SPECIES OF GALIUML. GENUS AS PROMISING ANTICANCER AGENTS

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A cosmopolitan genus Galium L. of RubiaceaeJuss. family comprises 659 officially registered species, 145 of which grow in Europe (*Flora Europaea*, 2010).*Galiumverum* L. and *Galiumaparine* L. are the most widespread species commonly used worldwide as ethomedicinal plants. According to *Hartwell*, 1971, *G. verum*was traditionally used in Europe and Northern America for the treatment of cancerous ulcers or breast cancer. In Palestine, an infusion from *Galiumaparine* L. leaves is usedin Hodgkin lymphoma (*Jaradatet al.*, 2016); *G. aparine*herb is used to treat cancer in Pakistan (*Tariqet al.*, 2017).

The present manuscript is aimed to provide summarized data available in public domain on anticancer activity of Galium L. genus species. Also, we focused our attention on individual phytochemicals with an established antitumor activity isolated from Galium spp. and/or other plants as a justification for further in-depth research into anticancer activity of species of Galium L. genus. In addition, with reference to the results of our previous research into chemotaxonomic studies of Galium L. genus (*Goryacha*, 2013, *Ilina*, 2013) we intend to estimatea number of Galium spp. as potential sources of antitumor phytochemicals.

According to opensources, the following human tumor cell lines were used in anticancer activity studies: E*hrlich* Ascites *Carcinoma* (EAC) *cell line;* nasopharyngeal *carcinoma* epithelioid*cell line*, CNE; non-small-cell lung*cancer cell line*, A549; colorectal *carcinoma cell line*, Hct-116; epitheloid cervix carcinoma, HeLa; liver *cancer cell line*, HepG-2; melanoma *cell lines*, HT168-M1 and A2058; subline of the ubiquitous keratin-forming *tumor cell line*,KB; gastric *carcinoma cell lines*, AGS and MGC-803; lung fibroblast *cell line*, MRC-5; lung *cancer cell line*, NCI-H460; colon adenocarcinoma cell lines, HT29 and Caco-2;hypopharyngealcell line, FaDu; larynx *carcinoma cell line*, HLaC78; breast cancer cell lines, MDA-MB-231 and MCF7; skin cancer cell lines, SK-MEL-5 and B16F10; leukemia cell line, K562; and immortalized *line* of T-lymphocyte cells, Jurkat cells.

In EAC *cell line*, *Galiumverum*L. herb aqueous extract purified from polysaccharides showed moderate cytotoxic activity (*Goryacha et al.*, 2013); decoction from *G.verum* leaves was found toxic in HLaC78 and FaDu cell lines, cytotoxicity being influenced by the expression of *p*-glycoprotein (MDR-1) in the carcinoma cell lines. The conclusion was made that decoction from *G. verum* leaves may be useful as a preventive and/or a concomitant therapeutic approach in head and neck cancer (*Schmidt et al.*, 2014). The results obtained by *Pashapour et al*, 2020 showed cytotoxic activity of the chloroform and petroleum ether fractional extracts of *G. verum* in HepG2 and HT29 cell lines. The chloroform extract showed cytotoxic effects on HT29 but increased the cell

viability of HepG2 cells. The petroleum ether extract had cytotoxic effects on HT29 and HepG2 cell lines and significantly decreased cell viability of both cancer cell lines compared to the control group.

Atmaca et al., 2016, investigated the potential anti-proliferative and apoptotic effect of *G.aparine*methanol extract on MCF-7 and MDA-MB-23 cell lines. The extract was cytotoxic in both cell lines in a concentration and time-dependent manner; the apoptosis was induced in MDA-MB-231 cells; whereas necrosis was induced in MCF-7 cells. The researchers assumed that an induction of non-apoptotic cell death besides apoptotic cell death by *G. aparine* methanol extract may enable the killing of apoptosis resistant breast cancer cells. *Shi et al.*, 2016, showed that *G. aparine* petroleum ether fractioncontains mainly daucosterol, *β*-sitosterol and dibutyl phthalate. Under experimental conditions, these compounds inhibited the proliferation of leukemia cell K562 with dose-effect and time-effect relationship, of which dibutyl phthalate had the strongest activity. *Aslantürk et al.*, 2017, established concentration-dependent cytotoxic/apoptotic effects of ethyl acetate and methanol extracts of *G. aparine*on MCF-7 and Caco-2 cell lines. The authors suggested that *G. aparine* extracts are capable of inhibiting cancer cell growth via apoptosis; they also assumed that alkaloids and saponins are responsible for high cytotoxic effect of ethyl acetate extract on Caco-2 cells, and phenolic compounds present in methanol extract may act selectively on MCF-7.

Amirghofranet. al., 2006, found *G. mite* to cause more than 40 % apoptosis in the K562 and Jurkat cells, and produce ladder formation in these cancer cell lines. The results indicated that antitumor activity of *G. mite*was due to apoptosis.

As is shown, *Galium* spp. are promising sources of different classes of biologically active compounds (BACs). In aerial parts, thebest-characterized group of BACsareiridoids, reported in more than 80 species. Iridioids are mainly represented by subgroups of asperuloside, loganin and monotropein. *Cameroet al*., 2018, reported on anti-angiogenic effects of iridoids from leaves of *G. tunetanum* Lam., namely, asperuloside, geniposidic acid and V1-iridoid inhibited angiogenesis in a dose-dependent manner. In the range of iridoids with established anti-angiogenic activity, all compounds are subsequent products of the same biosynthetic pathway, and we assume that more than 30 *Galium* spp. can be promising sources of iridoids and novel phytosubstances with an anti-angiogenic activity.

The second most abundant group of BACs in *Galium*L. genus are flavonoids, identified in more than 60 species. The dominant are diosmetin, luteolin and apigenin derivatives. *Zhao et al.*, 2011 reported that diosmetin from *G. verum* could inhibit tumor growth and protect tumor-induced apoptosis of the thymus, and the mechanism is closely associated with reduced cell death in the thymus and a Fas-FasL-dependent pathway. Diosmetin-7-O-β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside from *G.verum*could obviously inhibit the proliferation and induce the apoptosis in HepG-2 cellsthrough the modulation of the expression level of bax/bcl-2 mRNA (*Li et al*., 2013). Based on the given information, app.20*Galium*

spp., as plantsproducingdiosmetin and derivatives, thereof merit attention as prospective objects for in-depth phytochemical and specific pharmacological research.

A recent study reported the presence of ursane derivatives in *G. aparine* herb, the dominant compound beingeuscaphic acid; in the herb of *G. verum*saponins of lupane derivatives were found withlupeol predominant (*Ilina et al.*, 2018). *Dai et al.*, 2019, demonstrated that euscaphic acid reduced cell proliferation and induced apoptosis and cell cycle arrest by suppressing the PI3K/AKT/mTOR signaling pathway, which is related to cell activities such as proliferation, migration, and invasion. In the study by *Pitchai et al.*, 2014, lupeol induced an effective change in the cell viability of MCF-7 cells via apoptosis, induced cell death, change in cell morphology and population of the cancer cells, whereas normal cells were not affected. In HeLa cells, lupeol exhibited the growth inhibitory activity through induction of S-phase cell cycle arrest and apoptosis (*Prasad et al*., 2018).

In underground parts, the dominant group of BACs are anthraquinone derivatives of alizarin group, identified in more than 30 species. The most abundant are lucidine, lucidineprimveroside, alizarin, purpurinand rubiadin. The inhibitory activity of hybrids of alizarin and diamide scaffold, and novel alizarin α-aminophosphonate and O-methoxide derivatives against AGS, KB, NCI-H460, HepG-2, A549, MGC-803, Hct-116, CNE and Hela cells was shown (*Ye et al*.,2014*; Yao et al*.,2014*; Nguyen et al*.,2020), established with alizarin α-aminophosphonatederivatives was induction of apoptosis through a mitochondrion-dependent pathway. In the study by *Lajkóet al*., 2015, alizarin inhibited growth of MRC-5 cells; purpurin displayed a concentration and time-dependent growth inhibitory effect on A2058 and HT168-M1 cells and significantly reduced their number. *Bajpai et al*., 2018, reported on activity of xanthopurpurin and lucidin-ω-methyl ether against SK-MEL-5, B16F10, MCF7 and MDA-MB-231 cell lines.More than 15 *Galium* spp. as sources of alizarin and purpurin, as well as other biosynthetically related compounds, can be regarded as candidates for in-depth studies from both phytochemical and pharmacological points of view.

The present mini-review data give a theoretical contribution to a targeted search within *Galium* species as sources of phytochemicals with established anti-angiogenic and antitumor activities, and novel phytosubstancesas prospective objects for in-depth phytochemical and pharmacological research.