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REVIEW

Therapeutic Potential of Chamaejasmine: An Important Anticancer Metabolite of *Stellera Chamaejasme L.*

Chamaejasmine'in Terapötik Potansiyeli: Stellera Chamaejasme L. Bitkisinin Önemli Bir Antikanser Metaboliti

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Abstract

Human illnesses and secondary complications have long been treated with phytomedicine. The majority of herbal drugs were composed of numerous elements of medicinal plants that had therapeutic benefit for human health conditions. *Stellera chamaejasme* L., contains chamaejasmine as an important phytochemical. Chamaejasmine has potent pain-relieving potential and exerted antitumor activity. Scientific data about chamaejasmine pharmacological properties and therapeutic applications have been collected from a variety of scientific research databases. Additionally, scientific information has been gathered and examined to determine the advantageous function of chamaejasmine. Further, chamaejasmine has also been analyzed for their anticancer potential against cancerous disorders. Present review scientific data described the therapeutic effectiveness of chamaejasmine against cancers. Chamaejasmine scientific data also signified its biological potential in terms of its anti-cancer activity against osteosarcoma, breast cancer, cervical cancer, lung adenocarcinoma, hepatocellular carcinoma, larynx carcinoma, atopic dermatitis and glioblastoma. Present review also described pharmacokinetic parameters of chamaejasmine with its effectiveness on multidrug resistance. The present scientific data pertaining to review studies could be used to investigate the health beneficial aspects of chamaejasmine for their anticancer activity in the future.

Keywords: Anti-cancer; Atopic dermatitis; Breast cancer; Cervical cancer, Chamaejasmine; Glioblastoma; Hepatocellular carcinoma; Larynx carcinoma; Lung adenocarcinoma; Osteosarcoma; Pharmacokinetic

The Stellera is an important genus in herbal medicine and comprised more than of 10–12 species and better examples are *Stellera chamaejasme* L. and *Stellera formosana* Hayata ex Li. *Stellera chamaejasme* L., which is also called "Rui-Xiang-Lang-Du" in traditional Chinese medicine.[1–3] *Stellera chamaejasme* L., a perennial herb belonging to the Thymelaeaceae family is widely distributed in Nepal, China, Russia and Mongolia. *Stellera chamaejasme* L.

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roots have been widely used for the treatment of tuberculosis, psoriasis, inflamed lymph nodes, chronic tracheitis, skin ulcers, and diarrhea. *Stellera chamaejasme* have wound healing properties, anti-inflammatory, anti-bacterial, anti-viral, analgesic, cytotoxic, and anti-tumour potential.[4–10] *Stellera chamaejasme* contain significant amounts of lignans, diterpenes, and biflavonoids. However, other phytochemicals, including biflavonoids neochamaejasmin B, neochamaejasmin C, C-3/C-3″-biflavanone, chamaejasmenin B, isochamaejasmenin C, isochamaejasmenin B, were isolated from the root of *Stellera chamaejasme*.[11] The roots of *Stellera chamaejasme* L. has been utilized as a pesticide to control different types of pests on crops, and pastures against maggots, bugs, and flies. *Stellera chamaejasme* L. methanolic extract showed significant antitumor activities.[12–14] Biological effects of *Stellera chamaejasme* on microvascular density and apoptosis of cancer cells in rat bladder tumor models have been investigated. *Stellera chamaejasme* has a good therapeutic effect on rat bladder cancer, which may inhibit the progression of bladder cancer by inhibiting micro-angiogenesis and inducing the apoptosis of bladder.[15] Hollow fiber tumor model were used to evaluate the inhibitory and proapoptotic effects of *Stellera chamaejasme* L. extracts and found that *Stellera chamaejasme* L. extracts had inhibitory effects on tumor cells.[16] Methanol extract of *Stellera chamaejasme* L. was assessed for antitumor activity against murine leukemia P388 *in vivo*. The bioassay-directcd separation of the extract furnished seven diterpene compounds, including two biflavanone compounds neochemae-jasmin A and B.[17] In the current review, we have examined the medicinal importance of chamaejasmine by reviewing the literature on the pharmacological activity of chamaejasmine, after compiling all scientific data pertaining to the chamaejasmine. Therefore, the purpose of this review was to provide readers with a comprehensive explanation of the molecular mechanisms, pharmacological activity, and therapeutic importance of chamaejasmine.

Methods

The goal of this review is to discuss the scientific evidence about the pharmacological activities and therapeutic potential of chamaejasmine in order to determine its biological role in medicine. In order to explore the biological potential of chamaejasmine, this review uses relevant research articles from a number of scientific sources, including Science Direct, Google Scholar, and PubMed. The search criteria include scientific terms and terminology such as phytochemical, cancer, chamaejasmine, and herbal medicine. The authors also discuss the molecular mechanism of chamaejasmine in order to understand their pharmacological activity. Out of the 123 scientific articles, this review cited 38 well reviewed scientific papers and review articles.

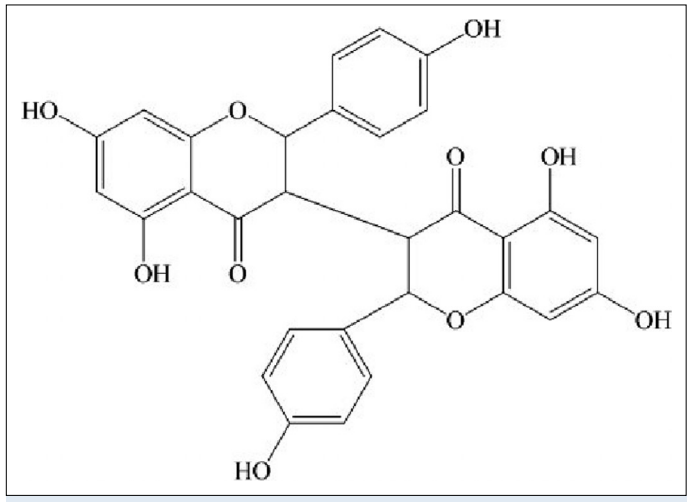

Figure 1. Chemical structure of chamaejasmine.

An Overview of Chamaejasmine

Chamaejasmine (Fig. 1) is one of the most significant phytochemical of *Stellera chamaejasme* L., which has been shown to have potent anti-proliferative effects on human osteosarcoma cells. Furthermore, by blocking the PI3K/Akt signaling cascade, chamaejasmine can also cause HeLa cells to undergo apoptosis.[18] In many animal models, chamaejasmine shown anti-inflammatory, analgesic, and anti-tumor effects. In a mouse model of atopic dermatitis (AD) produced by DNCB, chamaejasmine, which was isolated from *Wikstroemia dolichantha* Diels, was found to be beneficial.[19] Significant aldose reductase inhibitory capability was demonstrated by chamaejasmine that was isolated from the root of *Stellera chamaejasme* L.[20] Strong anticancer effects on osteosarcoma, human breast, lung, and laryngeal cancer cells were demonstrated by chamaejasmine.[21] Flavonoids, including 7,7′′-di-O-β-D-glucosyl-(–)-chamaejasmin has been isolated from *Ormocarpum kirkii*.[22] The detection of chamaejasmine in the extracts of *Stellera chamaejasme* has been accomplished by ultrafiltration liquid chromatography and mass spectrometry.[23] For the simultaneous measurement of chamaejasmine in rat plasma, an ultra-high liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) technique was employed.[24] *Wikstroemia dolichantha* was found to contain flavonoids, including

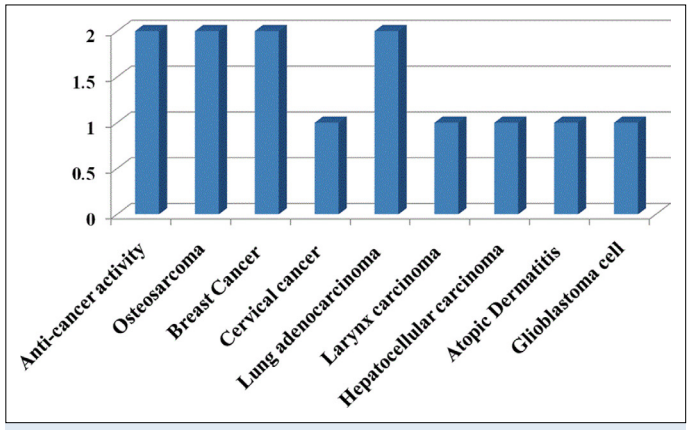

Figure 2. Anticancer potential of chamaejasmine in medicine.

chamaejasmine, according to HPLC-DAD/QTOF-MS analysis.[25] Based on the existence of chamaejasmine in their chemical composition, scientists have examined the variety in the *Stellera chamaejasme* population.[26] Human HEP-2 epithelial cells may be inhibited by chamaejasmin A, which may also stop the cell cycle, trigger apoptosis, and prevent nuclear NF-κB translocation in human breast cancer cell lines MDA-MB-231.[27]

Anticancer Activity of Chamaejasmin

Anti-Cancer Activity

Biological potential of chamaejasmin A for their anticancer activity has been investigated through different cell lines (CAL-27, UMSCC-1, UMSCCG19, HEP-2 and Vero cells). Chamaejasmin A showed significant anticancer activity against HEP-2 cells. Chamaejasmin A interacts with the binding site located at the top of β-TB.[28] Biological potential of chamaejasmine for their cytotoxic potential against several human cancer cell lines (MCF-7, A549, SGC-7901, HCT-8, HO-4980, Hela, HepG2, PC-3, LNCap, Vero and MDCK) have been investigated in order to know its anticancer potential. Chamaejasmine revealed significant anticancer activity than taxol against PC-3 cells.[29]

Osteosarcoma

The biological potential of chamaejasmine has been investigated in MG-63 cells by MTT assay in order to know its effects on the cellular proliferation, apoptosis, and autophagy. Chamaejasmine revealed pro-apoptotic and pro-autophagic effect and cellular growth inhibition in MG-63 cells which could be used for the treatment of osteosarcoma (OS).[13] Chamaejasmine revealed significant anti-proliferative potential on human osteosarcoma cells and also induced apoptosis in MG63 cells.[30]

Table 1. Biological source of chamaejasmine

S. No.	Biological source	Reference
1.	*Stellera chamaejasme*	[11, 20, 23, 24, 26]
2.	*Wikstroemia dolichantha*	[19, 25]
3.	*Ormocarpum kirkii*	[22]

Breast Cancer

Biological potential of chamaejasmine B extracted from *Stellera chamaejasme* L., has been investigated for its anti-angiogenic potential on breast cancer. Chamaejasmine B significantly suppressed the neovascularization potential in tumor-HUVEC co-culture model.[31] Biological potential of chamaejasmine has been investigated in the human breast cancer cell line, MDA-MB-231. Chamaejasmine treatment of MDA-MB-231 cells resulted in decrease in cyclins A and cyclins B1 and induction of WAF1/p21 and KIP1/p27, which suggested that chamaejasmine could be used as a chemotherapeutic agent for the treatment of breast cancer.[14]

Cervical Cancer

Biological potential of chamaejasmine isolated from *Stellera chamaejasme* L. on cervical cancer cells has been investigated in cervical cancer. Chamaejasmine was found to have potent antitumor potential on cervical cancer cell lines. Further, chamaejasmine could also induce apoptosis in HeLa cells, which could be mediated through the suppression of PI3K/Akt signaling cascades.[21]

Lung Adenocarcinoma

The biological potential of chamaejasmine on A549 human lung adenocarcinoma cells has been investigated. Chamaejasmine inhibited the growth of A549 cells and arrested the cell cycle in the G2/M phase and induced apoptosis. Chamaejasmine nduced Bax expression and also inhibited Bcl-2 expression which signified its cytotoxic potential towards A549.[32] In another scientific study, chamaejasmine also induced apoptosis in A549 cells through increasing the caspase-3, Bax/Bcl-2 ratio, and activating the Fas/FasL.[33]

Larynx Carcinoma

The biological potential of chamaejasmine on human HEp-2 larynx carcinoma cells have been investigated in order to investigate its effectiveness on larynx carcinoma. Chamaejasmine was found to show significant anticancer activity against NCI-H1975, HEp-2, SKOV-3, PC-3, and HT-29. Moreover, chamaejasmine also significantly inhibited HEp-2. Chamaejasmine significantly induced caspase-9 and caspase-3.[12]

Table 2. Molecular mechanism of chamaejasmin

S. No.	Biological activity	Molecular mechanism	Reference
1.	Anti-cancer	Chamaejasmin A possesses anti-cancer properties relating to β-TB depolymerization inhibition.	[28]
2.	Osteosarcoma	Chamaejasmine promotes apoptosis and autophagy by activating AMPK/mTOR signaling pathways with involvement of ROS in MG-63 cells. Chamaejasmine induced apoptosis in MG63 cells. chamaejasmine possesses anti-cancer properties relating to β-tubulin depolymerization inhibition.	[13, 29, 30]
3.	Breast cancer	Chamaejasmine treatment of MDA-MB-231 cells resulted in induction of WAF1/p21 and KIP1/p27, decrease in cyclins A and cyclins B1.	[14]
4.	Cervical cancer	Chamaejasmine could induce apoptosis in HeLa cells, and this apoptosis-inducing effect may be mediated through the suppression of PI3K/Akt signaling cascades.	[21]
5.	Human lung adenocarcinoma	Chamaejasmine inhibited Bcl-2 expression and induced Bax expression to desintegrate the outer mitochondrial membrane and causing cytochrome c release. It increasing the Bax/Bcl-2 ratio, caspase-3 and activating the Fas/FasL.	[32, 33]
6.	Hepatocellular carcinoma (HCC)	Chamaejasmenin E inhibited HCC cells. Furthermore, chamaejasmenin E caused oxidative stress and mitochondrial malfunction, which ultimately resulted in cellular death.	[34]
7.	Larynx carcinoma	Chamaejasmine significantly induced caspase-9 and caspase-3 activity. In vivo, chamaejasmine intake through gavage resulted in inactivation of Akt and induction of apoptosis in HEp-2 tumors.	[12]
8.	Atopic dermatitis	Chamaejasmine inhibited DNCB-induced increases in total IL-4 and IgE levels in serum, improved skin barrier function, and increased epidermis moisture.	[35]

TB: β-tubulin; AMPK: Adenosine 5'-monophosphate-activated protein kinase; HCC: Hepatocellular carcinoma; ROS: Reactive oxygen species; DNCB: Dinitrochlorobenzene.

Hepatocellular Carcinoma

The ability of five identified biflavones from *Stellera chamaejasme* root to inhibit hepatocellular carcinoma (HCC) Hep3B cells has been assessed *in vitro*. Of these biflavones, chamaejasmenin E showed the most potent inhibitory action. Additionally, chamaejasmenin E may inhibit HCC cells' capacity to migrate as well as proliferate and form colonies. Furthermore, chamaejasmenin E caused oxidative stress and mitochondrial malfunction, which ultimately resulted in cellular death. At the same time, chamaejasmenin E decreased the c-Met downstream proteins in HCC cells. In a tumor xenograft model, chamaejasmenin E is effective and non-toxic, and it has demonstrated an underlying tumor-suppressive mechanism.[34]

Atopic Dermatitis

Biological effectiveness of chamaejasmine isolated from *Wikstroemia dolichantha* on AD-like skin lesions has been investigated in a DNCB-induced murine model of AD to know its effectiveness on atopic dermatitis. Chamaejasmine attenuated the clinical symptoms of DNCB-induced dermatitis in the topical administration. In addition, 0.5% chamaejasmine also inhibited DNCB-induced increases in total IgE levels and IL-4 in the serum.[35]

Glioblastoma Cell

Biological potential of chamaejasmine isolated from *Stellera chamaejasme* L. for their anti-glioblastoma (GBM) have been investigated. 216 potential targets associated with GBM were identified, including chamaejasmine in the *Stellera chamaejasme* L.[36]

Multidrug Resistance

The fundamental mechanisms of chamaejasmin B anti-multidrug resistance (MDR) properties have been studied. Chamaejasmin B suppressed the development of cell lines. Additionally, chamaejasmin B demonstrated positive anti-MDR efficacy in xenograft mice of KB and KBV200 cancer cells. Later research revealed that chamaejasmin B caused apoptosis and G0/G1 cell cycle arrest in resistant KBV200 cancer cells as well as KB cells. However, the activation of caspase 3 and caspase 9 was necessary for the apoptosis produced by chamaejasmin B. The stimulation of the mitochondrial-dependent intrinsic apoptotic pathway may be one of the underlying reasons for chamaejasmin B strong anti-MDR efficacy, both *in vitro* and *in vivo*. These results offer a new MDR therapy leading drug and new evidence for the possible use of chamaejasmin B in MDR therapy clinical trials for cancer.[37]

Pharmacokinetic Study

A sensitive and selective ultra-high liquid chromatography -tandem mass spectrometry (UPLC-MS/MS) method was developed and validated for the simultaneous determination of five flavonoids, including chamaejasmine of *Stellera chamaejasme* L. in rat plasma. The validated method was successfully applied to a pharmacokinetic study of five flavonoids in rats after oral administration of *Stellera chamaejasme* L.[24]

Conclusion

The scientific information on chamaejasmine was collected from a variety of research databases. The current review discussed chamaejasmine possible medicinal uses. In the current review, the specific pharmacological actions of chamaejasmine have been examined for their anticancer potential against various types of cancer disorders. The biological role of chamaejasmine against several malignant illnesses was demonstrated by the scientific facts presented in this review. Scientific data of chamaejasmine in the present review signified its anti-cancer potential against osteosarcoma, breast cancer, cervical cancer, lung adenocarcinoma, larynx carcinoma, hepatocellular carcinoma, atopic dermatitis and glioblastoma (Fig. 2). The present review also described the pharmacokinetic parameters and its effectiveness on multidrug resistance. Furthermore, chamaejasmine natural occurrence and its molecular mechanisms were also described in Table 1 and Table 2. The scientific information provided in this review will be helpful in understanding the health benefits of chamaejasmine for the future creation of a novel family of anticancer medications.

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