

# Inhibition of invadopodia formation by diosgenin in tumor cells (Review)

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Received February 27, 2020; Accepted July 15, 2020

DOI: 10.3892/ol.2020.12148

**Abstract.** Diosgenin is a type of steroid extracted from the rhizome of *Dioscorea* plants. In traditional Chinese medicine, *Dioscorea* has the effect of ‘eliminating phlegm, promoting digestion, relaxing tendons, promoting blood circulation and inhibiting malaria’. Recent studies have confirmed that diosgenin exhibits a number of pharmacological effects, including antitumor activities. Through its antitumor effect, diosgenin is able to block tumor progression and increase the survival rate of patients with cancer; ultimately improving their quality of life. However, the mechanism underlying its pharmacological action remains unclear. Once tumor cells reach a metastatic phase, it can be fatal. Increased migration and invasiveness are the hallmarks of metastatic tumor cells. Invadopodia formation is key to maintaining the high migration and invasive ability of tumor cells. Invadopodia are a type of membrane structure process rich in filamentous-actin and are common in highly invasive tumor cells. In addition to actin, numerous actin regulators, including cortical actin-binding protein (Cortactin), accumulate in invadopodia. Cortactin is a microfilament actin-binding protein with special repetitive domains that are directly involved in the formation of the cortical microfilament actin cell skeleton. Cortactin is also one of the main substrates of intracellular Src-type tyrosine protein kinases and represents a highly conserved family of intracellular cortical signaling proteins. In recent years, great progress has been made in understanding the role of Cortactin and its molecular mechanism in cell motility. However, the diosgenin-Cortactin-invadopodia mechanism is still under investigation. Therefore, the present review focused on the current research on the regulation of invadopodia by diosgenin via Cortactin.

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*Key words:* diosgenin, invadopodia, Cortactin, tumor metastasis

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## 1. Introduction

Cancer is one of the leading causes of mortality worldwide, it was estimated that 14.1 million new cancer cases and 8.2 million cancer mortalities occurred in 2012, worldwide (1,2). Metastasis is the most dangerous stage in the occurrence and development of cancer (3). Clinically, numerous patients with malignant tumors present with metastases at the time of diagnosis (4). Therefore, the prevention and suppression of tumor metastasis is a critical issue that requires attention.

Tumor metastasis is a complex, multifactorial dynamic process (5). Tumor metastasis involves the activation and interaction of complex signaling pathways in the tumor micro-environment, the invasion and survival of tumor cells in the blood circulatory system or lymphatic circulatory system, and the proliferation of tumor cells at target-shifting sites (6).

Invadopodia is an important structure formed in cancer metastasis, therefore, it is considered promising to investigate the suppression of cancer metastasis from the perspective of inhibiting invadopodia. In addition, the topic concerning traditional Chinese medicine, including diosgenin suppressing cancer metastasis through inhibiting invadopodia has been paid more attention. The present review will discuss and summarize the potential molecular mechanism of diosgenin inhibiting the formation and function of invadopodia.

## 2. Formation and function of invadopodia

Several studies have demonstrated that invadopodia are formed in the early stages of invasion and metastasis of tumor cells (7,8). The invadopodium is an essential structure that is

involved in the invasion and metastasis of cancer cells (9). The invadopodium is a type of special membrane structure process that is rich in actin and involved in the degradation and remodeling of the extracellular matrix (10). Electron microscopy has revealed that invadopodia are slender, protruding structures (11).

The formation of invadopodia is generally divided into three stages (Fig. 1): i) formation of the core of the invadopodia precursor ii) stabilization of the invadopodia precursor and iii) maturation of the invadopodia (12). The core of the invadopodia precursor is formed by neural Wiskott-Aldrich syndrome protein (N-WASP), the Arp2/3 complex and cofilin recruitment around the actin-Cortactin complex (7). The core can be formed in a few seconds, but it is unstable (13). After the core is formed, tyrosine kinase substrate with 5 SH3 domains (Tks5) rapidly binds the core (within ~20 sec) (14). Tks5 mediates the binding of the precursor complex to PI(3,4)P2 located on the cell membrane to stabilize the precursor structure (14-16). Lamellipodin protein causes the MenaArg-SH2-domain-containing 5 inositol phosphatase (SHIP2) complex (Mena is a well-known cytoskeleton regulator that regulates the assembly of actin filaments and modulates cell adhesion and motility by interacting with Lamellipodin) (17) to be recruited as a precursor (15,16). SHIP2 promotes the production of PI(3,4)P2, which is beneficial for fixation of the precursor to the cell membrane and stabilization of precursors. Cofilin and Arp2/3 complexes mediate two different actin aggregation pathways, the cooperation of which greatly enhances further aggregation of actin (18). Actin polymerization then prolongs and forms the invadopodia, resulting in increased matrix metalloproteinase (MMP) content, degraded extracellular matrix and invadopodia maturation (12,14,19).

In other words, to break through the barrier of the extracellular matrix, tumor cells need to extend cellular protrusions, which reconstruct and degrade the extracellular matrix (13). These types of cell protrusions are essential for the ability of tumor cells to break through the basement membrane and vascular wall (10,13). The protruding structures (protrusions) formed by invasive tumor cells on one side of the basement membrane are the invadopodia, which are rich in actin regulatory proteins, adhesion molecules, signaling or receptor proteins, cell membrane recombinant proteins, and matrix proteolytic enzymes (10,13,19-23). Invadopodia are involved in the process of tumor cell invasion through the basement membrane as follows: i) The structure forms first, and then the invadopodia perforate the basement membrane; ii) the invadopodia then elongate and extend through and beyond the basement membrane; and iii) finally, the invadopodia lead to the migration of tumor cells (19).

As invadopodia are so important for cancer metastasis, an improved understanding of the formation of and regulatory mechanism controlling invadopodia is critical. Research results in this field are expected to provide new therapeutic targets and directions for tumor treatment.

### 3. Antitumor effects and mechanisms of diosgenin

Research on the effects of artemisinin against malaria by Youyou Tu (24) won the 2015 Nobel Prize in Physiology or Medicine. Therefore, the discovery of natural products from traditional Chinese medicine may be beneficial for the development of, and investigation into, innovative drugs for other diseases.

Diosgenin (Fig. 2) (25) is a type of steroid extracted from the rhizome of *Dioscorea* (26-28), it is the hydrolysate of dioscin and is abundant in *Dioscorea* (27,28). Its multiple pharmacological effects have been confirmed in previous studies; it has been demonstrated to exhibit antitumor (27,29,30) and anti-inflammatory activity (27,29,30), as well as improving cardiovascular function (27), lowering blood lipids (29,30), regulating immunity (27,29), and inhibiting platelet aggregation (31). Diosgenin can also decrease visceral injury and protect visceral organs, including the liver (29,30), kidney (29), brain (29) and gastrointestinal tract (29,30). Diosgenin represents an important raw material for the synthesis of various steroid drugs (27). Research has revealed that the toxicity and side effects of diosgenin are low (29,32).

Diosgenin inhibits the metastasis of various cancers, such as prostate (28,30,33-36), gastric (30,36-38), lung (39,40), breast (30,41), liver (30), renal (30) and colon (41) cancer, and melanoma (29). Diosgenin inhibits metastasis in multiple types of cancer primarily by suppressing constitutively-activated pro-inflammatory and pro-survival signaling pathways and factors (42), such as NF- $\kappa$ B-associated pathways (28,42,43), focal adhesion kinase (FAK)-associated pathways (44), p38/mitogen-activated protein kinase (MAPK) signaling pathways (42,45), and Src (46). Further studies have also found that diosgenin inhibits other functions in tumorigenesis, including tumor cell proliferation, apoptosis, epithelial-to-mesenchymal transition and angiogenesis (33,47-51). Shishodia and Aggarwal (42) revealed that diosgenin inhibits the invasion of human lung cancer H1299 cells via suppressing TNF-induced NF- $\kappa$ B activation. Li *et al* (28) found that diosgenin induces the expression of Src homology 2 phosphatase 2 (SH-PTP2), thus blocking the STAT3-associated signaling pathway, and also that it inhibits the development of human hepatocellular carcinoma. Diosgenin was demonstrated to inhibit tumor growth in both MDA-231 and MCF-7 xenografts *in vivo* by inhibiting Akt, the Raf/MEK signaling pathway and NF- $\kappa$ B activity to induce apoptosis (40,52,53). Therefore, diosgenin may be a potential option for the treatment of cancer (27,29,34,35,37,39).

### 4. Structure and regulation of Cortactin

Cortical actin-binding protein (Cortactin) has been demonstrated to be associated with cancer. Previous studies have demonstrated that Cortactin is upregulated in a variety of tumors, such as breast cancers and head and neck tumors (54,55). It is involved in a variety of cell activities, including invadopodia formation and cell adhesion, invasion, migration and division (54,56).

Human Cortactin is encoded by the CTTN gene (formerly known as the EMS1 gene), which is located on chromosome 11q13 (57). Cortactin protein has three main domains: i) The N-terminal acidic region (NTA); ii) filamentous actin (F-actin) repetitive domain (ABR) and iii) the SH3 domain in the C-terminal (54,58) (Fig. 3). The NTA binds with Arp in the Arp2/3 complex and can also regulate the polymerization and shrinkage of F-actin (54,56,58). The ABR is responsible for the binding of Cortactin to F-actin (58). The function of Cortactin is also regulated at the ABR via post-translational modifications (56,58). A study by Uruno *et al* revealed that

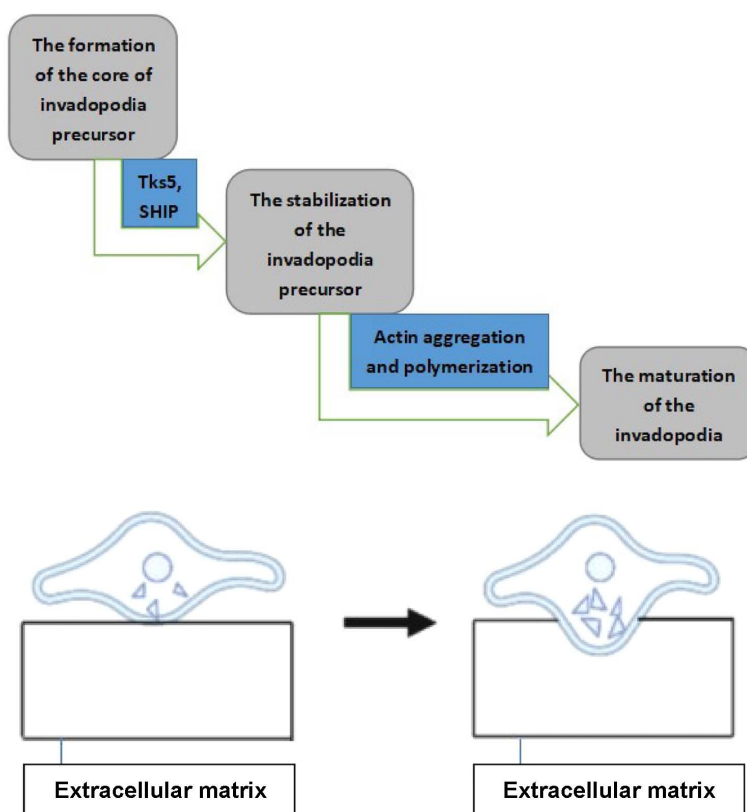


Figure 1. (A) Formation of invadopodia can be divided into three stages. (B) Schematic diagram of the formation and maturation of invadopodia. (created in BioRender.com).

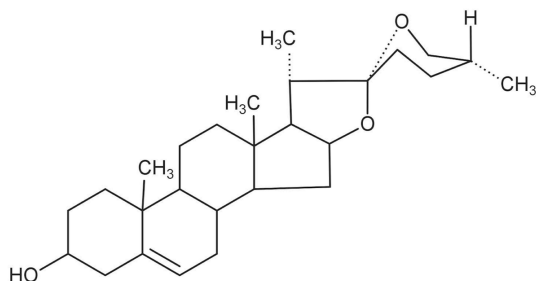


Figure 2. Chemical structure of diosgenin (25). (created with KingDraw).

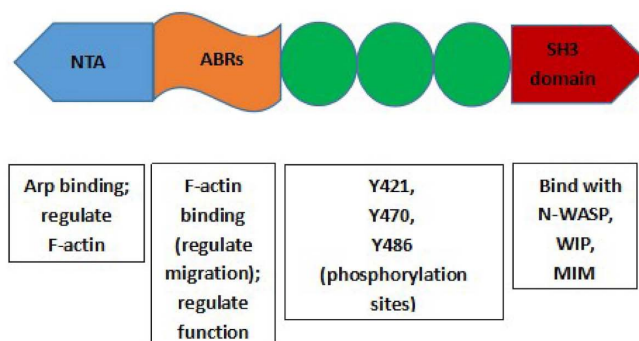


Figure 3. Cortactin consists of parts including NTA, ABRs, phosphorylation sites and SH3 domain (main expression of mentioned parts). NTA, N-terminal acidic region; ABRs filamentous actin repetitive domain; F-actin, filamentous actin; N-WASP, neural Wiskott-Aldrich syndrome protein; WIP, WASP binding protein; MIM, missing in metastasis.

the number of repeats in the ABRs determines the affinity of Cortactin to F-actin, as well as its ability to regulate cell migration (57). The SH3 domain is a conserved protein module found in various signaling proteins that mediates the interaction with various other proteins, such as neural Wiskott-Aldrich syndrome protein (N-WASP) (59), WASP binding protein (WIP) (60) and missing in metastasis (MIM) (61). The tyrosine phosphorylation of Cortactin is usually associated with the SH3 domain or proline-rich domain-binding proteins (58). The molecular structure of Cortactin changes after phosphorylation, bringing the SH3 domain closer to the SH3 binding protein, increasing the chances of binding (54,58). Cortactin is the main substrate of the Src family tyrosine kinases, and tyrosine phosphorylation serves an important role in the assembly of cortical microfilament actin (54). Cortactin phosphorylation via Src kinase is required for invadopodia formation mediated by

Cortactin (62,63); that is, the Src family tyrosine kinases may promote cell migration via the phosphorylation of Cortactin.

Cortactin and its associated proteins perform functions in the cortical areas associated with cell membrane deformation and the actin cytoskeleton; in pseudopods and cell wrinkles, these proteins enhance the formation and/or stability of dendritic actin networks (64).

### 5. Role of Cortactin in invadopodia formation and function

Invadopodia formation requires numerous proteins (65,66). Cortactin is an actin-binding protein that is closely

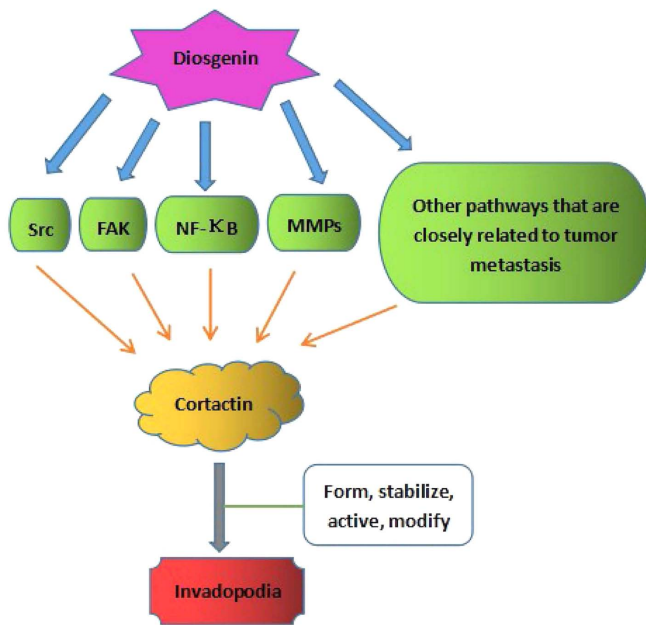


Figure 4. Potential diosgenin-Cortactin-invadopodia mechanism. FAK, focal adhesion kinase; MMPs matrix metalloproteinases; MAPK, mitogen-activated protein kinase.

associated with invadopodia through its interaction with other proteins (67). Cortactin is key for invadopodia formation and interacts with various proteins, such as Arp2/3, N-WASP, and F-actin (7,65,68). Furthermore, Cortactin activates and stabilizes the phases of branched actin assembly via the Arp2/3 complex of invadopodia (69-71). In addition, Cortactin can increase the endurance of invadopodia and promote molecular adhesion and cell movement (72,73).

Previous studies have reported that Cortactin phosphorylation is associated with the rate of cell migration in a number of different types of tumor cell (54,55,74,75). The upregulation of Cortactin promotes the formation of invadopodia, the degradation of the extracellular matrix and the invasiveness of cancer cells (54,61,76). Cortactin is positively correlated with tumor invasiveness and metastasis and is closely associated with the synaptic membrane structure of tumor cells (54,55,61,76).

Other studies have demonstrated that Cortactin binds the Arp2/3 complex and N-WASP and regulates the formation of invadopodia via the Nck1-N-WASP/Arp2/3 signaling pathway (76,77). WASP family proteins can induce the rearrangement of actin molecules in cells by activating Arp2/3 and thus promote the rapid formation and maturation of invadopodia (78). Genna *et al* (79) revealed that the tyrosine kinase Pyk2 activates Abl-related gene (Arg) through the EGFR-Pyk2-Src-Arg-cortactin signaling pathway, and directly or indirectly mediates the phosphorylation and polymerization of Cortactin induced by epidermal growth factor (EGF). This results in invadopodia actin polymerization, invadopodia maturation and enhanced invasion of breast cancer cells.

Overall, the aforementioned studies indicate that Cortactin serves a pivotal role in the formation of invadopodia and the degradation of the extracellular matrix to promote cancer cell migration and invasion.

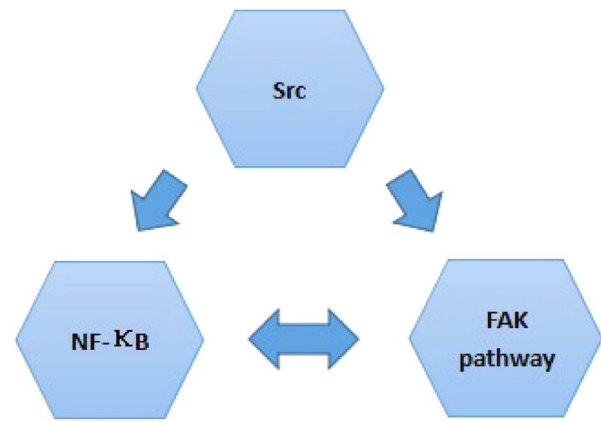


Figure 5. Interactions between NF- $\kappa$ B, the FAK pathway and Src. FAK, focal adhesion kinase.

## 6. Potential diosgenin-Cortactin-invadopodia mechanism

Invadopodium is a convergence point for a number of signals that regulate tumor cell behaviors, particularly systemic dissemination and metastasis (13). Cortactin is the switch that mediates invadopodia formation (54,55,67,74,75,80). It is regulated by numerous signaling pathways and factors, including the FAK pathway (81), Src (82), NF- $\kappa$ B (54,55), and other pathways that are closely associated with tumor metastasis (54,55,74,75,80). Several studies have reported that diosgenin is closely associated with the FAK pathway, Src, NF- $\kappa$ B and MMPs (43,83). A potential mechanism of action underlying diosgenin-Cortactin-invadopodia is presented in Fig. 4.

In prostate cancer, diosgenin inhibits MMP expression and, therefore, cancer metastasis (33), while MMP expression promotes cortactin, and both MMPs and cortactin are required for form and function of invadopodia (84). This suggests that the potential mechanism of diosgenin involves the downregulation of MMPs, and inhibition of Cortactin and invadopodia, ultimately inhibiting prostate cancer metastasis. It has also been demonstrated that diosgenin downregulates the NF- $\kappa$ B signaling pathway, thus inhibiting the metastasis of prostate cancer, suggesting another mechanism: Downregulation of the NF- $\kappa$ B signaling pathway results in inhibition of Cortactin, and hence, inhibition of invadopodia (33). In addition, diosgenin can inhibit colon cancer metastasis via regulating the Akt/MAPK signaling pathway (85), while Akt can activate Cortactin (86,87), thus suggesting that diosgenin downregulates the Akt/MAPK signaling pathway, which inhibits Cortactin and hence, inhibits invadopodia, resulting in inhibition of colon cancer metastasis. It was also reported that diosgenin can activate the p38 and JNK pathways and thus inhibit Cortactin in colon cancer (88), suggesting that diosgenin inhibits the formation and function of invadopodia via the downregulation of Cortactin via activating the p38 pathway (89). In breast cancer, it was revealed that diosgenin downregulates Akt, thus inhibiting the metastasis of breast cancer (40,90), similar to the mechanism in colon cancer. Diosgenin can serve as a dual inhibitor of the MEK/ERK and PI3K/Akt signaling pathways to overcome tyrosine kinase inhibitor resistance, resulting in clinical benefits for lung cancer treatment (91). Furthermore, diosgenin downregulates

the NF- $\kappa$ B-p65/p50 and p38-MAPK pathways and attenuates acute lung injury in mice (92). In human erythroleukemia, diosgenin inhibits the NF- $\kappa$ B signaling pathway and thus suppresses metastasis (43).

Diosgenin inhibits the activity and amount of transcription factor NF- $\kappa$ B (40,93), and can also inhibit the function of the FAK pathway (FAK is a regulator of cell migration, proliferation, survival and transcription) (44). In addition, it was found endothelial-cell FAK is required for DNA-damage-induced NF- $\kappa$ B activation (94). It was revealed that NF- $\kappa$ B activation can activate the FAK pathway, which is activated via FAK phosphorylation (95,96). Tyr397 is the main phosphorylation site of FAK; in addition to its autophosphorylation, Tyr397 can also interact with the SH2 domain of Src family proteins (97,98) to activate other phosphorylation sites, thus promoting the activation of the signaling pathway downstream of the FAK pathway and causing migration and invasion of tumor cells (97,99-101). Furthermore, Src promotes NF- $\kappa$ B transcriptional activity (102-104), and Src and FAK also serve as a signaling pathway, whereby Src promotes the FAK pathway activity (99-101). The interactions between Src, NF- $\kappa$ B and the FAK pathway are presented in Fig. 5. It was also revealed that diosgenin can decrease the activities of MMP-2 and MMP-9, and the two combined with NF- $\kappa$ B form an axis (105-108). Inhibiting MMP-2/-9 can suppress the activity of AKT/NF- $\kappa$ B in HeLa cells (107), while suppressing NF- $\kappa$ B can also down-regulate MMPs in nude mice which are injected HepG2-HBx cells (108,109). This suggests that the diosgenin mechanism of action may be extensive, involving multiple pathway links that are very complex.

## 7. Clinical application of diosgenin

On the basis of its various functions, diosgenin has been used medicinally to treat a number of diseases and improve several physiological functions. Diosgenin has been applied in many cases, such as treating inflammation (27,29,30), improving cardiovascular function (27), lowering blood lipid levels (29,30) and regulating immunity (27,29,30).

Traditionally, diosgenin was used for the treatment of various symptoms such as cold hands and feet (by its function of activating blood), loss of appetite caused by diseases including cancer, and frequent urination (by its function of protecting kidney) (27,29,30). Currently, diosgenin is widely used for the treatment of cardiovascular diseases (110,111). Several extensive clinical cases (particularly for cardiovascular diseases) have validated diosgenin as a drug for treating diseases (110). In addition, certain studies have demonstrated that psychobehavioral interventions of traditional Chinese medicine can benefit patients with cancer by multiple roles, such as decreasing functional impairments, leading to pain relief, easing depression, decreasing time to flatulence following surgery and improving sleep quality (112).

Several traditional Chinese medicines, such as artemisinin (113,114), Danshen (113,115), glossy Ganoderma (116), and Huangqi (117,118), have been used as anticancer therapies, and as being used as supplementary anticancer drugs and psychobehavioral interventions (112-118). This suggests the potential for diosgenin as a traditional Chinese medicine in clinical antitumor use.

At present, the incidence rate of some kinds of cancers in certain areas is increasing, such as colorectal cancer in Latin America, Asia, Eastern Europe, breast cancer in low-income countries, gastric cardia cancer in the United States and many European countries (119-121), besides, cancer remains a serious threat to human health and mortality (1). Cancer is often discovered in the late stages, and in the majority of cases, the primary cancer has metastasized into adjacent lymph nodes and other sites (3). Diosgenin, as a main component of a traditional Chinese medicine, has a suppressing effect on tumor metastasis. Numerous anticancer drugs that are currently used have toxic side effects, and certain types of cancer develop resistance to the drugs to a certain extent (30). Diosgenin may have the capability of avoiding these shortcomings (30,110).

The clinical use of diosgenin as an anticancer treatment requires further study and testing. Given the multiple pathways and various targets of diosgenin, future research should investigate its potential function in cancer inhibition.

## 8. Conclusions and prospects

Diosgenin may act on: i) Src by inhibiting its phosphorylation ii) the FAK pathway by inhibiting the expression of associated molecules and activation of the pathway; and iii) NF- $\kappa$ B by inhibiting its level and activity, in addition to other pathways. Furthermore, Src, the FAK pathway and NF- $\kappa$ B have inter-relationships. The inhibition of diosgenin on Src, the FAK pathway and NF- $\kappa$ B has a negative effect on the main switch Cortactin, thus inhibiting invadopodia formation in various cancer cells.

Future studies should examine the mechanism of diosgenin inhibition of invadopodia formation to suppress the metastasis of primary tumors. These findings will aid subsequent clinical applications, particularly pharmaceutical use.

## Acknowledgements

Not applicable.

## Funding

The present study was supported by Jilin University, (Changchun, China; grant nos. 2017QNYB016 and 201910183200) and the Department of Education of Jilin Province (Changchun, China; grant no. 2016456).

## Availability of data and materials

The data used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

## Authors' contributions

YL completed the collection and analysis of relevant literature and wrote the first draft of the manuscript. DW, XM and XW participated in the analysis and collation of the literature. HL, LH and HX critically analyzed the relevant literature and the manuscript structure. JZ revised the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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