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Research Progress on the Anti-tumor Effects of Euphorbia Humifusa

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1. Abstract

Euphorbia Humifusa is commonly known as ground spurge, contains various compounds such as flavonoids, triterpenes, coumarins, sterols, tannins, and phenolic acids. It exerts a wide spectrum of properties including anti-bacterial, anti-inflammatory, antioxidant, anti-viral, hypoglycemic, and anti-tumor. In this article, we focus on the antitumor effects of Euphorbia humifusa and its active constituents, providing evidence for further research on this medicinal herb.

2. Introduction

Euphorbia Humifusa was first recorded in Song dynasty's "Jiayou Bencao." It is a dried whole herb of Euphorbiaceae family, also known as ground spurge or spotted spurge. In the book "Jiayou Bencao," it is described as a plant that grows near fields and is particularly superior in the Chuzhou area. The stems are slender and creep on the ground, red in color, with green-purple leaves. It grows vigorously in midsummer and blooms with red flowers in June, followed by small fruits. The plant is collected by taking the seedlings. EHH has a pungent taste, a neutral property and flavor, and belongs to the lung, liver, stomach, large intestine, and bladder meridians. It exerts excellent anti-bacterial, anti-inflammatory, anti-oxidant, anti-viral, hypoglycemic, and anti-tumor properties (Figure 1). Euphorbia humifusa is widely distributed with abundant resources, making it a frequently-used medicinal herb in China, best harvest in summer and autumn. Made by removing impurities, spraying with water, slightly moistening, cutting into sections, and drying through sun exposure [1]. Studies have shown that the main constituents of Euphorbia humifusa are flavonoids, triterpenes, coumarins, sterols, tannins, and phenolic acid compounds [1,2]. It contains a large number of anti-tumor compounds, including ellagic acid, suillin, arbutin, apigenin, luteolin, β-sitosterol, gallic acid, quercetin, and kaempferol, etc [3]. Currently, there is growing achievements in the extraction of Euphorbia humifusa and its anti-tumor mechanisms. In this article, we provide a brief review of the anti-tumor mechanisms of Euphorbia humifusa in order to guide its clinical application.

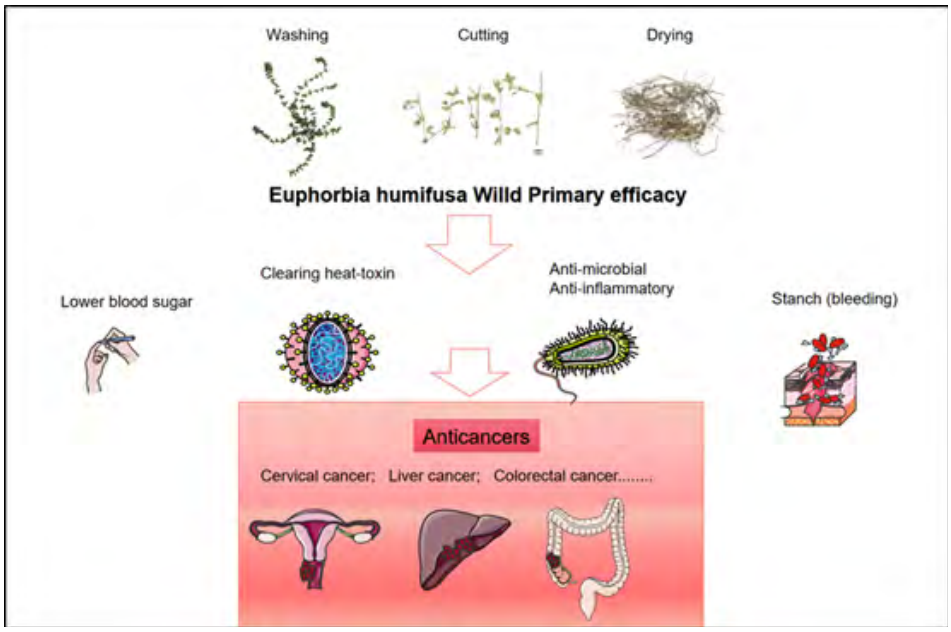

Figure 1: Groundnut, family Euphorbiaceae, has antibacterial, anti-inflammatory, antiviral, antioxidant, hemostatic, hypoglycemic, and anticancers effects,For example :Cervical cancer,Liver cancer,Colorectal cancer and so on.

3. Active Constituents of Euphorbia Humifusa

3.1. Flavonoids

Through the process of ultrasound-assisted reflux extraction and macroporous resin adsorption, Wang Shuping, Zhang Jianchao, and Jiang Chao [4-6] et al obtained total flavonoids from the aqueous extract of Euphorbia humifusa, including apigenin-7-O-glucoside, luteolin-7-O-glucoside, quercetin-3-O-arabinoside, quercetin, and kaempferol (Table 1). Wang Jinjun [7] used reversed-phase high-performance liquid chromatography to determine four flavonoid compounds in Euphorbia humifusa, which were similar to the aforementioned compounds. Cao Naifeng [8], isolated seven compounds from Euphorbia humifusa using silica gel column chromatography, including four flavonoids, three sterols, and triterpenes, identified as genistein, β-sitosterol, and palmitic acid. Further research revealed that flavonols have anti-tumor effects by inducing apoptosis of tumor cells in U14 cervical cancer mice, inhibiting S phase and G2/M phase retardation, and downregulating the expression of cyclin D1 [9].

3.2. Sterols and Triterpenes

Pei Yingge [10] separated the ethanol extract of Euphorbia humifusa using silica gel column chromatography (CC), preparative thin-layer chromatography (prep-TLC), and recrystallization, obtaining 35 compounds, including triterpenes, sterols, their glycosides, sesquiterpenes, (iso)coumarins, organic acids, glycerides, and long-chain alcohols. The structures of 28 of these compounds were identified, including 2 newly discovered compounds. Liu Runhui [2] etc used silica gel column chromatography to isolate 5 compounds from the aqueous extract of Euphorbia humifusa, including β-sitosterol, 4 sterols and triterpenes, which were identified as genistein, cycloart-23E-en-3β, 25-diol, cycloart-23E-en-3β, 25-diol, cycloart-25-ene-3β, 24-diol, and 1-glycerinhexadecylate (Table 1).

3.3. Tannins and Phenolic Acids

Tian Ying [11] et al employed polyamide, macroporous resin, Sephadex LH-20, and MCI GEL CHP20P chromatographic methods to isolate 7 phenolic compounds from the ethanol extract of Euphorbia humifusa, identifying them as shortleaf suillin, shortleaf suillin acid, shortleaf suillin methyl ester, sanguisorbic acid dilactone, 3,3'-dimethoxyellagic acid, and tannic acid. Li Hui [12] et al used high-performance liquid chromatography and ultraviolet-visible spectrophotometry, separated phenolic acid components from Euphorbia humifusa, including gallic acid, tannic acid, and shortleaf suillin (Table 1).

3.4. Lactones and Other Chemical Constituents

Hasierdun et al isolated lactones and coumarins, such as scopoletin, umbelliferone, trimaseranin, alkaloids, pyrrolidinones, unsaturated fatty acids, vitamins, inositols, palmitic acid-alpha-glyceride, (3R,6R,7E)-4,7-diene-3-hydroxy-9-violetone, 1-palmitoylglycerol, palmitic acid-alpha, alpha'-diglyceride, 1-palmitoyl-3-linoleoyl-sn-glycerol, and docosanol, from the ethyl acetate extract of Euphorbia humifusa [12] (Table 1).

Table 1: The main components of grass are flavonoids, sterols and phenolic acids and other compounds.

Classify	Compounds	Species	References
Flavonoids	Quereetin	Euphorbia humifusa Willd, Euphorbia maculate, Euphorbia thymifolia	(Wang, WU and Meng, 2007, Zhang, 2009, Jiang, 2008) (Wang and Zhang, 2009) (Cao, 2011) (Wang and Hu, 2023)
	Kaempferol		
	Apigenin 7-O-glucoside		
	Luteolin-7-O-glucoside		
	Quercetin 3-O-alpha-L-arabinoside		
	Lupeol		
	Daucosterol		
	Apigenin		
	Luteolin		
Steroid	β-sitosterol	Euphorbia humifusa Willd, Euphorbia maculate, Euphorbia thymifolia	(LIU and KONG, 2005, Pei, 2007)
	Legast-4-en-3-one		
Organic acids	Methylgallate	Euphorbia humifusa Willd, Euphorbia maculate, Euphorbia thymifolia	(Tian and Sun, 2010, Li, Xu, Xu, Guan, He and Wang, 2012)
	ellagic acid		
	geraniin		
	brevifolin carboxylic acid		
	3,4,5-trihydroxybenzoic acid		
	Palmitic acid		
	coumalic acid、Protocatechuic acid、linolenic acid		
	sanguisorbic acid dilactone		
Others	Scopolamine	Euphorbia thymifolia	(Hasi and Wuzhang, 2017)
	7-Hydroxycoumarin		
	Euparin.5(6)-gluten-3α-ol.alnincanol		
	MonopalMitin		

4. Anti-tumor Research of Euphorbia Humifusa

4.1. Cervical Cancer

Through the establishment of a U14 cervical cancer mouse model, Geng Guoxia (Hasi and Wuzhang, 2017)et al obtained the aqueous extract of Euphorbia humifusa using decoction and found Euphorbia humifusa could effectively inhibit tumor growth and the expression of P53 protein, induce cell cycle arrest at the G2/M phase, and subsequently induce apoptosis (Figure 2B). Similarly, Wang Peijun (Wang and Hu, 2023) et al also discovered that flavonol, one of the active components of Euphorbia humifusa, could effectively inhibit tumor growth in U14 cervical cancer mice, promote the upregulation of P16, Caspase-8, and Caspase-3, lead to cell apoptosis, and inhibit the expression of Cyclin D1. This may be achieved by modulating the Bcl-2/Bax ratio, promoting the release of cytochrome C, and initiating the mitochondrial-dependent pathway, thereby activating caspase cascade on the cell membrane and activating caspase-3, resulting in tumor cell apoptosis (Figure 2A).

4.2. Liver Cancer

By establishing a subcutaneous H22 hepatoma mouse model, Wang Xiaomin [13] et al treated Euphorbia humifusa at different concentrations via oral gavage and found that it significantly inhibited tumor growth, increased the spleen index, elevated the IL-2 level, activated T cells, and enhanced immune response against tumors (Figure 2D). Similarly, Zou Zhijian [14,15] found that oral administration of Euphorbia humifusa effectively suppressed tumor growth, increased serum SOD levels, decreased serum MDA levels, activated Caspase-3 enzyme activity, and induced tumor cell apoptosis. Euphorbia humifusa also reduced the expression of VEGF and MMP-9 proteins in tumor tissue (Figure 2E), thereby reducd tumor angiogenesis and matrix degradation. Hu Jianxin [16] et al further investigated and found that Euphorbia humifusa significantly downregulated CD31 expression in H22 hepatoma tumor tissue, inhibited the expression of NF-κB, TNF-α, VEGF mRNA (Figure 2C), and thus may reduce tumor neovascularization and weaken the expression of inflammatory factors in tumor tissue (Figure 2).

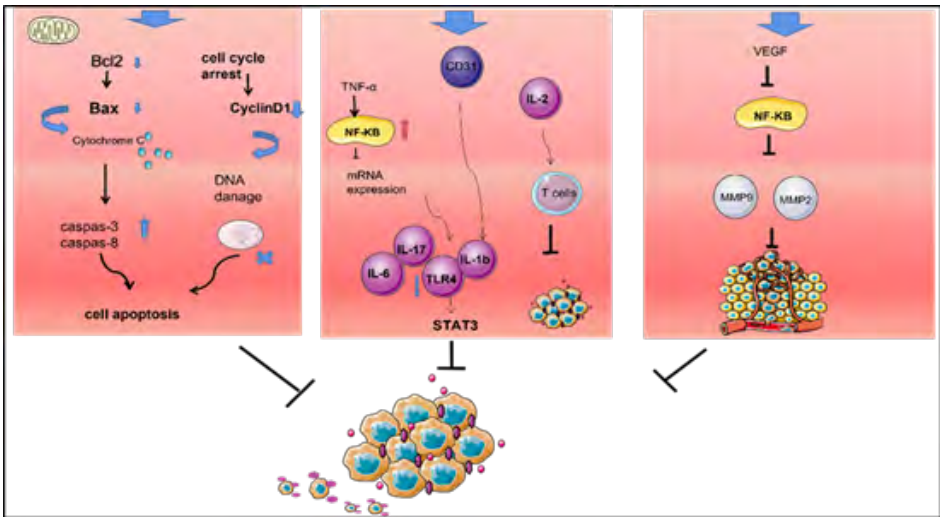

Figure 2: A. Digitonin may inhibit the release of cytochrome C through the mitochondrial pathway by inhibiting Bcl-2 and Bax, and activate caspase-3,causing apoptosis of tumor cells; B. Inhibit the expression of CyclinD1 in the cell cycle, which leads to DNA damage and apoptosis; C. Digitonin was able to down-regulate the level of CD31, inhibit the NF-κB, TNF-α, VEGF, mRNA expression, attenuate inflammatory factors IL-17, IL-6, IL-1b, TLR4, and inhibit STAT3 signaling pathway; D. Digitonin was able to improve immunity, enhance IL-2 level, activate T cells, and thus activate Caspase-3 to induce apoptosis in tumor cells; E. Digitonin was able to reduce VEGF in tumor tissues, inhibit NF-κB, and thus inhibit MMP-2, MMP-9 protein expression, to reduce tumor angiogenesis and matrix degradation may inhibit tumor.

4.3. Colorectal Cancer

By inducing colorectal cancer in mice using azoxymethane/dextran sulfate sodium (AOM/DSS), Wu Nawei (Hu, et al., 2018) et al administered Euphorbia humifusa at different concentrations via oral gavage after successful modeling. They found that Euphorbia humifusa may exert its anti-tumor effects by inhibiting endoplasmic reticulum stress and downregulating the expression of ATF4, CHOP, and Xbp1s, suppressing the expression of inflammatory factors IL-1β, IL-17, IL-6, and TLR4, and modulating the miR-17-5p-mediated STAT3 signaling pathway (Figure 2C). Fan Hongge [17] et al treated the human colon cancer cell line SW480 with ethanol extract of Euphorbia humifusa and found that it could downregulate MMP2/9 and regulate the expression of circRHOT1/miR-29a-3p axis through negative regulation of miR-29a-3p by circRHOT1 (Figure 2E), thereby inhibiting the proliferation, migration, and invasion of SW480 cells.

5. Anti-tumor Research on Major Constituents of Euphorbia Humifusa

5.1. Quercetin

Quercetin is a flavonoid compound derived from plants. Studies have shown that quercetin can upregulate Bax, caspase-3, and p21 to regulate cell apoptosis, while downregulating Akt, PLK-1, cyclin-B1, cyclin-A, CDC-2, CDK-2, and Bcl-2 to control cell apoptosis [18]. It can modulate p53, NF-κB, MAPK, JAK/STAT, PI3K/AKT, and Wnt/β-catenin pathways, inhibit the activity of ncRNAs, regulate the expression of miRNAs, and exhibit anticancer properties by inhibiting tumor proliferation, invasion, and metastasis [19] (Figure 3A). Quercetin has been found to regulate ROS production and control tumor and cancer stemness [20]. It can also regulates oxidative stress, controls inflammation, induces immune suppressive factors, promotes immune escape of cancer cells, and prevents disease progression in pancreatic cancer [21]. It has been reported that quercetin increases the degradation of STAT3 protein in liver cancer cells and reduces STAT3 activation, thereby inhibiting the progression of liver cancer [18]. Quercetin can modulate the β-catenin signaling pathway, inhibit epithelial-mesenchymal transition (EMT) in tumor cells, and suppress tumor metastasis, reducing metastasis in triple-negative breast cancer [22]. In summary, quercetin has shown significant inhibitory effects on lung cancer, liver cancer, breast cancer, colorectal cancer, prostate cancer, and hematological malignancies, making it a promising therapeutic agent [23].

5.2. Ellagic Acid

Ellagic acid is a polyphenolic compound with anti-oxidant, anti-inflammatory, and anti-tumor properties, and it helps overcome multidrug resistance in cancer by inhibiting epithelial-mesenchymal transition (EMT) [24-26]. Studies have shown that ellagic acid can inhibit the TGF-β signaling pathway by reducing the expression of Smad2, Smad3, and Smad4, thereby increasing gemcitabine (GCB) sensitivity and overcoming GCB resistance in bladder cancer [25] (Figure 3B). Ellagic acid regulates cell proliferation and induces apoptosis by inhibiting cyclin-dependent kinase 6 (CDK6) and acts as an effective CDK6 inhibitor in breast cancer cells [27]. It inhibits mitochondrial respiration and tumor growth in lung cancer, activates AMP-activated protein kinase (AMPK), reduces the expression of HIF-1α in lung cancer cells (Figure 3B), and shows potential as a chemotherapy drug targeting mitochondrial metabolism in lung cancer [28].

5.3. Arbutin

Arbutin is a bioactive hydrophilic polyphenol compound that includes α-arbutin 4-hydroxyphenyl-α-D-glucopyranoside and β-arbutin 4-hydroxyphenyl-β-D-glucopyranoside and has been

shown to be beneficial in treating tumor diseases [29]. Research has demonstrated that β-arbutin at IC50 concentrations induces apoptosis in MCF-7 human breast adenocarcinoma cells through p53 and Caspase 3 activation [30] (Figure 3C). Arbutin generates excess ROS and disrupts mitochondrial membrane, inducing cell apoptosis, reducing inflammation and PI3K/mTOR signaling molecules, inhibiting cell adhesion characteristics of glioma cells, and exhibiting anticancer effects [31]. Additionally, it reduces the expression of IL-1β and TNF-α genes, providing a potential treatment for prostate cancer [32].

5.4. β-Sitosterol

β-Sitosterol is a major bioactive component found in plants and exhibits anti-tumor effects against fibrosarcoma, colon cancer, breast cancer, lung cancer, and prostate cancer [33,34]. It inhibits tumor cell proliferation, migration, invasion, induces G0/G1 phase arrest and apoptosis, suppresses NF-kB activity, and downregulates epithelial-mesenchymal transition (EMT) markers and AKT/GSK-3β signaling pathway (Figure 3D), thereby exerting its anti-tumor effects [35]. It has been found that β-sitosterol induces apoptosis in ovarian cancer cells and inhibits their proliferation and cluster migration. This may be attributed to the loss of pro-apoptotic signals, mitochondrial membrane potential, increased reactive oxygen species (ROS) production, and calcium influx through the endoplasmic reticulum-mitochondria axis, leading to anti-tumor effects in ovarian cancer [34].

5.5. Gallic Acid

Gallic acid is a hydrolyzable organic acid with plentiful pharmacological activities. It inhibits the growth of T24 human bladder cancer cells in a concentration and time-dependent manner, induces apoptosis, upregulates the expression of Cleaved Caspase-3, Bax, P53, and Cyt-c proteins, downregulates the expression of Bcl-3, P-PI65K, P-Akt, P-IκBα, P-IKKα, and P-NF-κB, and inhibits tumor cell proliferation, metastasis, and promotes cell apoptosis (Figure 3E). This may be closely related to mitochondrial dysfunction and inhibition of PI3K/Akt/NF-κB signaling pathway [36]. Gallic acid can also induce apoptosis in HCC1806 cells through the mitochondrial apoptosis pathway, induce ROS generation, further inhibit the PI3K/AKT/EGFR pathway, and activate the MAPK signaling pathway [37]. It has been shown to inhibit colorectal cancer by regulating ferroptosis [38], and inducing apoptosis in breast cancer cells, exerting an anticancer effect [39]. Additionally, it has been proven to be effective in combination with paclitaxel for the treatment of cervical cancer [40].

5.6. Kaempferol

Kaempferol is a common natural compound belonging to the flavonoid class. It has been reported to exhibit various anticancer activities in breast cancer, prostate cancer, bladder cancer, cervical cancer, colon cancer, liver cancer, lung cancer, ovarian cancer, leukemia, and others [41,42]. Kaempferol promotes autophagy and cell death [43], inhibits PKM5-mediated glycolysis to reverse 5-FU resistance in human colorectal cancer cells [44] (Figure 3F), and reduces oxaliplatin resistance in colon cancer treatment [45. Kaempferol shows great function as an adjuvant therapy for overcoming tumor resistance and has potential clinical applications

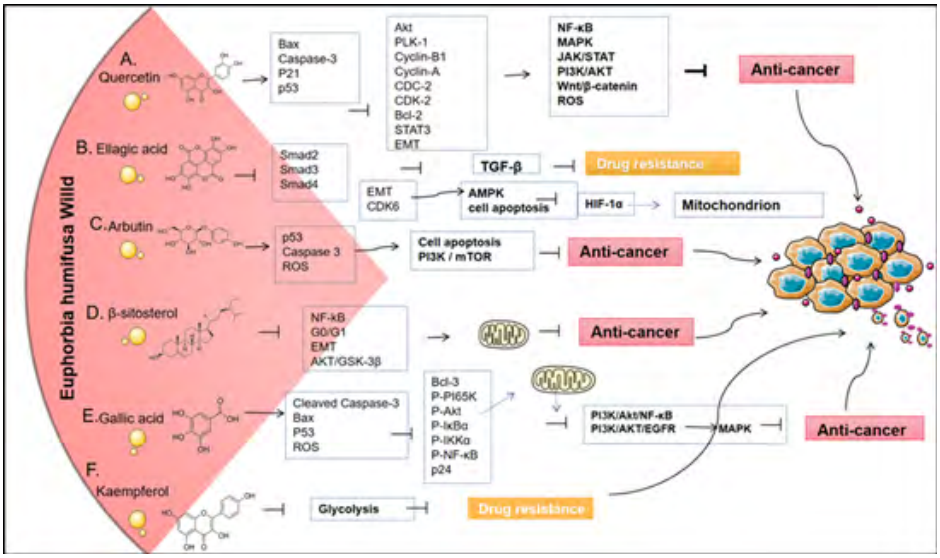

Figure 3: A. Quercetin up-regulates Bax, Caspase-3, P21, P53 and down-regulates Akt, PLK-1, Cyclin-B1, Cyclin-A, CDC-2, CDK-2 and Bcl-2 to regulate apoptosis; regulates p53, NF-κB, MAPK, JAK/STAT, PI3K/AKT and Wnt/β- catenin, inhibits ncRNA activity, and regulates miRNA expression; B. Ellagic acid reduces the expression of Smad2, Smad3, and Smad4, inhibits the TGF-β signaling pathway in vitro and in vivo; inhibits cell-cycle protein-dependent kinase 6 (CDK6)-induced apoptosis; and activates the AMPK signaling pathway; C. Arbutin induces apoptosis by activating p53 and Caspase 3 induced apoptosis; reduced inflammatory IL-1β and TNF-α and PI3K / mTOR signaling molecules; D. β-Sitosterol inhibited NF-kB activity, EMT, and activated the AKT/GSK-3β signaling pathway; E. Gallic acid up-regulated Cleaved Caspase-3, Bax, P53, and Cyt-c and down-regulated Bcl-3 , P-PI65K, P-Akt, P-IκBα, P-IKKα and P-NF-κB, p24 protein expression, inhibited tumor cell proliferation, metastasis and promoted apoptosis, inhibited PI3K/Akt/NF-κB signaling pathway and activated the MAPK signaling pathway; and regulated iron death; F. Kaempferol promoted autophagy and cell death, and inhibited glycolysis.

6. Conclusion

As a medicinal plant, Euphorbia humifusa contains various chemical constituents such as flavonoids, triterpenes, coumarins, sterols, tannins, phenolic acids, and lactones. Previous studies have demonstrated its anti-inflammatory, anti-microbial, anti-oxidant, anti-viral, hemostatic, hypoglycemic, and immunomodulatory properties. This article primarily focuses on its unique anti-tumor effects, provided certain valuable insights. The major active constituents of Euphorbia humifusa also have the potential to be utilized as adjunctive therapies in clinical treatment for various types of tumors, thus durther enhanced its their therapeutic value.

7. Funding Statement

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