Therefore *S. Chamaejasme* could suppress cellular immunity by inhibiting activation of T cells and secretion of cytokines [103].

4.7 Insecticidal activity

Chemical pesticides pose a a health and environmental challenge and and It is imperative to develop biorational pesticides for human, livestock and environmental safety. The insecticidal activity of *S. Chamaejasme* has been well established. The root of *S. Chamaejasme* was grinded into fine powder, and then placed it in the ditch to kill the underground

pests, such as armyworm and fly. The bioactive analysis for the asian corn borer by *S. Chamaejasme* displayed that the death of the larvae was due to the toxicity and anti-feeding effect of the drug [104]. *S. Chamaejasme* had contagious and systemic toxicity to the hawthorn spider mite. Many plants have been proved to be of insecticidal properties, but only a few had acaricidal activity. *S. Chamaejasme* has the potential to become plant pest control agent however, further research is needed in this area [105].

5. TOXICITY

S. Chamaejasme is a poisonous plant with the root being the most toxic. Cattle and sheep are prone to poisoning by accidental consumption of this plant. It Can cause vomiting, abdominal pain, diarrhea, limb weakness, whole body spasm, heart palpitations, and hyperthyroidism. In severe cases, collapse or convulsion of death can take place and in addition it can cause miscarriage if the female livestock comes into contact with *S. Chamaejasme*. Human contact can result in allergic dermatitis And its pollen can induce a strong and persistent spicy irritation to the eyes, nose and throat [106]. Therefore contact with *S. Chamaejasme* with must be kept to a minimum and managed carefully..

The LD_{50} value was 184.3 g/kg of SCLA, and SCLA was found to be almost nontoxic [84]. The LD_{50} value was 2.08 g/kg of ethanol extract of *S. Chamaejasme*, the mice were shown to be physically weak, curled up all over their bodies, twitched, struggled and even died, revealing that the drug was somewhat toxic [107]. The total extract of *S. Chamaejasme*, petroleum ether extract of *S. Chamaejasme*, ethyl acetate extract of *S. Chamaejasme* and n-butyl alcohol extract of *S. Chamaejasme* were subjected to acute toxicity experiments. These proved that that the ethyl acetate extract displayed the highest toxicity under the same dose of different polar parts, and the LD_{50} of the ethyl acetate extract was 4.66 g/kg.. These experiments also indicate that the the toxicity of different extracts of *S. Chamaejasme* are different [108]. No toxicity was found when neochamaejasmin B (until 156.25 μM) was added to madin-darby canine kidney (MDCK) and MDCK-human multidrug resistance gene 1 (hMDR1) cells for 3h. However its cytotoxicity was detected after 40 hours of continuous culture by MTT analysis (respectively n=3, 4), the IC_{50} was 20.60 $\mu mol \cdot L^{-1}$ for MDCK cells and 210.9 $\mu mol \cdot L^{-1}$ for MDCK-hMDR1 cells [109].

6. CONCLUSION

The flavonoids, coumarins, terpenoids, lignans and other chemical components have been isolated from *S. Chamaejasme*. Many of these monomer compounds have anticancer, antivirus, immunomodulatory, anti-inflammatory and other pharmacological activities. Therefore, it is possible to study the structure-activity relationship of these monomer compounds to find the lead compounds. In recent years, some more advanced extraction and separation technology, such as solid Phase extraction (SPE) and high-speed countercurrent chromatography (HSCCC), has been applied in the field of natural products, and one can apply this advanced technology for extraction and separation of chemical constituents of *S. Chamaejasme*. This will not only increase the separation efficiency, but also enhance the chance of discovery of new compounds. However the current pharmacological research of *S. Chamaejasme* has only been conducted in the evaluation of the pharmacodynamics of extracts and compounds, the direct mechanism of action and the targets need to be further explored. Although *S. Chamaejasme* is widely distributed, has a large density, is abundant and easy to obtain, the active constituents should be synthesized and developed. These compounds can then be evaluated for their pharmacological activities and in doing so will also protect the natural resources and be ecologically friendly. This synthetic approach will rationally utilize the natural resources and fully exploit the medicinal value of *S. Chamaejasme*.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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