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(54) Title: USE OF A HUMIC ACID–CONTAINING SUBSTANCE IN MEDICINE

(57) Abstract

The invention relates to the use of a humic acid–containing substance in medicine, to pharmaceutical compositions containing as active ingredient such a substance, and to a process for preparing this substance. The humic acid–containing substance according to the invention is preferably used in the form of a pharmaceutical composition containing 0.01 to 99.90 % by weight of humic acid–containing substance of peat origin as active ingredient together with carriers and/or other known additives. The invention also relates to a process for the preparation of a humic acid–containing substance of peat origin, which comprises using as the starting material a juvenile, preferably at most 10,000 years old, peat formed from a great bulrush and winter–sedge as peat–forming plants; preparing a suspension by stirring the peat with an aqueous alkaline solution of pH 7.5 to 10.5; utilizing the upper phase of the obtained suspension by adjusting its humic acid content to 10–100 g/L; concentrating it; or bringing it into solid form by dehydration.

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USE OF A HUMIC ACID-CONTAINING SUBSTANCE IN MEDICINE

The invention relates to the use of a humic acid-containing substance in medicine, to pharmaceutical compositions containing as an active ingredient such a substance, and to a process for preparing this substance. The pharmaceutical compositions are useful as a prophylactic to injuries of the haemopoietic system or for regeneration of the injured haemopoietic system.

It is known that humic acids are heteropolycondensates of widely various compositions, respectively, allomelanins, which can be found, e.g. in soils, carbon sorts and peat. Humic acids are formed through a slow decomposition process, respectively chemical and biological transformation of plant materials. [For details, see, e.g., W. Flaig: "The chemistry of humic substances", FA0/IAEA Tech. Meet. Brunswick-Völkenrode, p. 103 to 127 (1963); M. V. Cheshire et al.: "Humic Acids II. Structure of humic acids", Tetrahedron, 23, 1669-1682 (1967); M. Schnitzer and S. U. Khan: "Humic substances in the environment", Dekker, New York (1972); C. Steelinek: "What is Humic Acid?", J. Chem. Educ., 40, 379-384 (1963)]. The humic acids contain complex, polymerized macromolecules of phenolic structure; their composition depends strongly on the site and age of their formation. The metal ion-binding, particularly iron-binding, and chelate-forming properties of humic acids are well known.

Recognition of such pioneering character is disclosed in the Hungarian patent specification No. 158,252, which describes a

composition for satisfying the trace element demand of vertebrates. This composition contains at least 8% of humic acid and metal ions, being in a biologically available form for vertebrates.

Since the end of the 80's, more and more publications devoted to the biological effects of humic acids or humic acid-containing materials have appeared. Thus, the antiallergic effect (German patent specification No. 4,335,523) and antiviral action (German patent specification No. 4,134,378) of humic acids and their salts became known; in addition, within the category of their antiviral action, the humic acids also were found to be useful for the treatment of HIV infections (see the international patent application No. WO 95/08335). Furthermore, data regarding the dermatological, bactericidal, gastrointestinal, and anti-inflammatory effects of humic acids also can be found [for details, see, e.g., Cr. Heinrich: "Huminsäure und Permeabilität", Protoplasma 58, 402-425 (1964); R. Klöcking et al.: "Zur Biochemie der Huminsäuren V. Die Bindung der Huminsäuren an Serumproteine in vitro", Acta Biol. Med. German, 18, 9-13 (1967); R. Obenaus and R. Mücke: "Zur Biochemie der Huminsäuren aus ihren Eisenchelatverbindungen", Acta Biol. Med. German, 10, 233-238 (1963)].

Our initial experiments have been directed to produce a reproducible, standardized humic acid mixture which can be used in the preparation of therapeutical compositions. Thus, our aim was to provide a humic acid mixture obtained by recovery and extraction of a peat originating from a well-characterized source, said peat produced and pre-treated under controlled conditions according to a uniform technology.

It has been found, on the basis of data and recoveries taken from various peat areas, that a standardized base material suitable for the preparation of pharmaceutical compositions can only be achieved by selecting a peat of not more than 15,000 years old, according to

radiocarbon determinations, as the starting material. A homogeneous peat layer of between 3,000 and 7,000 years of age (based on radiocarbon data) and found at depth of between 0.5 to 2.5 m under the ground surface proved to be particularly advantageous. The fibrous structure of this material can be well perceived by the naked eye.

According to the palaeobotanic data, the main peat-forming plants of the starting material referred to above are 20 to 40% of great bulrush (Schoenoplectus lacustris) and 60 to 80% of winter-sedge (Cladium mariscus).

The biological effects of these humic acid-containing substances were studied in several series of experiments. It surprisingly has been found that the humic acid-containing substances prepared by the process to be described later favourably influence the regeneration of the haemopoietic system injured by external whole body ^{60}Co gamma irradiation of the experimental animals.

This recognition is novel and original since no literature data or references were found which would prove such biological activity of humic acid.

Detailed investigations were carried out on experimental animals by using various doses of whole-body gamma irradiation in order to develop a composition and a method of treatment that can be effectively used for human therapy as well.

The biological activity of humic acid-containing substances prepared by the process of the present invention was proven by the experimental results described below.

I. Experimental animals

At the beginning of the experiments, female Wistar rats of 190 to 220 g body-weight (Laboratory Animals Institute, Gödöllő, Hungary), randomized according to weight, were used in test groups. The animals

were kept in plastic cages (5 animals in each cage) at a controlled temperature of 23 ± 3 °C and relative humidity of 60 ± 10% under alternating illumination (12-hour cycles of light/darkness). The rats received standard diet (Code: 624, Altromin GmbH, D-32791 Lage/Lippe, Germany) and water ad libitum. The average daily food consumption was 20 g per animal.

The rats were acclimated to the experimental conditions for two weeks. During the experiment, the general physical condition of the animals was controlled daily.

II. Test material

The preparations were administered to the experimental animals in various doses through a gastric tube.

Natural humic acid product for feeding (in the following text: HA) was prepared by grinding the normal standard rat pellet (see earlier) mixed with the required amount of the material as prepared according to the following Example 1. The mixture was homogenized, regranulated and dried at room temperature.

III. ^{60}Co gamma whole body irradiation

The whole body exposure of rats was performed in a special plastic cage (40 animals/cage) with an irradiation dose of 7.0 Gray (Gy) (dose intensity = 0.82 Gy/min). The $LD_{50/30}$ value characteristic of the rat strain was found to be 7.5 Gy.

IV. Haematological investigations

On days 0, 7, 14, 21 and 28 of the experiment, the animals were anaesthetized by ether; the abdominal section of the aorta was prepared and blood samples were taken.

The haematological parameters, including white blood cell (WBC) count, red blood cell (RBC) count, haemoglobin (HGB), haematocrit (HTC), platelet (PLT) count, and reticulocyte (RET) count, were

determined by using MEDICOR PHA-1 and PHA-2 type haematologic automatic devices (MEDICOR Ltd., Budapest, Hungary).

V. Experimental groups

In our experiments, treatments were performed on 30 animals in each group with various doses of the natural humic acid (HA) product as defined in point II above. The mean haematological values characteristic of the WISTAR strain are shown as reference values in the Figures in every case.

Group 1: Whole body irradiated with 7 Gy of ^{60}Co gamma (standard feed + tap water).

Group 2: Pretreatment with HA for 7 days (240 mg/animal/day), then whole body exposure to 7 Gy and additional 4-week treatment with a dose of 240 mg/animal/day of HA.

Group 3: Whole-body exposure to 7 Gy, then a single treatment with a dose of 240 mg/animal/day of HA.

Group 4: Pretreatment with HA for 7 days (90 mg/animal/day) then whole-body exposure to 7 Gy and additional 4-week treatment with a dose of 90 mg/animal/day of HA.

Group 5: Whole-body exposure to 7 Gy, then a single treatment with a dose of 90 mg/animal/day of HA.

The experimental data were analyzed by using the Student's "t" test.

VI. Results

From the haematological parameters of the rats treated as above, the changes in WBC count and PLT count are shown in Figures 1 and 2 for the treatment with a dose of 240 mg/animal/day and in Figures 3 and 4 for the treatment with a dose of 90 mg/animal/day. In the Figures, the number of days post-exposure are indicated on the horizontal axes, whereas the cell counts as G/L (10 E 09/L) values are given on the vertical axes.

Results obtained by treatment with a dose of 240 mg/animal/day

It can be stated that the WBC and PLT counts were significantly ($p < 0.05$) decreased in the whole-body irradiated animals (group 1, control) as well as in animals treated once with HA after irradiation (group 3). A medium-grade enhancement of regeneration caused by a single HA treatment occurred only with respect to PLT starting from the 3rd week.

The regeneration of both the WBCs and PLTs of animals in the untreated control group (group 1) began only after the 3rd week following the irradiation.

No injury of the haemopoietic system occurred in the animals pretreated with 240 mg/animal of HA and then additionally treated with the same dose of HA after whole-body exposure to 7 Gy (group 2), and the number of WBCs and PLTs remained near the reference values characteristic for the WISTAR strain.

These experimental results demonstrate that the harmful biological effect of a high dose of ionizing radiation on the haemopoietic system practically can be avoided by administering a suitable dose (240 mg/animal/day) of the test material and by using a proper method of treatment [treatment preceding the irradiation, followed by a maintenance treatment] (c.f. Figures 1 and 2).

Results obtained by treatment with a dose of 90 mg/animal/day

It can be stated that both the WBC and PLT counts were significantly ($p < 0.05$) decreased in the case of either the once-treated or the continuously treated animals by one week following the whole-body exposure. A significantly decreased PLT count was measured in the animals both in the untreated control group (group 1) and also in the animals treated once with HA (group 5) also in the 2nd week post-irradiation.

The regeneration of WBCs as well as PLTs began in the animals in

the irradiated but untreated control group (group 1) only after the 3rd week following irradiation.

When pretreatment with HA was carried out on animals treated with a dose of 90 mg/animal/day of HA (group 4), the regeneration of both cell types already had started intensively after the first week and reached the values of the control animals by the end of the 2nd week (Figures 3 and 4).

A regeneration to a similar degree as that of the pretreated group (alteration of the PLT, Figure 4) occurred in the group treated once with a dose of 90 mg/animal/day (group 5) only from the 2nd week.

In summary, it can be stated that the test material applied exerts its effect in several therapeutical doses in the case of a high-dose ^{60}Co gamma whole-body exposure in the normalization of the irradiation-induced injuries of the haemopoietic system. The action becomes most favourable by also using the test material before irradiation as a pretreatment.

It is unambiguously proven by the above results that the humic acid-containing compositions according to the invention can be used advantageously to prevent injuries to the haemopoietic system of various origins or for an effective, increased regeneration of the injured haemopoietic system.

Due to their proven biological activity, the compositions according to the present invention can be effectively used in human therapy in cases in which the human body is affected by an ionizing radiation during therapy or because of other events (reactor accident, accidental radiation effect affecting the patient or the handling crew, etc.). Additional experiments indicate that the compositions according to the present invention can also be utilized to increase the regeneration of the haemopoietic system when it is injured during chemotherapy treatments.

Thus, the invention relates to a pharmaceutical composition useful

for the prevention of injuries of the haemopoietic system and for regeneration of an injured haemopoietic system, in which the composition comprises an effective amount, suitably 0.01 to 99.9% by weight, of humic acid-containing substance of peat origin together with the usual additives.

According to a preferred embodiment of the invention, the compositions contain 1.0 to 25.0% by weight of humic acid-containing substance of fen peat origin and 75 to 99% by weight of known, therapeutically acceptable additive(s) in solid, liquid, or gel form.

The invention further relates to a process for the preparation of a humic acid-containing substance. This process is characterized in that, as a starting material, juvenile peat of fen origin of not more than 15,000 years of age is used, which had been formed from at least 20% of great bulrush (Schoenoplectus lacustris) and at least 40% of winter-sedge (Cladium mariscus) as peat-forming plants. The peat is stirred with an aqueous alkaline solution of pH 7.5 to 10.5 to obtain a suspension. Suitably, at least a 2.5-fold amount of an alkaline solution, based on the weight of the peat, is used to form the suspension. An aqueous solution of alkaline metal hydroxides, preferably sodium or potassium hydroxide, and/or a basic aqueous solution of alkaline salts, like sodium carbonate, trisodium phosphate, or potassium pyrophosphate, may be used as the aqueous alkaline solution. The upper phase obtained after settling of the mixture is suitably adjusted to 10 to 100 g/L of humic acid content, or concentrated by dehydration, or brought into solid form. Evaporation under reduced pressure, drying with atomization, lyophilization, and other or similar technical procedures may be applied.

In more detail, the appropriately selected peat is homogenized by drying, crushing, and grinding; the peat grist containing humic acid is suspended in a mildly alkaline, i.e. pH 7.5 to 10.5, aqueous medium, and settled; after separation from the lower phase, the pH value of the

supernatant is, if desired, adjusted to pH 5 to 7, and then, if desired, the mixture is concentrated or dried by dehydration.

According to a preferred embodiment of the process of the present invention, the appropriately selected dried and homogenized peat is treated with a dilute, e.g. at most 5% by weight, alkaline solution of pH 7.5 to 10.5; then, the dry substance content of the recovered suspension is determined, and the humic acid-containing substance is transformed into the desired form, e.g. suspended or powdered.

The advantages of the invention can be summarized as follows:

1) The pharmaceutical compositions according to the present invention act within a novel and highly significant field by curing diseases related to injuries of the haemopoietic system; and
2) The invention provides a well-reproducible process for the preparation of the pharmaceutical compositions by ensuring a humic acid-containing substance of stable composition.

The invention is illustrated by the following non-limiting Examples.

Example 1

Production of a humic acid-containing substance

Peat of 3,000 to 7,000 years of age originating from a depth of 0.5 to 2.5 m was used as the starting material, containing 20 to 40% of great bulrush and 60 to 80% of winter-sedge as peat-forming plants.

The peat was treated with a 1% potassium pyrophosphate ($K_4P_2O_7$) solution at 45°C in an acid-resistant or enamel-lined vessel, fitted with a heater and a stirrer, under constant stirring. After dissolving 1 part by weight of potassium pyrophosphate in 100 parts by weight of tap water heated to a maximum of 45°C, 50 parts by weight of peat having a maximum moisture content of 30% were added. The suspension obtained contained about 10% of peat material. The recovery lasted not more than 48 hours. Within this period, after stirring for 1 hour, the mixture was

subjected to vigorous, particle-grinding stirring for an additional 2 hours in a Dispax reactor (IKA Werke, Germany) for achieving a homogeneous particle distribution.

After 48 hours, the suspension of recovered peat was pumped into a settling tank and settled for 24 hours. The upper phase was separated from the lower, solid sediment after 48 hours.

The humic acid-containing liquid removed from the settling tank by suction was stirred in the dilution tank for at least 30 minutes. In order to determine the dry substance content, 30 ml of homogeneous humic acid-containing suspension were dried to constant weight at 130°C in a drying oven. The suspension was adjusted to a humic acid content of 60 g/L concentration with a 1% potassium pyrophosphate solution (pH=9.4), based on the dry substance content determination.

Thus, a standardized humic acid suspension of 60 g/L concentration was obtained.

Example 2

Preparation of humic acid granulates

After adding 1400 g of maize starch and 70 g of polyvinylpyrrolidone to 1 L of a suspension according to Example 1, containing 30 g/L of humic acid, a granulation mixture was prepared, granulated through a screen of 1.2 mm, dried at room temperature, i.e. maximum at 25°C, and re-granulated to give grayish loose granules.

Example 3

Preparation of humic acid granules from a concentrate

A mixture of 1 L of starting material employed in Example 2, i.e. the suspension containing preferably 30 g/L of humic acid, was evaporated down to a volume of 100 to 120 mL, and, after adding 11 g of polyvinylpyrrolidone and 110 g of maize starch to the suspension, a granulation mixture was prepared. This mixture was granulated through a

1.2 mm screen, dried at room temperature, i.e. maximum at 25°C, and re-granulated to give grayish granules.

Example 4

Preparation of a microcapsulated humic acid composition

Four hundred grams of 30% Eudragit L 30 D dispersion (Röhm Pharma, Darmstadt, Germany) were added to a suspension containing the substance of Example 1 in an amount of 100 g of dry substance, and mixed thoroughly. The mixture obtained was dried through atomization by using an inlet drying air flow of maximum 40°C and a feeding rate of 750 g/hour to give a fine, nearly black, flowable powder.

What is claimed is as follows:

1. Use of a humic acid-containing substance of peat origin as a prophylactic to injuries of the haemopoietic system or for the regeneration of the injured haemopoietic system.

2. Use according to claim 1 in the form of a pharmaceutical composition comprising 0.01 to 99.90% by weight of humic acid-containing substance of peat origin as active ingredient together with, in an amount supplementing up to 100%, carriers and/or other known additives.

3. Use according to claim 1 or 2 in the form of a pharmaceutical composition containing 1.0 to 25.0% by weight of active ingredient.

4. A pharmaceutical composition useful for the prophylaxis of injuries of the haemopoietic system or for regeneration of the injured haemopoietic system, which *comprises* an effective amount of a humic acid-containing substance of peat origin as active ingredient.

5. A pharmaceutical composition according to claim 4, which *comprises* 0.01 to 99.90% by weight of active ingredient.

6. A pharmaceutical composition according to claim 4 or 5, which *comprises* 1.0 to 25.0% by weight of active ingredient.

7. Process for the preparation of a humic acid-containing substance of peat origin according to any of the preceding claims, which *comprises* using as the starting material a juvenile, preferably at most 10,000 years old, peat formed from at least 20% of great bulrush (Schoenoplectus lacustris) and at least 40% of winter-sedge (Cladium mariscus) as peat-forming plants; preparing a suspension by stirring the peat with an aqueous alkaline solution of 7.5 to 10.5 pH value; utilizing the upper phase of the suspension obtained after settling by adjusting its humic acid content to a value suitably between 10 and 100 g/L; concentrating it; or

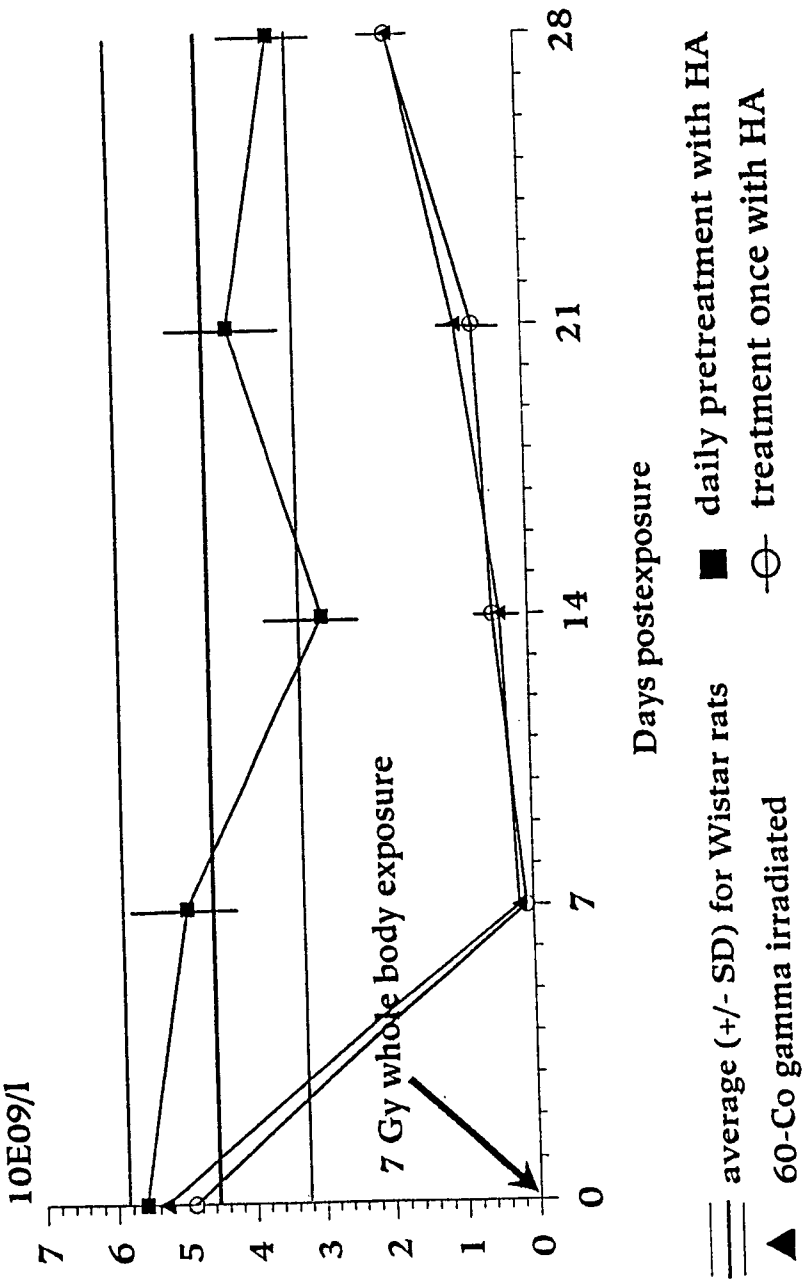
bringing it into solid form by dehydration.

8. A process according to claim 7, which *comprises* using an aqueous alkaline solution in an at least 2-5-fold amount, based on the peat weight, during formation of the suspension.

9. A process according to claim 7 or 8, which *comprises* using an aqueous solution of an alkaline metal hydroxide or a basic aqueous solution of an alkaline salt as aqueous alkaline solution.

10. Method for use as a prophylactic to injuries of the haemopoietic system or for the regeneration of the injured haemopoietic system, *characterized* by administering an effective amount of humic acid-containing substance of peat origin to the patient.

Fig. 1.: Combined effect of humic acid treatment (240 mg/rat) and a 7 Gy whole body exposure on the changes of white blood cell (WBC) number in Wistar rats



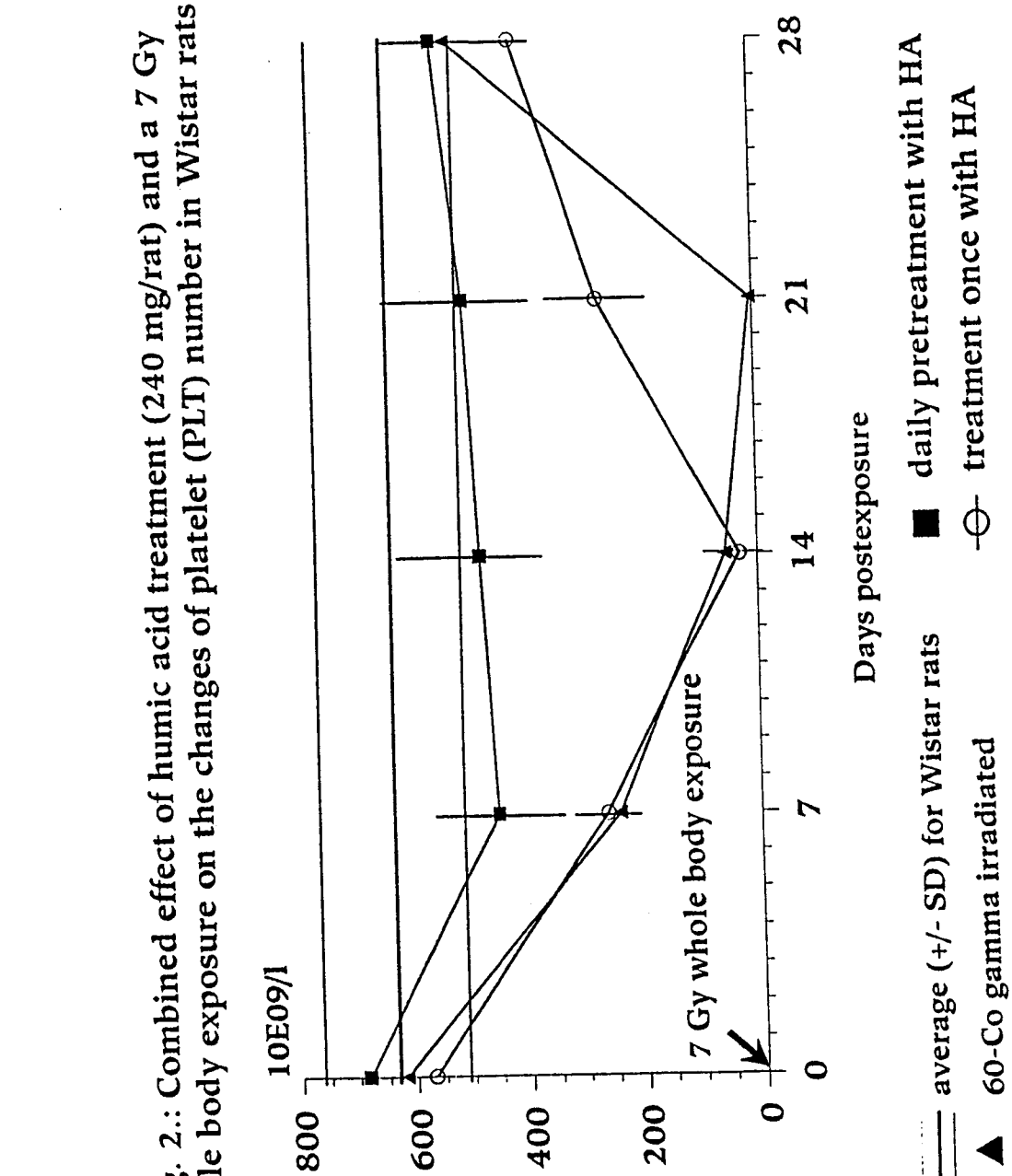
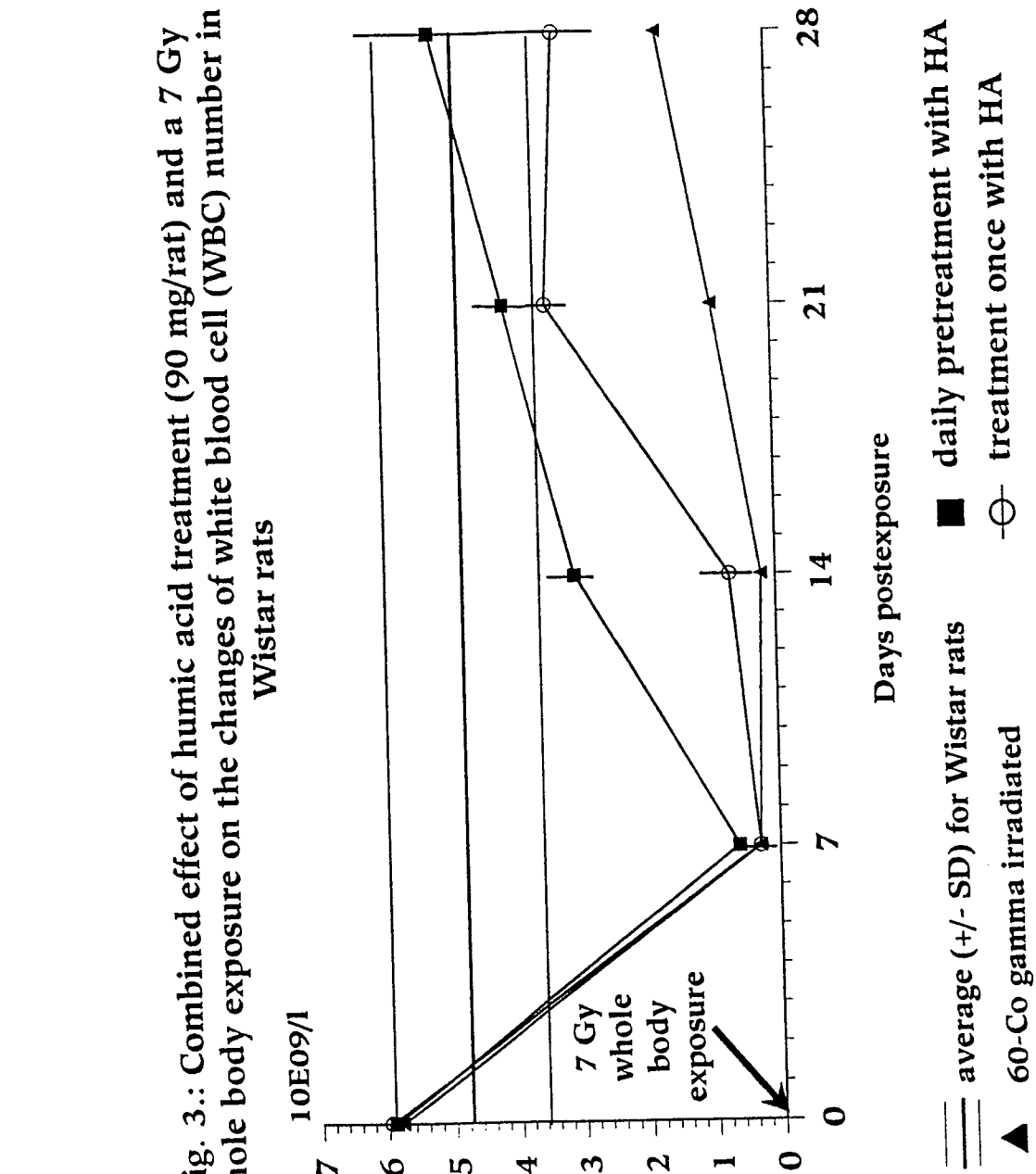


Fig. 2.: Combined effect of humic acid treatment (240 mg/rat) and a 7 Gy whole body exposure on the changes of platelet (PLT) number in Wistar rats

Fig. 3.: Combined effect of humic acid treatment (90 mg/rat) and a 7 Gy whole body exposure on the changes of white blood cell (WBC) number in Wistar rats



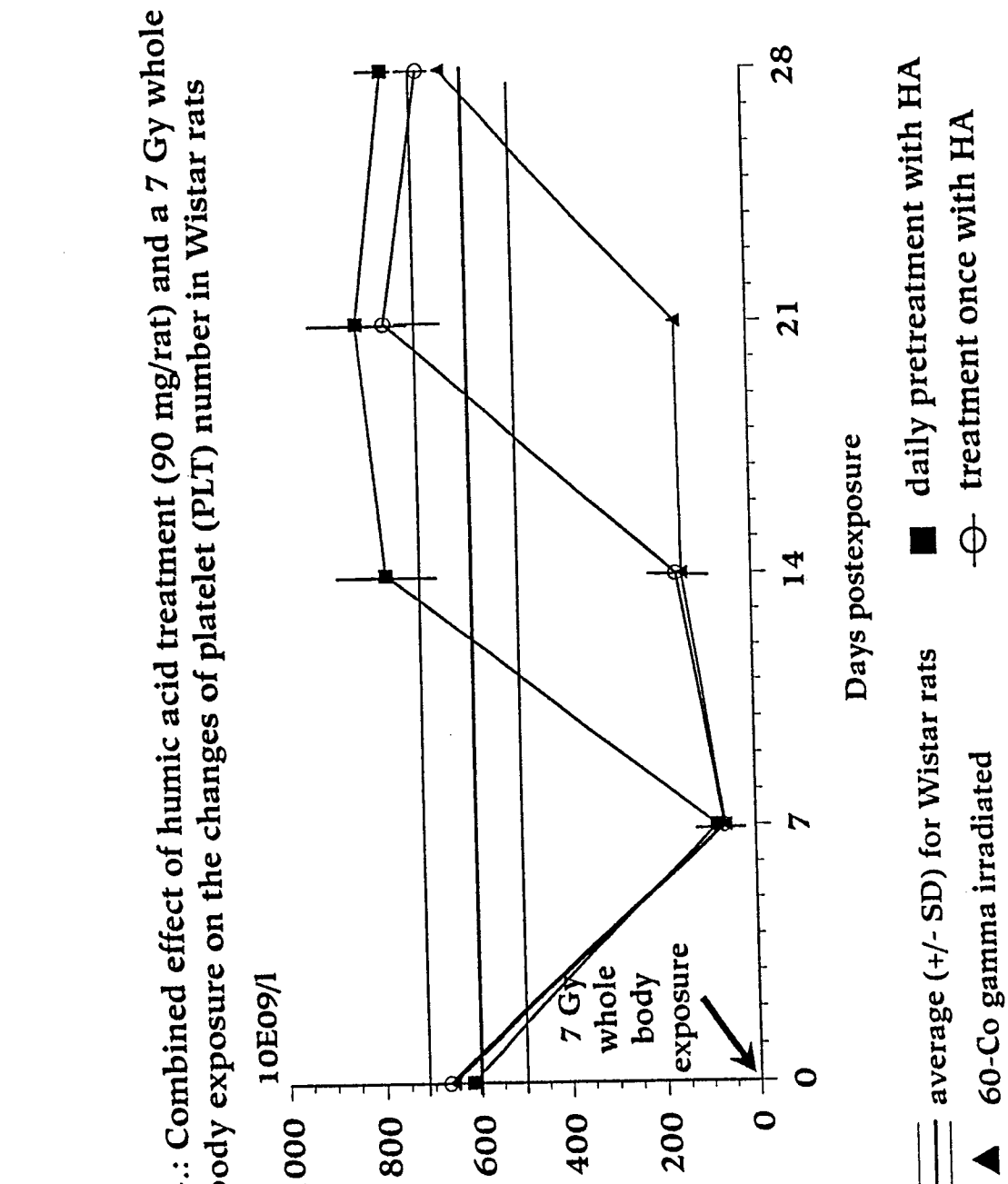


Fig. 4.: Combined effect of humic acid treatment (90 mg/rat) and a 7 Gy whole body exposure on the changes of platelet (PLT) number in Wistar rats

INTERNATIONAL SEARCH REPORT

Internati. Application No
PCT/HU 98/00059

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INGLOT A D ET AL: "TOLPA TORF PREPARATION (TTP) INDUCES INTERFERON AND TUMOR NECROSIS FACTOR PRODUCTION IN HUMAN PERIPHERAL BLOOD LEUKOCYTES" ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS, vol. 41, no. 1, 1993, pages 73-80, XP000619722 see the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1998	30/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreau, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/HU 98/00059

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US PUKHOVA G G ET AL: "'Effect of sodium humate on animals irradiated with lethal doses!. Vliianie gumata natriia na zhivotnykh, obluchennykh v letal'nykh dozakh." XP002080637 see abstract & RADIOBIOLOGIIA, (1987 SEP-OCT) 27 (5) 650-3, ---	1-10
A	WO 95 08335 A (ZANETTI M.) 30 March 1995 cited in the application see the whole document ---	1-10
A	WO 92 16216 A (TORF ESTABLISHMENT) 1 October 1992 see the whole document -----	1-10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 98/00059

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/HU 98/00059

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