ALOE TODAY

Part Four

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PHARMACOTOXICOLOGY OF THE ANTHRANOID CONSTITUENTS

1. THE CATHARTIC ACTION

Aloe and its constituents/derivatives is considered the most energetic laxative of the common purgative drugs (senna, cascara, frangula, rhubarb) and, as such, was greatly used in the past from time immemorial (the Ebers Papyrus from Thebes). Even today, in the presence of serious constipation and in individual, non-continuous cases, it can be used profitably (see below, under point 3, the undesired effects).

The Italian Pharmacopoeia, up to the 7th edition (FV II), contained the preparation for "Dragees of *Aloe compound*" (vol. III, p. 37) with the following composition.

Composition.		
One dragee contains:		
Aloe powder	mg	50
Dry aqueous extract	mg	50
Dry aqueous extract belladonna	mg	10
Preparation.		
1) Aloe powder	g	50
Lactose	g	10
Starch	g	10
2) Starch	g	4
3) Dry aqueous extract rhubarb	g	50
Dry aqueous extract belladonna	g	10
Silica gel	g	10
Starch	g	15
Lactose	g	11
4) Alcohol		q.s.
5) Silica gel	g	0.5
Talc	g	8
Magnesium stearate	g	1.5

The pulverized substances 1) are granulated with 2) in the form of starch water at 10%. The substances 3) are granulated with con q.s. of 4). The two granulates are dried and mixed with 5). It is homogenized and tablets with a weight of about 0.18g each are made using convex punches with a diameter of 8 mm. Dragees with a weight of approximately 0.36 g are made in a pan.

The "*Laxative tincture of aloe*" was also used which, due to its bitter flavour, was prepared with the addition of corrective drugs. The National Formulary IX (USP 17) gives, for example, the following formula (Aloe Tincture):

Composition.		
Aloe powder	g	100
Liquorice root powder	g	200
Extraction solvent:		
Alcohol 95 %	ml	500
Purified water	ml	500

Add to the drug 750 ml of solvent and extract by shaking, until exhaustion. Filter and wash on the filter, bringing to volume of 1000 ml with the same solvent.

Laxative dose: 2 ml.

The use of "Compound Tinctures" was also very common and they were widely used as digestives. In this regard see point 4 below.

According to the Commission E, the maximum recommended daily posology is equal to the quantity of product corresponding to 20-30 mg of aloin (see NATURAL 1, November 2002, page 45) whilst the exact individual dosage is the minimum one that can allow the formation of soft faeces.

As the above formulas show, there is a preference, in the treatment of constipation, to associate aloe with other drugs (rhubarb, as a corrective of the taste; belladonna, as an anti-spastic; boldo, as a cholagogue) rather than use it alone.

Some authors also consider that diet has an influence on the metabolism of aloin in man. Cereals, for example, are believed to slow it down (2), whilst protein foods seem to activate it (3).

2. THE MECHANISM OF THE LAXATIVE ACTION

Although there is little systematic research on the pharmacokinetics of the various anthranoid compounds, it is accepted opinion by the majority of researchers that their laxative action is to be attributed to the irritant stimulus that the free anthranols have on the mucous. After oral administration of a mixture of glycosides and aglycones, the latter are already absorbed in the upper tract of the tenuis, metabolised in the liver and eliminated by the kidneys in the form of sulphates or glucuronates. Only a small part of the glycosides follows the same metabolic path because the majority of them directly reach the large intestine where the bacterial enzymes hydrolyse them and transform them into anthrones, which are deemed active metabolites. These mainly influence the motility of the colon (the portion of the large intestine that goes from the cecum to the rectum) by means of the inhibition of stationary contractions and the stimulation of the propulsive ones with acceleration of the intestinal tract; in addition, through an activation of the secretion of chlorides, there is an accumulation of water and electrolytes. The glycosides (aloin) thus represent "prodrugs" that provide for the transport of the laxative ingredient (aloeemodin ‡ aloeemodinanthrone) until the site of action, avoiding their rapid metabolization as an aglycone.

The results of this empirical research already go back more than half a century (1) and are always referred to as such by all foreign literature. It is however thanks to the researchers of the Department of Experimental Pharmacology of the "Federico II" University of Naples (2) whose further in-depth research has produced, in recent years, a better explanation of the intimate mechanism of action of stimulus on the colon which includes the inhibition of Na-K-ATPase (sodium-potassium adenosintriphosphatase) and the release of nitric oxide (NO) which stimulate the secretion of electrolytes and the relaxation of the smooth intestinal muscles. These studies also outline a new physiopathological role of NO regarding PAF (Platelet Activating Factor), an endogenous lipid (which is originated inside the organism) and which causes the contraction of the smooth musculature.

3. UNDESIRED EFFECTS AND POTENTIAL TOXICITY

According to the E Commission, stimulating laxatives, such as aloe, should not be taken for prolonged periods (more than 1–2 weeks) without consulting a doctor. Chronic abuse may cause loss of electrolytes, especially of potassium (with subsequent disorders of the cardiac function and muscular hyposthenia), albuminuria and erythrocyturia; possible pigmentation of the intestinal mucous (*Pseudomelanosis coli*) and/or reddish colouring of urine are on the other hand atoxic and reversible at the end of treatment. Use during pregnancy and breastfeeding should also be avoided due to the increased blood flow of the pelvis, even if it has never been proved that it has an abortive action.

Tests of the mutagenic nature of the anthranoid aglycones, conducted in vitro (bacteria and cells of mammals) with emodin and aloeemodin by researchers at the University of Hamburg, appear to give partially positive results (5) whilst chrysophanol and physcion appeared, again in vitro, weakly genotoxic. (6). In 1994, these reports led the German Ministry for Health (then the BGA or Bundesgesundheitsamt) to limit as a precaution the presence of free aglycones in therapeutic products to the following percentages: rhein: 0.9-2.3; aloeemodin: 0.05-0.15; emodin: 0.001-0.006 or to request experimental tests in the absence of genotoxicity and/or mutagenicity in the product until registration (7). Not only these restrictions, still valid in Germany were not accepted by any other country (with the exception of Austria) but all the tests of genotoxicity in vivo (in rodents) conducted with sennosides and their aglycones (rhein, aloeemodin and emodin) were negative (8). This conclusion was also reached, after two years of experimentation, by the aforementioned researchers of the University of Naples, in a work of forthcoming publication (9). As a final result of the therapeutic debate on aloe, the precautions of use suggested by the E Commission (see above) can be considered as current and valid but the complex action at cellular level, observed in the aglycones, encouraged the discovery of their capacity to induce apoptosis in tumourous cells (see point 5).

4. THE STOMACHIC, AROMATIZING AND TONIC ACTION

Even if today, due to the difficulty of a certain diagnosis and a subsequent effective therapy, the problem of "tonic bitters" has gradually lost medical interest, tradition, above all in phytotherapy, counts several "bitter" plants which have always been used against dyspepsia which appears with various symptoms, including loss of appetite, sense of satiety and weight in the stomach and slight abdominal pain. The subjective elimination of these symptoms by "bitters" is based on their capacity to stimulate the digestive glandular secretion reflexively: namely, whilst a reflex originated by the lingual taste buds which are sensitive to a bitter taste would stimulate the saliva and gastric secretion (secretomotory effect), the liver, pancreas and bile should also as a consequence be activated due to the functional unity existing between the glands for digestion (cholagogue effect).

Mention has already been made under point 1 that aloe, at lower doses that the purgative one, was also often used as a tonic, digestive and aromatic bitter with cholagogue

Compound Tincture of aloe	
Tincture of aloe	Preparation: mix 3 grams of each tincture.
Tincture of quinquina	Posology: XV-XXV drops, before meals, as a digestive
Tincture of gentian	
Tincture of rhubarb	
Tincture of nux vomica	
Compound elixir of aloe	
Fluid extract of aloe	Posology: 2-3 small glasses a day
Fluid extract of rhubarb	each grams 30
Fluid extract of gentian	
Fluid extract zedoaria	each grams 5
Tincture of saffron	grams 25
Alcohol 95°	grams 150
Simple syrup	grams 500
Water q.s. to	grams 1000
Hager Elixir	
Fluid extract of aloe	Preparation: mix and filter
Fluid extract of myrrh	Posology: 2-4 grams twice a day
Fluid extract of rhubarb	
Tincture of saffron	each grams 20
Diluted hydrochloric acid	grams 10
Sweet white wine	grams 200

properties. For this purpose, the "compound tinctures" were mainly used, i.e. alcoholic solutions of aloe in association with various drugs which were coadjutant or corrective of the taste. They were very common in central and northern Europe under the popular name of "Swedish drops" (Schwedentropfen) to which a psychostimulant effect was also attributed, as well as the tonic action (10); the Italian use of bitters, elixirs and the so-called "Fernet" also derives from these tinctures. As an example, some formulas of these preparations are given (11). A very well documented research doctorate has recently been carried out on this subject at the University of Trieste (12).

5. THE ANTI-TUMOUROUS ACTIVITY OF EMODIN AND ALOEEMODIN

From as early as the 1970s, medical science had recognized the immunostimulant action (with probable anti-tumourous activity) of some preparations of aloe (13) in which it was necessary in the end to identify the active responsible ingredients. There have been numerous reports on the use, with encouraging results, of these preparations (made up of mixtures): amongst the latest reports, a recent paper at the 2002 S.I.T. conference (17) on two clinical tests carried out with aloe and melatonin (MLT) against melatonin on its own, following experimental statistical criteria, at the Oncology Radiotherapy Division of the San Gerardo Hospital of Monza. In the first (various advanced solid neoplasia, including with metastasis) a tincture of aloe (10% in alcohol at 40%) was used; in the second (neoplasia of the biliary tract) a preparation similar to the well known one of Father Zago, consisting of fresh aloe leaves 300g, honey 500 g and 40 ml of 40° alcohol, was used with the following results: "In the first study, the percentage of non-progression of the disease was significantly greater in patients treated with aloe + MLT (14/24 vs 7/26) as was the percentage of survival after 1 year (9/24 vs 4/26); in the second study, objective tumourous regression was obtained in 3/14 (21%) consisting of a complete response and only two partial responses, with an average duration of 18 months. Stabilization of the disease was also obtained in 6 patients, therefore with a percentage of non-progression of the illness equal to 9/14 (64%) of the patients. Overall, the administration of aloe, both as a mixture and as a tincture, was well tolerated and the only side effect was that of slight diarrhoea, well controlled by common treatments".

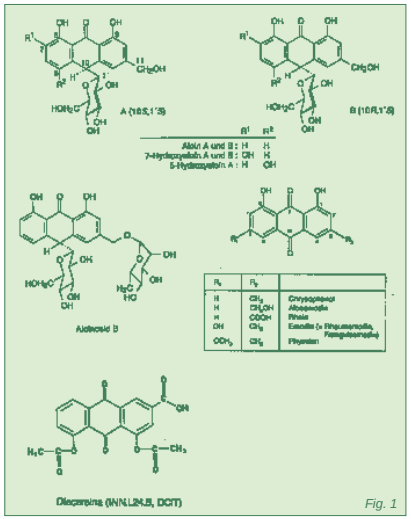

Fig. 1

Whilst the experimentation and applications were turned preferentially to the polysaccharides of aloe gel (see "Part five", forthcoming), there were surprising results of a group of Chinese researchers, active at the Anderson Cancer Center of the University of Houston, Texas, who identified in emodin (isolated from rhubarb) an anti-tumourous ingredient active in repressing the transformation and metastatic properties of the proto-oncogene Her-2/neu-overexpressing breast cancer cell (14) and which also makes Her-2/neu pulmonary overexpressing tumourous cells less resistant to chemiotherapy treatment (15).

Subsequent in-depth research carried out at University Institutes in Padua and Genoa (16) not only show that aloeemodin is a new type of anti-cancer agent that is selectively active against neuroectodermal tumours (typical of the paediatric age), but simultaneously its action is carried out through selective apoptosis (programmed cell death) of the carcinogenic cells and not those of the adjacent healthy tissue. The researchers such say the following in the Abstract: "It is shown here that aloeemodin…carried out, in vitro and in vivo, a specific antineuroectodermal antitumourous activity. The growth of neuroectodermal tumours is inhibited in the seriously immunodepressed mouse, without any toxic effect for the animal. The compound does not inhibit the proliferation of the normal fibroplasts nor that of the hemopoietic progenitor cells. The mechanism of action of aloeemodin consists of the induction of apoptosis and its selectivity for the neuroectodermal tumourous cells is linked with its specific incorporation, energetically correlated within the cell. Considering the uniqueness of its cytotoxic profile and its mechanism of action, aloeemodin can conceptually represent an innovative anti-tumourous substance".

With regard to the aforementioned energetically correlated incorporation of the aglucone within the cell, the authors subsequently specify, in the paper, that the glucoside (i.e. aloin) tested in the same way, is not incorporated and does not show anti-tumourous activity. As far as the difference of metabolism between glucoside and aglucone is concerned, see also under point 2, on the laxative mechanism of action.

Further research on the anti-tumouraous biological mechanisms of emodin and aloeemodin was carried out by the China Medical College of Taiwan (18) whose researchers wanted to check if the enzymatic processes, induced by the two anthranoids, in the carcinogenic cells reproduced the well known enzymatic processes which cause apoptosis. The results fully confirmed what the Italian researchers in Padua and Genoa (see above) had pointed out.

A group of cysteinic proteases (enzymes that catalyse the scission of the proteins into peptidic fragments) called "caspases", plays a fundamental role in the biochemical and morphological processes linked with apoptosis. The group of the caspases is in its turn divided into two sub-groups of initiator caspases, as caspases-8 and –9, and (effector) caspase as caspase-3; for there to be apoptosis, the action of effector caspase-3 is necessary but this must be activated, directly and indirectly, by an initiator caspase.

Subjecting to tests the action of emodin and aloeemodin in the apoptosis of the cells of human squamous cell lung carcinoma CH27 and non-small lung cancer cells H-460, the Chinese researchers were effectively able to highlight the aforementioned enzymatic mechanism obtaining further confirmation from other processes linked with the modification of the expression of isozymes of the protein kinase.

6. DIACEREINE

Diacereine is the diacetyl-derivative of rhein which, in its turn, is a product of oxidation of aloeemodin (see the formulas in the figure; its method of preparation is described in Part Three, in Natural 1, November 2002). Contrary to what has been considered so far, diacereine does not show the biological characteristics described for anthranoids, but is configured as the head of a new class of drugs with a prevalently anti-arthrosis activity. It has shown that it can inhibit the action of the proteolytic enzymes responsible for the disaggregation of the proteoglycans (glycoproteins of connective tissue with a cementing function) of the cartilage of the joints. It also inhibits the release and activity of lysosomial enzymes, the formation of peroxides and free radicals, responsible for the inflammatory arthrosis process.

Due to the anthraquinonic structure, the undesired effects may potentially include a laxative action, an increase in enterocolitic disorders already present and a reddening of urine.

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