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Pharmacological Exploration of Hypericum Annulatum Morris Subsp. Annulatum as a Source of Novel Antineoplastic Compounds

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Abstract

This mini-review gives an outline of the oncopharmacological projects focused on the identification of potential anticancer agents or lead compounds from Hypericum annulatum Morris subsp. annulatum, an endemic species inhabiting the Balkan Peninsula, Sardinia, East Africa and Saudi Arabia. A total of 14 phenolic compounds (incl. five benzophenones/benzophenone glycosides, one xanthone, and eight prenylated species), incorporating the core phloroglucinol scaffold were tested using different in vitro end-points to assess their antineoplastic potential. The prenylated acylphloroglucinols have shown prominent cytotoxic effects, whereas the benzophenones and the xanthone, albeit less cytotoxic proved to exert other interesting activities, incl. cytoprotective, antioxidant and MDR-reversal effects. These findings give us reason to consider Hypericum annulatum Morris subsp. annulatum as a valuable source of potential anticancer compounds.

Keywords: Cytotoxicity; Apoptosis; Phloroglucinols; Hyperatomarin; Hyperannulatins A-E; Hypericum; Multidrug resistance

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Introduction

The survey of the chemical diversity of plant-derived compounds as a source of novel antineoplastic agents is a research area of significant interest, fuelled by the clinical efficacy of a plethora of plant-derived drugs or their semisynthetic analogues, such as Vinca alkaloids, taxanes, epipodophyllotoxins, camptothecins, combretastatins, maytansionoids, Cephalotaxus alkaloids, among others [1,2]. Besides the plant natural products comprise a vast and largely unexplored source of anticancer molecules, whose structural complexity could not be matched even by the most sophisticated and rich combinatorial libraries, generated in a chemical lab [1-3].

Among the numerous plant compounds the prenylated acylphloroglucinols comprise an important class of biologically active compounds peculiar for the species from the related families Hypericaceae and Clusiaceae (Guttiferae) [4,5]. The complex substitution patterns involving different acyl and isoprenoid functions, glycosylation, oxidation, or cyclization of the phloroglucinol scaffold affords the tremendous structural diversity of these fascinating compounds [4-7]. This chemical diversity is translated into pleiotropic pharmacological effects, incl. antidepressant, antimicrobial, anti-inflammatory, antiangiogenic, and worth mentioning cytotoxicity against cancer cell lines [8, 9]. Besides the polyprenylated phloroglucinols plants synthesize simpler, more polar analogues, without isoprenoid functionalities, which are potent antioxidants with diverse biological activities [10].

Our natural phloroglucinol-based drug discovery program has been focused for decades on Hypericum species characteristic for the Bulgarian Flora, and noteworthy on Hypericum annulatum Moris subsp. annulatum, an endemic species inhabiting Sardinia, the Balkan Peninsula, East Africa and Saudi Arabia [6,11-18]. The phytochemical survey of this plant has identified the occurrence of flavonoids, catechins, hypericins, xanthones, benzophenones and phloroglucinols [13,19-23]. This paper gives a concise outline of the oncopharmacological studies of the phloroglucinols from this plant using different tumor models and read-out systems.

Prenylated acylphloroglucinols

Hyperatomarin (1) is a bicyclic prenylated acylphloroglucinol, isolated for first time in Serbia

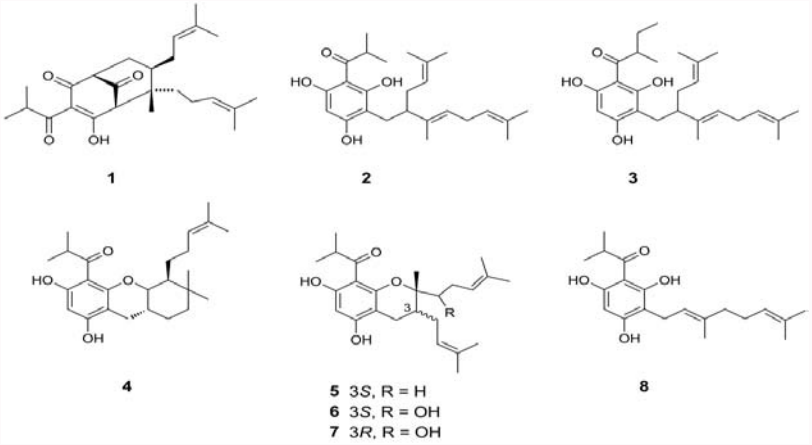

Figure 1: Chemical structures of the cytotoxic prenylated phloroglucinols, isolated from the plant.

by Šavikin-Fodulović et al., [13] from H (Figure 1). atomarium Boiss. ssp. degennii and eventually by Paraskev Nedialkov and colleagues from H. annulatum subsp. Annulatum, collected in Bulgaria [22]. The Serbian group has tested hyperatomarin for antibacterial activity, whereas we have conducted its extensive evaluation as an antineoplastic agent [13,15-17]. Its cytotoxic effects were tested in a large panel of tumor cell lines, whereby it was found to be a potent antineoplastic agent with IC_{50} values identical or even lower to those of the reference anticancer drug daunorubicin [15]. Moreover hyperatomarin proved to induce apoptosis in different tumor cell lines as evidenced by the hallmark DNA-fragmentation patterns [16,17]. Flow cytometric analysis of the effects of hyperatomarin in KG-1 cells confirmed the proapoptotic potential of the compound and its ability to induce G1 cell cycle arrest. Preliminary investigation of the antiangiogenic potential of hyperatomarin revealed that it inhibited the VEGF-induced proliferation of human umbilical vein endothelial cells and induced apoptosis in these cells which firmly indicates the need for further examination of the angiostatic effects of this compound [16]. These data well correlate with the well documented anticancer, apoptogenic, antiangiogenic and antimetastatic effects of hyperforin, a structurally related acylphloroglucinol, derived from St. John's wort (Hypericum perforatum) and to the antineoplastic potential of the polyprenylated phloroglucinols as an emerging class of natural anticancer agents [8, 24-27].

A very recent phytochemical survey of the plant has identified five new prenylated acylphloroglucinol derivatives hyperannulatins A-E in addition to the known hypercalyxone A and 3-geranyl-1-(2′-methylpropanoyl) phloroglucinol. The anticancer cytotoxicity of the newly isolated compounds was established in a panel of tumor cell lines (namely HL-60, HL-60/DOX, MDA-MB, SKW-3 and K-562). The hyperannulatins A and B proved to be the most potent cytotoxic agents, whose IC_{50} values against the chemosensitive cell lines ranged 3.42 μM to 5.87 μM and 1.48 μM to 8.21 μM, and were comparable to those of the potent anticancer drug etoposide [23].

All the eight polyprenylated acylphloroglucinols (1-8), isolated from Hypericum annulatum Moris subsp. annulatum, were eventually subjected to a computational ADME, pharmacokinetic and drug-likeness evaluation, using the web tool SwissADME, developed by the Swiss Institute of Bioinformatics [28,29]. The calculated physicochemical parameters indicated significant lipophilicity, and low water solubility. On the basis of the virtual screening findings the compounds are expected to have plausible oral bioavailability, and with the only exception of hyperatomarin are not expected to be P-glycoprotein substrates. The virtual evaluation of their inhibitory potential in several cytochrome P450 isoforms indicates all of them as potential CYP3A4 inhibitors, whereas the expected modulatory effects on other CYPs varied among the series. The drug-likeness evaluation employed five alternative rule-based filters and noteworthy all compounds complied with the Lipinski "rule of five" [28].

Non-prenylated benzoyl phloroglucinols

A series of benzophenones, namely annulatophenone (9), annulatophenonoside (10), acetylannulatophenonoside (11), neoannulatophenonoside (12), hypericophenonoside (13) and the structurally related xanthone gentisein (1,3,7-trihydroxyxanthone) (14), all incorporating the benzoyl-phloroglucinol scaffold were screened for cytotoxicity in a panel of human tumor cell lines: HL-60 (acute promyelocyte leukemia), HL-60/Dox (a multidrug resistant variant), K-562 (chronic myeloid leukemia) (Figure 2). These phenolic compounds exhibited concentration-dependent cytotoxicity and 14 proved to be the most potent agent among the series. A DNA fragmentation analysis showed that the observed cytotoxicity is mediated by induction of apoptosis. When applied at sub-cytotoxic concentrations the investigated benzophenones and gentisein restored the chemosensitivity of the multidrug resistant cell line HL-60/Dox cells to the anthracycline antibiotics doxorubicin, epirubicin, idarubicin and daunorubicin. These findings indicate that the tested compounds could be further evaluated as potential multidrug resistance reversal agents [17].

Within another project we sought to assess the protective effects of neoannulatophenonoside, annulatophenonoside and acetylannulatophenonoside against the myelosuppressive effects of epirubicin, using murine long term bone marrow cell cultures. The anthracycline antibiotic alone (at 1.25 μM) significantly inhibited the clonogenicity of the bone marrow cells. When co-administered with epirubicin neoannulatophenonoside decreased the detrimental effects of the anthracycline towards the bone marrow colony forming units, whereas neither annulatophenonoside nor acetylannulatophenonoside afforded significant cytoprotection. The myeloprotective effects are most probably mediated by antioxidant and glutathione-modulating activities, as shown by the conducted mechanistic studies [22].

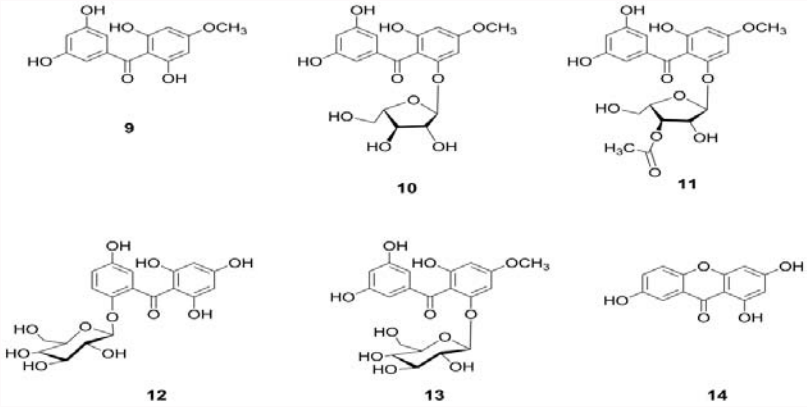

Figure 2: Chemical structures of the non-prenylated benzoyl phloroglucinols (benzophenones and a xanthone), isolated from the plant.

Conclusion

The briefly outlined oncopharmacological studies of phloroglucinols from Hypericum annulatum Moris subsp. annulatum unambiguously indicate these agents as a perspective set of biologically active compounds for further more detailed pharmacological and toxicological evaluation. A total of 14 phenolic compounds (incl. five benzophenones/benzophenone glycosides, one xanthone, and eight prenylated acylphloroglucinols), incorporating the core phloroglucinol scaffold were tested using different in vitro end-points to assess their antineoplastic potential. The prenylated acylphloroglucinols have shown prominent cytotoxic effects, whereas the benzophenones and the xanthone, albeit less cytotoxic proved to exert other interesting activities, incl. cytoprotective, antioxidant and MDR-reversal effects. These findings give us reason to consider Hypericum annulatum Morris subsp. annulatum as a valuable source of potential anticancer compounds. Of the hitherto identified agents hyperatomarin is of special pharmaceutical interest, due to its potent cytotoxic and apoptogenic effects on one hand and, on the other hand because of its abundance in the aerial parts of the plant in relatively high amounts.

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