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New anti-cancer agent S-1: metabolism based drug combination

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S-1 is a novel oral form of a tegafur (FT, a prodrug of 5-fluorouracil)-based antitumor agent combination. It combines two compounds, 5-chroro-2,4-dihydroxy-pyridine (CDHP) which inhibits DPD(dihydropyrimidine dehydrogenase, rate limiting enzyme of 5-FU catabolism) and mono-potassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate(Oxo) which reduces gastrointestinal toxicity by inhibiting ORPT(orotate phosphoribosyl-transferase, it phosphorylates 5-FU) in the gastrointestinal tract.

We have investigated the pharmacokinetics of each S-1 component and 5-FU in rats and dogs to evaluate the control of 5-FU metabolism and Oxo targeting.

The AUC and C_{max} values of 5-FU, the active metabolite of FT, increased markedly in dogs, 40 times in AUC and 50 times in C_{max}, after administration of the combined preparation than after administration of FT alone. After oral administration of S-1 to tumor (Yoshida sarcoma) bearing rats, the concentrations of FT, 5-FU, CDHP and Oxo in plasma, tumor and small intestine were determined. The concentration of 5-FU in the tumor, which is the target tissue for anti-tumor action, was highest among the tissues, and showed a long duration. The concentration of Oxo, which is added to reduce the toxicity in the digestive tract was high in the small intestine. On the other hand, the concentration of Oxo in the tumor was low, and was not considered to reduce the anti-tumor effect of 5-FU.

Pharmacokinetically the marked species difference in AUC and C_{max} values of 5-FU corrected by the dose in each body surface area was not observed in dogs and rats.

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Retrometabolic approaches in phytobiochemistry

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Our aim was to examine to what extent the principles of the retrometabolism-based drug and chemical design [1–3] may be applied or extended to the phytophysiological processes. As a basis of this hypothesis is the recognition that in living beings the fundamental biological laws and those of them that describe the enzyme systems, are the same. It seems that the possibilities of the soft drug approach are particularly promising. We have first expected immediately accessible results from the study of phytohormones, namely auxins.

The research of phytohormones represents the central field of the up-to-date phytophysiological investigations, where in the last decades two fundamental statements were born [4–10]:

1) the hormones of plants form a coherent functional system,

2) the phytohormones act on both genetical and metabolic levels.

Auxins are implicated in a wide variety of developmental processes in plants, including elongation growth, photo- and gravitropism, apical dominance, lateral root initiation, the differentiation of vascular tissues, embryogenesis and fruit ripening. Auxin has an autoregulating activity, i.e. it induces the formation of decomposing enzymes (e.g. auxin-oxydase) increasingly with the age of the plant. By this regulation the equilibrium between the growth and metabolism is ensured, too.

The action mechanism of auxin is disputed. Experimentally it is known that their growth-stimulating activity as a function of the concentration passes over a maximum (optimum). For its explanation frequently the "two points theory" is accepted. The occurrence of the phenomenon (the appearance of the maximum) could be explained by the inhibitory effect of the gradually multiplied free radicals having appeared due the decompositions caused by auxin-oxydase, too. These two cause-effect relations are not compulsorily independent on each other.

This image is more complicated by a fact known from literature [11]: indole-acetic acid (IAA), above the optimal concentration, induces formation of ethylene, being itself a growth factor, mainly an inhibitor. Possibly, auxin releasing ethylene influences the m-RNA synthesis, thus of the enzymes, too.

Our hypothesis was that replacing the $-CH_2-CH_2-$ structural unit in the "hard" indole-butyric acid (IBA) molecule with the isosteric/isoelectronic $-C(=O)-O-$ and $-O-C(=O)-$ group (ester or reversed ester functions), according to the usual synthesis of "soft" analogues [2], the amount of the phytotoxic metabolic products will decrease. If the oxidative metabolic products inhibit the growth-stimulating effect, one should wait for a modification of the growth-concentration curve form in the case of soft analogues, and the character of these modifications will supply information to the more detailed understanding of the action mechanism.

Our preliminary research results are represented concisely by the curves in Figs. 1 and 2. We followed the stimulating effect by measuring the growth in length of the etiolated oat coleoptiles, in different hormone concentrations, in

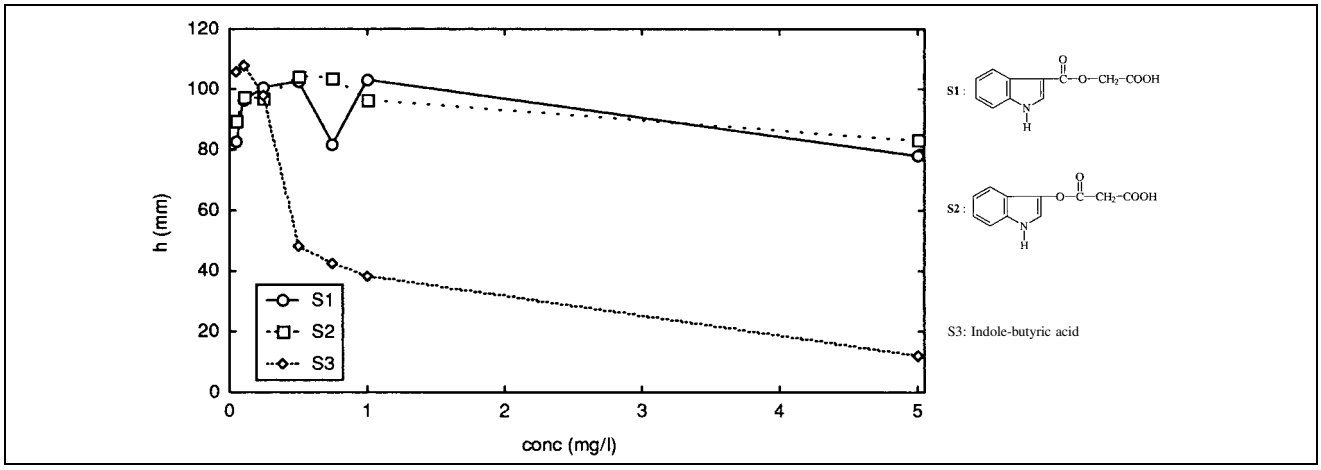

Fig. 1: The growth stimulating activity of IBA and its soft analogues as a function of hormone concentration (the length of the principal root). Average std. err: S1 = 4,7 mm, S2 = 3,2 mm, S3 =3,5 mm

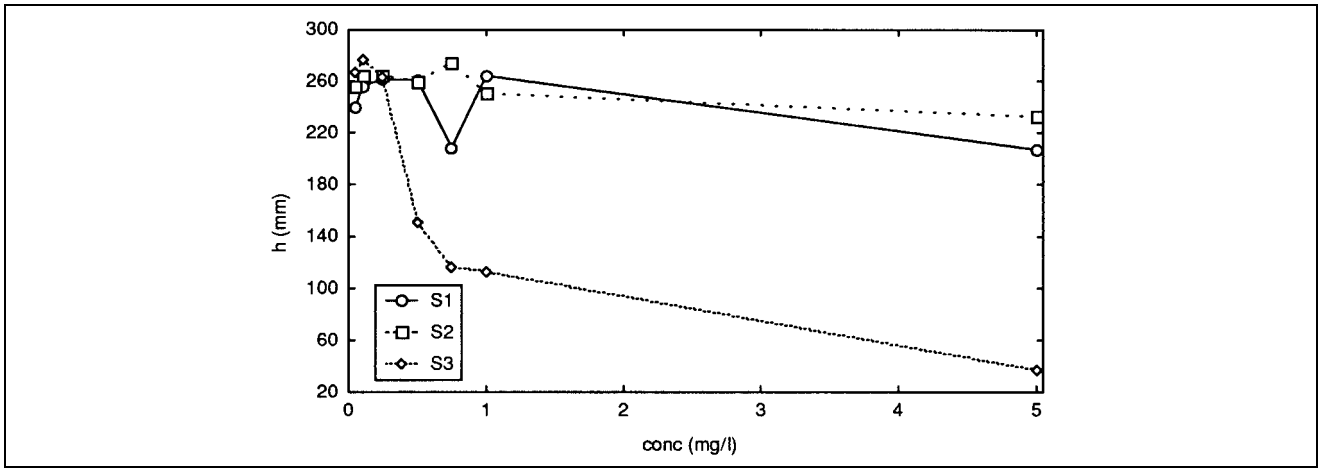

Fig. 2: The growth stimulating activity of IBA and its soft analogues as a function of hormone concentration (the whole length of roots)

aqueous solutions. We have measured both the growth rate and the whole root length developing in 7 days. Since in the course of the experiment secondary roots also developed in an increasing number, in order to compare them, we recorded both the principal and the whole root-length. In the graphs it is visible that while IBA, like IAA, passes over a sharp maximum, tboth soft analogue curves differs essentially: the maximum is flat and reminds nearly of a saturation curve. This last curve type is analogous with the function of average bonding number of biologically active compounds in protein sites from ligand concentration, which opens perspectives for new interpretations [12]. In this case the "two points" hypothesis is not necessary. The decreased activity observed in hard lead compounds agrees with the phytotoxic free radical formation, i.e. it agrees with their inhibiting action as a function of the concentration. In the soft analogues such inhibition practically does not appear even in great auxin concentrations, thus certifying our original hypothesis.

An interesting and reproducible deviation (minimum) is observed in a certain concentration (C = 0.75 mg/l) on both curves for the Indole $-C\overset{\overset{O}{\|}}{-}O-CH_2-COOH$ ester. As an explanation, we suppose that the both types of metabolism simultaneously take place, and their effects will overlap one another. In the above concentration the phototoxic effect dominates, but then the soft character of the hydrolytic metabolism will prevail. To decide in detail this problem, supplementary measurements are necessary. It seems that this phenomenon does not agree with the "two points", theory, either.

These results, beside their principial and theoretical importance, open promising horizons in plant production.

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