New aspects regarding efficacy and safety of sennoside drugs in Eucarbon®

The brilliant formula of Mr. Trenka (I)
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1. Introduction
Eucarbon® is a traditionally used combination of laxative drugs containing sennosides (Senna and Rhubarb) and vegetable charcoal (carbo ligni).

EUCARBON, based on the above ingredients, has proven its efficacy in a wide spectrum of applications that can be summed up under the term “General regulation of digestion”. This includes the following indications (depending on the marketing authorisations):
- Sluggish intestinal transit
- All forms of constipation
- In decomposition and fermentation processes of the small intestine
- Meteorism (elevation of diaphragm)
- Flatulence
- Intestinal auto-intoxication
- Haemorrhoidal constipation
- Irritable bowel syndrome

Eucarbon® stimulates the entire digestive system, has a mild laxative and spasmolytic effect and relieves gas pains.

This review presents new results for the active laxative sennoside drugs in EUCARBON based on new scientific research published regarding efficacy and safety and its implication for EUCARBON.

2. Development made by the pharmacist F. Trenka in 1909:
The most important and interesting achievement of the scientist and pharmacist, Mr. Trenka, was the development of a new formula combining the following drug substances:
- Combination of 2 Sennoside drugs
- Combination of laxative drugs with the mild adsorbent compound

“Vegetable charcoal”, a kind of non-activated charcoal (will be discussed in a follow-up publication)

Up to some years ago it was unclear, why Mr. Trenka, see fig 1,

Figure 1: Mr. Trenka developed EUCARBON

used two Sennoside drugs with very similar active components (as known so far) in one pharmaceutical product.

Especially as this makes it not very easy for the manufacturer to
1. show evidence that the presence of both drugs in EUCARBON is justified.
2. demonstrate and measure the content of the amount of each drug used as part of the quality documents. This point could be overcome by using an analytical method suitable for the determination of the total amount of the active components of the sennosides, the aglycons, which were estimated as total anthraquinone derivatives (TAD).

3. Chemical and pharmacological properties of the sennoside drugs (traditional, established use)
Senna and rhubarb, which are constituents of Eucarbon®, are popular purgative crude drugs and have been employed for centuries as laxatives.

EUCARBON contains the following amount of active ingredients of Sennoside drugs:
- Senna leaf (Pol. sennae specified acc. European pharmacopoeia): 105,00 mg/tab.
- Rhubarb Extract (Extractum Rhei spec. acc. German Pharmacopoeia): 25,00 mg/tab.

Senna Leaf, the dried leaflets of Cassia senna L. (C. acutifolia De Lile) and Rhubarb extract, manufactured from the dried rhizome and root of Rheum officinal Baillon or of Rheum palmatum Linné (Fam. Polygonaceae) using 70% ethanol for the extraction contain similar active principles:
The main active constituents are sennosides A and B; further sennosides, C and D are present to smaller amounts. Sennosides are glucosides possessing two moles of glucose and the so-called 1,8-dihydroxyanthracene - aglycons, the pharmacological active substance, such as Rheum-emodin, rhein, aloë-emodin, chrysophanol and Physcion.
Pharmacodynamic – pharmacokinetic properties (monograph ESCOP, 1999):
1,8-dihydroxyanthracene derivatives possess a laxative effect. The b-linked glucosides (sennosides) are not absorbed in the upper gut; they are converted by the bacteria of the large intestine into the active metabolites (rhein anthrone). There are two different mechanisms of action:
1) Increase of the motility of the large intestine (stimulation of peristaltic contractions and inhibition of local contractions) resulting in accelerated colonic transit, thus reducing fluid absorption.
2) Influence on secretion processes (stimulation of mucus and active chloride secretion) resulting in enhanced fluid secretion.
Defecation takes place after a delay of 8 – 12 hours due to the time taken for transport to the colon and metabolisation into the active compounds (aglycons).

4. Pharmacological Properties of Rhubarb according new scientific research
A literature update of the scientific research activities for the last years up to end of 2004 revealed very new and interesting aspects of the properties of rhubarb, either used as root powder or extract, and of some of the active ingredients, respectively.

4.1 Adstringend effect
Rhubarb is known to have also tanning ingredients: glucogallin and tetrarin which yield glucose gallic acid and other products upon hydrolysis.
These ingredients can lead to the opposite effect of the anthraquinones: constipation. It is assumed that the adstringend, antilaxative effect will play a role in low doses (Wichtl, 1997). In Chinese medicine these low doses of rhubarb root (0.05 – 0.5g/day) are used for the treatment of chronic diarrhoea (Hänsel und Haas, 1983). This is in complete correlation with the dual action of EUCARBON®, known for many years and which up to now primarily has been addressed to the content of vegetable, non-activated charcoal.

4.2 Anti-bleeding and antiphlogistic effects
Studies have demonstrated that Rhubarb reduces bleeding in the upper and lower part of the intestine (gastro-intestinal part). This may also be the result of the content of tanning agents as well as to the antiphlogistic effect of some other ingredients (Hager’s Handbuch, 1993).
In addition 3 studies published in the last years have given evidence that rhubarb and its active principles are effective against inflammation and are protective against pancreatitis and hepatic encephalopathy:
Zhang et al, 2002 have demonstrated that an extract of rhubarb prevented and cured experimental hepatic encephalopathy in rats.
In another study (Peng et al, 2002) it could be shown on 40 patients with systemic inflammation reaction syndrome (SIRS) – a very severe illness which is the reaction to a massive systemic infection and might lead to septic shock and death – that treatment with rhubarb powder improved the prognosis of patients: Cure rate in the treated group was significantly higher than that in the control group accompanied with lesser occurrence of multiple organ dysfunction syndrome (MODS) and lower mortality.
In the 3rd study Zhao et al, 2004 published their results of the protective effects of rhubarb on experimental severe acute pancreatitis (SAP) in rats:
Rhubarb can exert protective effects on SAP, probably by inhibiting the inflammation of pancreas, improving pancreatic microcirculation, and altering exocrine secretion.

4.3 Antimicrobiological and antiviral effects:
In the study published by Wang et al, 2003 it could be shown that an extract of rhubarb root (RE) was as effective as acyclovir for the treatment of experimental herpes simplex virus infection in mice:
In addition candida albicans und trichophytes have been stopped in their growth activity (Cyong et al., 1987). In several studies it was reported that anthranoids from rhubarb have antiviral activity against human cytomegal-, herpes- und influenza-Virus (Chen, 1974; Barnard et al.,1992; Hsiang et al., 2001).

4.4 Antioxidative effects
Rhubarb also contains small amounts of (-) Epicatechin3-gallat and Procyanidines, that means substances which are regarded to be antioxidants. This group of substances is especially interesting these days as so-called radical scavengers which can reduce free radicals (instable, very aggressive molecules to cells, membranes, proteins and DNA) and prevent cell damage (from Wichtl, 1997 and Hager’s Handbuch, 1993).
In a study (Lizuka et al, 2004) it was shown that aloe-emodin, chrysophanol and emodin-1-O-beta-D-glucoside exhibited antioxidative activities on Low density Lipoprotein LDL (R=0.914, P<0.01) when 30 specimens of rhubarb of different origin were tested on a spontaneous familial hypercholesterolemia model of rabbits.

4.5 Antitumor and antimutagenic activity

In recent literature many publications and issues were found to prove the use of anthraquinoids and derivatives as anticancer agents (Dunn et Goa, 1996).

Wiseman et al, 1997 showed in their publication the antitumor effect of the anthraquinone mitoxantrone in prostatic cancer. The antineoplastic agent mitoxantrone in combination with a corticosteroid (either prednisone or hydrocortisone) has shown clinical efficacy as palliative treatment for a proportion of patients (about 35 to 40%) with hormone-resistant advanced prostate cancer.

In the meantime mitoxantrone, which exhibits the structural similarity to the aglycons of the sennosides, is an established antitumor agent. Also for Rhein, using human hepatoblastoma G2 (Hep G2) cell line and Emodin using Human promyelooleukemic HL-60 cells the antitumor activity has been demonstrated in recently published studies (Kuo et al, 2004 and Chen et al, 2002).

5. Combination of Senna and rhubarb in EUCARBON: Efficacy and safety

5.1 Efficacy

The efficacy of EUCARBON has been proven throughout nearly 100 years by the long term experience of the many patients who used the medicine. This has also been confirmed by a great number of clinical studies and reports in the different indications. Taking just the last 5 years, a number of studies on EUCARBON have been completed in various countries for the following indications:
1) Austria, Belgium, Morocco and Israel: Treatment of irritable bowel syndrome (IBS), 2000 - 2002
2) Lithuania: Treatment of IBS, 2003
3) Lithuania: Treatment to prepare for emptying of bowel, 2003
4) Georgia: Treatment of IBS, 2003
5) Rumania: Treatment to prepare for emptying of bowel, 2003
6) Austria: mainly constipation, 2003

5.2 Safety

5.2.1 Result of literature research update regarding Senna leaf as an active ingredient in Eucarbon®:

In the publication of Siegers et al in 1993 it was described that the use of anthraquinone containing drugs as laxatives with aloe, cascara (Senna), frangula and rheum might be associated with the development of Pseudomelanosis coli, and further on maybe with adenocarcinoma and colorectal carcinoma. In the same study reference is made to a report with a model of dimethylhydrazine-induced colorectal tumors in male mice where aloin- or sennoside-enriched diets (0.03%) did not promote incidence and growth of adenomas and carcinomas after 20 weeks.

6. Conclusion

The evidence of the efficacy and safety of EUCARBON, which is on the market in two formulations, with and without sulfur (herbal version: EUCARBON herbal), has been demonstrated in this review by literature update regarding safety of the active sennoside drugs rhubarb and senna leaf and by the practical experience from studies and from long term use.

But Mr. Trenka, one hundred years ago, developed a product which has turned out to be a mild but effective medicine with by far more beneficial effects than originally perceived. New scientific results for the active ingredient rhubarb may give evidence to the common saying that “healthiness starts in the gut with a good digestion”, especially if using the multi-active phyto-pharmaceutical EUCARBON for general regulation of digestion.

7. References

On request from the author