

Review of the Anticancer and Cytotoxic Activity of some Species from Genus *Euphorbia*

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Summary

Euphorbiaceae is a widely spread family. To genus *Euphorbia*, from that family, belongs more than 2000 species. The plants of this genus have been used for a long time in traditional medicine. Their main active components: alkanes, triterpenes, phytosterols, tannins, polyphenols and flavanoids are supposed to be responsible for different types of activity. *Euphorbia formosana* Hayata is a medicinal plant used to treat rheumatism, liver cirrhosis, herpes zoster and it is used as tumor suppressor. *Euphorbia tirucalli* L. have been used to obtain methanolic extracts. Their cytotoxic activity have been examined against many different types of cancer cells, such as colon cancer cell line, liver cancer cell line, ovarian cancer cell line and prostate cancer cell line. Leukemic cell lines, THP-1 and HL-60, were inhibited after 24 h of treatment with 400 µg/mL *E. formosana*. *In vitro* anticancer activity assays of *E. formosana* suggest potent anticancer effects that cause both cell cycle arrest and apoptosis of leukemic cancer cells. The ethanolic extract of *Euphorbia helioscopia* L. inhibited the growth of only three cancer cell lines, Hep-2 (27%), T-47D (7%) and PC-5 (11%). Cell viability assays were conducted on the pancreatic cancer primary tumor cell line to assess the relative toxicity of the *E. tirucalli* extracts. The toxicity of both aqueous and methanolic extracts was found to be dose dependent, with cell viability decreasing with increasing extract concentration. Both extracts demonstrated similar activity at 50 µg/mL with a viability of 50%, while only the methanol extract exerted a significant decrease in cell viability at concentration of 25 µg/mL. The pronounced cytotoxic activity of these few species from the genus *Euphorbia*, suggests that it could be very interesting to investigate more deeply about their potent anticancer ability. So, the aim of this study was to make a review of the anticancer activity of some of the *Euphorbia* species that were examined experimentally, using different *in vitro* or *in vivo* assays.

Key words

anticancer effects, cytotoxic effects, *Euphorbia* spp., medicinal plants

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Received: May 20, 2018 | Accepted: July 20, 2018

Introduction

Natural products, especially medicinal plants, have played a significant role in drug discovery and development of therapeutic agents. Plants contain many biologically active compounds that have potential for development of therapeutic agents. More than 35,000 plant species have been used in various regions around the world for medical purposes (Al-Faifi et al., 2017). The Euphorbiaceae family comprises about 300 genus and 10,000 species. Euphorbiaceae is among the largest flowering plant families consisting of a wide variety of vegetative forms including trees, succulents and herbaceous plants. Some of the plants from that family are of great importance (Gupta et al., 2013). Different species of *Euphorbia* grow all over the world either wild or as cultivated. The genus *Euphorbia* is the largest genus of the medicinal plants widely distributed in China, India, Bangladesh and Pakistan (Nyeemet et al., 2017). It was reported that plants from Euphorbiaceae family are used in folk medicine against venomous bites and trichiasis, and as wart removers. Species of *Euphorbia* are characterized by high ecological amplitudes in tropical, subtropical and warm temperate regions, and they are widely spread around the world. They grow in North Africa and also in the temperate parts of Asia, but mainly in the Mediterranean region (Shaaban et al., 2018). Several plants of Euphorbiaceae family were tested for their anticancer property, but most of them have been used in traditional medicine as treatment for various human diseases. Antitumor activity against sarcoma and ascites, leukemia in mice and cytotoxic activity against certain cancer cell lines were also observed (Prakash and Gupta, 2013). Some species have been used in treatment of dermatosis, paralysis and pain of human body as well as poultice for broken bones ulceration, swelling and hemorrhoids. A number of interesting biological activity was also reported such as cytotoxic, hepatoprotective, antispasmodic, anti-inflammatory, antibacterial, antifungal, anti-mutagenic, antiviral, pesticide, molluscicidal and larvicidal activities. Interestingly, the latex of these plants have shown cocarcinogenic and anticarcinogenic activities.

Euphorbia hirta L. is an annual herb 15-50 cm high, erect or ascending, hispid with long often yellowish crisped hairs; stems usually terete; leaves often lanceolate or obovate-lanceolate, acute or subacute, serrulate or dentate, dark green above, pale beneath, base usually unequal sided acute or rounded. It is a common weed found throughout the hotter part of India and most of tropical and subtropical countries (Lin and Hsieh, 1991). The plants are characterized by the presence of milky latex. The extract of *E. hirta* has sedative effect on the mucous membrane of the respiratory and genito-urinary tract. The plant has been also used in treatment of bowel complications, worm infestations, kidney stones and as galactogogues. The whole plant has also been reported to possess anti-bacterial, anti-amoebic, anti-fungal, antiviral, spasmolytic, anti-diarrheal, sedative, anxiolytic, analgesic, anti-pyretic, anti-inflammatory, anti-malarial and anti-hypertensive properties (Nyeemet et al., 2017). One study also demonstrated that hydroalcoholic extract of *E. hirta* was effective in protecting the liver from toxic hepatitis (Brindhaet et al., 2010).

Euphorbia tirucalli L. is probably the best known and most widespread of all *Euphorbia* species. It is a shrub or a small tree endemic to tropical areas with pencil-like branches from which it derives its vernacular name, the pencil-tree. *E. tirucalli* is generally

evergreen since its stems and branches remain green all year round and are rarely fed on by herbivores (Lin and Hsieh, 1991). It bears white poisonous latex, which may possibly account for the low herbivore pressure and medicinal features (Gupta et al., 2013). The use of *E. tirucalli* latex in traditional medicine as a treatment for cancer has attracted the recent interest. However, according to Munro et al. (2015), whole plant aqueous extracts have shown interaction with antioxidant enzyme systems in human leukocytes via up-regulation of key antioxidant enzyme genes. This could lead to increased cytotoxicity, confirming the need for precise investigations considering dose and administration of *E. tirucalli* extracts for medicinal purposes (Munro et al., 2015).

Euphorbia formosana Hayata is a Taiwanese native medicinal plant. It is an herbaceous branched plant with erected glabrous stem. Leaves are sessile, linear-lanceolate, 50-120 mm long and 5-15 mm wide. They are wide, acute at the apex of the plant and attenuate at the base; glabrous on both surfaces. The inflorescence of this plant is a cyathium in terminal compound pleiochasia. Rhizomes of this species are found as characteristic subterranean parts (Lin and Hsieh, 1991). This plant have been used in treatment of rheumatism, liver cirrhosis, herpes zoster, scabies and photoaging leukemia. Hsieh et al. (2013) tried to explain the molecular targets and mechanism of action of *E. formosana* that could be responsible for its apoptotic effect on leukemic cells.

Euphorbia helioscopia L. known as sun spurge is herbaceous plant that is widely distributed in Europe, Asia and Northern Africa. The stem of *E. helioscopia* contains a milky liquid that can produce a toxic reaction on the skin and mucous membranes. The leaves are simple, lobed or unlobed, but not separated in leaflets. They are arranged alternate, one leaf per node along the stem. Flowers are radically symmetrical and petals or sepals are barely present. As a traditional Chinese medicine, *E. helioscopia* has been widely used to treat different disease conditions, such as ascites, tuberculosis, dysentery, scabies, lung cancer, cervical carcinoma and esophageal cancer. *E. helioscopia* is featured with slightly toxic and wide pharmacological effects. There are no obvious toxic effect when patient takes orally its decoction in dose of 150 g/day. Up to date, numerous studies revealed that the secondary metabolites of *E. helioscopia* included diterpenoids, flavonoids, triterpenoids, polyphenols, steroids and lipids (Cheng et al., 2015).

Anticancer and cytotoxic activity of species of genus *Euphorbia*

Euphorbia hirta L.

E. hirta contains flavonoids, terpenoids, phenols, essential oil and other compounds (Nyeemet et al., 2017). These authors have described the rich chemical composition of this plant. In the group of flavonoids, *E. hirta* contains: quercetin, quercitrin, quercitol and derivatives, rhamnase, quercetinrhamnoside, a chlorophenolic acid, rutin, leucocyanidin, leucocyanidol, myricitrin, cyaniding 3,5-diglucoside, pelargonidin 3,5-digucoside, camphol, hentriacontane, myricyl alcohol, inositol, teraxerol, friedelin, β -sitosterol, ellagic acid and kaempferol. Triterpenoids: α -amyrin, β -amyrin, friedelin, teraxerol, taraxerone, 11 α , 12 α -oxidoteraxerol, cycloartenol, 24-methylene-cycloartenol and euphorbolhexacosonate were also found in this plant (Chi et al., 2012). Other isolated terpenoids are sterols, including

β -sitosterol, campesterol, cholesterol and stigmasterol. Many tannins were present in the extract obtained from this plant: dimeric hydrolysable dehydro ellagic tannins, euphorbins A, B, C, E and terchebin; the monomeric hydrolysable tannins geraniin, 2,4,6-tri-*o*-galloyl- β -D-glucose and 1,2,3,4,6-penta-*O*-galloyl- β -D-glucose and the esters 5-*O*-caffeoyl quinic acid (neo chlorogenic acid), 3,4 -di-*o*-galloyl quinic acid and benzyl gallate. *E. hirta* L. also contains ellagic, gallic, maleic and tartaric acids. Major constituents of essential oils include: 3,7,11,15-tetra methyl-2-hexadecan-1-ol, 6,10,14-trimethyl-2-pentadecanone, hexaacanal, phytol and n-hexadecanoic acid (Nyeemet et al., 2017).

Shao-Ming Chi et al. (2012) isolated a new cyclopentanone derivative (1'R,5'R)-5-(5-carboxymethyl-2'-oxocyclopentyl)-3Z-pentenyl acetate from *E. hirta*. Based on spectroscopic analysis 1D and 2D NMR their structure were elucidated. They have also evaluated the cytotoxicity of ethanol extract against K562 (human leukemia) and A549 (lung cancer) cell lines. From their results, the ethanol extract exhibited a weak activity against A549 cells and it was inactive against K562 cells (Shao-Ming Chi et al., 2012). Sandeep et al. (2011) studied antitumor activity of *E. hirta*. They used the aerial parts of the plant to obtain ethanol, chloroform and petroleum ether extracts. All of the extracts contained tannin, saponin, alkaloids and flavonoids. Chloroform and ethanol extract enhanced mean survival time and reduced solid tumor mass in mice. According to Sandeep et al. (2011) this antitumor activity was shown due to presence of flavonoids. Ping et al. (2012) investigated the genotoxic effect of methanol extract of *E. hirta* using *Allium cepa* Assay. The extracts (125, 250, 500 and 1000 μ g/ml) were tested on root meristems of *Allium cepa* L. Ethylmethane sulfonate and distilled water served as positive and negative control, respectively. A decreased mitotic index and increased chromosome aberrations were observed as the concentrations of *E. hirta* extract increased. Some abnormalities like stickiness, mitosis, bridges and vagrant chromosomes were also observed. At interphase stage, micro nucleated cells were also observed. This result confirmed that *E. hirta* methanol extract (1000 μ g/ml) exerted a significant genotoxic and mitodepressive effect (Ping et al., 2012).

Euphorbia tirucalli L.

Gupta et al. (2013) discovered the major constituents of latex of *E. tirucalli*. They are isomers of triterpenes, such as euphol, tirucalol, cycloeuphordenol, euphorginol, amyryn, lanosterol, cycloartenol and others. Munro et al. (2015) showed the anticancer properties of tetracyclic triterpene euphol extracted from *E. tirucalli* latex. They found that this compound exhibited dose and time dependent cytotoxic effects against a significant number of cell lines, with most prominent effects against oesophageal squamous cell and pancreatic cell carcinomas. Euphol, the main constituent of the sap of *E. tirucalli*, can be extracted by ethanol. It exhibits diverse biological activities, such as anti-viral, anti-inflammatory and anti-cancer (basal cell carcinomas, leukemia and lung, prostate and breast cancers) (Chen et al., 2015).

Munro et al. (2015) examined the *in vitro* activity of extracts of *E. tirucalli* on human pancreatic cancer cell line Mia-PaCa2. They worked with methanolic and aqueous extracts of *E. tirucalli*. These extracts were obtained from grounded whole plant material (20 g) extracted by stirring in 400 mL of 80% (*v/v*) methanol for 17 h

(for methanolic extract) and 27 min (for aqueous extract) at room temperature. Cell viability was determined using the Dojindo Cell Counting Kit-8. Different concentrations of *E. tirucalli* methanolic or water extracts (200, 100, 50, 25, 12.5 and 6.25 μ g/mL) were used in their experiments in order to examine their cytotoxic activity. They concluded that toxicity of *E. tirucalli* methanolic extract was dose dependent, and cell viability was decreasing by increasing the extract concentration. Both aqueous and methanol extracts demonstrated similar activity, and by dose of 50 μ g/mL the cells resulted in viability of ~50%. The methanol extract exerted a significant decrease in cell viability even in a dose of 25 μ g/mL (Munro et al., 2015).

Euphorbia formosana Hayata

E. formosana have been used in folk medicine for the treatment of snakebite as well as dermatosis in Taiwan. *E. formosana* Hayata has rich chemical composition that includes: polyphenols (ellagic acid, 3,3'-Di-*O*-methyllellagic acid-4'-*O*-bxylopyranoside, 3'-*O*-methyl-3,4-methylenedioxyellagic acid, methyl brevifolincarboxylate, dehydrochebolic acid trimethyl ester, gallic acid, brevifolin, octacosylferulate), steroids (β -Sitosterol, β -Sitosteryl-3-*O*-glucoside, β -Sitostenone and ergosterol peroxide), peptide (aurantiamide acetate), furan (5-hydroxymethylfurfural), coumarins (scopoletin, euoniside and 6-methoxy-7,8-methylenedioxcoumarin), diterpenes (helioscopinolide E, isopimara-7,15-dien-3-one, epi-manool and larixol), triterpenes (euphol, glutinone, cycloart-23-ene-3b,25-diol and tirucalla-8,25-diene-3,24-diol) and flavonoids (quercetin-3-*O*- α -L-rhamnoside and kaempferol-3-*O*- α -L-rhamnoside) (Hsieh et al., 2013). Yu et al. (2012) described the isolation and identification of a series of *ent*-abietane-type diterpenoids 1 – 6 from *E. formosana*. These series of *ent*-abietane-type diterpenoids showed cytotoxic, antimicrobial, spasmolytic, antioxidant and gastroprotective activities (Yu et al., 2012). Yu et al. (2012) prepared extract of *E. formosana* by extracting from dried aerial parts (11.8 kg) three times with methanol (100 L). They concluded that *ent*-abietane-type diterpenoids such as compounds 3–5 (helioscopinolide A, helioscopinolide B, helioscopinolide C, respectively) significantly up-regulated the expressions and activation of MMP-2 and -9 (matrix metalloproteinases) in human fibrosarcoma cell line HT1080, so they could potentially lead to development of novel wound-healing drugs.

Hsieh et al. (2013) used water extract from *E. formosana* and they assessed its anticancer and cytotoxic activity on human lung carcinoma cell line A-549, human bladder papillary transitional cell carcinoma, cell line BFTC905, human monocytic leukemia-derived cell line THP-1 and human promyelocytic leukemia cell line HL-60. They concluded that both leukemic cell lines, THP-1 and HL-60, had dose-dependent growth inhibition of 40% and 30%, respectively, after 24 h of treatment with 400 μ g/mL of *E. formosana* water extract (EFW). On the other side, the highest EFW concentration of 400 μ g/mL did not inhibit growth of the lung carcinoma line A-549 and the bladder carcinoma line BFTC905. When peripheral blood mononuclear cells (PBMCs) were treated with 40 μ g/mL EFW over 50% of their growth survived. These results showed that EFW selectively inhibited the growth of leukemic cancer cells; solid human cancer cells are not sensitive to EFW and EFW has low toxicity in normal cells (Hsieh et al., 2013).

Euphorbia helioscopia L.

E. helioscopia has high content of quercetin, a plant-derived flavonoid, but also contains heliosterpenoids A and B. The extracts of *E. helioscopia* L. effectively inhibited the growth of human hepatocellular carcinoma lines SMMC-7721, BEL-7402, HepG2, gastric carcinoma cell line SGC-7901 and colorectal cancer cell line SW-480 (Cheng et al., 2015). According to Mai et al. (2017) the terpenoid compounds from *E. helioscopia* are potent inhibitors of P-glycoprotein (ABCB1), and they have also exhibited cytotoxic activity against MDA-MB-231 cell lines.

Prakash and Gupta (2013) examined the cytotoxic activity of *E. helioscopia* ethanolic extract (EHE) against different human cancer cell lines as well as colon cancer cell line (Colon HT-29, SW-20, SiHa), liver cancer cell line (Hep-2), breast cancer cell line (T-47D), cervix cancer cell line OVCAR-5 and prostate cancer cell line (PC-3). These authors concluded that ethanol extract of *E. helioscopia* inhibited the growth of three human cancer cell lines: Hep-2, T-47D and PC-5 for 27%, 7% and 11%, respectively. Cheng et al. (2015) examined hepatocellular carcinoma growth inhibition by *E. helioscopia* ethyl acetate extract (EAE) in nude mice xenografts. They concluded that tumor growth was inhibited and the volume significantly decreased after being subjected to EAE treatment. These effects were dose dependent (doses from 50 to 200 µg/mL EAE). The authors observed a significant downregulation of Cyclin D1 protein expression after treatment with EAE, and the staining in the cytoplasm was reduced compared with controls. Cell cycle data showed that EAE primarily arrested cells in the G1 phase in a dose and time dependent manner and reduced the percentage of cells in the S phase. Therefore, Cheng et al. (2015) concluded that the effect of growth inhibition is mainly mediated by inhibition of cell proliferation, which is associated with a profound modulation of the expression of cell cycle mediators and the cell cycle machinery disruption. In addition, EAE treatment displayed a dose dependent inhibitory effect on tumor cell invasion *in vitro*. Wang et al. (2012) evaluated the anticancer effects of *E. helioscopia* extracts on five different human cancer cell lines. In their study they showed that EAE significantly inhibited the proliferation of SMMC-7721 cells in a time- and dose-dependent manner. EAE treatment arrested cell cycle in G1 phase and EAE used at the concentration range of 100-200 µg/mL induced a marked increase of sub-diploid peak. After EAE treatment at the concentrations of 150 and 200 µg/mL the percentage of apoptotic cells was increased. At the EAE concentration of 200 µg/mL the typical morphology of early apoptotic change was observed in SMMC-7721 cells. The EAE treatment displayed a dose-dependent inhibitory effect on tumor cell invasion and MMP-9 expression. The data showed that the flavonoids could be the main constituents of EAE responsible for its effects. Based on this data, Wang et al. (2012) concluded that EAE of *E. helioscopia* could have chemopreventive potential against the human cancer.

Conclusion

The extracts of *Euphorbia* are rich in many secondary metabolites that possess different biological or pharmacological effects. This has been shown through the traditional medicine in the recent years. But, the evidence based medicine does not gave us many data about its usage. When we speak about the anticancer and cytotoxic properties, we have to say that many

factors should be taken in consideration. From this review it could be concluded that its extracts selectively inhibited the growth of leukemic cancer cells, while solid human cancer cells are less sensitive to EFW, and EFW has low toxicity to normal cells. Up to now, *Euphorbia* extracts have shown cytotoxic activity mainly to leukemic cell, fibroblastoma cell line, pancreatic, hepatocellular, gastric and colorectal carcinoma cells. The pronounced cytotoxic activity of this very few species from the genus *Euphorbia* suggests that it could be very interesting to investigate more deeply their potent anticancer ability. According to the results of this study, *E. hirta* showed the weakest cytotoxic activity to the assessed cancer cell lines, while other species of *Euphorbia* have shown strong to moderate activity.

There are different references that emphasize the potential use of the extracts obtained from the genus *Euphorbia*, but these studies are not enough to confirm the anticancer and cytotoxic properties for all types of cancer. We should stress out that it is very important to know which species will be used for extraction of the active cytotoxic compounds, which procedures will be used in order to obtain the extracts, and main question is selectivity to different types of cancer that should be further studied. More clinical studies are necessary in order to confirm *Euphorbia* extracts anticancer effect and potential use as chemotherapeutic agents.

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acs84_01