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A Natural Anthraquinone Plants with Multi- Pharmacological Activities

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Abstract: Anthraquinone derivatives are naturally occurring compound, extracted from medicinal plants (Cascara, Frangula, Aloe, Rhubarb, Senna, and Rumex) of consolidated use in folk medicines as well as in modern medical practice, which have attracted attention of scientists, and still represent remarkable remedies in the treatment of many diseases, especially acute and chronic constipation.

Key words: Anthraquinones, Anthraquinones-containing Plants, Pharmacological Activity.

Introduction:

Natural anthraquinones are distinguished by a large structural variety, wide range of biological activities, and low toxicity. They possess astringent, purgative, anti-inflammatory, moderate antitumor, and bactericidal effects; they participate in the processes of metabolism, respiration, division of cells, oxidative phosphorylation, complexation with DNA and RNA, and, perhaps, in other physiological processes of vital importance; they are parts of many medicines of the plant origin [1].

Anthraquinone derivatives have been found in wild and cultured higher plants, mosses, lichens, fungi as well as in sea animals and algae. In fungi and lichens, these are anthracycline antibiotics and anthracyclines. In higher plants, anthraquinones are present in oxidized, reduced, glycosides, and condensed forms, as a rule, together with their precursors [2].

When searching for new medicinal preparations, it is extremely important to know the ways and methods of working with different plants and biological objects, in particular, the methods of isolation, separation, purification, and identification of individual compounds.

Besides medicinal preparations, anthraquinones have found application as dyes, pigments, luminophores, analytical reagents, chemical means for plant protection, and so on… .

Natural anthraquinone plants

plants which containing natural phenol compounds used in traditional medicine for a long time, have always attracted the attention of scientists.

Herbs and especially those kinds of herbs which contain natural anthraquinone derivatives, have been effectively used in both traditional medicine as well as in modern medicine practice. Some plants belong to this kind of herbs: “Cascara sagrada, Senna, Frangula, Rhubarb, Rumex, Hypericum, and Aloe” [3,4].

Aloe:

Chemical constituents:

Aloe contains as its major and active principle hydroxyanthracene derivatives, mainly of the aloe-emodin-anthrone 10 –C- glucoside type. The major constituents are known as barbaloin (aloin). It also contains hydroxyl ions. Barbaloin (aloin) is in fact a mixture of aloin A and B [5,6].

Aloe ferox also contain aloin side A and B, aloin A and B interconvert through the anthranol form as do aloinoside A and B.It also contains emodin, aloe-emodin, aloesin and its aglycone aloesone [7].

Pharmacological actions and uses:

The laxative effects of Aloe are due primarily to the 1,8-dihydroxyanthracene glycosides, aloin A and B. After oral administration aloin A and B, which are not absorbed in the upper intestine, are hydrolysed in the colon by intestinal bacteria and then reduced to the active metabolites (aloe-emodin-9-anthrone) which like senna acts as a stimulant and irritant to the gastrointestinal tract. The laxative effect of Aloe is not

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generally observed before 6 hours after oral administration, and sometimes not until 24 or more hours after [1,5,8].

Aloes are recommended for the treatment of atonic constipation and suppressed menstruation [2].

In folk medicine, Aloe are used for treatment of seborrheic dermatitis, peptic ulcers, tuberculosis, fungal infections, and reduction of blood sugar levels [9].

Hypoglycemic actions have been documented for Aloes extracts. Aloe Vera gel is widely used for the external treatment of minor wounds and inflammatory skin disorders [4].

The gel is used in the treatment of minor skin irritations, including burns, bruises, and abrasions [9].

The gel is further used in the cosmetics industry as a hydrating ingredient in liquids, creams, sun lotions, shaving creams, lip balms, healing ointment, and face packs.

Aloe vera Gel has been traditionally used as a natural remedy for burns, and has been effectively used in the treatment of first and second degree thermal burns and radiation burns [3].

In folk medicine, aloe vera is used for the treatment of acne, haemorrhoids, psoriasis, anemia, glaucoma, blindness, eczema, and fungal infections.

The aloe vera extracts exhibited an anaesthetic reaction, antibacterial action, and increased local microcirculation [10].

It has been experimentally proven that aloe vera liquid is effective in treating ulcers in the oral cavity.

In experiments, it has been proven that aloe-emodin has an antitumor effect, and that the effect of the laxative anthracinone has been known for a long time, and there are some experiments that indicate that aloe vera extract in diarrhea is more severe than the effect of senna and cascara [8].

The active substance in aloe vera is obtained from the tissue in the middle of the aloe vera leaf and consists of fats and some sugars.

Aloes is obtained by evaporating water from the yellow sap, which is obtained from the leaf

Aloe vera does not act as a laxative because it does not contain any anthraquinone compounds

Hypericum:

Chemical constituents

Hypericum contains as its major and active principles hydroxy-anthrone derivatives, mainly of the dehydrodianthrone compound.

The major constituents are known as hypericin, iso hypericin, and protohype ricin [11].

Pharmacological actions and uses:

In folk medicine, Hypericum is used for the treatment of mouth infections. The Hypericum extracts exhibited antibacterial action, anti-inflammatory activity, and antiseptic effect [2,3,11].

Rhamnus:

Chemical constituents

Rhamnus contains as its major and active principles hydroxy-anthraquinone derivatives, mainly of the emodin glycosides and diglycosides type. The major constituents is known as Frangulosides including frangulin A and B and glucofrangulin A and B (emodin diglycosides, emodin derivatives including emodin dianthrone and its mono rhamnoside, palmidin C and its mono rhamnoside, emodin glycoside, It also contains the glycosides of chrysophanol and physcione [12,13].

Pharmacological actions and uses

The active of Rhamnus is characterized by the anthraquinone glycosides constituents. The laxative action of these compounds is well knowen and it supports the herbal use of rhamnus as a laxative medicine [4].

Rhamnus is stated to active as mild purgative properties and has been used traditionally for constipation [2,14].

Rheum:

Chemical constituents

The major constituents are hydroxyanthracene derivatives including emodin, physcion, aloe-emodin and chrysophanol glycosides, along with di-O, C-glucosides of the monomeric reduced forms (rheinosides A- D), and dimeric reduced forms (sennosides A-F). The level of the oxidized forms is maximal in summer and almost nil in winter.

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It also contains heterodianthrones including palmidin A (aloe-emodin, emodin), palmidin B (aloe-emodin, chrysophanol), palmidin C (chrysophanol, emodin), sennidin (rhein, aloe-emodin), rheidin B (rhein, chrysophanol), and rheidin C (rhein, physcion) [15-18].

Pharmacological actions and uses

Rhubarb has been used in traditional medicine both as a laxative and antidiarrhoeal agent.

The laxative action of anthraquinone derivatives is well-recognized and Rhubarb also contains tannins, which active like an astringent action [16,19].

In low doses, is stated to act as an antidiarrhoeal because of the tannin components, whereas at higher doses it exerts a cathartic action.

In folk medicine rhubarb is used to treat hypotension, increase peripheral vasodilatation, and inhibit blood coagulation. This activities are not supported by experimental or clinical data [20,21].

Rubia:

Chemical constituents

Rubia contains as its major and active principles hydroxy-Anthracene derivatives, mainly of the oxy and - oxy –methyl anthraquinone glucoside type. The major constituents are known as Alizarin, rubiacin, purpurin [22,23].

Pharmacological actions and uses

In folk medicine, extracts from under the ground of Rubia have been used for the treatment of kidney stones. Rubia possess antispasmodic activity, and urolith action.

The activities of rubia can be attributed to the alizarin constituents of radix rubia tinctorum [2,3,24].

Rumex:

Chemical constituents

Rumex contains as its major active principles hydroxy-anthraquinone derivatives, such as emodin, physcion, chrysophanol, and aloe-emodin. It also contains glycosides of chrysophanol and emodin [25-27].

Pharmacological actions and uses

Rumex has been used traditionally as a laxative and antidiarrhoeal agent [25].

Rumex also contains tannins, which exerts an astringent action. At low doses, it is stated to act as an antidiarrhoeal because of the tannin components, whereas at higher doses it exerts a cathartic action. In folk medicine, rumex is used to treat hypotension, and haemorrhoids. These activities are supported by medical experiment [27].

Senna:

Chemical constituents

Senna contains as its major a family of hydroxyanthracene glycosides, the most plentiful of which are sennosides A and B. There are also small amounts of aloe-emodin and rhein 8-glucosides. It also contains free anthraquinones such as aloe-emodin, chrysophanol and rhein with their glycosides [4,28-30].

Pharmacological actions and uses

The effects of folium sennae as a laxative are due primarily to the hydroxyanthracene glycosides, especially sennosides A and B. which are converted by bacteria of the large intestine into the active derivatives. (rhein-anthrone) [2].

In folk medicine, senna used as an expectorant, a wound dressing, an antidysenteric, a carminative agent, a treatment of gonorrhea, skin diseases ,dyspepsia, fever, constipation and haemorrhoids [3].

Antihepatotoxic activity has been documented for naphtho- α - pyrone and naphtho- γ - pyrone glycosides, and for the anthraquinone glycosides isolated from a related species Cassia tora. Greatest activity was documented for the naphtho- γ - pyrone glycosides. Significant inhibitory activity against leukemia has been documented for aloe – emodin [29].

The results of author's studies:

Author has studied a lot of plants of Flora Ukraina, Jordan, Uzbekistan, Russia and Palestine.

***Senna (Cassia)*:**

Author and co-workers used thin layer chromatography and paper chromatography for the separation of anthraquinone derivatives from Cassia angustifolia vahl. Flora of Uzbekistan; using

- n-Toluene –acetone – 50% acetic acid (4: 1: 0.5)
- N-butanol – acetic acid – water

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(4:1:5) or (4:1:2)

- N-propanol – ethyl acetate – water

(40 : 40 : 30) as eluent for both the glycosides and the aglycones.

Aloe –emodin, emodin, rhein, chrysophanol, sennoside A,B, rhein-glycosid , and aloe –emodin glycoside have been identified [31].

Also antimicrobial activity of extracts from folium Cassia angustifolia Vahl, has been evaluated in *vitro* against: Staphylococcus aureus, Escherichia coli, Bacillus subtilis, and one yeast (Candida albicans) which are known to cause dermic and mucosal infections, beside other infections in humans. All extracts showed antimicrobial activity towards the Gram- positive, Gram-negative bacteria and fungicidal activity against C.albicans [32].

Aloe :

Author from folium Aloe arborescens has been isolated aloin, emodin, and aloe-emodin, by using thin layer and paper chromatography, and authentic samples [33].

Rumex :

Author and co-workers used thin layer chromatography, paper chromatography, column chromatography, preparative chromatography on paper and authentic samples, for the separation of anthraquinone derivatives from rumex. (Table 1)

(Table 1) Species of rumex that have been studied

Flora of Ukraine and Russia	Rumex crispus
	Rumex confertus
	Rumex thyrsiflorus
Flora of Palestine	Rumex cyprius
	Rumex dentatus
	Rumex pulcher

Using :

- N-Toluene –acetone – 50% acetic acid (4: 1: 0.5)
- Hexane – ethyl acetate – acetic acid

(90 : 5 : 5).

- N-butanol – acetic acid – water

(4:1:5) or (4:1:2) as eluent for both the glycosides and aglycones.

The chemical structure of the compounds (emodin, chrysophanol, physcion, aloe-emodin, chrysophanein, and glucuemodin) isolated has been identified on the basis of their chemical transformations UV-, and IR- spectra [27].

Also the antimicrobial activity of aqueous-alcoholic extracts from all species above, has been studied with the help of different microbiological methods, in vitro; against: Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Candida albicans, Streptococcus pyogenes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter aerogenes, Shigella flexneri, Salmonella enteritidis, and Bacillus subtilis.

It has been established that the extracts from Rumex thyrsiflorus and Rumex pulcher have the highest bactericidal and fungicidal activities; it allows us to consider their perspective to produce new phyto-remedies [3].

Rheum (Rhubarb):

From Rheum palmatum –flora Ukraine- author and co-workers used thin- layer chromatography for the separation of anthraquinone, using as eluent:

- N-Toluene –acetone – 50% acetic acid (4: 1: 0.5)
- N-butanol – acetic acid – water (4:1:5) or (4:1:2)

It has been identified as chrysophanol and chrysophanein.

The ethanolic extracts from Rheum palmatum, showed antibacterial activity against (3) bacterial species, and showed anticandidal activity [34].

Rubia tinctorum:

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Author used thin layer chromatography, paper chromatography, for the separation of anthraquinone derivatives from rubia. It has been identified alizarin and alizarin -1- methyl ether [35-36].

The Pharmacological Activity of Natural Anthraquinone

The naturally occurring anthraquinone can be divided into two groups on the basis of their biosynthetic pathways, a division which parallels therapeutic use. The first of the group is the anthraquinones, which is found in the Leguminosae (Cassia sp.), Rhamnaceae (Rhamnus sp.), and Polygonaceae (Rheum sp.- Rumex sp.) and is widely used in medicine because of their laxative action. This group of anthraquinone occurs mostly in the form of glycosides. The second group of anthraquinone is found in the Rubiaceae (Rubia sp.) and some related families, (Bignoniaceae, Scrophulariaceae, and Verbenaceae) have been used in traditional medicine. For example, in Germany extracts of the roots of Rubia tinctorum L. have been used for the treatment of kidney stones [3,4,37].

Some of the natural anthraquinones, however, exhibit very interesting biological in vitro and in vivo activities: antimicrobial, hypotensive, and antileukemic properties have been reported.

This part of paper has been written in order to discuss all pharmacological and biological activity of natural anthraquinone derivatives and to update literature of these properties.

Laxative action

The anthraquinone and related glycosides are stimulant cathartics and exert their action by increasing the tone of the smooth muscle in the wall of the colon and stimulate the secretion of water and electrolytes into the large intestine. After oral administration, the anthraquinone glycosides are hydrolyzed in the colon by the enzymes of the microflora to the pharmacologically active free aglycones which usually produce their action in 8 to 12 hours after administration[1-4,8].

These agents are individual for constipation in patients who do not respond to milder drugs and for bowel evacuation before investigational procedures or surgery. Stimulant laxatives are habit-forming, and long-term use may result in laxative dependence and loss of normal bowel function.

Glycosides of anthranols and anthrones elicit a more drastic action than do the corresponding anthraquinone glycosides, and a preponderance of the former constituents in the glycosidic mixture can cause discomforting gripping action[25,37].

The drugs of choice are cascara sagrada, frangula, and senna.

Aloe and rhubarb are not recommended because they are more irritating which increases the chance for gripping action[1-4,8,25,37].

Antidiarrheal action:

The oxidized forms of anthraquinone have clearly demonstrated the antidiarrheal effect. Grytsyk A.R. was offered to the underground organs of Rumex alpinus L. as a new medicinal plant with hepatoprotective and antidiarrheal activity[2,3,25,37].

Anti-psoriasis activity :

Chrysarobin is a mixture of neutral principles obtained from the roots of Rumex tianschanicus and Rhubarb tanguticum, the constituents are various anthraquinone, such as chrysophanol, emodin, physcion and their anthranols, anthrones forms[2,3,25,37].

Although the drug possesses cathartic activity. Chrysarobin is used externally, usually in an ointment as a keratolytic in the treatment of psoriasis, trichophytosis, and chronic eczema[25,37].

Antibacterial and Antifungal activity:

It has been established that the aqueous – alcoholic extracts from Rumex thyrsiflorus and Rumex pulcher have bactericidal and fungicide activities.Derivatives of anthraquinone such as rhein, emodin, aloe-emodin, alizarin, chrysophanol and physcion showed various inhibitory effects against streptococci and staphylococci[25,32,34,38-40].

Antiviral activity :

Compounds of dianthronic nature, which were obtained from Hypericum perforatum, demonstrated anti-virus activity in vivo. Emodin, physcion, aloe-emodin which was obtained from Aloe vera, Frangula, and Cassia angustifolia are used for treatment of many diseases caused by virus Herpes simplex[2,3,19,41-42].

Ntihypertensive and Sedative action:

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It has been established that tincture from the root of Rumex confertus has hypotensive and sedative action. This activity is characterized by the anthraquinone derivatives[25,37].

Antinephritic action:

Dry extract from Rubia tincture has been used in traditional medicine for the treatment of kidney stones and bile stone.

As a result of experiments, it has been established that alizarin and its derivatives have anti-urolith action, which was obtained from Rubia tinctorum [1,25,37].

Diuretic effect:

Asphodelus fistulosus is a plant used in folk medicine as diuretic, and the effects of this plant are due primarily to the anthraquinone derivatives[1,3,37].

Antispasmodic and Hepatoprotective activity:

From the underground organs of Rumex alpinus was obtained extract which contained derivatives of anthraquinone, and possessed hepatoprotectant and antispasmodic action. Emodin, which is obtained from many plants, showed anticholiric and antispasmodic effects[1,6,37].

Photodynamic and Radioprotective effect:

As a result of experiment, it has been established that dimmer- emodin type hypericin, which was obtained from Hypericum perforatum, possess photodynamic activity[1,3,37].

Antineoplastic activity:

They are a lot of antibiotics, which constituents anthraquinone, used for their antibacterial and antineoplastic action, for example: Antibiotic 289F and X-14881C -1,2,4,6,8-pentahydroxy-anthraquinone, showed high antineoplastic activity against cancer Cartsinoma. Emodin and Rhein stopped growing Melanoma and Ehrlich's cancer. Antineoplasyic activity has been documented for alizarin and some derivatives of chrysophanol [2,3,20,43-44].

Anti-inflammatory activity:

It has been documented for derivatives of anthraquinone obtained from frangula, rumex, rhubarb and aloe. Extracts from these plants used in traditional medicine for treatment of wounds, burns, ulcers, eczema and skin illnesses. Aqueous extract of the roots of Rumex patientia exhibited strong anti-inflammatory, antipyretic and analgesic activities[1,45-46].

Antidepressant activity:

Capsules antidepressant obtained from Hypericum perforatum, the constituents are compounds of dianthronic nature. Exhibited strong antidepressant activity[1,37].

Lipotropic activity:

Many derivatives of anthraquinone are able to activate or inhibit many enzymes and fermental systems, for example: It has been reported that emodin has an effective inhibitor of many enzymes like trypsin and lipase.

Derivatives of anthraquinone (chrysophanol, emodin, rhein, and frangulin) have been studied for their lipotropic activity on enzyme lipase in vitro, a result of experiments showed that all anthraquinone possess inhibit or activate lipase[1,13].

Other activities:

The derivatives of anthraquinone exhibited

- Hypoglycemic actions.
- Anti-arthritic activity.
- Antitumor activity.
- Antiemetic.
- Carminative action.
- Antileukemia.
- Antimalarial activity.
- Antioxidant action.
- Anti Helminthiasis.
- Analgesic.
- Antipyretic.

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antihistaminic, anticholinergic, and anti bradykinin activity[47-61].

The toxicity:

The toxicity of anthraquinone derivatives is very low. After oral administration in animals, no mortalities are seen at dosages up to 2000-3000mg/kg, depending on the type of extract used .In chronic toxicity studies for up to 6 months, at dosages which do not produce too marked laxative effects, no toxic effects can be demonstrated in the various organs and apparatus. Controlled clinical studies conducted in patients of all ages (including children and elderly patients) and in conditions such as pregnancy and the puerperium, have clearly documented the therapeutic efficacy and the good tolerability of anthraquinone derivatives. In patients requiring prolonged treatment, these old drugs appear to be tolerated better than the synthetic laxatives with irritant/ detergent action, which when administered chronically, are known to exert toxic effects on the intramural innervations of the intestine [2,3].

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