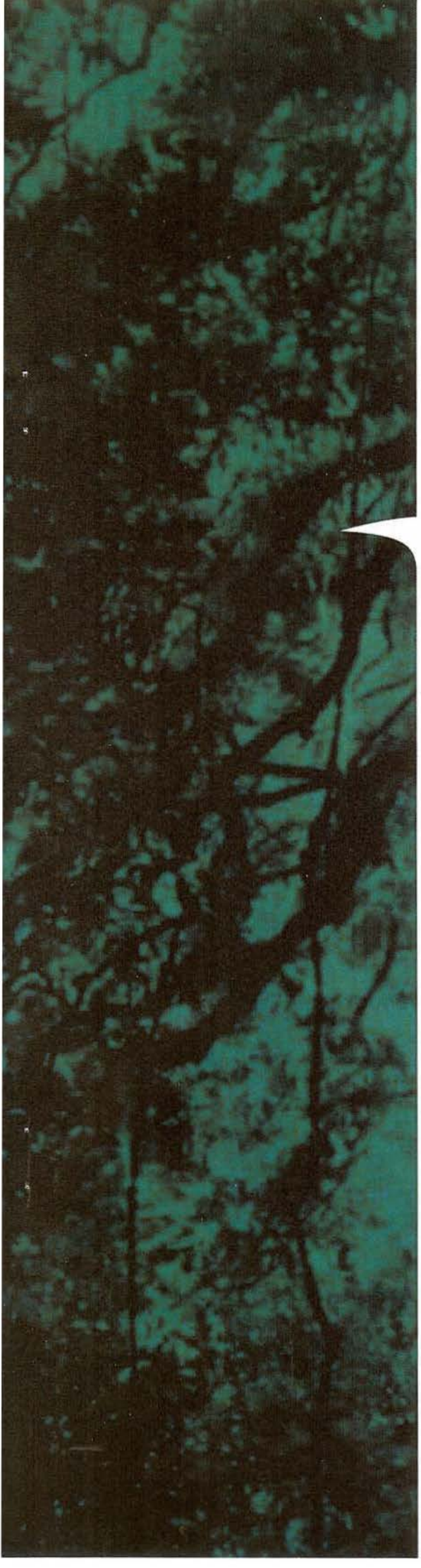

Uncaria tomentosa

(Willd.) DC., pentacyclic chemotype

Product Monograph

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IMPORTANT NOTE

KRALLENDORN® is a **registered trademark** of the company IMMODAL Pharmaka GmbH, Volders, Tyrol, Austria, and refers exclusively to **standardised, quality-tested preparations** from the root of the **pentacyclic chemotype of *Uncaria tomentosa* (Willd.) DC**.

The term "Krallendorn" is often wrongly referred to as the "German name" for *Uncaria tomentosa, Uncaria guianensis* or even completely unrelated plants, as well as being used for an assortment of uncontrolled products, many of which are offered illegally in the market. Such preparations have no connection whatsoever with the registered medicinal drugs developed and manufactured by IMMODAL Pharmaka GmbH.

Under the applicable jurisdiction, any such misleading use of the name "Krallendorn" constitutes an infringement of the copyright and trademark rights of IMMODAL Pharmaka GmbH and will be legally prosecuted if discovered.

Please note that the tests described in the following were performed exclusively using standardised, quality-tested extracts, extract fractions and preparations produced exclusively from the pentacyclic chemotype of *Uncaria tomentosa* (Willd.) DC. Any referencing of these test results or derivations therefrom to substantiate the effects or side effects of other products is inadmissible.

INTRODUCTION

The designation KRALLENDORN® defines standardised extracts produced by IMMODAL Pharmaka GmbH from the root of the pentacyclic chemotype of "*Uncaria tomentosa* (Willd.) DC", a traditional South American medicinal plant which exerts an effect on the immune system.

The pentacyclic oxindole alkaloids contained in KRALLENDORN® induce endothelial cells to release a lymphocyte growth factor which inhibits the proliferation of transformed and highly activated T and B lymphoblasts while increasing the proliferation of resting and weakly activated T and B lymphocytes. Isopteropodine, an isomer of the pentacyclic oxindole alkaloids, increases the phagocytotic activity of granulocytes and RES cells.

Furthermore, initial studies have shown that extracts standardised for pentacyclic oxindole alkaloids inhibit the release of the pro-inflammatory cytokines TNF-alpha, IL-1 and IL-6 from activated macrophages.

Besides stimulating the non-specific immune system, KRALLENDORN® therefore also exerts a targeted modulatory effect on the specific immune system. The proliferation of T and B lymphocytes with pathologically modified proliferation behaviour – whether pathogenically or iatrogenically caused – is stimulated or inhibited, i.e. regulated in response to the pathological modification.

This mechanism of action allows KRALLENDORN® to be used for the treatment of diseases caused by hypofunction of the non-specific immune system or dysfunction of the cellular or humoral specific immune system, as well as diseases in the course and/or therapy of which such dysfunctions occur. [1]

UNCARIA TOMENTOSA (WILLD.) DC

Uncaria tomentosa (Willd.) DC in its native rainforest habitat on the eastern slopes of the Peruvian Andes

Botany and pharmacognosy

Uncaria tomentosa (Willd.) DC is one of the species of the genus Uncaria indigenous to South America and is a member of the Rubiaceae family. The genus Uncaria has a pantropical distribution and is found mainly in Asia, although it is also represented in Africa. Only two species of this genus are known in South America. [2]

Uncaria tomentosa (Willd.) DC and *Uncaria guianensis* (Aubl.) Gmel., the second representative of the genus which is often confused with *Uncaria tomentosa*, are huge woody lianas. They occur in the tropical Amazonian rainforest in an area extending from northern Bolivia through Peru, Brazil, Ecuador, Colombia and Venezuela to Honduras and Belize. [3]

Thorns of Uncaria tomentosa

When growing in the wild, the stems of both Uncarias frequently reach a length of several hundred metres with a diameter of over 20 cm. When they reach direct sunlight the plants form short shoots on which the leaves are arranged in pairs. The leaf axils bear curved thorns, the characteristic shape of which earned them the Spanish folk name "Uña de gato" (German "Kralle des Katers" or "Katzenkralle", Engl. "Tomcat's Claw" or "Cat's Claw"), which they share with around 17 other non-related plants from the same region.

The climbing organs of *Uncaria tomentosa* are sharp, slightly curved thorns which are not sensitive to touch, while *Uncaria guianensis* has soft, heavily curved, touch-sensitive tendrils.

During the blossoming period the two plants produce panicles of ball-shaped flower heads in place of the thorns: in *Uncaria tomentosa* these are whiteish to yellow-coloured with a cinnamon-like fragrance, in *Uncaria guianensis* they are yellow to orange-coloured and about double the size.

Although the two South American Uncarias are highly similar in appearance and habitat, karyosystematic studies have revealed clear differences in their chromosome patterns: accordingly, a close relationship between *Uncaria tomentosa* and *Uncaria guianensis* can be ruled out. [4]

Apart from ubiquitous plant components, quinovic acid glycosides, plant sterols and catechins have been isolated from the two South American Uncarias. The pharmacological action of these substances, which are common to both Uncarias, gives some indication of why the two plants are frequently treated as equivalents in lay medicine. However, the therapeutic relevance of these groups of substances remains to be discussed.

Two groups of highly pharmacologically active oxindole alkaloids have been isolated from the roots of *Uncaria tomentosa*: the group of pentacyclic oxindole alkaloids and the group of tetracyclic oxindole alkaloids. [5]

When growing in the wild, *Uncaria tomentosa* occurs in two chemical variants (chemotypes) with different genetically determined oxindole alkaloid compositions. One chemotype contains pentacyclic oxindole alkaloids (POA), the other tetracyclic oxindole alkaloids (TOA). Mixed forms are not uncommon. [6]

Pentacyclic oxindole alkaloids (POA) have a pronounced regulatory effect on the body's immune system. They increase the phagocytotic activity of RES cells and exert a modulatory effect on the proliferation of T and B lymphocytes. [7]

Tetracyclic oxindole alkaloids (TOA), on the other hand, are Ca^{2+} channel blockers. They act on the central nervous system, possess hypotensive qualities and show negative chronotropic and negative inotropic effects. Toxic effects have been described for TOA in higher doses. Furthermore, TOA exert a competitive antagonistic effect on the immune-modulatory properties of the POA. [7,8,9,10]

Due to the different pharmacological action of the TOA, and especially in view of their competitive antagonistic effect on the action of the POA, special production processes have been developed and careful quality controls are performed to ensure the manufacture of safe, highly effective medicinal drugs containing POA only.

Use in traditional South American medicine

Aqueous decoctions from the roots of selected plants of the species *Uncaria tomentosa* have been used therapeutically for centuries by high-ranking healers of the Asháninka Indians, an indigenous people of the Amazonian basin in Central Peru. They are used in the treatment of illnesses accompanied by disturbances of the immune system, particularly including all forms of rheumatic diseases, viral and bacterial infections as well as tumour-related diseases and allergic disorders. [6, 11, 12]

Illustration from Poma de Ayala's "Chronicle of the Incas" (16th century)

The plant remained unknown to Western medicine until the second half of the 20th century. Recent ethnomedical studies provide an explanation for this:

Knowledge about the therapeutic use of *Uncaria tomentosa* was not generally disseminated among the Asháninka people, but was exclusively reserved to their highest-ranking healer-priests. Owing to its strong spiritual orientation, the knowledge of these healer-priests met with a lack of understanding on the part of the conquerors and missionaries, resulting in rejection and persecution. Today, illustrations from the period of the *Conquista* showing devil-like figures still testify to the power of the indigenous healers, which was perceived as a "demonic threat" by the Spanish invaders. It is assumed that the greater part of their knowledge was destroyed during the period of the Spanish conquest and that only fragments were passed on to the successive generations as closely guarded secrets. [6, 13]

The first scientifically published indications of a medicinal use of the South American Uncarias were provided by the English botanists Phillipson and Hemingway in their 1978 taxonomic study of all *Uncaria* species worldwide: "... Una de gato (*Author's note: No specification as to whether Uncaria tomentosa or Uncaria guanensis is meant*) is used for its antitumour activity by the Campa Indians (*Author's note: Spanish colonists' name for the Asháninka*) of the high Amazonian basin in Peru. ..." [14]

Discovery for Western medicine

Klaus Keplinger, the founder of IMMODAL Pharmaka GmbH, first gained a vague knowledge of the mystery-shrouded healing plant of the Asháninka in the course of a Tyrolean expedition to the Peruvian *Cordilliera* in 1959. Around the mid-1970s he began intensive ethnological studies of the traditional medicine system and medicinal plants of the Asháninka Indians. In the course of this research work *Uncaria tomentosa* was subjected to comprehensive botanical tests, pharmacognostical studies and pre-clinical trials, and the clinical efficacy of the drug was documented in a double-blind, placebo-controlled study at the University of Innsbruck. These convincing research findings finally led to the development of KRALLENDORN® extract, and the plant began to arouse growing interest among pharmaceutical researchers.

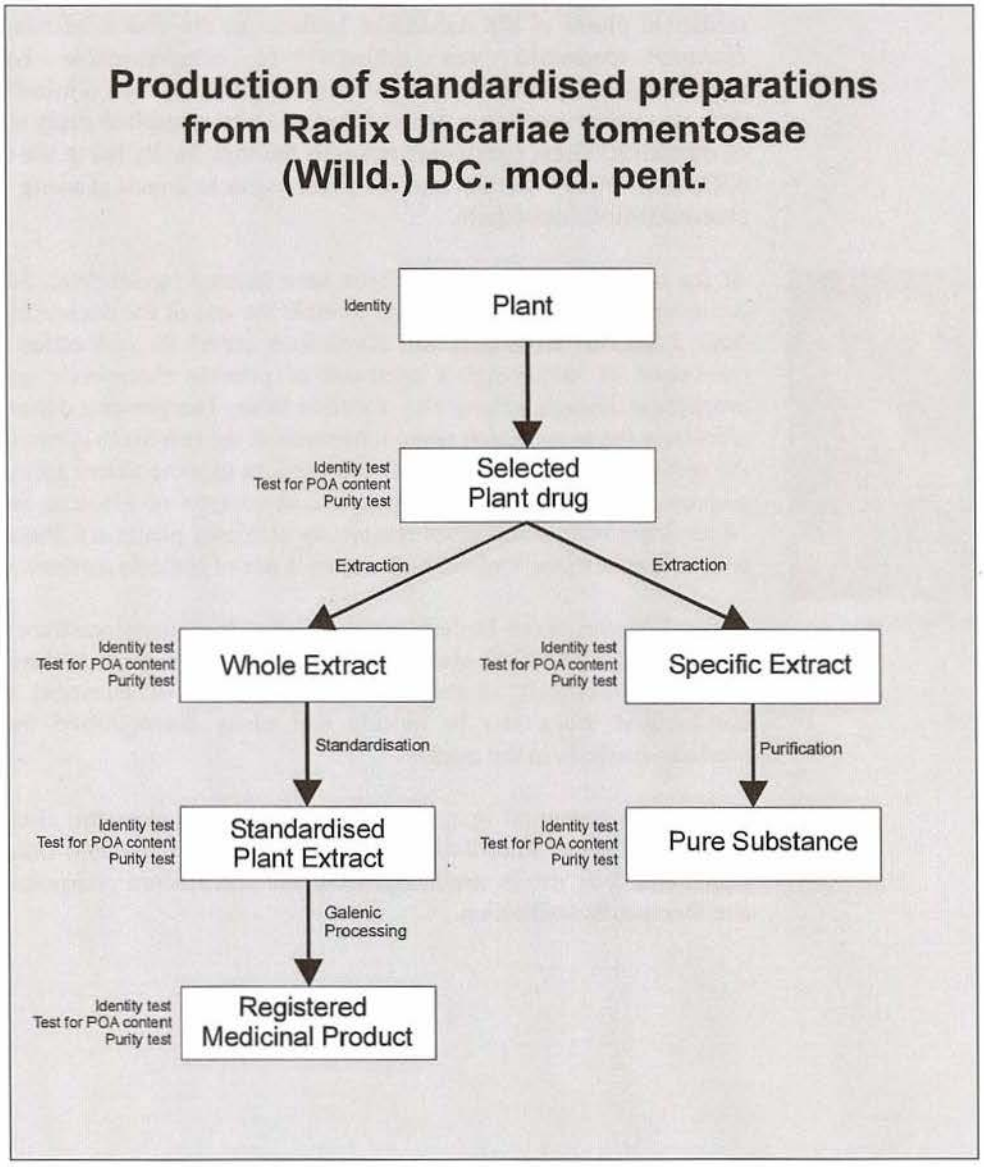
Flowers of Uncaria tomentosa

At the beginning of the 1990s there were isolated reports from South and North American trading companies, and towards the end of the decade increasingly also from European importers, of "miraculous cures" in connection with *Uncaria tomentosa*. A wide-ranging spectrum of possible therapeutic applications was propagated, though without any scientific basis. The growing demand for the drug ultimately led to confusion and adulteration of the two South American Uncarias in the market and in science, which still persists to some extent today. For instance, preparations made from the tetracyclic chemotype of *Uncaria tomentosa*, from *Uncaria guianensis* and other completely unrelated plants are frequently marketed with reference to the traditional therapeutic use of *Uncaria tomentosa.* [15]

Today, however, it can be demonstrated that only preparations from the pentacyclic oxindole alkaloid (POA) chemotype of *Uncaria tomentosa* are therapeutically safe and immunologically highly active. By means of chemical analyses these standardised drugs can be quickly and easily distinguished from adulterated products available in the market.

The studies presented in the following finally complete the circle between the Asháninka healers' knowledge about the selection of individual *Uncaria tomentosa* plants and their use in traditional medicine and modern pharmaceutical research and therapeutic application.

CHEMISTRY



Schematic diagram of the production of standardised preparations from the root of Uncaria tomentosa (Willd.) DC mod. pent.

Active substance

Isopteropodine crystal

KRALLENDORN® is an aqueous acid-extracted dry extract from the root of the pentacyclic chemotype of *Uncaria tomentosa* (Willd.) DC. The extract is standardised for the immunologically active pentacyclic oxindole alkaloids and tested for the absence of tetracyclic oxindole alkaloids, which exert an antagonistic effect on the action of the POA.

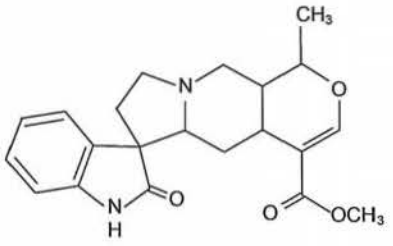
The pharmaceutical quality of the product is assured by comprehensive quality controls on the raw plant material, starting prior to harvesting, by patented extraction and standardisation processes, and by in-process controls throughout the entire production process and during the batch release procedure.

Lead substance – pentacyclic oxindole alkaloids:

The group of pentacyclic oxindole alkaloids consists of a mixture of four isomeric forms of the oxindole alkaloid pteropodine and two isomeric forms of the oxindole alkaloid mitraphylline.

The isomerisation behaviour of the oxindole alkaloids was investigated; following chromatographic separation and partial syntheses the molecular structure of the individual isomers was determined by melting point comparison, mass spectroscopy, two-dimensional NMR and IR spectroscopy, elemental analyses and X-ray analysis. Their effect on the immune system was demonstrated. [16, 17, 18, 19, 20, 21, 22]

Chemical structure:



Empirical formula: $C_{21}H_{24}N_2O_4$

Isomeric forms:

Pteropodine group:

pteropodine, isopteropodine, speciophylline, uncarine F

Mitraphylline group:

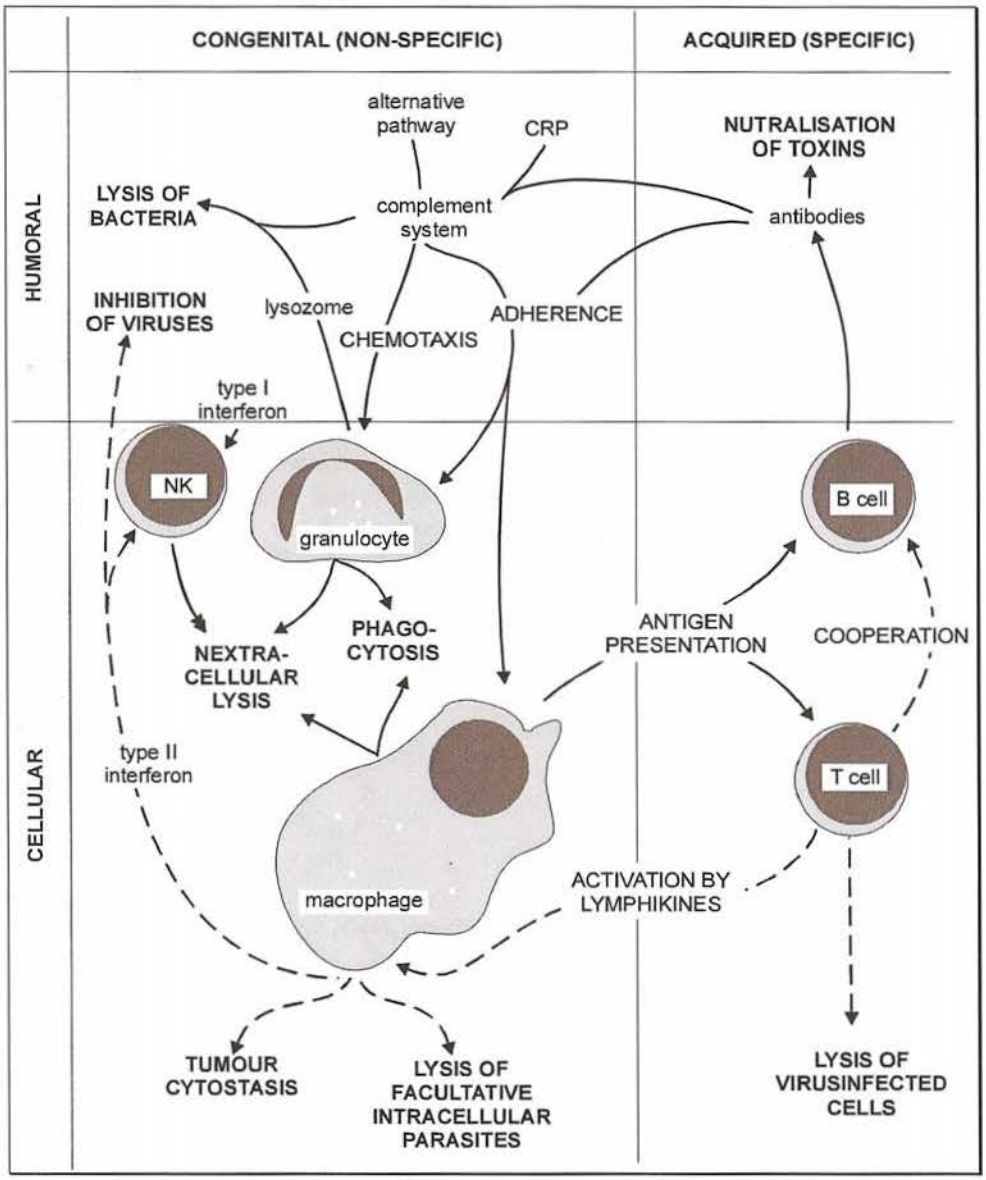
mitraphylline, isomitraphylline

Molecular weight: 368.43 g/mol

Description: colourless, crystalline substance

Solubility: slightly soluble in water, readily soluble in alcohol, chloroform and aqueous acids

THE IMMUNE SYSTEM



Simplified diagram showing the interaction of the specific and non-specific immune systems (from Cytokine und Interferone. Spektrum Akademischer Verlag *(1993))*

Function and purpose of the immune system

With the immune system, the human body is equipped with an extremely complex system for reacting to exogenic and endogenic influences. A series of closely interconnected identification, response and defence mechanisms interact in this system, protecting the body against infections as well as forming the basis for differentiation between "own" and "foreign" matter.

The immune system is subdivided into a phylogenetically older **non-specific immune system** and a phylogenetically younger **specific immune system**. When functioning normally the two components work in close synergy, adapting optimally to external influences by means of numerous positive and negative feedback mechanisms.

Phagocytes, cells of the non-specific immune system, are triggered into action in the elimination of many antigens. Antigens invading the organism are surrounded by phagocytotic cells which lyse and kill off the antigens.

Should the antigens manage to overcome this protective barrier, T lymphocytes are activated through antigen presentation by the macrophages, a type of phagocyte. The activation of these cells of the specific immune system leads to their clonal expansion, to the formation of helper T cells, suppressor T cells, cytotoxic T cells and killer T cells, as well as to the clonal expansion of B lymphocytes. Activated B lymphocytes are transformed into plasma cells which then produce antibodies to mark the antigens for attack and elimination by the phagocytotic cells of the non-specific immune system or by the complement system. [23, 24]

Significance of the immune system in pathogenesis and therapy

The responsiveness and perfect interplay of the interacting cells in the immune system play an essential role in maintaining or restoring the health of the human organism.

Pathogenic, iatrogenic or genetic influences can lead to malfunction or failure of these regulatory and defence mechanisms in the form of:

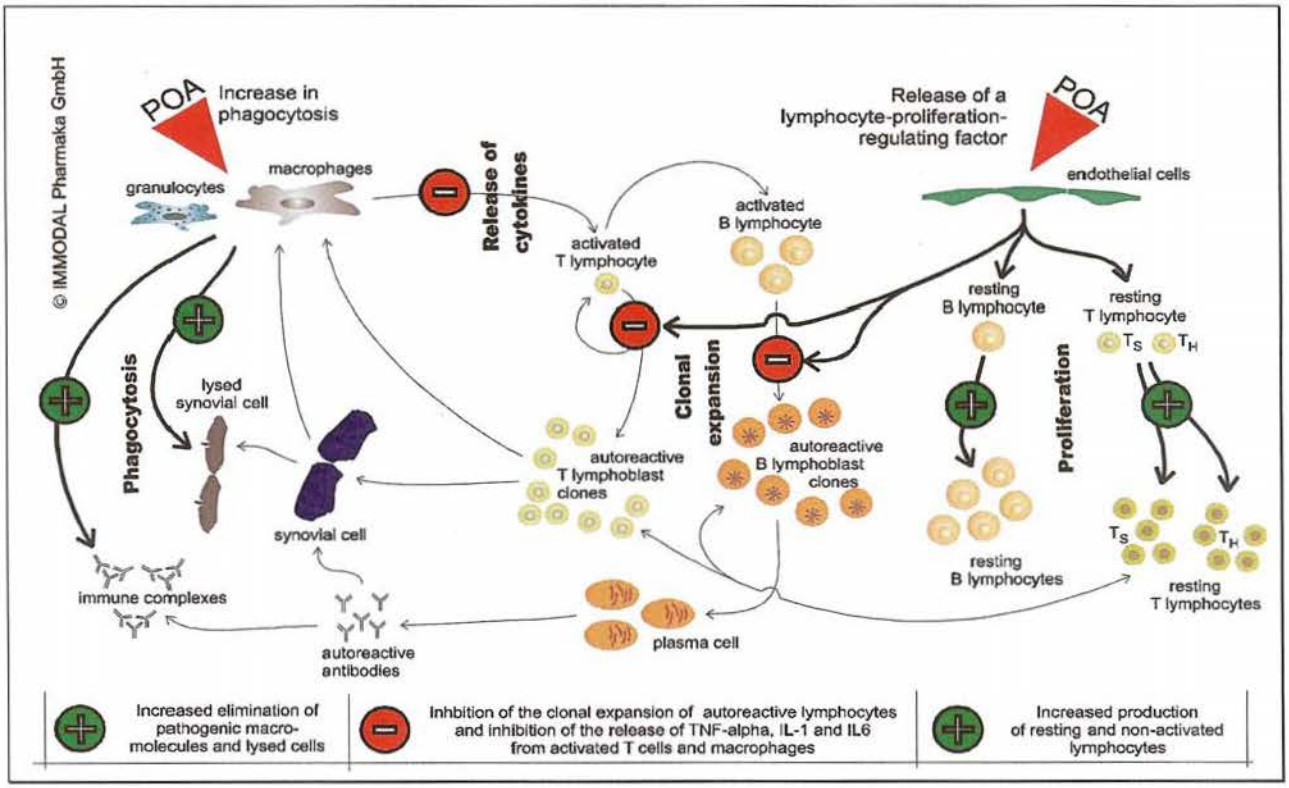
- **Hypofunction of the non-specific immune system**
  (pathogenic substances and lysed cells are not or not adequately eliminated), and/or
- **Hyperfunction of the specific immune system**
  (the immune system reacts to the body's own tissues or to substances that are intrinsically harmless to the organism) or
- **Hypofunction of the specific immune system**
  (the immune system is unable to recognise and eliminate invading antigens)

The consequences of immune malfunction become particularly evident in autoimmune diseases or allergies and in the course of viral or bacterial infections, but also in the treatment of tumour-related diseases (chemotherapy, radiotherapy), which may result in therapy-induced immunosuppression.

Owing to the complexity of the feedback mechanisms, the disturbance of one component of the immune system usually also leads to impairment of the function of other components, thus triggering a chain reaction of different complications.

To date, most approaches to immune therapy have been limited to either stimulation or suppression of individual components or functions of the immune system. However, immune dysfunction and deficiency should rather be viewed and treated systemically.

The aim is to restore immunological tolerance and/or immunological competence as a whole system.



Mechanism of action of the pentacyclic oxindole alkaloids (POA) contained in KRALLENDORN® in rheumatoid arthritis

KRALLENDORN® not only stimulates or inhibits individual components and functions of the complex immune system; the mechanism of action of **KRALLENDORN® permits systemic intervention in the immune response process:**

- the **enhanced phagocytotic activity of the macrophages** leads to improved antigen presentation at the start of the immune response cascade in viral and bacterial infections;
- the **increased proliferation of resting and weakly activated T lymphocytes** improves the immune response against intracellular bacteria, parasitic micro-organisms, viral infections and malignantly transformed endogenous cells;
- through clonal expansion, the **increased proliferation of resting and weakly activated B lymphocytes** leads to increased production of antibodies that are better able to ward off infections;
- the **inhibition of the proliferation of highly activated T and B lymphoblasts** plays an essential role in autoimmune diseases, as it results in diminished formation of inflammation mediators;
- the **inhibition of the release of TNF-alpha, IL-1 and IL-6** from activated macrophages leads to a **reduction in inflammatory responses**;
- at the end of the immune response cascade, the **increased phagocytotic activity of the RES cells** leads to faster elimination of antigen-antibody complexes and lysed and transformed cells.

PHARMACODYNAMICS

Effects of standardised extracts from the pentacyclic chemotype of Uncaria tomentosa (KRALLENDORN®):

In-vitro:

- **Inhibit the proliferation** of highly activated and transformed T and B lymphocytes
- **Increase the proliferation** of resting T and B lymphocytes
- **Inhibit the release** of TNF-alpha, IL-1 and IL-6 from activated macrophages
- **Increase the phagocytotic activity** of macrophages and granulocytes

In-vivo:

- **Increase the phagocytotic activity** of RES cells
- **Inhibit the inflammatory response**
- **Positively influence the course of viral infections**

Effect on the specific immune system

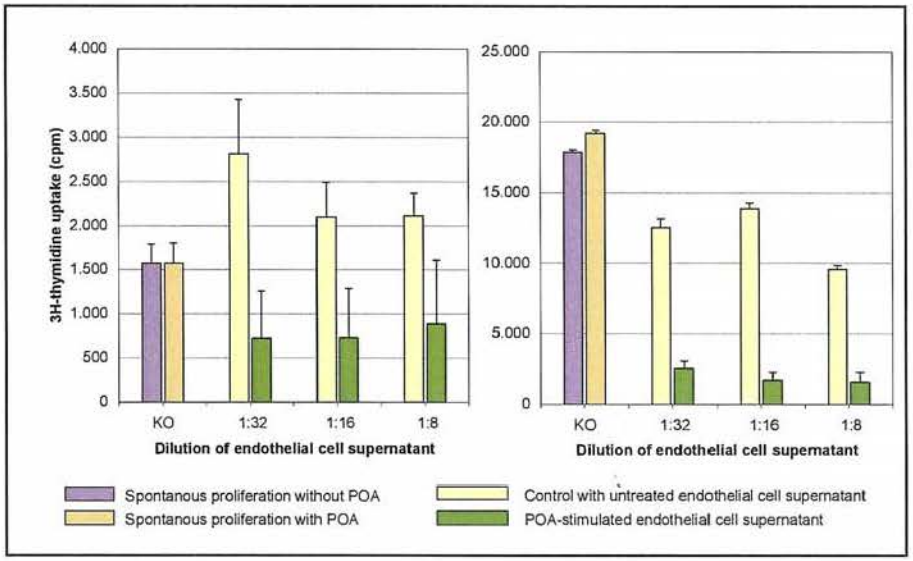
Regulation of proliferation of T and B lymphocytes depending on their degree of activation

Results of clinical observations and animal studies suggested that substance fractions of the pentacyclic chemotype of *Uncaria tomentosa* had an effect on the specific immune system. Accordingly, preliminary studies focused on their direct action on the proliferation and function of cells of this part of the immune system.

The results remained inhomogeneous, however, reflecting the different immunological status of each individual donor. Further multi-stage tests were therefore developed to investigate the effect of the pentacyclic oxindole alkaloids on T and B lymphocytes taking the degree of T and B lymphocyte activation into account. [7,25]

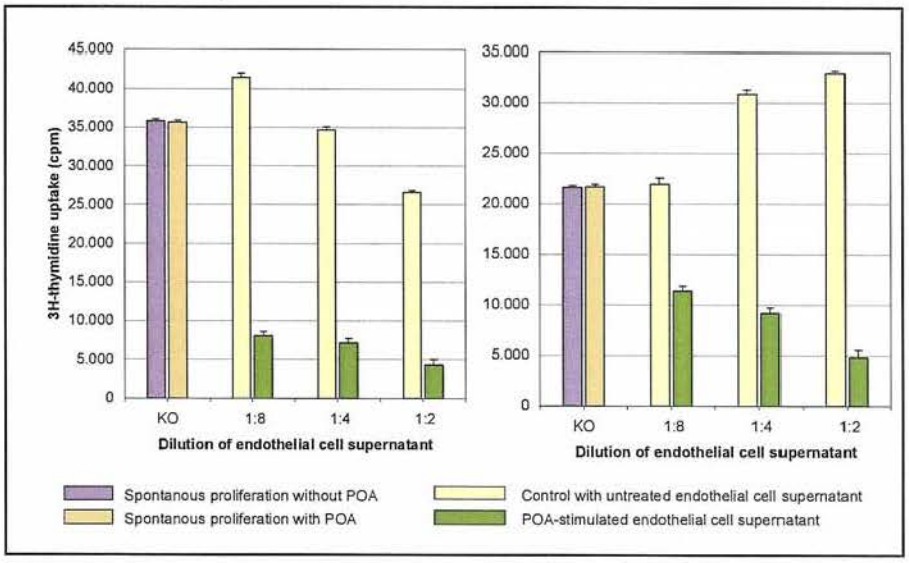
Human endothelial cells (EA.hy926) were cultivated in vitro for 7 days with equilibrated mixtures of isomers of the pentacyclic oxindole alkaloids (POA) isolated from the root of *Uncaria tomentosa* in a concentration of 0.4 µg/ml to produce POA-stimulated endothelial cell supernatants. T and B lymphocytes isolated from the peripheral blood of human donors were then separated according to their degree of activation by means of Percoll gradients and incubated with the POA-stimulated endothelial cell supernatant in a dilution series. The proliferation of the lymphocytes was measured by 3H-thymidine uptake. Supernatant of untreated endothelial cells, both with and without addition of POA, was used as control. [25]

Activated T and B lymphocytes reacted differently to the addition of untreated endothelial cell supernatant, but incubation with POA-stimulated endothelial cell supernatants **inhibited proliferation by up to 54%** in **activated T lymphocytes** and **by up to 92 % in activated B lymphocytes** in comparison with the spontaneous proliferation rate.



Inhibition of the proliferation of activated human T lymphocytes (left) and activated human B lymphocytes (right) by POA-stimulated endothelial cell supernatants

Comparable results were achieved in the same test batch with **the human B lymphoblastoid cell line "Raji"** and the **human T lymphoblastoid cell line "Jurkat"**. Here too the untreated endothelial cell supernatant was observed to exert different effects on proliferation, depending on the concentration. Incubation with the POA-stimulated endothelial cell supernatant, on the other hand, **inhibited proliferation by 88 % in the cell line "Jurkat" and by up to 78% in the cell line "Raji"** in comparison with the spontaneous proliferation rate.

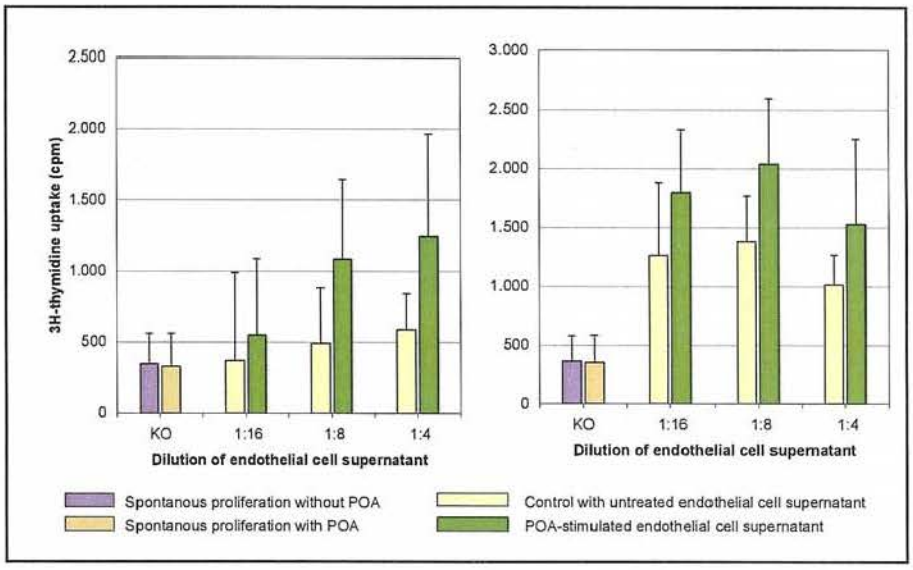


Inhibition of the proliferation of transformed human T lymphocytes ("Jurkat", left) and transformed human B lymphocytes ("Raji", right) by POA-stimulated endothelial cell supernatants

In order to exclude the possibility that the proliferation-inhibiting effects of the POA-stimulated endothelial cell supernatants observed in the experiments were caused by non-specific toxicity, the **viability of the cells** was tested. It was **more than 90 %,** which meant that a potential cytotoxic effect of the POA-stimulated endothelial cell supernatants could be ruled out.

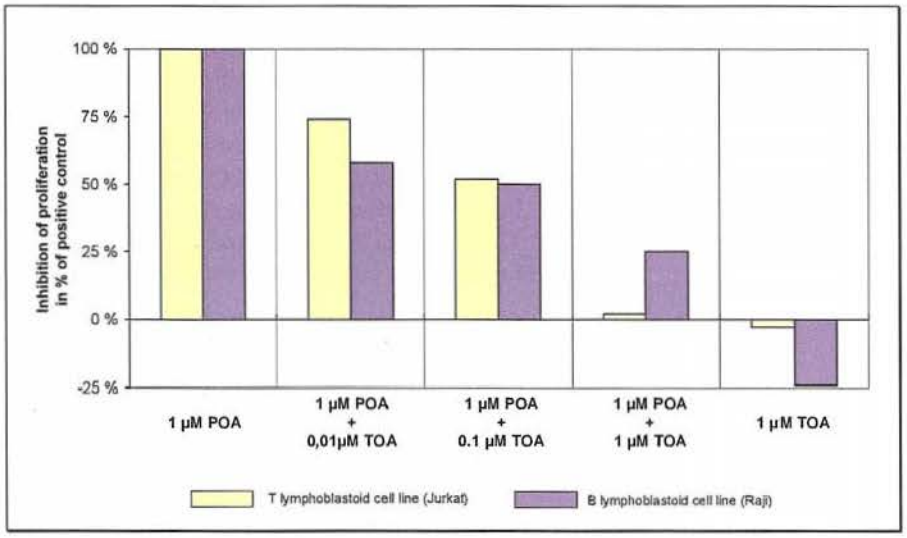
	Viability (%)			
	Raji		Jurkat	
	Day 1	Day 2	Day 1	Day 2
Medium	93.5	95.1	95.8	93.7
1µg IMM-2414	96.8	90.1	95.2	95.8
SN medium (1:2)	95.4	95.3	96.4	92.0
SN medium plus IMM-2414 (1:2)	98.4	92.2	94.4	92.2

The POA-stimulated endothelial cell supernatant exerted the opposite effect on **resting and weakly activated T and B lymphocytes**. T and B lymphocytes already reacted to the untreated endothelial cell supernatant with a slight increase in proliferation, but the **POA-stimulated endothelial cell supernatant** led to a higher **increase of 50% in the proliferation rate** in **B lymphocytes** and even to a **120% increase in the proliferation rate** in **T lymphocytes** in comparison with the positive control (= untreated endothelial cell supernatant).



Enhancement of the proliferation of resting human T lymphocytes (left) and resting human B lymphocytes (right) by POA-stimulated endothelial cell supernatants

The effects of the tetracyclic oxindole alkaloids (TOA) occurring in the other chemotype of *Uncaria tomentosa* as well as different mixtures of pentacyclic and tetracyclic oxindole alkaloids were also investigated in the same test batch. The results showed **that TOA have no effect on the proliferation of T and B lymphocytes**. The tests using different **mixtures of POA and TOA** rather demonstrated that **the TOA have a pronounced competitive antagonistic effect** on the POA-induced release of the lymphocyte-proliferation-regulating factor from endothelial cells.



Competitive antagonistic action of TOA on the proliferation-inhibiting effect of POA-stimulated endothelial cell supernatants on the human T and B lymphoblastoid cell lines Raji und Jurkat

Effect on the non-specific immune system

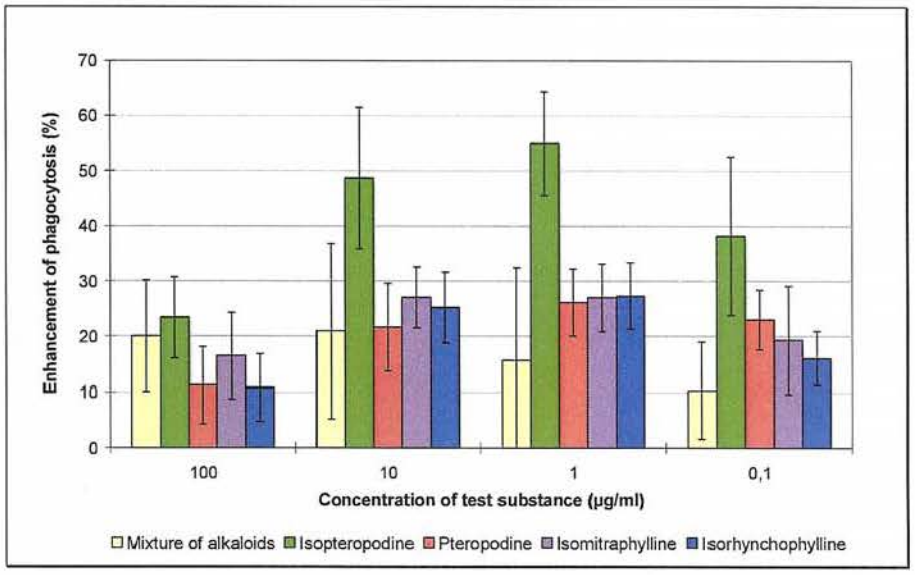
Stimulation of the phagocytotic activity of granulocytes and macrophages

The stimulatory effect on the non-specific immune response was demonstrated in vitro using the **granulocyte test** modified according to Brandt and the **chemoluminiscence test**, and in vivo using the **carbon clearance test** according to Biozzi. [26, 27, 28]

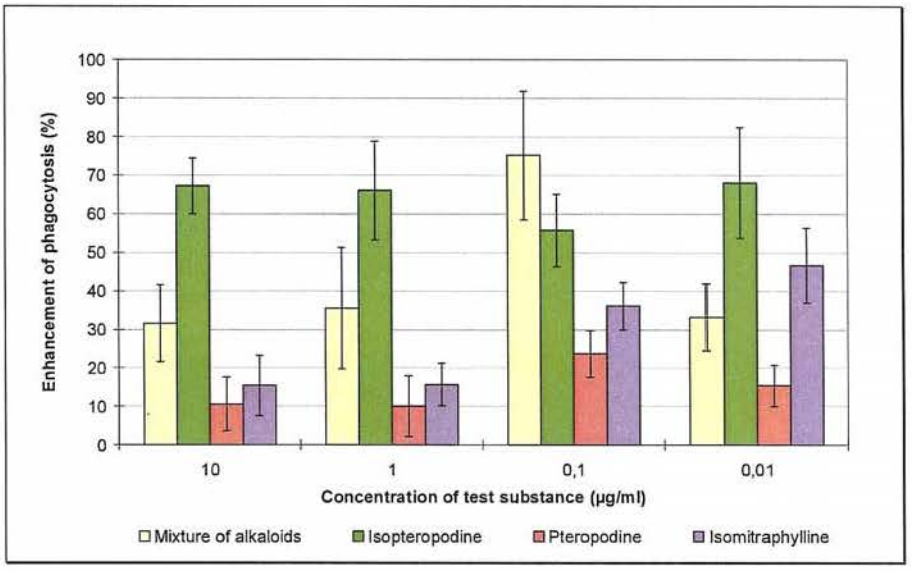
In the granulocyte test according to Brandt, yeast particles were added to granulocyte fractions obtained from the blood of healthy human donors, which were then incubated with the test substance. After 45 minutes the number of phagocytised yeast particles was determined. In the chemoluminiscence test the determinable quantity of superoxide radicals whose secretion by polymorphnuclear leukocytes was increased upon contact with mitogens was measured after 45 minutes' incubation with the test substance.

Both tests were carried out on whole extracts and fractions from the root of *Uncaria tomentosa*, the pentacyclic oxindole alkaloids isopteropodine, pteropodine, mitraphylline, and the tetracyclic oxindole alkaloids isorhynchophylline and rhynchophylline.

In both tests, **isopteropodine** as a pure alkaloid **showed** the **most pronounced stimulatory effect on phagocytosis**. Pteropodine and isomitraphylline also showed activity. Isorhynchophylline produced contradictory results in the granulocyte test and the chemoluminiscence test. Mitraphylline and rhynchophylline remained inactive in both test models.



Enhancement of phagocytosis in the granulocyte test according to Brandt

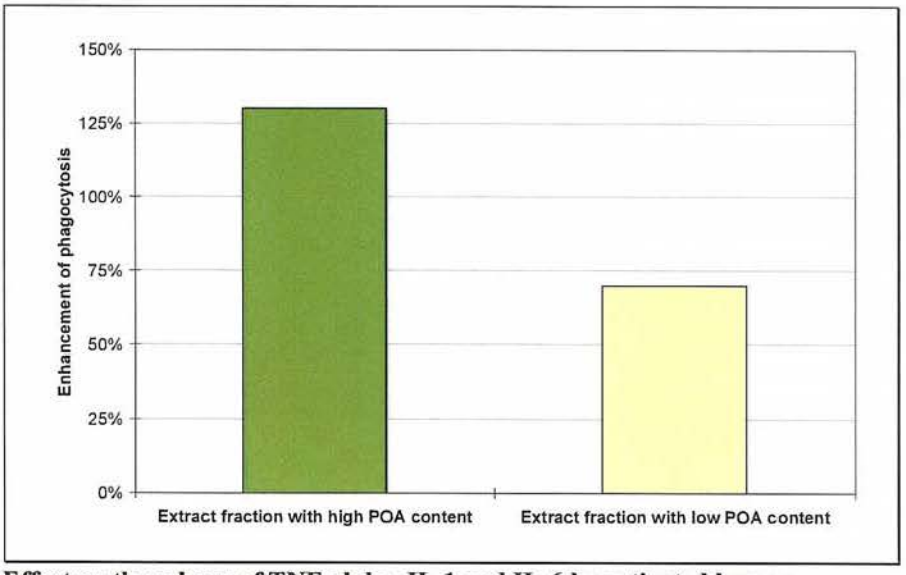


Enhancement of phagocytosis in the chemoluminescence test

The effect on the phagocytotic activity of the cells of the reticulo-endothelial system (RES) was investigated using the carbon clearance test according to Biozzi. Gelatine-stabilised carbon particles were intravenously injected into the test animals; blood was taken from the retro-orbital venous plexus at defined time intervals and the rate of elimination of the carbon particles determined by photometric measurement.

The tests were performed using extracts from the root of *Uncaria tomentosa* with varying concentrations of POA, administered intraperitoneally to mice at a dosage of 10mg/kg body weight (bw) 24 hours before the start of each test. Untreated animals served as control.

The test showed a **pronounced increase in phagocytotic activity** in comparison with the control **for the extract fraction with high POA content** and a moderate enhancement of phagocytosis for the low-alkaloid extract fraction.



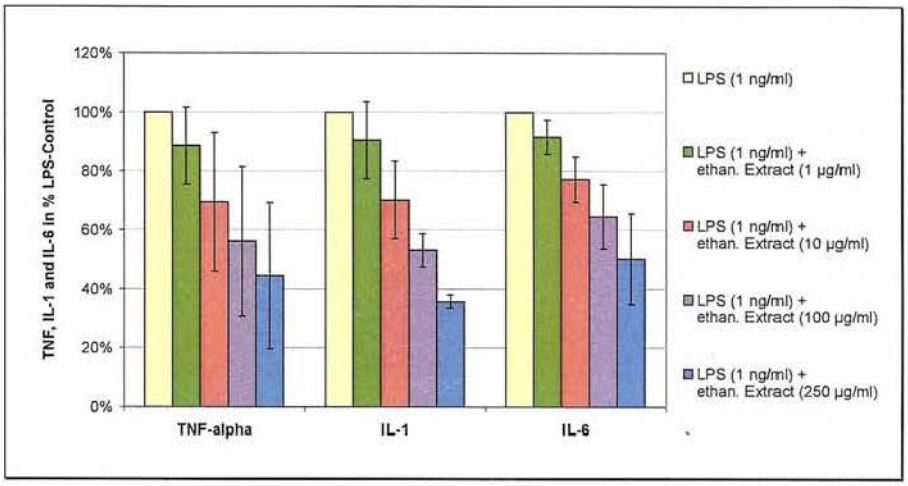
Enhancement of phagocytosis in the carbon clearance test

Effect on the release of TNF-alpha, IL-1 and IL-6 by activated human macrophages and monocytes

In preliminary orientation tests, an ethanol extract from the whole root of *Uncaria tomentosa* comparable to KRALLENDORN® (standardised to 1.3 mg/g pentacyclic oxindole alkaloids and free of tetracyclic oxindole alkaloids) was tested for its effect on the release of TNF-alpha, IL-1 and IL-6 by LPS-activated human monocytes.

Monocytes were isolated from the blood of healthy human donors and incubated for 30 minutes with an ethanol extract from the root of *Uncaria tomentosa* dissolved in DMSO at dosages of 1, 10, 100 and 250 µg/ml. The cells were then activated for 24 h with 1 ng/ml LPS, the supernatants obtained and the concentration of pro-inflammatory cytokines determined by enzyme immunoassay (ELISA).

A significant, **dose-dependent reduction in the concentrations of TNF-alpha, IL-1 and IL-6** was observed, to about half of the concentrations in the control culture treated with LPS only. [29]



Inhibition of LPS-induced release of TNF-alpha, IL-1 and IL-6 by primary human monocytes (n=9)

Comparable results were achieved in the investigation of the release of TNF-alpha by RAW 264.7 cells, a murine **macrophage cell line, after stimulation by**

lipopolysaccharides (LPS). The macrophages were pre-treated with a freeze-dried aqueous extract from *Uncaria tomentosa* at dosages of 1, 10, 100 and 1000 ng/ml for two hours and then stimulated with LPS (50 ng/ml) for 1 hour. After removal of the medium the cells were incubated for a further 16 hours at 37°C, the cell supernatant obtained and the concentration of TNF-alpha determined. A **dose-dependent, statistically significant inhibitory effect on the release of TNF-alpha** was observed at an EC_{50} value of 10.2 ng/ml. [30]

The published studies on the inhibition of LPS-induced iNOS gene expression, nitrite formation, and, in particular, the inhibition of NF-kappaB activation, are of interest for the evaluation of these results. Since NF-kappaB controls the expression of a whole series of pro-inflammatory molecules, including adhesion molecules and cytokines, its inhibition could be the cause of the reduced release of IL-1, IL-6 and TNF-alpha in the tests described above. [30,31,32]

Effect on inflammatory response

The pentacyclic oxindole alkaloids from *Uncaria tomentosa,* administered subcutaneously and orally, were tested for their anti-inflammatory potential compared with the control substances indomethacin and dexamethasone in two in-vivo test models in rats, the carrageenan-induced paw oedema test and the adjuvant arthritis test. [28]

In both test models, subcutaneous administration of the test substance resulted in a significant, dose-dependent reduction in oedema, though the values did not reach the positive control values for indomethacin and dexamethasone. With oral administration of the test substance the effect was still present, but much less pronounced than with subcutaneous administration.

Test sample	Dose	Route of administration	Oedema reduction in %	
			2.5 h	5 h
Mixture of alkaloids	10 ml	s.c.	8.2	13.0
Mixture of alkaloids	30 ml	p.o.	39.0	27.5
Indomethacin	10 mg	p.o.	51.7	42.2

Oedema reduction in the carrageenan-induced paw oedema test in rats; the test substances were administered 30 min. prior to carrageenan injection

Test sample	Dose	Route of administration	Oedema reduction in %	
			Paw 1	Paw 2
Mixture of alkaloids	5 ml	s.c.	42.1	58.7
Dexamethasone	0.5 mg	s.c.	61.3	35.7
Mixture of alkaloids	10 ml	p.o.	5.1	17.0
Dexamethasone	1 mg	p.o.	80.7	57.7

Oedema reduction in the adjuvant arthritis test in rats; the test substances were administered for five successive days following adjuvant injection

Legend:

Mixture of alkaloids *Suspension in 10 % gelatine*

Underlined figures *The underlined figures are significantly different from the control group with $p < 0.05$ (Student's t-test for paired samples).*

In further studies, the anti-inflammatory effects of extracts from *Uncaria tomentosa* with high POA content and low TOA content (see page 5 ff.) were compared with those of *UT* extracts with low POA and high TOA, with indomethacin as control. The POA-rich fraction exhibited a significantly higher anti-inflammatory activity than the one with low POA content, and in higher dosages even exceeded the effect of indomethacin.[33]

Effect on viral infections

Aqueous extracts, alkaloid fractions and quinovic acid glycosides from *Uncaria tomentosa* were tested for direct **anti-viral activity** against HSV-1, HSV-2, VSV, rhinovirus 1B and HIV IIIB in various in-vitro screening models. The POA-stimulated endothelial cell supernatant (see page 15) was also tested for its effect against HIV IIIB. [34,35]

Aqueous extracts from *Uncaria tomentosa* showed in-vitro activity against both HSV-1, with MIC_{50} values ranging between 0.1 µg/ml for Vero cells and 3 µg/ml for HEp-2 cells, and HSV-2, with MIC_{50} ranging between 0.03 µg/ml for Vero cells and 10 µg/ml for HEp-2 cells. The MTC_{50} value for the same extract was 100 µg/ml for Vero and 330 µg/ml for HEp-2.

No reproducible, dose-dependent effects of extracts or individual substances from *Uncaria tomentosa* against HIV were elicited. However, a 1:4 dilution of the supernatant from endothelial cells stimulated with 0.4 µg/ml pentacyclic oxindole alkaloids inhibited HIV replication as measured by p24 antigen release by 50%.

In order to investigate the therapeutic potential of preparations from the root of the pentacyclic chemotype of *Uncaria tomentosa* in lethal virus infections, experimental therapy was carried out in **cats infected with FeLV, FIV and/or FIP**. FeLV, FIV and FIP are feline retroviral infections that are generally considered untreatable and lead to death of the infected animal in over 90 % of cases.

In **experimental therapy in 24 cats**, intra-muscular injection of pentacyclic oxindole alkaloids (POA) in a dosage of 30 µg POA in 0.5 ml physiological saline administered on days 1, 3 and 5 of the treatment period resulted in a reduction in symptoms in 85 % of the infected animals. In 44 % of the FeLV-infected animals loss of viraemia was reported after 5 months of observation. [36]

A subsequent **screening study on 31 cats infected with FeLV, FIV and/or FIP** confirmed the results of the experimental therapy. The animals were also administered intra-muscular injections of pentacyclic oxindole alkaloids in a dosage of 30 µg POA in 0.5 ml physiological saline on days 1, 3 and 5. In individual cases the therapy was continued at 48-hour intervals until clinical improvement was achieved. The study showed clinical recovery in 65 %, progression of the disease in 3 % and exitus in 26 % of the cats. Follow-up screening could not be carried out in 6 % of the studied population because the cats' owners had moved away. [37]

	Sero-neg. (n=9)	FeLV (n=11)	FIP (n=6)	FIV (n=1)	FeLV/FIV (n=1)	FeLV/FIP (n=3)
Remission	5	7	4	1	1	2
Persistent disease	0	0	1	0	0	0
Exitus	4	2	1	0	0	1
Moved away	0	2	0	0	0	0

TOXICOLOGY

Single-dose toxicity

The acute toxicity of a freeze-dried aqueous decoction from the root of the pentacyclic chemotype of *Uncaria tomentosa* was investigated in a limit test in mice following oral administration in the maximum dosage of 16 000 mg/kg body weight (corresponds to 16 000 times the recommended daily dose). Lower substance concentrations were not tested.
One out of the five mice in each of the two (male and female) test groups died within 4 hours of treatment. Autopsy revealed haemorrhage of the stomach and intestines and pallor of the liver and spleen. Death and the abnormal histological findings most likely resulted from the high substance concentration combined with the large volume administered (1 ml / 25 g), which means that hardly any clinical relevance can be attached to these findings. The survivors made a complete recovery within five days of treatment and were then identical to the control group. Post-mortem examination of the euthanised animals revealed no unusual findings. [38]

In further tests, whole aqueous extracts and alkaloid fractions from the root of *Uncaria tomentosa,* administered orally and intraperitoneally, were tested in dosages of 1 000, 2 000 and 5 000 mg/kg body weight. The animals were observed for 14 days after treatment. No changes from normal behaviour were observed. [28]

Moreover, an aqueous dry extract from the stem bark of *Uncaria tomentosa,* comparable to KRALLENDORN®, was tested on Wistar-Furth rats in dosages of 0, 1 000, 2 000, 4 000 and 8 000 mg/kg body weight in comparison with two commercially available products (pulverised bark of a not further specified preparation and an aqueous whole ethanol extract from *Uncaria tomentosa* with a total alkaloid content of 4%).
The animals were observed for a period of 14 days for signs of toxicity. All the test animals survived the single oral dose of the three different preparations in the given dosages. No signs of toxicity were observed. [39]

Test substance	Animals	Dosage (mg/kg bw)	Application	Mortalities m / f	Changes from normal behaviour / Signs of toxicity
Freeze-dried aqueous decoction from the root of UT	5 m + 5 f NMRI mice per dose	16 000	oral	1 / 1	none
Whole aqueous extract from the root of UT (POA)	5 m + 5 f NMRI mice per dose	2 000, 5 000	i.p. / oral	0 / 0	none
Mixture of raw alkaloids from the root of UT	5 m + 5 f NMRI mice per dose	1 000, 2 000	i.p. / oral	0 / 0	none
Aqueous dry extract from the stem bark of UT (POA)	5 Wistar-Furth rats per dose	1 000, 2 000, 4 000, 8 000	oral	0	none
Non-characterised bark powder of UT	5 Wistar-Furth rats per dose	250, 500, 1 000, 2 000	oral	0	none
Aqueous ethanol extract from UT (total alkaloid content 4%)	5 Wistar-Furth rats per dose	630, 1 250, 2 500, 5 000	oral	0	none (sedation, diarrhoea)

Multiple-dose toxicity

The sub-acute toxicity of KRALLENDORN® extract (aqueous acid extract from the root of the pentacyclic chemotype of *Uncaria tomentosa*) was tested in a 28-day toxicity study performed as a limit test on 10 male and 10 female rats with a daily oral dose of 1,000 mg/kg bw (corresponds to 1,000 times rec. daily dose). The test substance was administered by means of an oesophageal probe. Body weight, food consumption and haematological parameters were monitored and signs of ill health and any behavioural changes recorded. Following completion of treatment the rats were subjected to a complete post-mortem examination. The kidneys, liver, adrenals, testes, heart and spleen were dissected and weighed, and all organs with macroscopically visible changes were additionally subjected to histological examination.
No mortalities occurred during the study, and no clinical or behavioural changes were observed. There were no differences between the test group and the control group in terms of body weight and food consumption. In the test group, the haematological examination showed a slight but statistically significant decrease in the percentage of neutrophile granulocytes and a slight but statistically significant increase in the percentage of lymphocytes. The histology of the kidneys was normal in all cases. [40]

In addition, an aqueous dry extract from the stem bark of *Uncaria tomentosa,* comparable to KRALLENDORN®, was tested in different dosages for a period of up to 8 weeks. The animals were monitored for clinical changes, weight gain, food consumption and haematological parameters and the organs were weighed following autopsy. [39]

a) For a period of 4 weeks, groups of 9 female W/Fu rats were gavaged daily with an aqueous solution of the test substance in doses of 160 mg/kg body weight or sterile tap water.

b) For a period of 8 weeks, groups of 8 female W/Fu rats were gavaged daily with an aqueous solution of the test substance in doses of 0, 5, 10, 20 or 40 mg/kg body weight.

c) For a period of 8 weeks, groups of 5 female W/Fu rats were gavaged daily with an aqueous solution of the test substance in doses of 0, 40 or 80 mg/kg body weight.

No signs of toxicity were observed in any of the three tests within the observation period of up to 8 weeks. There were no differences between the test groups and the control groups in terms of body weight and food consumption. In addition, post-mortem examination after all three tests showed no differences in either the organ weight coefficients or the histopathological findings.
In test a) with a daily oral dose of 160 mg/kg body weight for 4 weeks, the haematological analysis showed that white blood cells were significantly elevated in the test group compared with the control group. In test b) a significant increase in white blood cells was likewise recorded in the group which received the highest dose of 40 mg/kg for 8 weeks, and in test c) an elevated WBC count was also observed at a dose of 80 mg/kg.

Mutagenicity / Genotoxicity

A freeze-dried aqueous extract as well as 5 extracts and 6 fractions of a chloroform/ethanol extract from *Uncaria tomentosa* were tested for mutagenic properties using the Ames test (*Salmonella*/mammalian microsome test). *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 were used, both with and without metabolic activation, and the substances were tested in concentrations of 50, 500, 1500 and 5000 µg/per plate. There was no evidence of a possible mutagenic effect at any of the tested concentrations. [41, 42]

KRALLENDORN® extract (aqueous acid extract from the whole root of the pentacyclic chemotype of *Uncaria tomentosa*) was tested for genotoxicity in a micronucleus test using HepG2 cell cultures. The substance was tested in concentrations of 1,500 µg/ml, 150 µg/ml, 15 µg/ml, 1.5 µg/ml and 0.15 µg/ml, with benzo[a]pyrene (1.6 µmol/l) as positive control and double-distilled water as negative control. The assay was performed using 4×10^6 HepG2 cells per batch in 10 ml DMEM culture medium. The substance showed no genotoxic effect in the assays performed. However, at the lowest concentration of 0.15 µg/ml, a statistically significant lower micronucleus frequency than the negative control was observed, which suggests that the test substance may have an anti-mutagenic effect. [43]

The test on repair of radiation-induced DNA strand breaks produced further indications of a possible anti-mutagenic potential of standardised extracts from *Uncaria tomentosa*. [39]

Three groups of 10 female W/Fu rats were gavaged daily with 40 or 80 mg test substance per kg bw or sterile tap water for 8 consecutive weeks. Half of the rats from each group were then whole-body irradiated with 12 Gy from a ^{137}Cs source and allowed to repair for 3h in vivo. The animals were then sacrificed and spleen cell suspensions prepared to examine the repair of the DNA strand breaks.

In the rats treated with sterile tap water for over 8 weeks the number of DNA strand breaks in the irradiated animals was still significantly higher than in the non-irradiated controls, even after being allowed to repair for 3h in vivo. However, in the rats treated with the highest dose of test substance DNA single-strand breaks were almost completely repaired. The eight-week pre-treatment with the test substance was shown to enhance repair of both single and double-strand DNA breaks in a dose-dependent pattern.

CLINICAL TRIALS

The clinical trials performed on standardised extracts from the pentacyclic chemotype of Uncaria tomentosa (Willd.) DC. (KRALLENDORN®) comprise:

Double-blind, placebo-controlled trial:

- Adjunctive therapy in r**heumatoid arthritis**

Case studies / Case reports:

- Therapy of **herpes simpex** und **varicella zoster**
- Adjunctive therapy in **HIV-infection** und **AIDS**
- Adjunctive therapy in **tumour-related diseases**

KRALLENDORN® in the treatment of rheumatoid arthritis

Randomised, double-blind, placebo-controlled trial in 40 patients with rheumatoid arthritis

Study design: Randomised, double-blind, placebo-controlled trial in 40 patients with Steinbrocker functional class II or III rheumatoid arthritis [44]

Duration of study: 6 months

Medication: All patients had been undergoing basic anti-rheumatic therapy with sulphasalazine or hydroxychloroquine for a period of at least 6 months prior to the study; stable doses of these drugs had to be taken in the 6 weeks prior to enrolment and for the entire duration of the trial. Additional administration of NSAIDs or analgesics was permitted as needed.

Test group: above plus 1 KRALLENDORN® capsule three times daily

Control group: above plus placebo

Clinical assessment: At 0, 4, 8, 16 and 24 weeks

Criteria: Main outcome measures:

- Number of painful joints assessed by ARA functional classification and Ritchie articular index
- Number of swollen joints assessed by ARA functional classification
- Tenderness and swelling of joints assessed by VAS

Secondary outcome measures:

- Functional capacity assessed by HAQ
- Patients' VAS assessment of subjective pain
- Duration of morning stiffness
- Surrogate markers: erythrocyte sedimentation rate, acute phase C-reactive protein and rheumatoid factor

Statistical analysis: "According to protocol"
Deductive statistical methods were used, adapted to the respective efficacy and safety criteria. The placebo group and the test group were statistically identical at the start of the study.

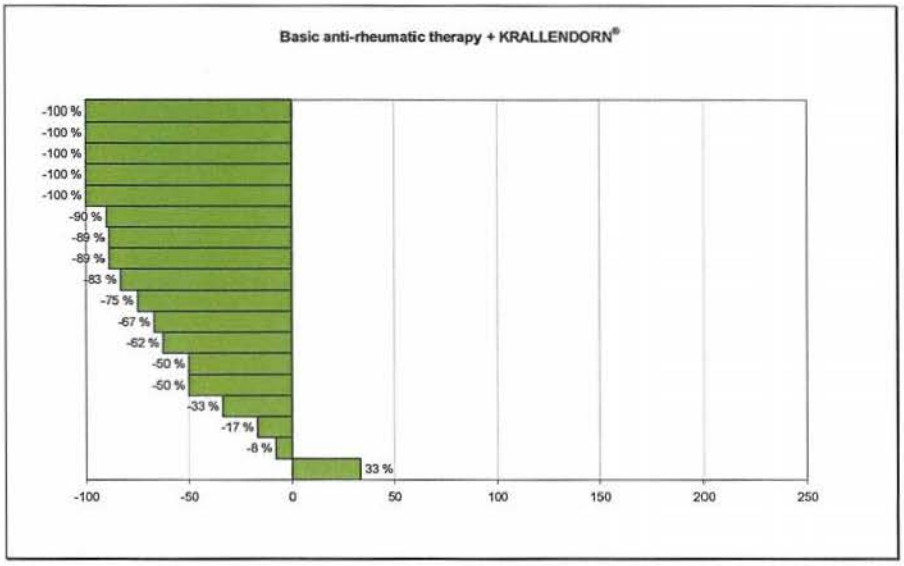
Adverse events / Side effects:

No adverse events or side effects associated with KRALLENDORN® were observed.

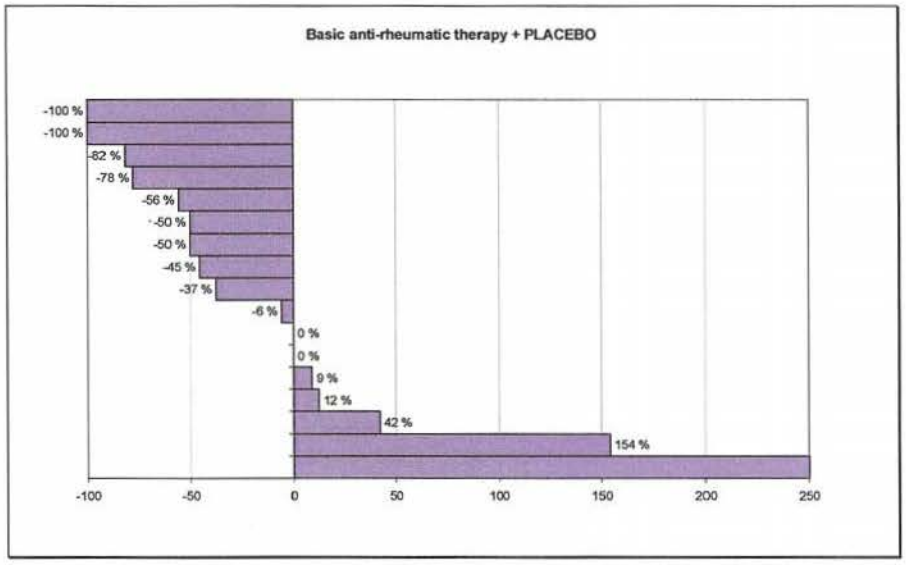
Clinical outcome at end of study:

- Significant reduction in the number of tender joints ($p = 0.035$)
- Significant reduction in the number of painful joints and intensity of pain ($p = 0.004$)
- Significant reduction in the duration of morning stiffness ($p = 0.021$)
- Stabilisation of rheumatoid factor ($p = 0.030$)
- Increase in functional capacity (though without reaching the pre-defined statistical significance level)

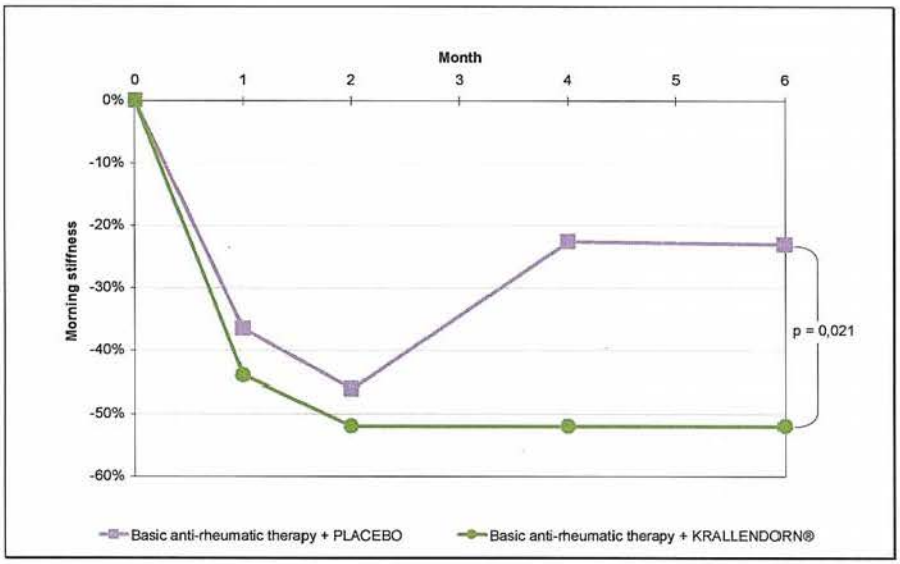
➢ No adverse interaction with the basic medication



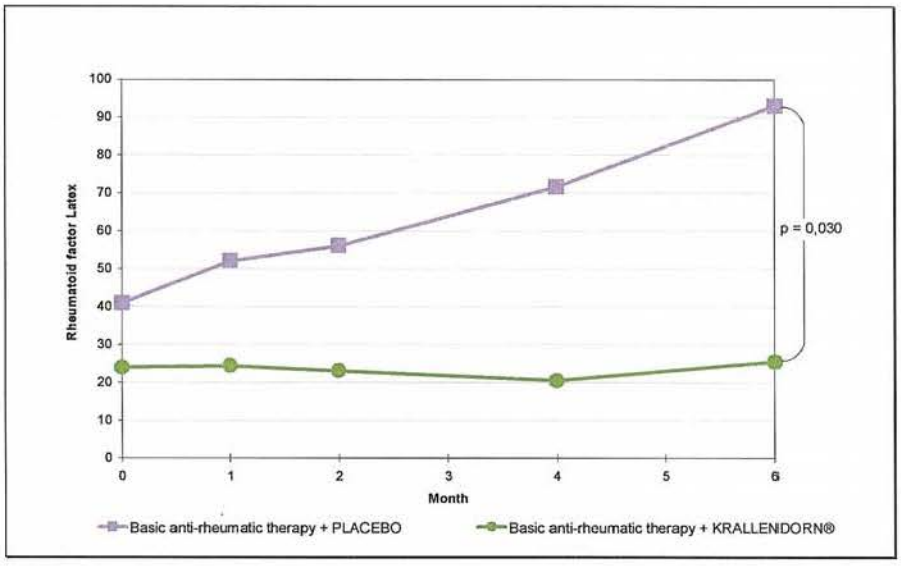
Reduction (negative values) or increase (positive values) in the outcome measure "ARA Pain Index" at week 24 in percent of the baseline value in the test group



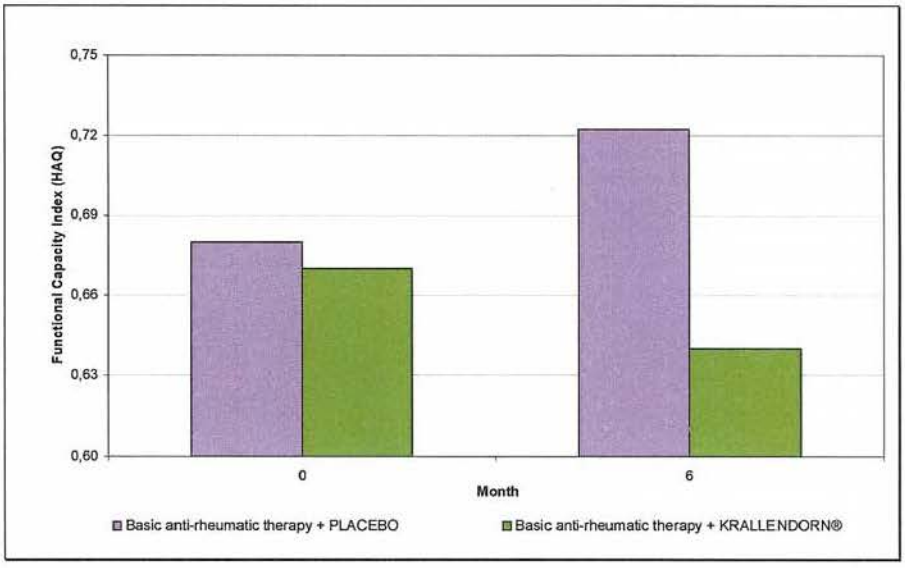
Reduction (negative values) or increase (positive values) in the outcome measure "ARA Pain Index" at week 24 in per cent of the baseline value in the placebo group



Development of the duration of morning stiffness in % of the baseline value



Development of latex rheumatoid factor



Functional Capacity Index as assessed by Health Assessment Questionnaire at the beginning (Mo. 0) and end (Mo. 6) of the trial

Open follow-up of double-blind trial (see above) in 30 patients with rheumatoid arthritis

Study design: Open, controlled follow-up of double-blind trial [45]

Duration of study: 6 months

Medication: All patients had been undergoing basic anti-rheumatic therapy with sulphasalazine or hydroxychloroquine for a period of at least 6 months prior to the study; stable doses of these drugs had to be taken in the 6 weeks prior to enrolment and for the entire duration of the trial. Additional administration of NSAIDs or analgesics was permitted as needed.

Group A: above plus 1 KRALLENDORN® capsule three times daily for the entire duration of the trial

Group B: above plus placebo in weeks 0-24
KRALLENDORN® capsules in weeks 24-52

Clinical assessment: At 24, 38 and 52 weeks (after start of double-blind phase)

Criteria: As in double-blind phase (see page 27)

Statistical analysis: "Intent to treat"
Non-parametric tests (Mann-Whitney, Wilcoxon, Kolmogorov-Smirnov) were used.

Adverse events / Side effects:

No adverse events or side effects associated with KRALLENDORN® were observed.

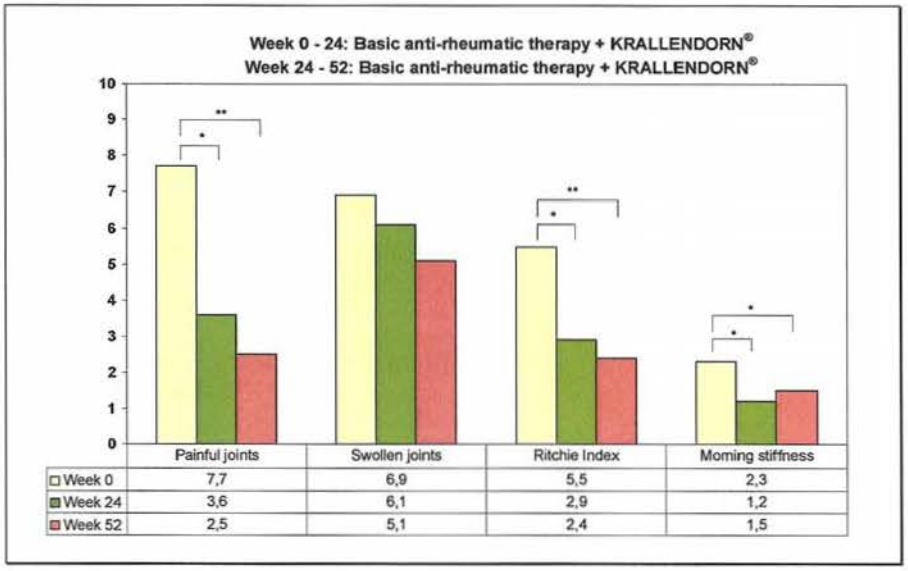
Clinical outcome at end of study:

In former test group:

- Further reduction in the number of tender joints ($p < 0.001$)
- Further reduction in the number of painful joints and intensity of pain ($p < 0.001$)
- Further reduction in the number of swollen joints (though without reaching the pre-defined statistical significance level)
- Slight increase in morning stiffness compared with end of double-blind trial (without statistical significance)

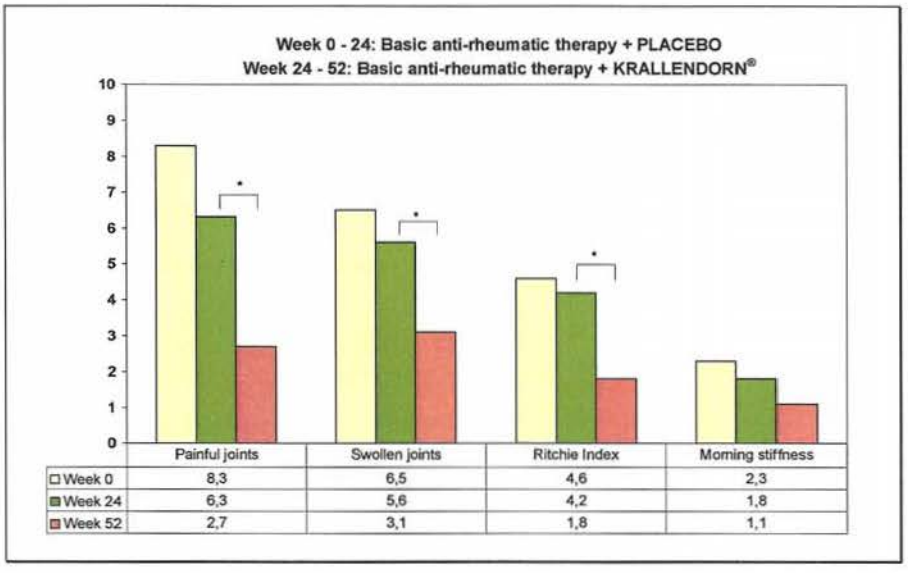
In former placebo group:

- Significant reduction in the number of tender joints ($p < 0.01$)
- Significant reduction in the number of painful joints and intensity of pain ($p < 0.01$)
- Significant reduction in the number of swollen joints ($p < 0.01$)
- Reduction in the duration of morning stiffness (though without reaching the pre-defined statistical significance level)



	Painful joints	Swollen joints	Ritchie Index	Morning stiffness
Week 0	7,7	6,9	5,5	2,3
Week 24	3,6	6,1	2,9	1,2
Week 52	2,5	5,1	2,4	1,5

Group A:
Mean outcome measures at 0, 24 and 52 weeks in patients receiving treatment with KRALLENDORN® in addition to basic anti-rheumatic medication for the entire duration of the trial
($p < 0.01$; ** $p < 0.001$)*



	Painful joints	Swollen joints	Ritchie Index	Morning stiffness
Week 0	8,3	6,5	4,6	2,3
Week 24	6,3	5,6	4,2	1,8
Week 52	2,7	3,1	1,8	1,1

Group B:
Mean outcome measures at 0, 24 and 52 weeks in patients receiving placebo from Week 0 to Week 24 and treatment with KRALLENDORN® from Week 24 to Week 52 in addition to basic anti-rheumatic medication ($p < 0.01$)*

Clinical observation study on 6 patients with rheumatoid arthritis

Study design: Clinical observation of 6 patients with rheumatoid arthritis (4 patients in Steinbrocker functional class II / III, 2 in Steinbrocker functional class I / II), conducted by a general medical practitioner [46]

Duration of observation: 24 months of KRALLENDORN® therapy
8-year observation period

Medication: 1 KRALLENDORN® capsule once to three times daily
or equivalent dose of aqueous decoction of *Radix Uncariae tomentosae* (Willd.) DC. mod. pent.
Prior to the onset of therapy the patients received medication in the form of gold injections, NSAR, steroidal anti-rheumatics and analgesics.

Adverse events / Side effects:

No adverse events or side effects associated with KRALLENDORN® were observed.

Clinical outcome:

After 3 months:

- Increased symptoms in 3 patients
- Reduced symptoms in 3 patients

After 6 months:

- Reduction in pain, joint stiffness and symptoms of inflammation in all patients

After 12 months:

- 3 patients largely symptom-free
- Other 3 patients completely symptom-free
- Reduction of dosage of basic medication in some patients

After 18 months:

- All patients completely symptom-free

In 2 patients in Steinbrocker functional class I / II the good clinical status persisted for an average of 6 (5 – 7) years without any further therapy. In the patients in Steinbrocker functional class II / III the freedom from symptoms persisted for an average of 1.7 (1 – 2) years following the end of therapy. The patients reported that – in contrast to the course of the disease prior to therapy – no generalised episodic attacks occurred during the symptom-free period.

Upon recurrence of symptoms the therapy with KRALLENDORN® was resumed with the same therapeutic success as in the first phase of treatment.

KRALLENDORN® in the treatment of viral infections

Multi-centre clinical observation study on patients with varicella zoster and herpes simplex

Study design: Multi-centre clinical observation study on 20 patients with varicella zoster and 17 patients with herpes simplex [47]

Duration of observation: 17 days

Medication: Topical application of KRALLENDORN® (ointment, cream, spray, gel) in a dose equivalent to 4 mg/g, applied once daily in patients with herpes simplex and 16 patients with varicella zoster; in 4 patients with varicella zoster KRALLENDORN® was applied at two-hour intervals during the waking phase

Adverse events / Side effects:

No adverse events or side effects associated with KRALLENDORN® were observed.

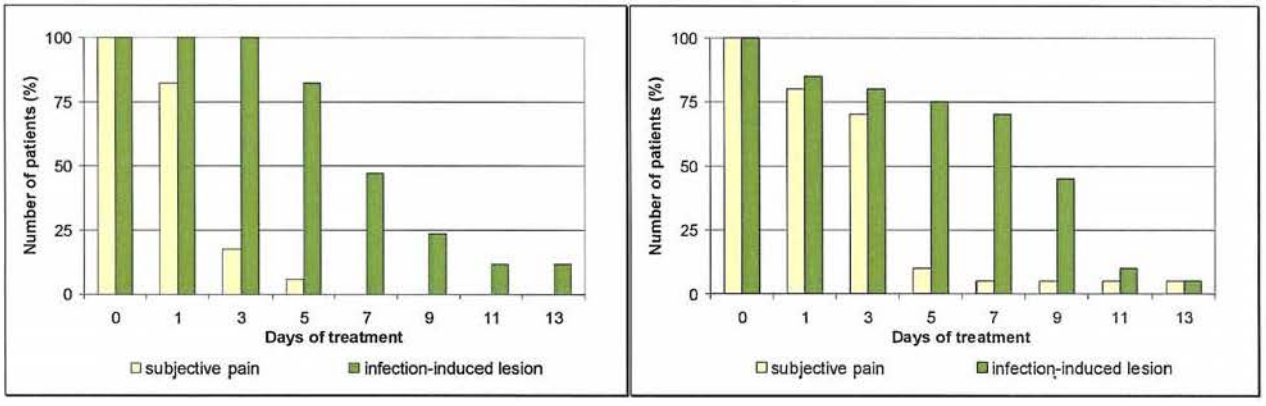
Clinical outcome at time of data analysis:

Patients with herpes simplex:

- Subjective freedom from pain in 18 % of the patients at day 1 and in 100 % at day 7 after start of treatment
- Healing of infection-induced lesion in 18 % of the patients at day 5 and in 88 % at day 11 after start of treatment

Patients with varicella zoster:

- Subjective freedom from pain in 20 % of the patients at day 1 and in 95 % at day 7 after start of treatment
- Healing of infection-induced lesion in 15 % of the patients at day 1 and in 95 % at day 13 after start of treatment
- One patient did not respond to the therapy
- The group who received multiple daily applications responded significantly better to the therapy than the group who received a single daily application



Reduction in subjective pain and healing of infection-induced lesion in 17 patients with herpes simplex (left) and 20 patients with varicella zoster infection (right)

Multi-centre clinical observation study on 44 patients with HIV infection

Study design:	Multi-centre clinical observation study on 44 patients with HIV infection in stages CDC A (n=16), CDC B (n=13) and CDC C (n=15) following adjunctive administration of KRALLENDORN® [48]
Duration of observation:	12 to 60 months
Medication:	1 KRALLENDORN® capsule once to six times daily or equivalent dose of KRALLENDORN® drops or equivalent dose of aqueous decoction of *Radix Uncariae to*mentosae (Willd.) DC. mod. pent, in addition to antiretroviral therapy and opportunistic prophylaxis
Adverse events / Side effects:	No adverse events or side effects associated with KRALLENDORN® were observed.

Clinical outcome at time of data analysis:

- Enhanced vitality and mobility in all patients
- No adverse interaction with the basic medication or opportunistic prophylaxis
- Stabilisation of the CD4 cell count in patients in stage CDC A
- Stabilisation of or increase in the CD4 cell count in patients in stages CDC B and CDC C
- Direct correlation between development of CD4 cell count and development of total leukocyte count and CD8 cell count
- Loss of concomitant clinical symptoms in patients in stage CDC B
- Limitation of disease progression in stage CDC C

Retrospective data analysis of 16 patients with HIV infection

Study design:	Retrospective data analysis of 16 patients with HIV infection in CDC stages A1, A2, B1, B2, B3 and C3 following adjunctive administration of KRALLENDORN®; conducted in cooperation with the AIDS Outpatient Clinic at the Pulmonological Hospital and the AIDS-Hilfe support organisation, both in Vienna [49]
Duration of observation:	1 to 5.8 years
Medication:	1 KRALLENDORN® capsule once to six times daily in addition to antiretroviral therapy and opportunistic prophylaxis
Adverse events / Side effects:	
	No adverse events or side effects associated with KRALLENDORN® were observed.

Clinical outcome at time of data analysis:

KRALLENDORN® with antiretroviral therapy:

- Clinical stability in all patients
- Stabilisation of or increase in the CD4 cell count

KRALLENDORN® without antiretroviral therapy:

- Clinical stability in a majority of the patients
- Stabilisation of the CD4 cell count

Both therapeutical schemes with KRALLENDORN®:

- Enhanced vitality and mobility in all patients
- No adverse interaction with the basic medication or opportunistic prophylaxis

KRALLENDORN® as an adjunctive therapy to chemotherapy and radiotherapy

Retrospective data analysis of 60 patients with brain tumours

Study design: Retrospective data analysis of 60 patients with brain tumours following adjunctive administration of KRALLENDORN®, conducted at the Department of Neurosurgery, Innsbruck University Hospital [50]

Duration of observation: 14 to 34 months

Medication: Alcoholic solution of KRALLENDORN® extract in a dose equivalent to 1 KRALLENDORN® capsule once to three times daily in addition to tumour resection, radiotherapy or chemotherapy

Adverse events / Side effects:

No adverse events or side effects associated with KRALLENDORN® were observed.

Clinical outcome at time of data analysis:

- Significant increase in vitality and well-being in all cases, especially with regard to improved tolerance of chemotherapy and radiotherapy
- Confirmed non-recurrence in patients with medulloblastoma WHO grade IV, mixed glioma WHO grade II, oligodendroglioma WHO grade II*)
- No recurrence in 83 % of the patients with ependymoma WHO grades III and II*)
- No recurrence in 75 % of the patients with astrocytoma WHO grade II*)
- Suspected recurrence in the patient with oligoastrocytoma WHO grade II*)
- No prolongation of life in patients with glioblastoma multiforme WHO grade IV*)
- No adverse interaction with the basic medication

	Patients	Increased vitality	Recurrence*)	Exitus*)	Remission*)
Glioblastoma multiforme WHO grade IV	40	100 %	93 %	93 %	8 %
Medulloblastoma WHO grade IV	1	100 %	0 %	0 %	100 %
Ependymoma WHO grades III and II	6	100 %	17 %	0 %	83 %
Astrocytoma WHO grade II	8	100 %	25 %	0 %	75 %
Mixed glioma WHO grade II	1	100 %	0 %	0 %	100 %
Oligoastrocytoma WHO grade II	1	100 %	100 %	0 %	0 %
Oligodendroglioma WHO grade II	1	100 %	0 %	0 %	100 %
Malignant meningioma	2	100 %	100 %	50 %	0 %

*) *Status at end of observation period*

Case reports on 22 patients with various tumour-related diseases

Study design: Multi-centre clinical observation study on 22 patients with various tumour-related diseases following adjunctive administration of KRALLENDORN® [51]

Duration of observation: 12 months to 10 years

Medication: 1 KRALLENDORN® capsule once to three times daily or equivalent dose of aqueous decoction of *Radix Uncariae to*mentosae (Willd.) DC. mod. pent. in addition to tumour resection and radiotherapy or chemotherapy

Adverse events / Side effects:

No adverse events or side effects associated with KRALLENDORN® were observed.

Clinical outcome at time of data analysis:

- Increased vitality and well-being in all cases
- Improved tolerance of chemotherapy and radiotherapy
- Remissions for a period of up to 10 years were observed in patients in the early stages of disease
- No adverse interaction with the basic medication

	n =	Therapy	Exitus	Partial remission	Complete remission	Survival period (years)*
Myelodysplasia	1	PP	0	0	1	1
Histiocytic medullary reticulosis (Letterer-Siwe disease)	1	PP,IFN	0	0	1	1
Acute myeloid leukaemia	1	PP,CT	0	0	1	10
Brain stem glioma	1	PP,RAD	0	0	1	8
Oligodendroglioma	1	PP,SUR	0	1	0	1.5
Tonsillar carcinoma	1	PP,SUR	0	0	1	1.5
Bronchial adenocarcinoma	1	PP	0	1	0	1
Intestinal adenocarcinoma	3	PP,SUR	1	0	2	4 (1-9)
Urothelial carcinoma, stage pT3a, NO, Mo, G3	1	PP,CT	0	0	1	1.5
Testicular teratoma	2	PP,CT	0	0	2	10 (10, 10)
Cervical carcinoma, stage 4A	1	PP,SUR	0	0	1	7
Ovarian carcinoma	2	PP,SUR	0	1	1	1.5 (1, 2)
Recurrence of mammary carcinoma, stage M1	3	PP,SUR, CT	1	2	0	1.7 (1 – 2)
2nd recurrence of melanosarcoma, stage MI	1	PP, SUR, CT	1	0	0	3.5
2nd recurrence of medulloblastoma	1	PP	0	0	1	8

*PP = KRALLENDORN®; IFN = interferon; CT = chemotherapy; RAD = radiotherapy; SUR = surgery; *) = status at end of observation period*

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