N E W S
OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
SERIES OF BIOLOGICAL AND MEDICAL
ISSN 2224-5308
Volume 3, Number 333 (2019), 11 – 15 **https://doi.org/10.32014/2019.2519-1629.25**

UDC 615.1.4 (175)

K. D. Rakhimov

«National Medical University» JSC, Almaty, Kazakhstan.
E-mail: kdrakhimov@inbox.ru

STUDIES OF ANTIBLASTOMA NATURAL PRODUCTS ON THE ORIGINAL AND DRUG-RESISTANT VARIANTS OF TUMORS

Abstract. Preclinical studies in laboratory animals have shown that polyflavans possess high antitumor activity: 70-92% growth inhibition of Pliss lymphosarcoma, sarcoma 180, Erlich solid tumor, alveolar mucous cancer of the liver PC-1, Guerin carcinoma, sarcoma 45 resistant to sarcolysin and prospidin.

Key words: Pliss lymphosarcoma, Guerin carcinoma, sarcoma 45, P-388 lymphocytic leukemia, breast cancer (BC), antineoplastic drugs.

The antiblastoma effect of many plant extracts under experimental conditions is explained by the presence of dimeric catechins, condensed flavanols, ellagotanins in them [1-3, 6, 8].

A targeted search for anticancer drugs among these groups of compounds is carried out on a large scale in pharmacotherapy at the Kazakh Research Institute of Oncology and Radiology, together with the Department of Chemistry of the Natural Compounds of the al-Farabi Kazakh State University. The researches have revealed some data on the relationship of structure and antitumor activity in a number of different groups of flavanoids, hydrolyzable and condensed tannins [3, 6, 10].

A number of flavanols among monomeric catechins (flavon-3-ol), monomeric (+) - catechin and (-) - epacatechin, when injected intravenously in mice with sarcoma 180 and rats with Walker carcinosarcoma, don'tt have antitumor action. Dimeric compounds (catechins from Persia gratissima, Ouvatea) inhibit the growth of tumors by up to 50%. More pronounced antitumor activity was found in polymeric flavanols. In works [1, 3, 7, 20, 21] it was shown that monomeric (-) - epicatechin (+) - catechin are low active in antitumor relation, dimeric catechins (from Coataster vulgaris, Larix sibirica A.) reliably (up to 50-63 %) inhibit the growth of sarcoma 180 and considerable Ehrlich tumor. The condensation products of flavanes with 3', 4, -di-, 3', 4', 5, -triooxy groups with a molecular weight of between 10,000 and 20,000 showed a higher antitumor activity (63-90% of the growth inhibition of a number of transplantable animal tumors). As the authors point out, in this group of polyflavane substances (proanthocyanidins) the degree of their specific activity increases with increasing molecular weight of the polycondensate. In high doses, they exhibit an antitumor effect, in medium doses they are radiosensitizing, and in small doses have an antiradiation effect [1, 3, 5, 6, 19].

Phytopreparations were isolated at the Department of Chemistry of Natural Compounds of the Kazakh State University from various plants - tanning ram (Polygonum coriarium grig.), mountain ephedra (Rumex confertus Willd.), tatar rhubarb (Rheum tataricum L.), siberian larch (Larix sibirica A. Ledeb. Tien Shan sorrel, Tien Shan cuff (Rumex, Alchimilla L. tianschanicum), camel thorn (Alhagi kirgisorum A. Schrenk.) and others. Leukoefdin from ephedra mountain [21], Alhidin from a camel's thorn [12, 14, 17] was previously recommended by the Laboratory for Experimental Therapy of Tumors of the Kazakh Research Institute of Oncology and Radiology (KazRIOR) for preclinical study.

In the study of the acute toxicity of leucoefdin, it was administered intraperitoneally once as a 2% aqueous solution in doses of 220, 300, 400, 500, 600, 700, 900, 1100 mg / kg. Alhidine in 2% concentration in 0.1% solution of sodium bicarbonate in doses of 600, 1000, 1400, 1800, 2000, 2500 mg / kg.

For male mice, the maximum tolerated dose (MTD) for leucoefdin was 345 mgm / kg, LD50-610 (552 ÷ 668 mg / kg); Alhidin MTD - 510 mg / kg, LD50-840 (710 ÷ 876 mg / kg). After the introduction of drugs, excitation was observed, followed by ruffled coat and depression (within 3-5 hours); in the future, the remaining living mice had these phenomena. Mice died in a state of oppression at 1-5 days after their introduction.

Intolerable single doses of intraperitoneal administration of leucoefdine and alhidine, from which female mice died, the terms of their death from them are close to those of males. Therefore, special titration of single doses on white outbred mice-females was not performed.

At the dissection of the fallen mice, the fullness of the liver and spleen, hyperemia of the abdominal vessels, distention of the intestine are macroscopically noted.

The body weight of the mice in the first two weeks after the administration of leucoefedin in doses exceeding LD_{50} somewhat decreased and then its recovery occurred. After the introduction of the drug in doses of lower LD_{50}, this indicator increased in accordance with the physiological developmental norms.

The maximum tolerable dose of leucoefdin when administered intraperitoneally for rats was 320 mg / kg, LD_{50}-530 (500 ÷ 560) mg / kg for alhidine 480 mg / kg, LD_{50} - 690 ÷ 770 mg / kg. In toxic doses (700-1000 mg / kg), leucoefdin after administration caused excitement, then ruffled coat and depression (3-6 hours), rats died 1-5 days after exposure to the drug. At the dissection of dead rats from intolerance to leucoefdin, the same pathological picture was noted as in the case of experiments on mice with a single intraperitoneal injection.

A 10% aqueous solution of lyophilized leucoefdin after a single injection into the bladder at a dose of 250 mg / kg did not cause the death of rats, dysuric events, abnormalities in the pathological and morphological studies of the internal organs and bladder. Single doses of 550 and 890 mg / kg resulted in the death of rats by 40 and 50%. The death of animals from intolerable doses mainly occurred on the 8-10 day after administration, starting from 3-4 days. Toxic effects developed slowly and were caused by a pronounced irritant effect on the bladder mucosa; incomplete bladder content was observed. Common symptoms of intoxication were lethargy, loss of appetite, and general depression. Restoration of these changes in the surviving animals occurred for 15-20 days with the subsequent normalization.

With the introduction of a 10% aqueous solution of leucoefdin in the MPD in the bladder to rats daily for 10 days was 50 mg / kg and for the next 30 days there was no toxic effect of the drug [1, 11, 16].

Alhidine at a 2% concentration in a 0.1% solution of sodium bicarbonate was tested with a single intraperitoneal intravenous (tail vein) of mice and rats.

The MTD was 45 mg / kg, LD_{50} 90 mg / kg. The therapeutic latitude of alhidine for mice is small: the value of MTD is close to the lower boundary of the confidence interval for LD_{50}. The indicated toxicity parameters in female mice of line F_1 (CBA x C57Bl 6) are identical to the data on white outbred male mice.

The main death of animals from intolerance to doses began after 2-15 minutes and after 1-3 hours (below LD_{50}) and occurred 1-3 days after a single injection of the drug, but individual mice died on 8-12 days of experience [1, 4, 9, 13]. Exceeding the permissible concentration of alhidine (4% versus 2%) did not cause a local irritating action (no infiltration of the subcutaneous tissue of the tail). At the autopsy of rats suffering from intolerance to doses of alhidine, the same pathological-anatomical picture was observed as in the case of experiments on mice with a single injection of the drug.

Parameters of acute toxicity of sea buckthorn polyflavones and cuff grass are of low toxicity.

Chronic toxicity. In experiments on rats with transplantable tumors, the maximum tolerated dose (MTD) of a 2% aqueous solution of leucoefdin with daily intraperitoneal administration for 10 days was 50 mg / kg for mice, 40 mg / kg for rats, oral: 200 mg / kg for mice, 500 mg / kg for rats.

For 2% alhidine in a 0.1% sodium bicarbonate solution with daily intraperitoneal administration for 10 days, a single dose was 70 mg / kg for mice and rats; intravenous was 50 mg / kg for mice, 40 mg / kg for rats.

The MTD of a 2% aqueous solution of sea buckthorn polyflavan with daily intraperitoneal administration for 10 days for mice is 70 mg / kg, for rats it is 90 mg / kg.

With daily intraperitoneal administration for 5 days of a 2% aqueous solution of polyflavane alchemine-1, the MTD was 30 mg / kg, of alchemy II, 40 mg / kg in experiments on mice; 40 mg / kg in rats. In these doses, no marked toxic effects on animals and their death were observed. At autopsy of

animals slaughtered at the end of the experiment, no pathological changes from the internal organs were revealed.

The antitumor activity of polyflavans: leucoefdin, alhidin, alchemina I and II was studied in mice and rats with the original tumor strains, as well as in rats with drug-resistant variants.

It has been established that intraperitoneal and intravenous injections in MTD, leucoefdin and alhidin, have significant antitumor activity in experiments on rats with Pliss lymphosarcoma (LSP), Guerin carcinoma (K.Geren), carcinoma of Walker (KSU), alveolar mucous liver cancer (PC-1) (62-95% growth inhibition, P <0.02-0.001) to a lesser extent - M-1 sarcoma (CM-I), 45 sarcoma (C45) and breast cancer (RMK-1) (26-60%). A reliably pronounced inhibitory effect was obtained in the treatment of these drugs in MTD mice with sarcoma 37 (C37), sarcoma 180 (S180), a considerable Ehrlich tumor (Erlih tumor), gastric cancer of OZh-5 (OZh-5), adenocarcinoma of the mammary gland (CA) 755), cervical cancer (CCR-5) and Lewis lung carcinoma (LL) (60-84% growth inhibition, P <0.01-0.05). At the same time, in increase in life expectancy (ILE) of the mice with lymphocytic leukemia P-388 (P-388) (by 46-87%) with respect to the control was noted. Lymphoid leukemia L 1210 (L1210) (UPJ - 11-12%) and hepatoma 22a (12-36%) are not very sensitive.

Sea buckthorn polyflavone had a significant inhibitory effect in MTD in experiments on five tumors: breast cancer (RMK-1) and Pliss lymphosarcoma (88 and 60% growth inhibition, respectively), C-180, Ehrlich solid tumor (55 and 49%, respectively), P-388 (UPZh-50%). The remaining tumors of mice and rats were insensitive to this drug.

Alchemine-I had a high antitumor effect in comparison with alchemine-II in MTD on KSU, a solid tumor of Erlich, K.Heren (90-56% growth inhibition, P <0.001-0.05); both alchemine and C 45, LSP growth (72-76%) were equally inhibited. The remaining tumors were insensitive to them.

Thus, polyflavans have a high antitumor activity: 70-92% growth inhibition of Pliss lymphosarcoma, 180 sarcoma, Erlich solid tumor, alveolar mucous liver cancer PC-1, Guerin carcinoma.

Leukoefdin, alhidin and polyflavin from sea buckthorn with intraperitoneal daily use (for 10 days) caused a significant reliable therapeutic effect in relation to the resistance to rubomicin of Pliss lymphosarcoma (59-80% inhibition). As one can see, the initial sensitivity (60-88%) of the given strain to drugs is retained. The substrains of sarcoma 45, resistant to rubomycin and 5-fluorouracil were insensitive to polyflavins. On the contrary, in a comparative study, the tested polyflavans (at doses of 45, 70, 90, and 40 mg / kg, respectively) up to 90% inhibited the growth of sarcoma 45 resistant to prospodine. High sensitivity (up to 83% inhibition) and sarcoma 45 resistant to 5-fluorouracil have been revealed for alhidine [1, 4, 6, 7].

Sarcoma 45, resistant to sarcolysin, showed hypersensitivity to leukoefdin. The drug inhibited the growth of the original strain by 38%, and drug-resistant by 80% (P <0.001). Whereas on this strain, alchidin and polyflavin from sea buckthorn caused cross-resistance.

Similar results were obtained in the treatment of leucoefdin rats with Pliss lymphosarcoma resistant to prospidin. In experiments with this tumor strain, the initial sensitivity (92 and 56%, respectively) was retained when exposed to alhidin and alchemine-I (76 and 74%, respectively).

High antitumor activity was detected when leucoefdine and alhidine were administered (in MTD by intraperitoneal administration) to mice with lymphoid leukemia L 1210, resistant to methotrexate (MTX), nitrosomethylurea (NMU) [15], 6-mercaptopurine (6-MP) 146% ILE in relation to the control. A moderate increase in the life expectancy of the mice was found during treatment with a polyflavin of sea buckthorn and alchemine I (up to 35% ELE).

The studied polyflavans, in addition to tannins (82%), flavanoids (5%), glucose (2.2%), arabinose (1%), contain polysaccharides (1.6%).

Thus, with the use of drug-resistant transplantable rat tumors, Pliss lymphosarcoma and sarcoma 45, resistant to rubomicin and prospidin, were susceptible to polyflavans; sublines of leukemia L 1210, resistant to 6-mercaptopurine, nitrosomethylurea, methotrexate.

Of the polyflavans used, the more active (on 6-8 strains) were alhidin and leucoefdin. On sarcoma 45, resistant to sarcolysin and prospidin, collateral sensitivity to leucoefdine is manifested, and sarcoma 45, resistant to 5-fluorouracil – to alhidin.

Қ. Д. Рахимов

«ҰМУ» АҚ, Алматы, Қазақстан

ТАБИҒИ ПРЕПАРАТТАРДЫҢ БІРІНШІЛІКТІ ЖӘНЕ ДӘРІГЕ ТҰРАҚТЫ ҚАТЕРЛІ ІСІКТЕРГЕ АНТИБЛАСТОМДЫҚ ӘСЕРІН ЗЕРТТЕУ

Аннотация. Зертханалық жануарларға клиникаға дейінгі зерттеу кезінде полифлавандар қатерлі ісікке қарсы әсері жоғары екені дәлелденді: сарколизинге және проспидинге тұрақты Плисс лимфосаркомасы, саркома 180, Эрлихтың солидті ісігі, бауырдың альвеолярлы сілемейлі ісігі, РС-1, Герен карциномасы, саркомы 45 өсуін 70-92% тежеді.

Түйін сөздер: Плисс лимфосаркомасы, Герен карциномасы, саркома 45, лимфоцитарлы лейкемия Р-388, сүт безі қатерлі ісігі (РМЖ-1), қатерлі ісікке қарсы препараттар.

К. Д. Рахимов

АО «Национальный медицинский университет», Алматы, Казахстан

ИССЛЕДОВАНИЯ АНТИБЛАСТОМНЫХ ПРИРОДНЫХ ПРЕПАРАТОВ НА ИСХОДНЫХ И ЛЕКАРСТВЕННО РЕЗИСТЕНТНЫХ ВАРИАНТАХ ОПУХОЛЕЙ

Аннотация. Доклинические исследования на лабораторных животных доказали, что полифлаваны обладают высокой противоопухолевой активностью: 70-92% торможения роста лимфосаркомы Плисса, саркомы 180, солидной опухоли Эрлиха, альвеолярного слизистого рака печени РС-1, карциномы Герена, саркоме 45, резистентной к сарколизину и проспидину.

Ключевые слова: лимфосаркома Плисса, карцинома Герена, саркома 45, лимфоцитарная лейкемия Р-388, рак молочной железы (РМЖ-1), противоопухолевые препараты.

Information about author:

Rakhimov Kairolla Dussenbayevich, Doctor of medicine, Professor, Academician of the National academy of sciences Republic of Kazakhstan, Honored Worker of Republic of Kazakhstan, Lauteate in field of science and technology, chairman of the department of clinical pharmacology JSC «National medical university», Director of the center of Clinical Pharmacology JSC «National medical university», Almaty, Kazakhstan; kdrakhimov@inbox.ru; https://orcid.org/0000-0003-3125-6845

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