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RED GINSENG AND ITS PHARMACOLOGICAL PROPERTIES

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ABSTRACT

Panaxitriol and its derivatives are biologically active substances isolated from a natural product - red ginseng root. It was found that they are responsible for its main pharmacological properties, namely: cytotoxic, chemoprotective, chemopreventive, antiplatelet and anti-inflammatory. This review will consider the substrate for such a broad action.

Keywords: ginseng, panaxitriol, panaxitriol acetonide, cytostatics, chemoprotectors.

INTRODUCTION

Nature has proven that it is a rich source of structurally diverse biologically active compounds from which valuable preparations can be obtained. Scientists have been trying for a long time to identify the active components of various medicinal plants, in the hope of using them as leading components for further drug development. For thousands of years, ginseng root has been one of the traditional medicines in its native regions of Asia and is still widely used to treat a number of ailments today.

METHODOLOGY

Currently, the search for substances with antitumor activity continues. At the end of the twentieth century, the results of studies of the properties of red ginseng in this area were described. In particular, it was found that the main chemicals in red ginseng, in one way or another, responsible for its pharmacological effect are ginsenosides (plant steroids from the saponin class), polysaccharides (ginsanonans), glycopeptides (panaxanes) and volatile oils. that such substances as panaxitriol, panaxidol and panaxinol are of primary importance, and among them (3R, 9R, 10R) - panaxitriol is of particular interest (Fig. 1).

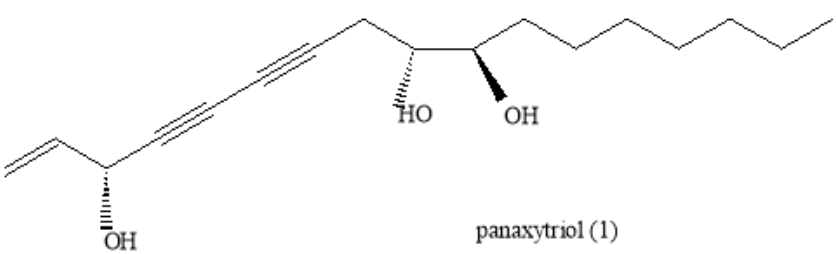


Fig. 1. Structural scheme of (3R, 9R, 10R) –panaxitriol

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It was found to have inhibitory activity against human gastric carcinoma (MK-1), mouse lymphoma (P388D1), human breast carcinoma (Breast M25-SF), and melanoma cells. The ability of panaxitriol to suppress tumor activity is due to the fact that it induces phase 2 enzymes. Since these enzymes promote detoxification reactions, their induction modulates the metabolism of cancer cells, neutralizing electrophilic agents that can exhibit carcinogenic and mutagenic properties. It was suggested that the presence of a hydroxyl group at the third carbon atom is not necessary for such an effect, and a special cytotoxicity and an increase in antitumor activity is achieved when the hydroxyl groups at 9 and 10 carbon atoms are bound into acetonide. Moreover, in in vitro experiments it was found that the obtained derivatives of panaxitriol (substances 12, 13, 14 in Fig. 2) have a greater inhibitory effect than itself, and the acetonide (13) surpasses panaxitriol itself in pharmacological activity by about 6 times.(Fig. 2).

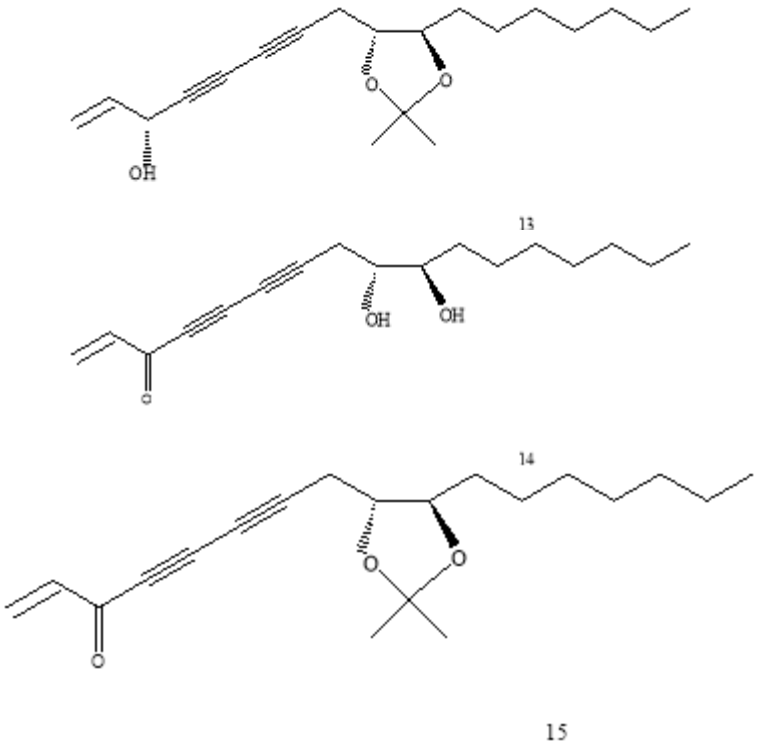


Fig. 2. Structural diagram of (3R, 9R, 10R) -panaxitriol derivatives

The cytotoxicity of panaxitriol and its derivatives was assessed in vitro using the MTT test. The MTT reagent is thiazolium blue tetrazolium bromide (3 (4.5 dimethylthiazol 2 yl) 2.5 diphenyltetrazolinium bromide). For this purpose, tumor cells are incubated in the absence (control) or in the presence of various concentrations of the studied cytostatic drugs. After 72 hours of culturing the cells and the corresponding test substances for cytotoxicity (panaxitriol and its derivatives) in a culture medium at 37 ° in a humid atmosphere, 3- [4,5-dimethylthiazolyl-2-el] -

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2,5-diphenyltetrazolium is added to each well bromide (MTT). After 4 h of exposure at 37 ° C, living cells reduce yellow MTT to dark purple formazan granules. Formazan granules are dissolved in isopropanol or dimethyl sulfoxide (DMSO), the amount of the reduced product is measured photometrically at 540 nm.

Panaxitriol significantly reduced the conversion of the tetrazole dye even at very low concentrations, which proves a significant level of cytotoxicity of panaxitriol towards tumor cells.

RESULTS

In laboratory conditions, panaxitriol and its derivatives (13, 14, 15) were studied on sensitive (CCRF-CEM \ VBL cell line) and on the contrary, cells that are immune (CCRF-CEM cell line (human leukemia cells) to multidrug resistance = MDR) cells. It is known that P-glycoprotein is a multidrug resistance protein, it is localized in the plasma membrane of normal tissues (renal epithelial cells , large intestine, adrenal glands), as well as tumor cells (Fig. 3, 4). It consists of 12 domains, of which on the side of the cytosol there are 2 sites that bind cytostatics.

It is important that each of the four investigated components (1,13, 14, 15) retained their effect against the CCRF-CEM / VBL cell line, which clearly shows multidrug resistance. These results prove that panaxitriol and its derivatives are not substrates for P-glycoprotein, and thus are not vulnerable due to multidrug resistance of cells.

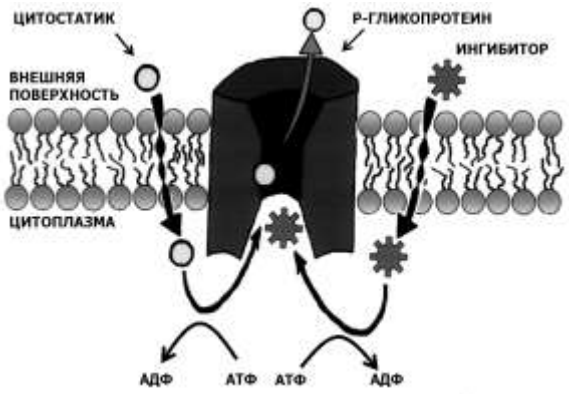


Fig. 3. P-glycoprotein

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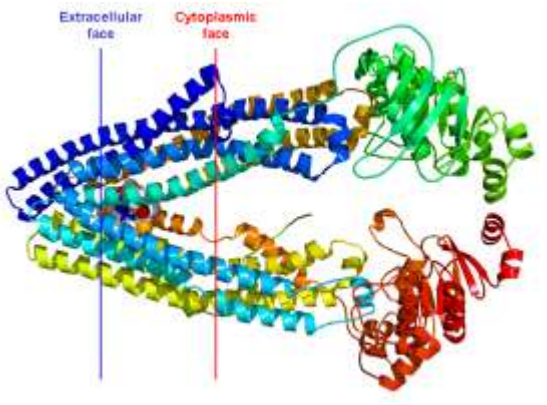


Fig. 4. P-glycoprotein

The presence of an acetonide functional group, apparently, affects the increase in cytotoxicity, as evidenced by the fact that both acetonide derivatives (13 and 15) showed greater activity in vitro than its diol analogs (1 and 14). This is due to the spatial structure of molecules in solution: panaxitriol bent in the C9-C10 region and relative to linear acetonide. Based on these data, it can be assumed that a noticeable increase in the biological activity of panaxitriol acetonide relative to panaxitriol itself may be reflected in the influence of the conformation of the C9-C10 region. (fig. 5)

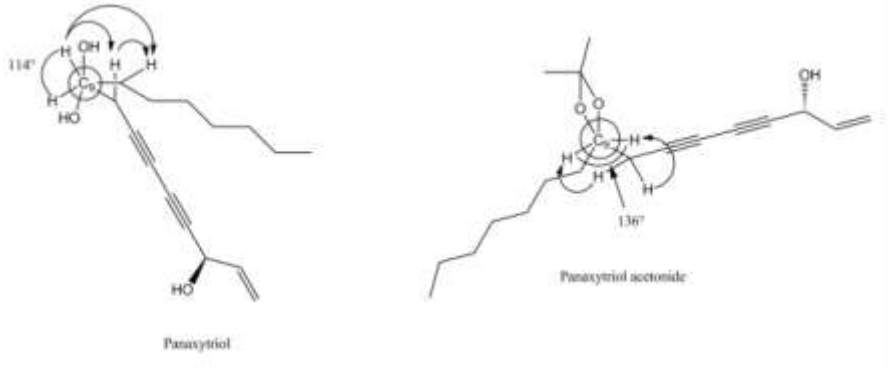


Fig. 5. Structure of panaxitriol and panaxitriol acetonide

Further, the in vivo efficacy of panaxitriol and panaxitriol acetonide was tested. Nude mice carrying human breast xenograft carcinoma were treated with various doses with slow intravenous infusion of panaxitriol (1) and panaxitriol acetonide (13). Cessation of tumor growth during the treatment with panaxitriol was observed at a dosage of 30 mg / kg, and in the treatment of panaxitriol with acetonide - already at 10 mg / kg. No significant tumor shrinkage was observed even at a dosage of 100 mg / kg.

DISCUSSION

It should be emphasized that these definitions of biological activity deserve attention not because of the high cytotoxicity, but because of the marked tumor

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suppression observed in vivo with the use of dietary supplements. Therefore, the antitumor effect of panaxitriol is not accompanied by any side effects, even at high dosages.

Anticancer and Potential Chemopreventive Effects of Panaxitriol Mammalian cells have evolved numerous mechanisms to detect and respond to various processes that disrupt homeostasis and threaten cell viability. Such stress-inducing stimuli can be biological, chemical (drugs, toxins) and physical (radiation). An important cellular defense pathway includes the following elements: ARE (antioxidant-responsive element), transcription factor Nfr2 Nrf2 / NFE2L2 [= nuclear factor (erythroid-derived 2) -like 2, nuclear factor (erythroid derivative 2) -like 2]. (binds to ARE), Keap1 - inhibits Nfr2. The inseparable connection of these molecular structures allows them to be combined into a single redox-sensitive signaling system Keapl / / Nrf2 / ARE, the main purpose of which is to maintain internal homeostasis during apoptosis-inducing, carcinogenic and stressful effects. This is a chemopreventive pathway in which panaxitriol is involved. (Fig. 6)

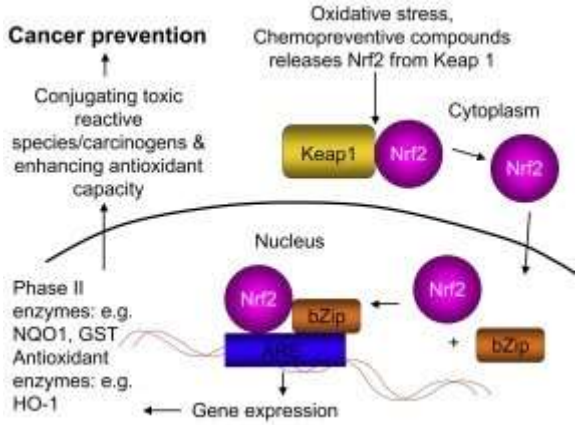


Fig. 6. Keap1 / Nrf2 / ARE system

The newly synthesized Nrf2 is located in the cytoplasm and binds to Keap1, forming the Nrf2-Keap1 dimer. Keap1 is a protein in the cytosol that inhibits Nrf2. When oxidants or a chemopreventive (panaxitriol) substance reacts with a special center in Keap1, Nfr2 is released and this allows the transcription factor to penetrate into the nucleus. (Phase of two proteins). Nfr2 binds to ARE and causes transcription of ARE-regulated genes. The decisive role of Nfr2 in the protection of cells under the influence of oxidative stress and carcinogens is the enhancement of expression and maintenance of homeostasis (oxidative) by the production of antioxidative enzymes. The directed cascade of Nrf2 reactions is an important achievement in the study of the anticancer chemopreventive activity of ginseng, including some of the oxidative stress and inflammatory response processes responsible for the initiation, stimulation and development of carcinogenesis.

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CONCLUSION

Chemoprotection Panaxitriol and its derivatives are chemoprotective in addition to cytotoxic agents. Chemoprotector is a substance that protects healthy tissues from the toxic effects of anticancer drugs. Panaxitriol analogs were given to patients in subtherapeutic doses along with the main cytotoxic drug, resulting in an increase in the combined drugs, and weight loss and nausea, as side effects of the main anticancer drugs, were sharply reduced.

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