

Physiological Action of Anthraquinone-Containing Preparations

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Abstract—In review the generalized data about biological activity of anthraquinone-containing plants and specimens on their basis is presented. Data of traditional medicine, results of bioscreening and clinical researches of specimens are analyzed.

Keywords—Anthraquinones, physiologically active substances, phytopreparation, Ramon.

I. INTRODUCTION

MANY anthracene-containing plants belong to the group of medicinal plants with wide spectrum of physiological activity and are described in State Pharmacopeias of many countries. 160 phytopreparations with natural anthraquinones in their composition are known. Along with officially-used plants, folk medicine uses other anthracene-containing plants and medicines prepared from them. For example, since ancient times medical practice has used soft purgative and antidermatic preparations whose active components are hydroxy-, methoxy- and glycoside derivatives of anthraquinone. Though there are cheaper synthetic purgative preparations, preparations from plants are still widely used as they act softly, painlessly, do not cause irritation of organs and tissues, are easily extracted from the organism and do not cause side effects.

Chemotherapeutical and pharmacological tests as well as experience of folk medicine show that individual natural anthraquinones and their synthetic analogues have versatile physiological activity, and the highest effect was registered for glycosised mono-, dimer and reduced forms and for anthracycline antibiotics. Oxidized forms of aglycones exhibit depending on dose astringent and (or) purgative effect, moderate antitumour, anti-inflammatory, antibacterial and radioprotective action.

II. RESULTS AND DISCUSSION

In Pharmacopeias of many countries the highest grade got purgative medicinal preparations containing dimer anthraglycosides. However, chemists could not prove their

advantage as compared with oxidized, glycosized or reduced forms, therefore Pharmacopeias of Poland, Austria and Hungary use as an estimation of purgatives percentage of “anthraquinone derivatives” converted into chrysophanol or other standard samples.

In some countries widely-spread local herbs are used as therapeutic agents. For example, in India instead of Chinese rhubarb roots of *Rheum emodi* Rh. Werbinum are used, in Japan roots of *Rheum indulatum* are used as a purgative. As a rule, in folk medicine the same preparation is used for different purposes [1]. For example, many species of cassias are used as purgatives: *Cassia absus* L. and *C. fistula* L. in India, *C. acutifolia* Del., *C. angustifolia* Vahl. in most countries of the world, *C. holosericea* Fr. in Aden, *C. marilandica* L. in the USA, *C. Moschata* in Columbia, *C. obovata* L. in Italy and Jamaica, *C. carnaval* Sped., *C. corimbosa* Lam., *C. hookeriana* Gill., *C. subulata* Gris in Argentina, *C. obtusifolia* L., *C. tora* L., *C. sophora* L. in tropical countries of Africa, Asia and America. As a bactericide preparation cassia is used in Western Africa, where dry leaves are crushed to powder and put on burns or ulcers. Seeds of *Cassia absus* L. and leaves of *C. occidentalis* L., *C. sophora* L., *C. tora* L. are used in Southern Africa and India as a remedy from coelminths. As an anti-parasitic remedy and as a preparation for treating skin diseases the folk medicine in Zimbabwe uses *Odura pulchra* [2].

Tincture from the roots of *C. alata* L. is used in Guatemala for treating rheumatism; decoction from the roots of *C. sieberiana* D.C. is used as a diuretic in Gambia, decoction from the leaves of *C. oxyphylla* Kunth. is used as a emetic drug in the countries of Central America and Mexico, leaves of *C. mimosoides* L. are used as tea in Japan. Seeds of *C. laevigata* Willd., *C. occidentalis* L., *C. sericea* Sw, *C. moza* L. are used as a substitute of coffee in Guatemala, Brasilia and Mexico [3]. Leaves of different species of senna, senna extract (anthrasennin); a compound powder of “liquorice”, cassia anthrones (cascosides), cassia leaves and fruit are used as purgatives [4]. It is also known that extract of cassia seeds and pods has a fungicide effect. Cassia roots and seeds are recommended as an antimicrobial agent, combined preparation from *Cassia pumila* (physcion, chrysophanol, emodin) has spasmolytic effect [2]. Rhubarb root and rhizome have tonic, purgative and astringent action. Therapeutic properties of rhubarbs are caused by anthraglycosides, chrysophanol, emodin, rhein, rheinosides and tannoglycosides. Preparations from rhubarb are used independently or in combination with other preparations. Most well-known – “rhubarb powder”, “dry rhubarb extract”, “water-alcohol

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extract", "alcohol rhubarb tincture", "rhubarb syrup" are used to treat bowels atony, meteorism and to improve digestion [5].

Mitotic activity of water-soluble fractions of *Rheum officinale* was discovered. Extracts of many *Hypericum* species have photodynamical activity and are used as a part of the corresponding preparation "Imanin". Anthraquinones from *Morinda parvifolia* and *M. officinalis* have an antileukemic effect [6]. From the bark of the brittle the buckthorn preparation "cofranal" is produced, its chemical investigation showed that it contains emodin and glucofrangulin, which in the organism in the process of acid hydrolysis turns into emodin, D-glucose and L-ramnose and in the process of enzymatic conversion turns into D-glucose and frangulin [7]. In medical practice the extracts of buckthorn Imeritinskaya and buckthorn fruit are used as decoctions and tinctures, "ramnil" containing up to 60% of anthraglycosides is used not only as a purgative but also as a preparation for treating gastric diseases. A combined preparation "cholagol", having emodin as a component, has choleric and spasmolytic action [8].

Finely-ground buckthorn bark is a component of preparation "Vicalin" used for treating stomach and duodenum ulcer and a component of medical mixtures with conventional names "stomach preparation" No. 3, 5, 11, "purgative preparation" No. 1-6, tablets "Altra", "Normogran", "Neonormacol", "Nepbapol" and others [4].

Dyeing madder contains free and bound anthraquinones and is used in folk medicine as astringent and diuretic preparation, for treating rachitis, joint diseases, children's tabes, jaundice, rheumatic pains. Dry madder extract has diuretic and spasmolytic action, it is also used to loosen nephroliths consisting of potassium and magnesium phosphates. For example, "Cistenal" and "Spasmocistenal" is complex preparations containing extract of dyeing madder relax muscular system of ureters and facilitate passing of small concretions [9]. Due to the presence of anthraglycosides Preparations "Frangin" from buckthorn and "Frangulaxin" from aloe have soft purgative action and are prescribed in pediatry. At all times leaves of aloe were used to make medicinal preparations; "Sabur" is concentrated and hardened juice from aloe leaves containing aloin, free and bound anthraglycosides. In folk medicine, homoeopathy, veterinary "Sabur" as well as aloe leaves is used for different purposes: it is generally recognized strong purgative, it is applied in treatment of tuberculosis, abscesses, lichens, headaches, eye diseases and many other diseases.

High efficiency of biogenic preparations from aloe was discovered. These researches opened new way in the usage of aloe in biogenic therapy as stimulators [1], [6].

The extract from aloe leaves is used in treatment of progressive myopia, miotic chorioretinitis, conjunctivitis, keratitis, opacity of vitreous body, bronchial asthma, rheumatic pains, and for wound healing. The "syrup of aloe with iron" is used as a preparation influencing the processes of tissue metabolism. Aloe syrup is used to prepare a special extract containing biogenic stimulators. "Aloe liniment" is used in ophthalmology, for treatment of septic wounds and inflammatory skin diseases [10]. The authors of a number of

papers describe the usage of an extract from aloe leaves for treatment of stomach and duodenal ulcer, bronchial asthma, some otolaryngologic diseases and parodontosis in complex with Novocain [4]. It was proposed to make a preparation for recreation and strengthening of autogenic forces in humans and animals as well as for skin protection.

There was patented a preparation for healing wounds and burns in the form of aloe gel with 0.9% of anthraglycosides. Oxanthraquinones are the base for sticking anti-inflammatory pharmaceutical plasters. To treat virus diseases caused by herpes simplex physicians use aloe-emodin extracted from the barks of *R. frangula*, leaves of *Cassia* > *J. angustifolia* and other plants [11].

Water extracts of fruit and roots of some sorrel species are known in medical and veterinary practice as anti-inflammatory and wound-healing preparations, anthraquinones from sorrels, rhubarbs and other medicinal plants are used for treatment of skin diseases and hypertension. Pharmacological studying of various sorrel species showed their high activity against enterocolitis with blood bleeding and confirmed the evidences of folk medicine about possibility of usage sorrels for treatment of scabies, fungi, lichens as well as antiscorbutic and antiseptic remedy [12].

To treat psoriasis, dry eczema and allergic diseases were used water solutions of anthraglycosides from leaves and inflorescences of *Tanacetum balsamite* and stems of *Persicaide douce*, *Coptis chinensis* [4].

Among natural reduced derivatives a very important role in medical practice plays "Chrizaborin", a complex preparation consisting of oxidized and reduced forms of anthraquinones which are stored in cavities of tropical trees such as *Andira oraroba*. Chrizaborin and its synthetic analogues "Anthraline" (Ditranol), "Cignolin" and some others are also used to treat psoriasis and dermatomycoses. They also have anti-inflammatory and anti-itching action, and it should be noted that long-term follow-up of the patients did not reveal any advantages of steroid-containing ointments as compared with ointments containing reduced anthraquinone derivatives. Various sorrel species are used in medical practice in Turkey, India and China; it was noticed that among 200 examined species therapeutic effect had 23 species and 5 hybrids with different concentration of the sum of anthraquinone derivatives [13]. Extraction of 17-19% of chrysarobin-like substance from rhizomes of some species of rhubarbs and sorrels growing in Hungary was described in. An analogue of chrysarobin was obtained from Tangutsk rhubarb but clinical examination showed its high toxicity, contraindications in case of liver and kidney diseases and irritant action on eye mucous membrane [14]. Many-year clinic observations of the action of chrysarobin from Tien-Shan sorrel revealed no adverse action or contraindications; this preparation was recommended for treatment of herpes, psoriasis, eczemas and some other skin diseases of children and adults. Antimalarial activity, antimicrobial and cytotoxic actions were described for anthraquinones *Cinchona* [15].

Growth-regulating activity of chrysophanol for food plants and hormonal activity for vetch was established in. The

authors [16] observed stimulating effect of quinalizarine and quinizarine on formation of cress roots. The above-mentioned and other oxyanthraquinones exhibit in this respect higher activity than now used heteroauxin, uglon and other substances. In order to increase productivity of cultivated plants including food plants, it was proposed to put into soil or to treat aboveground plant parts with 1,2-anthraquinone or hexahydroxy-, pentahydroxy- and 1,4-dihydroxyanthraquinones. Heteroprotolytic properties of hydroxyanthraquinones were studied, and on the base of 1-bis-anthraquinones an herbicide against water vegetation was proposed. 3-propyl-1,6,8-trihydroxyanthraquinone in concentration 1.5-7.0 g/ml shows activity against gram-positive bacteria. Alizarin and its derivatives show nephrolithic action [17].

The influence of rhein on the reactions of electron transfer in homogenates, intact and destroyed mitochondrion of liver and kidneys was studied and it was revealed that rhein actively blocks oxidation of substrates with NAD.

Rhein, aloe-emodin and emodin inhibit lactate dehydrogenase, whereas emodin, physcion and their 8-glycosides inhibit protein and tyrosine kinase [18].

Combination of hydroxyanthraquinones with ergotein in cytostatic therapy enables to reduce toxic effects. Natural antibiotic – 289F has antibacterial and antitumour action. 1,2,4,6,8-pentahydroxyanthraquinone showed antitumor activity against Twort carcinoma. Emodin and rhein inhibit 76% of melanoma growth, emodin inhibits growth of cancer of mammary gland, and rhein inhibits development of Ehrlich's ascites tumor. 2-isoprenilemodin and its dimeric form, antibiotic X-14881c and ochromicinone, produced as *Streptomyces* [18] are used as antileukemia preparations.

High antibacterial activity was shown on 26 strains of various pathogenic bacteria causing anthrax, hay fever, diphtheria, dysentery and other diseases. Anthraquinone derivatives inhibit growth of streptococcus and staphylococcus [19]. Such anthraquinones as aloe-emodin, aloin, chrysophanol and some others are used in cosmetology for skin and hair treatment [20]. β -D-glucopyranoside-1,3,6,7-tetrahydroxy-anthron was proposed to treat lichens.

It was proposed to use laccinic, carminic acids and boletol as natural food coloring agents and, due to their low toxicity, as preparations potentiating action of chemotherapeutic agents and antibiotics, suppressing immunological reactions arising as a result of injection of corticosteroids and anticancer medicines [4]. Aloe-emodin, chrysophanol, physcion are used to reduce pains in treating burns [21].

Mitochondrial activity of anthraquinones, anthrones, anthrones and glycosides may act as the base for their both purgative and antipsoriatic actions. For example, "Ditrinol" (1,8-dioxytranol) hampers supply of oxygen to psoriatic epidermis and its cell division, inhibits enzyme of gluco-6-phosphatdehydrogenase, phosphofructogenase and other enzymes, which shows its mitochondrial action [22].

Aloe-emodin and other anthraquinones possess virucidal action against virus of simple lichen. Chrysophanol, physcion and their methoxy-derivatives, knifolon, known for many ethnic groups in Africa, are used as antimicrobial agents [23].

Another patent was issued to treat tumor and virus infections including AIDS carmine acid, its glycosides, quinhedrone, tetraoxyanthraquinones in concentrations $\sim 10^{-3}$ mol/l [24].

Synthetic derivatives of anthraquinone also have a wide spectrum of biological activity. 9,10-anthraquinone turned out to be active repellents protecting flowers, fruits and, particularly, buds from birds. Semi-synthetic analogues of aloin and aloe-emodin with ethers of carboxylic acids prevent formation of melanine. 9-aminoalkoxy- and 9,10-dihydro-ethanoanthracenes exhibit antiallergic action. R-imides of ethanoanthracene-carboxylic acids exhibit spasmolytic, sedative, hypotensive, depressant and antitumour activity [25].

Many nitrogen-containing derivatives of anthraquinone are active inhibitors of aminopeptidases. N-hydroxyoxy-9-NH-9,10-dihydro-9,10-ethanoanthracenes and their salts with acids show antihistamine, antitussive and antiemetic action; ethers of ethano-dehydroanthrones-9 have similar and local anaesthetic action, whereas anthracenes of this type exhibit diuretic and cough-depressant effects [26].

Bis-anthracyclines are function inhibitors for nucleic acids, 7-deoxy- and 7-O-alkyl-derivatives of anthraquinones, their diols, acids, oximes, hydrazones, amino- and alkylamino-derivatives have high antitumor action [19].

Studying of bioactivity of the products of wide modifications in the structures of natural anthracyclines showed that insignificant changes in the structure caused significant changes in therapeutic activity. For example, reduction of C=O group of daunorubicin gave dihydrodaunorubicin with higher antitumour activity, whereas its 14-alkyloxy-derivatives exhibited cytostatic effect [27].

In order to reduce adverse effects in treatment of primary and secondary neoplasms in liver it was proposed to introduce doxorubicine into liposomes [12].

A number of authors noticed common nature of antitumor action for anthracycline antibiotics and bis-aminoalkylamino- or hydroxyamino-derivatives of anthraquinone. Especially active are amino-substituted derivatives such as 1,4-NHR-, NHR(OH)₂- and 1,4-aminoalkoxyamino-derivatives, which have lower toxicity, form more stable complexes with DNA and possess higher selectivity with respect to brain tumors [28]. Hydroxyamino-anthraquinones are more active against big tumors, while anthracyclines are not effective in this case. For example, "Mitoxanthron" is recommended for usage both in chemo- and radio-therapy of tumors. Condensation of natural quinizarine with alkylendiamines or 2,3-dihydro-1,4,5,8-tetrahydroxy-1,10-anthracendiones enabled to obtain over 60 1,4-bis-(alkyl-aminoalkylamino)-9,10-anthracendiones and their 2,3-dihydro-derivatives, which exhibit high activity against leukemia and big tumors on mice and give 4-10-fold increase in the lifetime in case of melanoma B-16, leukemia p-388 and LLS; their strength and therapeutic indices are equal or higher than those of adriamycin, cyclophosphamide, daunorubicine, metotrexate and other preparations used in medicine [28].

To dye and treat hair, skin, nails, to treat herpes, psoriasis and lichens it is recommended to use acylamino-derivatives,

formulations with "Anthraline", oxyacylanthrones, "Ditranol", "Ramon" and other preparations [4].

Antiestrogenic action is exhibited by substituted benzaanthracene 3,9-diols, whereas polysulfonates of sennosides A and B suppress complementary system of warm-blooded animals [29].

Antitumor activity is also observed for derivatives of anthra-(1,2)-pyran, in which anthraquinone nucleus is angularly annelated with γ -pyran cycle according to the scheme: 1,8-dihydroxy-9-anthron-10-yl of maleinic and other acids and their ethers are used in medicine, veterinary and cosmetics as highly active anti-inflammatory agents [30].

For treating parkinsonism preparations on the base of dihydroanthracenes are patented. 2,6-bis-(aminoacetyl-amino)-anthraquinones and their salts with acids have antiviral action, amidines 2,6- and 2,7-hydroxyanthraquinones have entamoebic activity and anti-inflammatory action. It was proposed to use 1-hydroxy-2-(N,N-dimethylaminomethyl)-anthraquinone for treating arthritis. Anthraquinonecarbamates, hydrazo-compounds, some azo-derivatives have herbicide action, 2-nitro-9,10-dihydro-9,10-ethanoanthracenaldehyde and its derivatives have psychotropic and antidepressant action. Oximes of anthrone, chrysophanol, physcion, emodin, rhein are used as peristaltic stimulators, 1,5,6,7,8-pentahydroxy-3-methyl-, 1,5,8-trihydroxy-3-methyl-, 1,5-dihydroxy-3-methylanthraquinones have anthelmintic action; bis-(aminoalkylsulfomail)-anthraquinones and their salts with acids have virucidal activity. Dialkylamino-alkylamino-derivatives of anthraquinone can be used as preparations against schistosomiasis. Derivatives of methylaminomethyl-9,10-ethanoanthracenes and their salts act on the central nervous system and are antagonists of cocaine and mescaline, histamine and acetylcholine [31].

Antimicrobial activity was exhibited by derivatives of 9,10-hydrozones and 1-hydroxy 4-aminoanthraquinones [17].

Immunological activity is exhibited by derivatives of anthraquinone with nitrogen-containing hetero-ring. O-diethylaminoethyl derivatives of di- and polyoxy-anthraquinones, in particular, alizarin ether, are antitumor stimulators, derivatives of hydroxycarboxylic acids and their glycosides enhance immunizing action. Derivatives of tiocarboilanthraquinone inhibit growth of leukemic cells and solid tumors. Compositions on the base of 1,8,9-triacetoxy-anthracene are proposed as antitumor preparations [32].

Aminoethers of some anthraquinones have antiallergetic action, oxims and alkylamino-derivatives of anthraquinones and naphthoquinones exhibit radio-sensitising, amebicidal and bacteriostatic activity, sulfur-containing derivatives of anthraquinones act as radio-protectors, compounds of anthraquinone containing substitutes with unsaturated bond impose sedative action on the central nervous system [33].

Many natural and synthetic types of quinine have high antimicrobial activity which is assumed to be caused by the presence of carbonyl groups in the molecule and ability of these substances to form hydrogen bonds. As an example of studying antimicrobial properties of quinines one can present

researches carried out with anthraquinones (tektoquinone, purpurine, emodin, rhein, combined anthraglucosides, etc).

Antileukemic activity is exhibited by derivatives of chrysophanol and emodin, which can act as alkylating agents.

51 new C-methyl-derivatives on the base of chrysophanol and emodin or their methyl ethers were studied to establish interrelation "structure – activity" against leukemia of mice L1210 and human leukemia HL-60. Alkyl- and dialkylamino-derivatives of chrysophanol inhibiting homoisomerase were proposed for treating cancer [34].

III. CONCLUSION

The aforesaid enables to consider the anthraquinone derivatives as a perspective class of biologically active compounds with a number of useful properties.

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