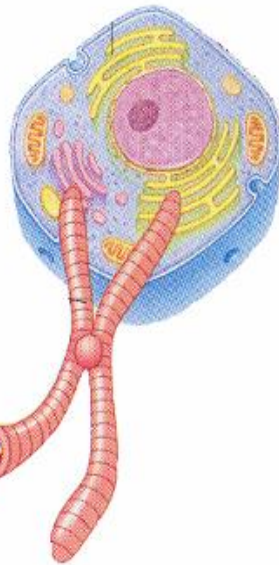




MÁS ALLÁ DEL MANEJO HOLÍSTICO DEL CÁNCER

Álvaro Andrés Ramírez Ochoa

Cada vez que una célula se divide en dos células hijas, estamos en un riesgo potencial de un error en la duplicación de su ADN: esto nos ocurre

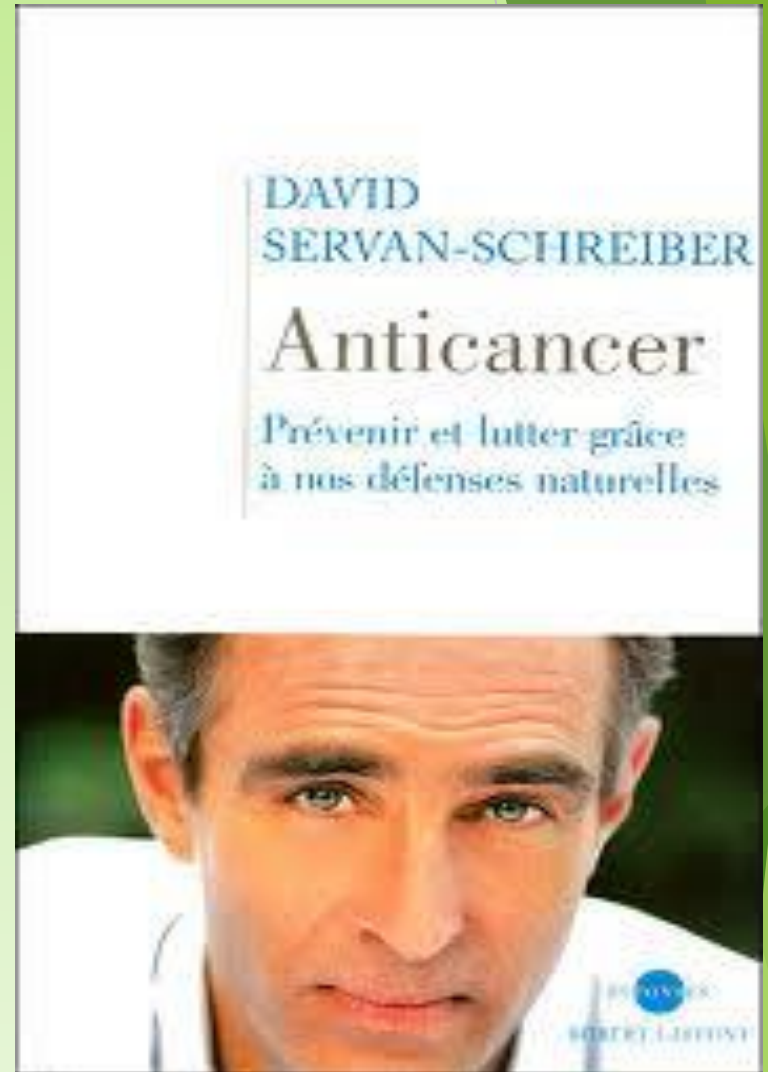


70 millones
de veces x día.

Cada célula de nuestro cuerpo debe fabricar mas de 800 veces por segundo, un juego completo de 46 cromosomas.

CÁNCER

Cuando el Doctor David Servan conoce el diagnóstico de cáncer cerebral comienza el camino de los consultorios y de los especialistas en cabeza de su oncólogo.



CÁNCER

- ▶ Pedí consejo a mi oncólogo: “Que tenía que hacer si deseaba tener una vida sana?”.
- ▶ “¿Que precauciones debía tomar para evitar una recaída?”.
- ▶ La respuesta de aquella lumbrera de la medicina moderna fue:
- ▶ “Vive con toda normalidad, haremos TAC´s cada equis tiempo y si vuelve a formarse un tumor, lo detectaremos antes de que sea tarde”.

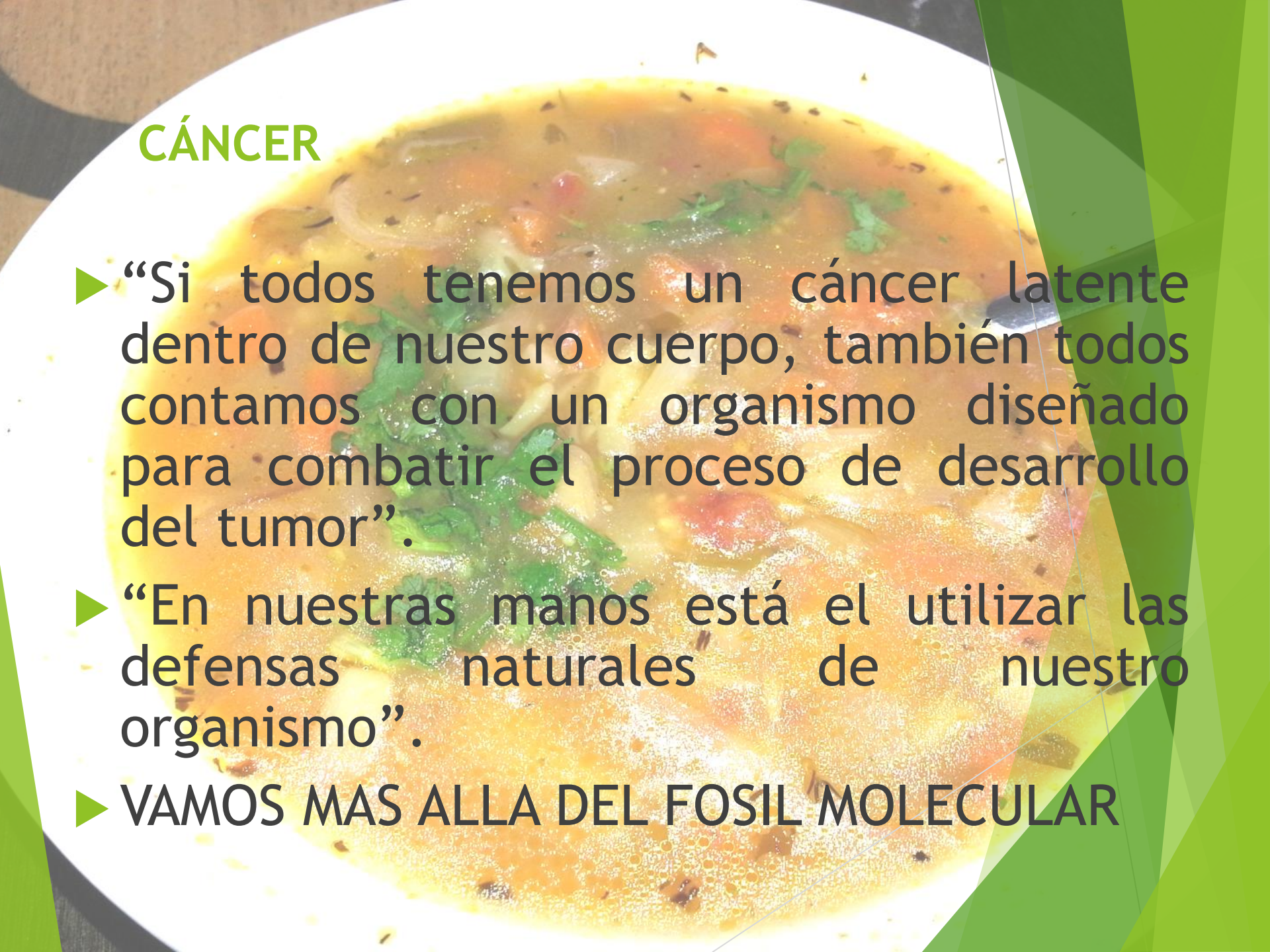
CÁNCER

“¿Pero?, no hay algún ejercicio que pueda hacer, alimentos contraindicados, o bien Un régimen alimenticio favorable?, no debería trabajar MI ACTITUD MENTAL?”.

- ▶ Su respuesta:
- ▶ “En este ámbito haz lo que te parezca, daño no te va a hacer, pero no se ha demostrado científicamente que esos enfoques sirvan para prevenir una recaída”.

NUTRICION Y CÁNCER

- ▶ “En cuanto a los enfoques que concedían importancia a la relación del cuerpo y la MENTE, o los enfoques que concedían importancia a la ALIMENTACION, mi oncólogo evidentemente no tenia ni tiempo ni ganas de explorar esas avenidas”.
- ▶ “Busqué este tipo de medicina que, además de tratar enfermedades, trabaje con el TERRENO”.
- ▶ Y la ENERGIA
- ▶ Y mi YO?
- ▶ Y EL ALMA?

A bowl of vegetable soup with tomatoes, onions, and herbs. The soup is served in a white bowl and is garnished with fresh green herbs. The background is a green geometric pattern.

CÁNCER

- ▶ “Si todos tenemos un cáncer latente dentro de nuestro cuerpo, también todos contamos con un organismo diseñado para combatir el proceso de desarrollo del tumor”.
- ▶ “En nuestras manos está el utilizar las defensas naturales de nuestro organismo”.
- ▶ VAMOS MAS ALLA DEL FOSIL MOLECULAR

► QUE PROPONE LA MEDICINA OCCIDENTAL



► QUE PROPONE LA MEDICINA OCCIDENTAL



► QUE PROPONE LA MEDICINA OCCIDENTAL



► QUE PROPONEMOS
NOSOTROS:

ASEDIAR
APOPTOSIS

Le quitamos el agua y la comida

Acorralar el tumor:

Alcalinizando al paciente

Dieta hipo-sódica

Enzimas proteolíticas, para destruir
proteínas dextróginas

Hiper-oxigenar el sistema

Recuperar función de los filtros

Eliminar toxinas acumuladas en el
espacio intersticial.

TODOS LOS ALIMENTOS ANTICANCER

Dieta cruda en una mayor proporción



HAY ALGO MAS
QUE HACER?



Kelly A. Turner, Ph.D.

RADICAL REMISSION

The Nine Key Factors That Can Make a Real Difference

SURVIVING CANCER
AGAINST ALL ODDS



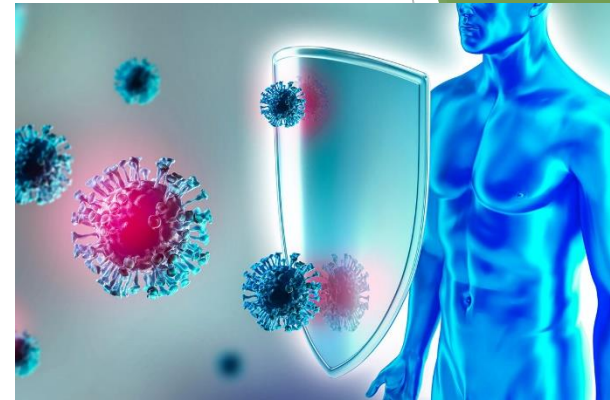
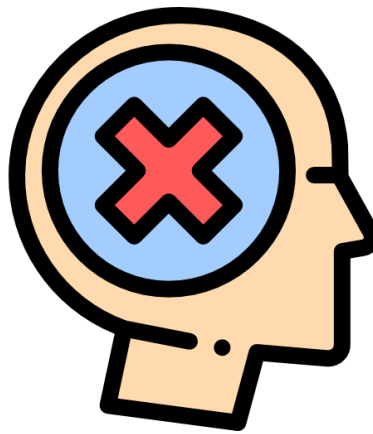
Supervivientes y sus terapeutas fueron entrevistados

- Los médicos les habían pronosticado X cantidad de vida
- Los pacientes les demostraron que estaban equivocados
- Y que las estadísticas son impersonales
- Nadie sabe de lo que eres capaz
- Si solo hay un 1% de posibilidad de sanar como puedo hacer parte de ese 1%?



Supervivientes y sus terapeutas fueron entrevistados

- Todo comportamiento o actitud negativa evita que tu sistema inmune trabaje de manera óptima
- Disponerte a mirar las partes oscuras de tu pasado
- Tu dieta
- Tus relaciones



FACTORES CLAVES EN LA REMISIÓN QUE PASÓ?

- La Medicina Occidental puede incidir en tu poder o capacidad:
- Es diferente decirle al paciente que hace
- Se le preguntó que hizo?
- Se encontraron mas de 75 cosas diferentes que los pacientes hicieron adicionales en busca de su sanación
- Peo hubo 9 factores básicos que se repitieron en casi todos ellos



75

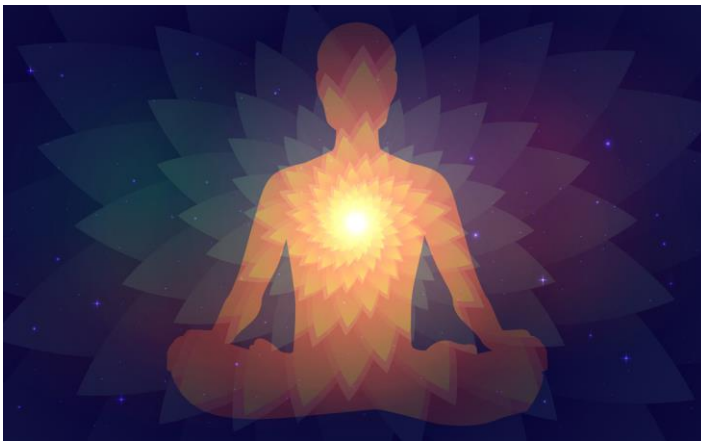
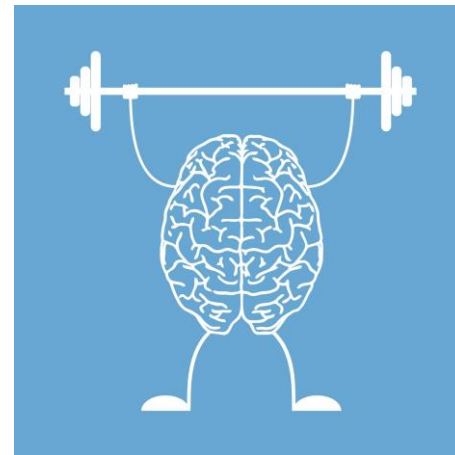
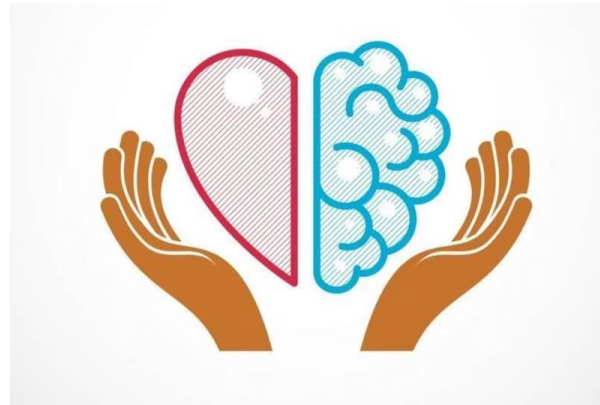
9

DE LOS 9 DOS FUERON FÍSICOS Y EL RESTO EN EL CAMPO EMOCIONAL MENTAL Y ESPIRITUAL

Se llegó a la conclusión que la clave es incidir en el SISTEMA INMUNOLOGICO que se puede activar con el trabajo:

- EMOCIONAL
- MENTAL
- ESPIRITUAL

FACTORES CLAVES EN LA REMISION TOTAL



CAMBIOS CLAVES EN LA REMISIÓN TOTAL

CAMBIOS FÍSICOS

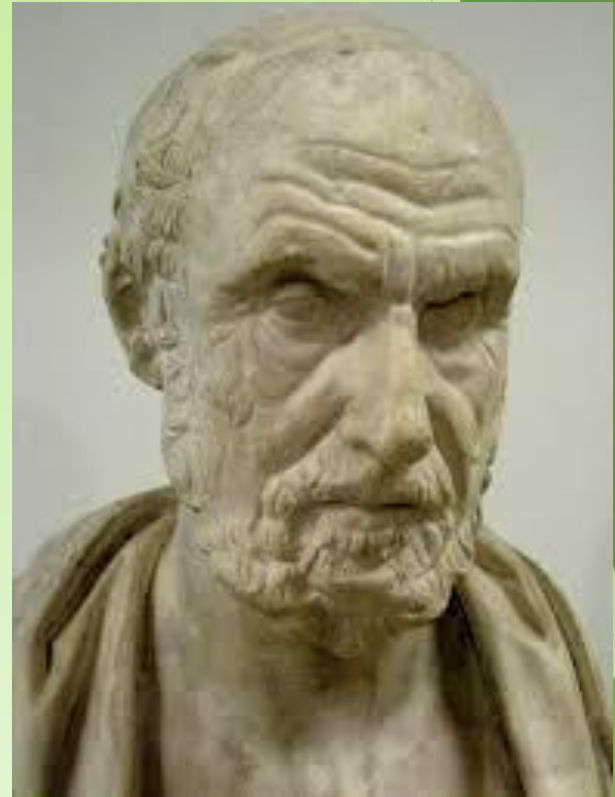
- CAMBIOS RADICALES EN LA DIETA
- REDUCIR alimentos potencialmente dañinos:
 - Carnes
 - Azúcares
 - Trigo
 - Lácteos
 - Comer orgánico
 - Verduras
 - Beber agua filtrada
 - Diferentes tipos de dietas bien dirigidas y diseñadas



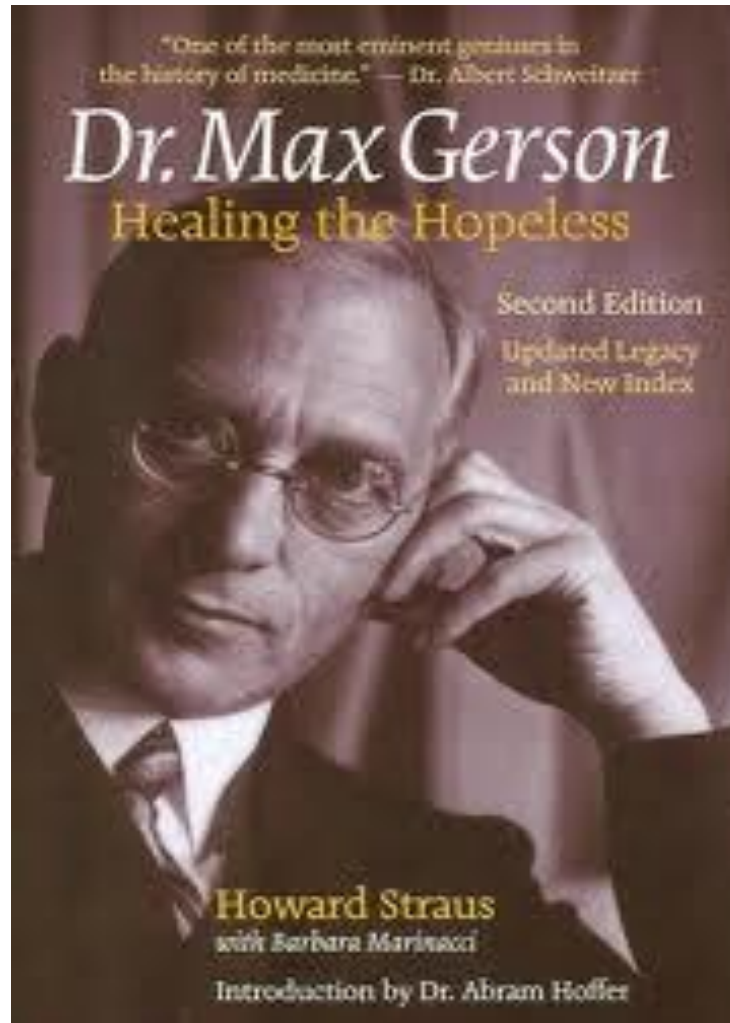
NUTRICIÓN Y CÁNCER

“QUE TUS ALIMENTOS
SEAN TU MEDICINA,
QUE TU MEDICINA SEAN
TUS ALIMENTOS”.

Hipócrates



MAX GERSON





ALIMENTOS ANTICÁNCER



CÁNCER Y PH

- ▶ Dr Soren Peter Lauritz Sorensen en 1909 habla por primera vez del pH.
- ▶ Dr. Albert Szent Gyorgui premio nóbel por descubrir la Vit C “El cuerpo es alcalino por diseño, pero todas sus funciones son acidificantes”.



CÁNCER Y PH

PH SANGUINEO



CÁNCER Y PH

www.Alkalinecare.com

Science Daily (Tumor cell Engineer Acidity to Drive cell invasion)

“ Monitoreamos los animales de laboratorio conforme avanzaba el tiempo usando microscopios y encontramos que las zonas donde había mayor invasión tumoral correspondía a las áreas donde el pH era mas Bajo”

5 Alimentos que destruyen el cancer



Té Verde



Tomates



Uvas

Gratificados



Curcuma

Todo tipo de Verduras



ALIMENTOS ANTICÁNCER

TÉ VERDE

- ▶ Contiene polifenoles llamados catequinas (epigallocatequina galato) EGCG.
- ▶ El té no fermentado.
- ▶ Bloquean recetores de inducción de angiogénesis.
- ▶ Leucemia, mama, piel, próstata, riñón, boca.
- ▶ Desintoxicante hepático.
- ▶ Sensibiliza células del SNC a la Radioterapia.



ALIMENTOS ANTICÁNCER

CURCUMA Y CURRY

- ▶ Es un potente antiinflamatorio.
- ▶ Molécula Curcumina.
- ▶ Inhibe Ca de colon, hígado, estómago, mama, ovarios y leucemia.
- ▶ Estimula la Apoptosis.
- ▶ Mezclar con pimienta (Curry)
- ▶ Sesibiliza a la Quimioterapia.
- ▶ Interfiere contra el NF-kappa B.
- ▶ Elimina toxinas



ALIMENTOS ANTICÁNCER

VERDURAS CRUCIFERAS

- ▶ La Col (De Bruselas, repollo Chino, brécol, coliflor)
- ▶ Contienen Sulforafano e indo-3-carbinoles (I3C), la ebullición los destruye
- ▶ Moléculas anticáncer
- ▶ Anti-Angiogénesis
- ▶ Promueven Apoptosis.



ALIMENTOS ANTICÁNCER

RAIZ DE JENGIBRE

- ▶ Potente Antioxidante Antiinflamatorio.
- ▶ Anti-Angiogénesis.
- ▶ Alivia náuseas por Quimioterapia y Radioterapia.
- ▶ Aderezar con ralladura o hacer infusión.



ALIMENTOS ANTICÁNCER

SETAS

- ▶ Estimulan sistema Inmune.
- ▶ Molécula lentinano.
- ▶ Complementan Quimioterapia en Japón.
- ▶ Seta de cardo, oreja blanca, Enoitake, Cremini, Shiitake, Portobello, champiñón en Ca de mama.



ALIMENTOS ANTICÁNCER

FRUTOS ROJOS

- ▶ El Acido Elágico de fresas y Frambuesas es un polifenol que ralentiza el crecimiento tumoral (Avellanas y nueces)
- ▶ Anti-angiogénesis.
- ▶ Elimina toxinas Celulares.
- ▶ El Acido Glucárico de la Cereza Desintoxicante.
- ▶ Antocianidinas y proantocianidinas de los arándanos: Apoptosis.



ALIMENTOS ANTICÁNCER

AJO, CEBOLLA, PUERRO,
CEBOLLETA

- ▶ Propiedades Antibacterianas.
- ▶ Sus compuestos de azufre reducen los efectos cancerígenos de las nitrosaminas y los compuestos n-nitroso (carne asada y tabaco).
- ▶ Apoptosis en Ca de colon, mama, pulmón, próstata, leucemias.
- ▶ Regulan azúcar en la sangre.



ALIMENTOS ANTICÁNCER

- ▶ El Licopeno y la VIT A inhiben el crecimiento de las células cancerosas.
- ▶ La Luteína, el Licopeno, el Fitoeno y la Cantaxantina estimulan el sistema inmune, estimulan las células NK.



ALIMENTOS ANTICÁNCER

ZUMO DE GRANADA

- ▶ Propiedades antiinflamatorias.
- ▶ Antioxidante.
- ▶ En cáncer de próstata se recomienda un vaso diario con el desayuno.



ALIMENTOS ANTICÁNCER

CHOCOLATE NEGRO

- ▶ Mas de un 70% de cacao
- ▶ Antioxidantes.
- ▶ Proantocianidinas.
- ▶ Polifenoles.
- ▶ Frenan el crecimiento de las células cancerosas.
- ▶ Limitan la angiogénesis.
- ▶ Su mezcla con productos lácteos anula sus beneficios.



ALIMENTOS ANTICÁNCER

CÍTRICOS

- ▶ Las naranjas, mandarinas, limón, pomelo contienen flavonoides antiinflamatorios.
- ▶ Desintoxican sustancias cancerígenas por parte del hígado.
- ▶ La piel de la mandarina tiene efecto sobre el cáncer cerebral.



ALIMENTOS ANTICÁNCER

ROMERO

TOMILLO

OREGANO

ALBAHACA

HIERBABUENA

- ▶ Los terpenos promueven la apoptosis de las células cancerosas.
- ▶ Son antioxidantes y antiinflamatorios.



DIETA CETOGENICA

AYUNO

- Efecto Wargurg, las células cancerígenas se nutren muy bien de la glucosa pero no pueden utilizar bien los cuerpos cetónicos para generar energía
- Hay vulnerabilidad en el cáncer al daño metabólico a partir de la generación mitocondrial de energía que tolera menos los cuerpos cetónicos
- La hiperglicemia es un factor de mal pronóstico en cáncer
- Mejora la resistencia a la insulina
- Disminuye IGF-1 IGF-2 que aumentan el riesgo de varios tipos de cáncer
- El BHB principal CC tiene un efecto antitumoral
- Las células se ponen en modo supervivencia con mayor resiliencia a estresores externos
- Disminuye la angiogénesis



ALIMENTOS ANTICÁNCER

ALGAS

- ▶ Apoptosis.
- ▶ Inmunoestimulantes, aumentan células NK.
- ▶ La Fucoxantina en Ca de próstata.
- ▶ La nori contiene Omega3 de cadena larga.
- ▶ Otros. Ca de mama, piel, colon.



COMPLEMENTOS NUTRICIONALES

OMEGA 3

- ▶ De cadena larga en pescados grasos reducen inflamación, cáncer de pulmón, mama, próstata, colon, riñón y metástasis.
- ▶ De cadena corta en la linaza y la semilla de Lino molida.



COMPLEMENTOS NUTRICIONALES

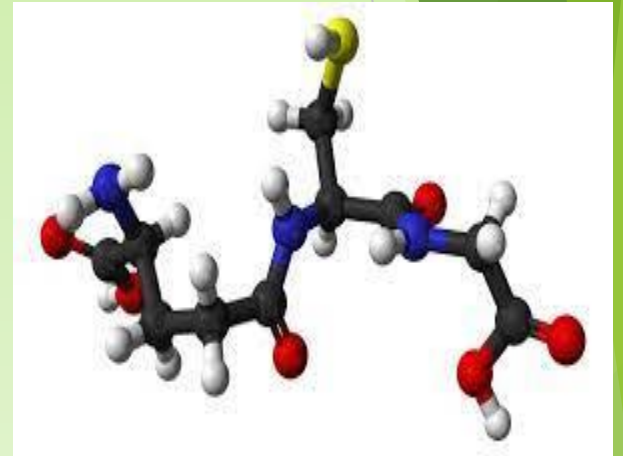
MELATONIA

- ▶ Dosis altas entre 10-15 mg/día
- ▶ Protector mitocondrial que al acumular suficiente melatonina mejora la producción de energía, la reparación de daños y previene la disfunción celular
- ▶ Potencia los efectos oncostáticos de los otros tratamientos disminuyendo los efectos adversos y la quimioresistencia



COMPLEMENTOS NUTRICIONALES GLUTATION

- ▶ Antioxidante maestro
- ▶ Activa inmunidad
- ▶ Controla la inflamación
- ▶ Se encuentra depletado en las células cancerígenas
- ▶ Disminuye con la edad
- ▶ Idealmente prescribir en forma liposomal



METFORMINA

- ▶ Reduce la producción hepática de glucosa, aumenta su absorción por el músculo y reduce niveles de insulina plasmática reduciendo así la producción de células pre y neoplásicas
- ▶ Activa el AMPK inhibiendo la mitosis y activando la apoptosis
- ▶ Inhibe la lipogénesis, reduciendo la disponibilidad de ácidos grasos para a células tumorales
- ▶ Efecto antia angiogénico disminuye VEGF



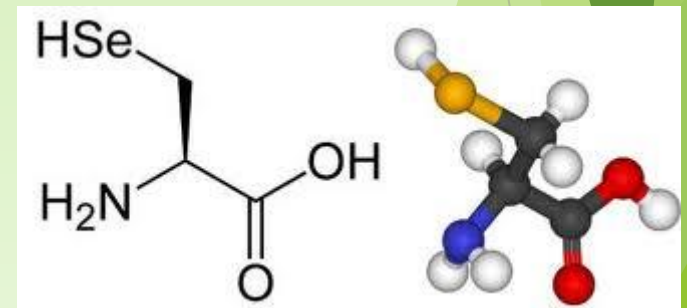
ESTATINAS

- ▶ El colesterol es un precursor en la síntesis de hormonas e isoprenoides involucrados e el desarrollo de algunos tipos de cáncer
- ▶ Previene la conversión de HMGCoA a mevalonato precursor de algunos tipos de cáncer
- ▶ Suprimen el crecimiento tumoral induciendo apoptosis y autofagia
- ▶ Inducen apoptosis y autofagia

COMPLEMENTOS NUTRICIONALES

SELENIO

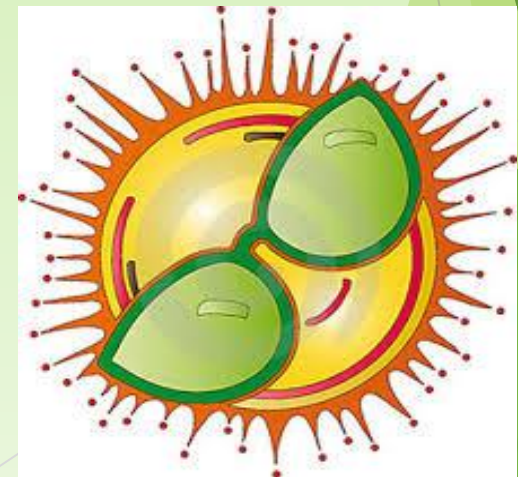
- ▶ Estimula el sistema inmune, células NK.
- ▶ Antioxidante.
- ▶ Presente en la tierra, verduras, cereales ecológicos, pescado, marisco, menudillos



COMPLEMENTOS NUTRICIONALES

VITAMINA D

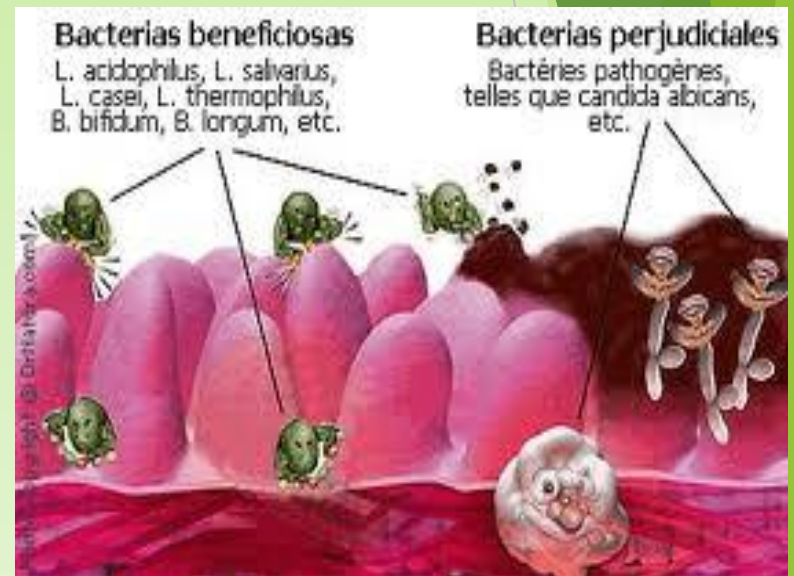
- ▶ 1000 Uis diarias de 25 hidrox vit D disminuye en un 75% el riesgo de padecer cáncer.
- ▶ 15 minutos de exposición al sol por día.
- ▶ Aceite de hígado de bacalao, salmón, caballa, sardina, anguilas.



COMPLEMENTOS NUTRICIONALES

PROBIÓTICOS

- ▶ *Bacillus acidophilus* y *Lactobacillus bifidus* inhiben ca de colon.
- ▶ Desintoxicación.
- ▶ El ajo, cebolla, tomate, espárragos, plátano, trigo son prebióticos



OZONO

CAMBIOS CLAVES EN LA REMISION TOTAL

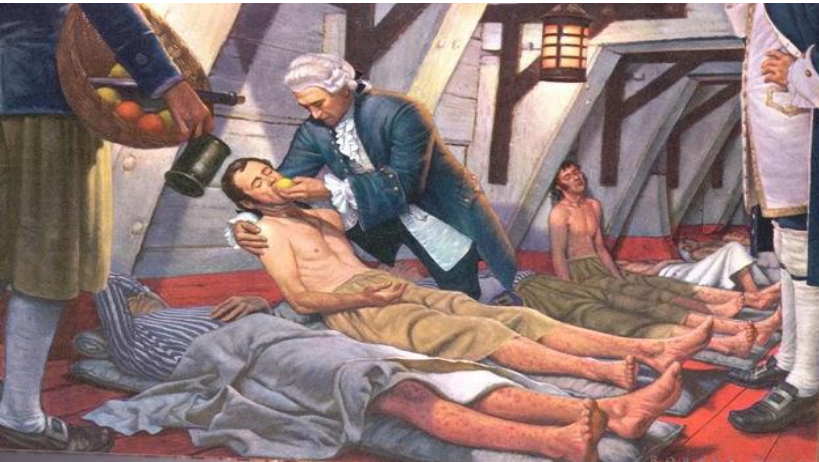
- Efectivo en enfermedades degenerativas con estrés oxidativo
- Mejora calidad y esperanza de vida
- Mejora la progresión de la enfermedad
- Las células tumorales y sus descendencias respiran por la vía glucolítica
- El ozono aumenta el transporte de O_2 a los tejidos
- Bien manejado es libre de efectos secundarios

VITAMINA



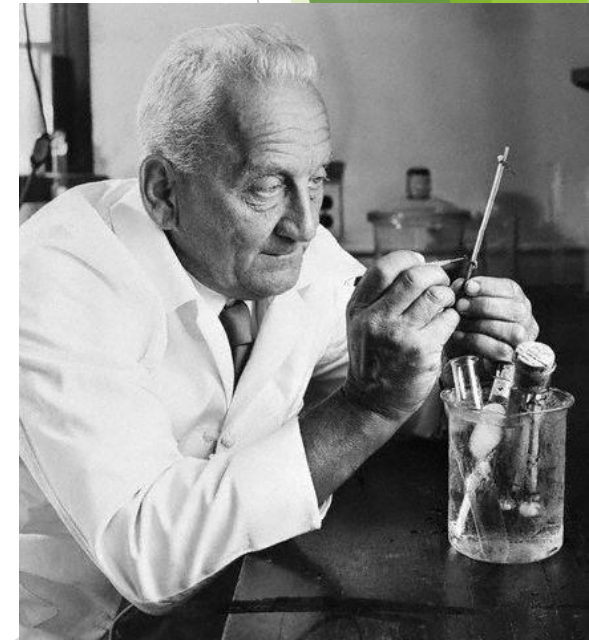
VITAMINA C - Historia

- ▶ Hace mas de 40 millones de años los primates y el hombre no sintetizan la vitamina C (**mutación - enzima gulonolactona oxidasa**)
- ▶ A finales del **siglo XV** se presenta una enfermedad propia de las **tripulaciones de los viajes transatlánticos**



- ▶ **Siglo XVIII** se demostró que el **escorbuto era una enfermedad carencial**, **James Lindt**, un médico de la marina inglesa descubrió el remedio de la enfermedad, **administrando zumo de limón y naranja** como parte de la dieta de pacientes con escorbuto.

- **1923** fue aislada por primera vez por el bioquímico húngaro y premio nobel **Albert Szent-Gyorgyi** a partir de las naranjas, limones, coles y cápsula suprarrenal.



VITAMINA C - FUENTES

- ▶ Las **dosis diarias recomendadas** de ácido ascórbico son de **75 mg/día (mujeres)** y **90 mg/día (varones)**
- ▶ Su **vida media** oscila entre los **10 y 20 días**
- ▶ Las **frutas, verduras y legumbres** constituían el **86 % del total del aporte**. Las bebidas, salsas, lácteos y huevos proporcionaban un 12,5 % del ácido ascórbico. Los frutos secos y las grasas no contribuyeron a dicho aporte
- ▶ El consumo de 5 raciones de frutas y verduras al día aporta una cantidad superior a **60 mg/día**.

Vitamina C (mg por 100g)					
					
Acerola 1677 mg	Escaramujo salvaje 426 mg	Guayabas 228 mg	Grosella negra 181 mg	Perejil 133 mg	Kiwi 92 mg
					
Longan 84 mg	Guisantes 60 mg	Fresa 58 mg	Moras 36 mg	Espinacas 28 mg	Lentejas 16 mg

VITAMINA C – Cáncer

Ascorbato y la prevención del cáncer

- La evidencia epidemiológica sugiere que los alimentos ricos en vitamina C juega un papel protector contra desarrollo del cáncer



- *Vitamin supplements and cancer risk: the epidemiologic evidence. Cancer Causes Control. 1997; 8:786-802.*
- *Diet and cancer prevention: contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Euro J Cancer. 2010; 46:2555-2562.*
- *Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. Lancet. 2004; 364:1219-1228.*

VITAMINA C – FARMACOCINÉTICA

- ▶ Después de la **ingestión oral**, las concentraciones plasmáticas de vitamina C están estrechamente controlados en **70 a 85 $\mu\text{mol} / \text{L}$** para las cantidades que puede obtenerse de los alimentos al día (300 mg/día)
- ▶ Una **dosis oral única de 3gr** produce una concentración plasmática máxima de **206 $\mu\text{mol} / \text{L}$** . Con 3 g por vía oral cada 4 horas, el máximo tolerable, el pico de concentración plasmática fue de aproximadamente 220 $\mu\text{mol} / \text{L}$
- ▶ Por el contrario, después de la **administración intravenosa**, el pico en plasma de concentraciones de vitamina C fue de aproximadamente **1,760 $\mu\text{mol} / \text{L}$ para 3 g; 2,870 $\mu\text{mol} / \text{L}$ para 5 g, 5580 $\mu\text{mol} / \text{L}$ de 10 g, 13 350 $\mu\text{mol} / \text{L}$ de 50 g, y 15 380 $\mu\text{mol} / \text{L}$ de 100 g**

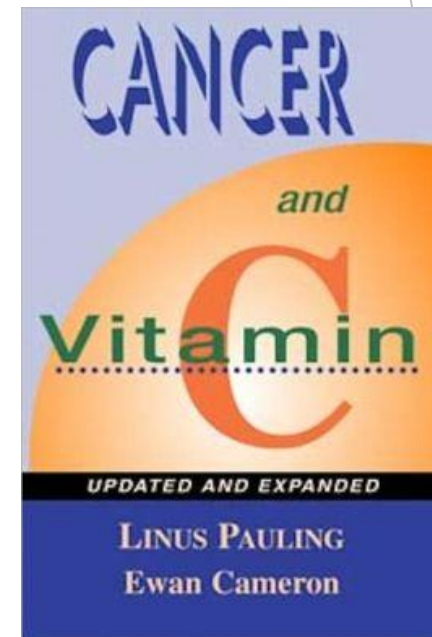
Vitamin C pharmacokinetics: implications for oral and intravenous use. . Ann Intern Med 2004; 140: 533–537

VITAMINA C - CÁNCER

- El uso de altas dosis de ascorbato en el **tratamiento de pacientes con cáncer** comenzó en la década de **1970**. Estos primeros estudios demostraron efectos beneficiosos de altas dosis de ascorbato

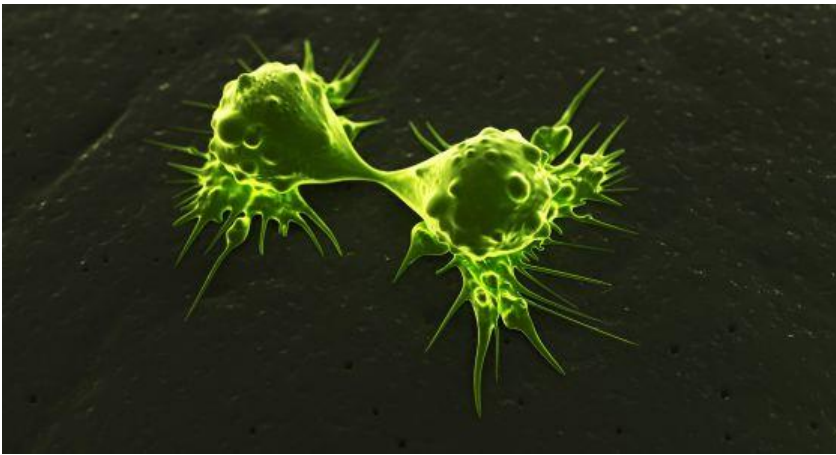
- Cameron E, Campbell A. The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. **Chem Biol Interact.** 1974; 9:285–315.

- Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. **Proc Natl Acad Sci U S A.** 1976; 73:3685–3689



VITAMINA C – FARMACOCINÉTICA EN CÁNCER

- ▶ La evidencia in vitro demostró que la vitamina C indujo la muerte de las células cancerosas a concentraciones extracelulares mas altas que 1.000 $\mu\text{mol} / \text{L}$



- Apoptosis-inducing activity of vitamin C and vitamin K. **Cell Mol Biol (Noisy-le-grand)**. 2000; 46:129-43
- Cytotoxic effect of ascorbate and its derivatives on cultured malignant and nonmalignant cell lines. **Anticancer Res**. 1993; 13:475-80.

VITAMINA C – FARMACOCINÉTICA EN CÁNCER

- ▶ Los mas recientes estudios farmacocinéticos **10 g IV de AA** producen **concentraciones en plasma de casi 6 mM**, que eran 25 veces mayores que las concentraciones resultantes de la misma dosis oral.
- ▶ Las dosis más altas (**50-100 gr**) administrados por vía intravenosa han dado lugar a concentraciones en plasma de aproximadamente **14 mM**
- ▶ Para muchas de las líneas celulares de cáncer, las concentraciones de ascorbato causan una disminución del 50% en la supervivencia celular

The Effects of High Concentrations of Vitamin C on Cancer Cells **Nutrients** 2013, 5, 3496-3505

VITAMINA C – FARMACOCINÉTICA EN CÁNCER

LINEA CELULAR	IC50 (mM)
Human myeloid leukemia	0.33 ± 0.18
Human acute promyelocytic leukemia	0.75 ± 0.3 *
Human myeloblast	0.79 ± 0.22 *
Human chronic myelogenous leukemia	0.5 ± 0.11 *
Human histiocytic lymphoma	0.3 ± 0.16 *
Ovarian cancer	>10 *
Human lymphoma	<1
MCF7 human breast cancer	2
MB231 human breast cancer	7
Hs587t human breast cancer	20

LINEA CELULAR	IC50 (mM)
Mouse lung cancer	<1
Mouse kidney cancer	<2
Mouse colon cancer	4
Mouse melanoma	7
LL/2, mouse lung cancer	11
Hs587Bst, human normal breast cells	>20
CCD34SK, human normal fibroblast cells	>20
Human normal lymphocyte	>20
Human normal monocyte	>20

The Effects of High Concentrations of Vitamin C on Cancer Cells **Nutrients** 2013, 5, 3496-3505

The Mistletoe



The Founders of Mistletoe Therapy in Oncology

He developed



Rudolf Steiner, PhD (1861-1925)
Scientist, Founder of Anthroposophy

She developed and administered
the first mistletoe injection products:



Ita Wegman, MD (1876-1943)
Physician, Head of the Clinical-Therapeutic
Institute (Switzerland)



From an idea to a pharmaceutical company

About 1969

Research for a new mistletoe product started

1975

Foundation of Helixor Heilmittel GmbH & Co. in Marburg

1979

Constitution of the non-profit foundation HELIXOR

1980

Relocation of Helixor company to Rosenfeld (Fischermühle)





Young mistletoe in Autumn on a fir tree

Helixor® A



Fir mistletoe

Helixor® M



Apple tree mistletoe

Helixor® P



Pine mistletoe

HELIXOR® mistletoe preparations are pure, sterile filtered, aqueous fresh plant extracts of viscum album l. (white-berried mistletoe)

Biologically Active Constituents of *Viscum album* L.

Structural types	Constituents	Effects on cancer cells	Effects on the immune system
Glycoproteins	Mistletoe lectins ML I, II, III	Cytotoxicity by inhibition of the ribosomal protein synthesis + induction of apoptosis	Local injection site reaction Increase in eosinophils Release of TNF- α , IL-1, IL-2, IL-6
	Visalb CBA		Stimulation of lymphocytes
Polypeptides	Viscotoxins A ₁₋₃ , B, 1-PS, U-PS	Cytotoxicity by lysis of cell membrane	Activation of macrophages Enhanced phagocytosis activity of granulocytes
Oligo- and Polysaccharides	Arabinogalactane Rhamno- galacturonane		Stimulation of T-helper-cells Enhanced NK-cell activity (TH ₁ , IFN γ)
Flavonoids	Derivates of quercetine	Induction of apoptosis	Antioxidative + cell protective effects
Triterpenoids	Oleanic, ursolic and betulinic acid	Induction of apoptosis and cell differentiation, Anti-angiogenesis	Anti-inflammatory + antioxidative effects Immune protection
Phytohormones	Jasmonic acid	Induction of apoptosis Inhibition of cell proliferation	?

Analytical Profile of Helixor® A, M and P 50 mg

(most important constituent groups)

		Helixor® A	Helixor® M	Helixor® P
CARBOHYDRATES	Monosaccharides (MW < 5 kD, glucose, fructose, galactose)	1.0 – 3.0 mg/ml	0.9 – 2.7 mg/ml	1.2 – 3.5 mg/ml
	Polysaccharides (MW > 5 kD)	0.2 – 0.6 mg/ml	0.1 – 0.3 mg/ml	0.1 – 0.3 mg/ml
PROTEINS	Mistletoe Lectins (mainly ML-III) (ELLA)	100 – 350 ng/ml	200 – 500 ng/ml	500 – 1,500 ng/ml
	Visalb CBA (ELISA)	approx. 100 ng/ml	approx. 250 ng/ml	approx. 100 ng/ml
	Viscotoxins (HPLC)	< 0.5 µg/ml	< 0.5 µg/ml	< 0.5 µg/ml
PHENYLPROPAN-GLYCOSIDES (HPLC)	Syringin	+	+	+
	Syringenin-4'-O-apiosylglucoside	+	+	+
FLAVONOIDS (as glycoside) (HPLC)	Rhamnazin	+	+	+
	Homoeriodictyol	+	+	–
	5,7-Dimethoxy-4'-hydroxyflavanon	–	–	+
TRITERPENOIDS	Oleanolic acid	approx. 0.45 µg/ml	approx. 0.20 µg/ml	approx. 0.25 µg/ml
	Betulinic acid	approx. 0.15 µg/ml	approx. 0.10 µg/ml	approx. 0.15 µg/ml

– = not detectable

+ = detected, means that the constituent(s) were found either in variable amounts or only in traces and were not determined quantitatively

Abbreviations:

MW = molecular weight

ML = mistletoe lectin

HELIXOR PHARMACOLOGICAL EFFECTS IN ONCOLOGY

EFFECTS	MODE OF ACTION
<i>TUMOR INHIBITION</i>	Direct: induction of apoptosis, induction of autophagy, suppression of miRNA activity thus allowing the function of RIPs to inhibit tumor growth, anti-angiogenesis and cell membrane protein synthesis alteration Indirect: immunological effector cells stimulation
<i>IMMUNOPROTECTION</i>	DNA stability and DNA repair on peripheral immune cells Protection from immunosuppressive effect of chemotherapy
<i>IMMUNOMODULATION</i>	Activation of macrofagos, dentritic and natural killer cells Cytokine release Enhancement of phagocytosis Increase of eosinophils, lymphocytes and T-helper cells
<i>IMPROVEMENT OF QoL</i>	Normalisation of neuroendocrinium Beta endorphin release

Effects of Helixor[®] A/M/P on 38 Different Human Tumour Cell Lines

Methods

- Study of anti-proliferative effects in a panel of 38 representative human tumour cell lines
- Helixor[®] A, M and P were added at 5 different concentrations (0.015 – 150 µg/ml)
Negative control: culture medium without Helixor[®]
Positive control: Doxorubicin (0.00003 – 0.3 µg/ml) and ML-1 (0.00001 – 0.1 µg/ml)
- After 4 days exposure, proportion of living cells in treated and control groups was determined and expressed as percentage ratio (% T/C)
- Clear anti-tumour activity: T/C < 50 %
stimulation of cell growth: T/C > 125 %

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journal homepage: www.elsevier.com/locate/biocel



Review

Plant lectins: Targeting programmed cell death pathways as antitumor agents

Lei-lei Fu¹, Cheng-cheng Zhou¹, Shun Yao¹, Jia-ying Yu, Bo Liu*, Jin-ku Bao*

School of Life Sciences & State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China

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ABSTRACT

Lectins, a group of highly diverse, carbohydrate-binding proteins of non-immune origin that are ubiquitously distributed in plants, animals and fungi, are well-characterized to have numerous links a wide range of pathological processes, most notably cancer. In this review, we present a brief outline of the representative plant lectins including Ricin-B family, proteins with legume lectin domains and GNA family that can induce cancer cell death via targeting programmed cell death pathways. Amongst these above-mentioned lectins, we demonstrate that mistletoe lectins (MLs), Ricin, Concanavalin A (ConA) and *Polygonatum cyrtonema* lectin (PCL) can lead to cancer cell programmed death via targeting apoptotic pathways. In addition, we show that ConA and PCL can also result in cancer cell programmed death by targeting autophagic pathways. Moreover, we summarize the possible anti-cancer therapeutic implications of plant lectins such as ConA, *Phaseolus vulgaris* lectin (PHA) and MLs that have been utilized at different stages of preclinical and clinical trials. Together, these findings can provide a comprehensive perspective for further elucidating the roles of plant lectins that may target programmed cell death pathways in cancer pathogenesis and therapeutics. And, this research may, in turn, ultimately help cancer biologists and clinicians to exploit lectins as potential novel antitumor drugs in the future.

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Pharmacological Effects of Mistletoe Products Relevant for Cancer Patients

Immunomodulation

Depends on host tree, preparation, compound

Monocytes/macrophages: cytotoxicity, phagocytosis, antigen presenting function, cytokines

VAE-activated macrophages tumoricidal in Balb/c mice with Ehrlich ascites tumor
[Immunol Investigations 1993; 22:431-440]

NK-cells: Activation, cytotoxicity, sensitivity of tumor cells

Adoptive application of VAE-activated NK-cells inhibit lung B16F10 metastases in mice
[Immunol Investigations 1999;28:1-8 & 2000;29:219-31]

T-lymphocytes: Proliferation, maturation, cytotoxicity, locomotory activity, cytokines, (CD4+, CD8+, $\gamma\delta$ -cells)

Effector-cell/tumor-cell bridging by VAE-rhamnogalacturonan
Cancer Res 1990; 50: 3646-3651.
Anticancer Res 1994; 953-962. Immunol Letters 1993; 38: 111-119.

Overview: Kienle GS: Die Mistel in der Onkologie. Stuttgart 2003.
Büssing A: Mistletoe. The Genus *Viscum*. Amsterdam 2000

Granulocytes: activation of phagocytosis by Viscotoxins Anticancer

Res 1999; 19: 1037-1042. Biochim Biophys Acta 1999; 1426: 80-90

Cytokines (esp. pro-inflammatory): IL-1, IL-6, TNF- α
IL-2, IL-4, IL-5, IL-10, IL-12, IFN- β , GM-CSF

Adjuvant: Augmentation of humoral and cellular immune response to other antigens Planta Med 1982; 46: 221-227. Scand J Immunol 2000; 52: 422

Dendritic cells: Maturation Anticancer Res 2002; 22: 267-274

Fever, acute phase proteins

Complement system

ML-antibodies

→ G-CSF

Overview: Kienle GS: Die Mistel in der Onkologie. Stuttgart 2003.
Büssing A: Mistletoe. The Genus Viscum. Amsterdam 2000



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Immunomodulating effects of Korean mistletoe lectin *in vitro* and *in vivo*

Chan-Ho Lee^a, Joon-Ki Kim^a, Hyo-Yeon Kim^a, Sung-Min Park^b, Sun-Mee Lee^{a,*}

^a College of Pharmacy, Sungkyunkwan University, 300 Cheoncheon-dong, Jangnan-gu, Suwon, Gyeonggi-do 440-746, Republic of Korea

^b CascedBioPharm Co., Ltd., 106 Chungbuk Oriental Medicine Center, Jecheon 390-250, Republic of Korea

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Korean mistletoe lectin

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NK cell

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Cold stress

ABSTRACT

The immunomodulatory effects of Korean mistletoe lectin (KML), one of the major active components in *Viscum album* L. var. *coloratum*, were investigated *in vitro* in immune cell proliferation and natural killer (NK) cell- and macrophage-mediated cytotoxicity, and *in vivo* in the forced swim test and cold stress. In mitogen-induced lymphocyte proliferation of murine splenocytes, concanavalin A and lipopolysaccharide significantly increased the proliferation of T cell and B cell lymphocytes, respectively. KML exposure increased lymphocyte proliferation in response to mitogen. KML also increased the splenic NK cell and macrophage activities *in vitro*. Exposure to KML increased production of cytokines such as interleukin-1 and interleukin-6 by macrophages. Two-week treatment with KML (30, 100, 300 and 600 µg/kg) increased the recruitment of lymphocytes, monocytes and macrophages. In the forced swim test, the immobility time was significantly attenuated by treatment with KML (300 and 600 µg/kg). In a cold stress experiment, spleen and thymus weight increased in KML-treated mice, while the weight of adrenal gland was lower than that in vehicle-treated mice. The levels of serum aminotransferases, lactate dehydrogenase and alkaline phosphatase were decreased by KML treatment. KML treatment also induced increases in the percentages of CD4⁺ and CD8⁺ cells in thymus. Our results suggest that KML enhances the immune system through modulation of lymphocytes, NK cells, and macrophages.



Gene Network Analysis on the Effect of *Viscum album* var. *coloratum* in T Cells Stimulated with Anti-CD3/CD28 Antibodies

Su-Yun Lyu¹ and Won-Bong Park²

¹Department of Pharmacy, Sunchon National University, Suncheon 540-742, Korea and ²Department of Chemistry, Seoul Women's University, Seoul 139-774, Korea

(Received August 31, 2010/Revised April 27, 2011/Accepted June 8, 2011)

A galactose- and N-acetyl-D-galactosamine-specific lectin (*Viscum album* L. var. *coloratum* agglutinin, VCA), which is known for its anticancer activity, was isolated from Korean mistletoe. This study reports a microarray analysis of the effects of VCA on an activated human T cells under various times and concentrations. A total of over 3000 genes were identified whose expression levels were significantly altered against controls after treatment with VCA and anti-CD3/CD28 antibody stimulation on human T-cells over an 8 h period. An analysis of the gene expression profile induced by VCA following incubation in human T cells revealed the activation and inhibition of genes involved in a wide range of immune functions in line with the broad mechanisms of action of VCA. These functions include cytokine gene expression, cell adhesion, cell motility, cell growth and maintenance, cell death, and the response to stress and to external stimulus. This report is aimed at providing the mistletoe research community with a robust database on which further studies could be built.

Key words: DNA microarray, Korean mistletoe, Lectin, Gene expression, T lymphocytes

Article

Differential Effects of *Viscum album* Preparations on the Maturation and Activation of Human Dendritic Cells and CD4⁺ T Cell Responses

Chaitrali Saha ^{1,2,3}, Mrinmoy Das ^{1,3,4}, Emmanuel Stephen-Victor ^{1,3,4}, Alain Friboulet ², Jagadeesh Bayry ^{1,3,4,5,*} and Srinivasa V. Kaveri ^{1,3,4,5,*}

¹ Institut National de la Santé et de la Recherche Médicale Unité 1138, Centre de Recherche des Cordeliers, 15 rue de l'Ecole de Médecine, Paris F-75006, France; chaitrali.roy@gmail.com (C.S.); mdasmicro@gmail.com (M.D.); esvkai@gmail.com (E.S.-V.)

² Université de Technologie de Compiègne, UMR CNRS 6022, Compiègne F-60205, France; alain.friboulet@utc.fr

³ Centre de Recherche des Cordeliers, Immunopathologie et Immuno-Intervention Thérapeutique, Paris F-75006, France

⁴ Sorbonne Universités, UPMC Univ Paris 06, UMR S 1138, Paris F-75006, France

⁵ Université Paris Descartes, Sorbonne Paris Cité, UMR S 1138, Paris F-75006, France

* Correspondence: jagadeesh.bayry@crc.jussieu.fr (J.B.); srini.kaveri@crc.jussieu.fr (S.V.K.); Tel.: +33-1-4427-8203 (J.B. & S.V.K.); Fax: +33-1-4427-8194 (J.B. & S.V.K.)

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Abstract: Extracts of *Viscum album* (VA); a semi-parasitic plant, are frequently used in the complementary therapy of cancer and other immunological disorders. Various reports show that VA modulates immune system and exerts immune-adjuvant activities that might influence tumor regression. Currently, several therapeutic preparations of VA are available and hence an insight into the mechanisms of action of different VA preparations is necessary. In the present study, we performed a comparative study of five different preparations of VA on maturation and activation of human dendritic cells (DCs) and ensuing CD4⁺ T cell responses. Monocyte-derived human DCs were treated with VA Qu Spez, VA Qu Frf, VA M Spez, VA P and VA A. Among the five VA preparations tested VA Qu Spez, a fermented extract with a high level of lectins, significantly induced DC maturation markers CD83, CD40, HLA-DR and CD86, and secretion of pro-inflammatory cytokines such as IL-6, IL-8, IL-12 and TNF- α . Furthermore, analysis of T cell cytokines in DC-T cell co-culture revealed that VA Qu Spez significantly stimulated IFN- γ secretion without modulating regulatory T cells and other CD4⁺ T cytokines IL-4, IL-13 and IL-17A. Our study thus delineates differential effects of VA preparations on DC maturation; function and T cell responses.

Keywords: *Viscum album*; innate cells; dendritic cells; maturation; cytokines; T cell response; IFN- γ ; Th17; Th1; Th2; regulatory T cell

Viscum album neutralizes tumor-induced immunosuppression in a human *in vitro* cell model

Carmen Steinborn¹, Amy Marisa Klemm¹, Ann-Sophie Sanchez-Campillo¹*, Sophie Rieger¹*, Marieke Scheffen¹*, Barbara Sauer¹, Manuel Garcia-Käufer¹, Konrad Urech², Marie Follo³, Annekathrin Ücker¹, Gunver Sophia Kienle¹, Roman Huber¹, Carsten Gründemann¹‡

1 Center for Complementary Medicine, Institute for Infection Prevention and Hospital Epidemiology, Faculty of Medicine, University of Freiburg, Freiburg, Germany, **2** Verein für Krebsforschung, Arlesheim, Switzerland, **3** Lighthouse Core Facility, Department of Medicine I, Medical Center—University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

‡ These authors contributed equally to this work.

* carsten.gruendemann@uniklinik-freiburg.de



OPEN ACCESS

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Abstract

Tumor cells have the capacity to secrete immunosuppressive substances in order to diminish dendritic cell (DC) activity and thereby escape from immune responses. The impact of mistletoe (*Viscum album*) extracts (VAE), which are frequently used as an additive anti-cancer therapy to stimulate the immune response, is still unknown. Using a human cellular system, the impact of two different VAE (VAEA + VAEI) on the maturation of human dendritic cells and on T cell function has been investigated using flow cytometry, automated fluorescence microscopy and cytokine bead array assays. Furthermore, we examined whether VAEI was able to counteract tumor-induced immunosuppression within this cellular system using a renal cancer cell model. The role of mistletoe lectin (ML) was analyzed using ML-specific antibodies and ML-depleted VAEI. VAEI and VAEA augmented the maturation of dendritic cells. VAEI abrogated tumor-induced immunosuppression of dendritic cells and both processes were partially mediated by ML since ML-depleted VAEI and ML-specific antibodies almost neutralized the rehabilitative effects of VAEI on DC maturation. Using these settings, co-culture experiments with purified CD4⁺ T cells had no influence on T cell proliferation and activation but did have an impact on IFN- γ secretion. The study provides a potential mode-of-action of VAE as an additive cancer therapy based on immunomodulatory effects. However, the impact on the *in vivo* situation has to be evaluated in further studies.

Review Article

Mistletoe and Immunomodulation: Insights and Implications for Anticancer Therapies

Shiao Li Oei ¹, Anja Thronicke¹, and Friedemann Schad ^{1,2}

¹Research Institute Havelhöhe, 14089 Berlin, Germany

²Oncological Centre, Hospital Havelhöhe, 14089 Berlin, Germany

Correspondence should be addressed to Shiao Li Oei; shiaoli.oei@havelhoehe.de

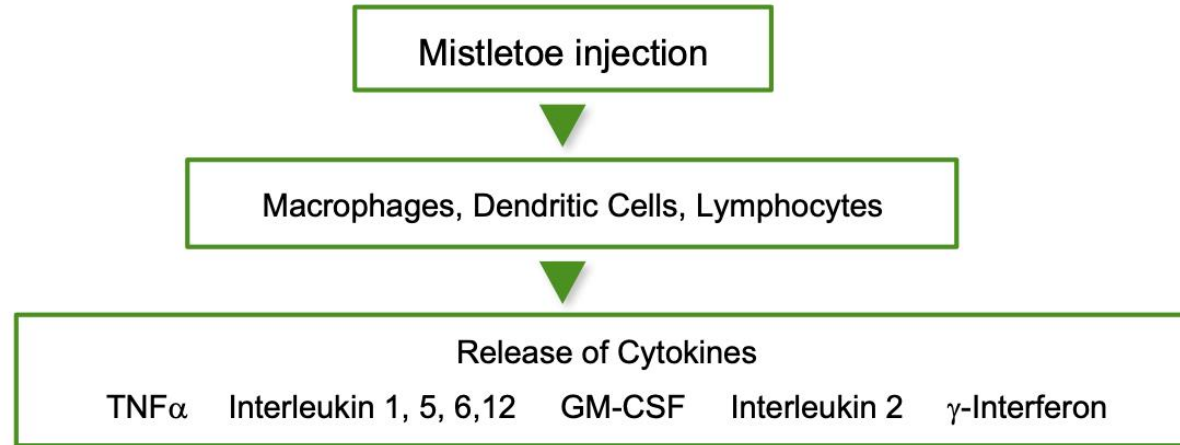
Received 21 September 2018; Revised 20 March 2019; Accepted 14 April 2019; Published 17 April 2019

Guest Editor: Hyo-jin An

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In early tumor development, cancer cells develop a plethora of strategies to escape surveillance from the adaptive and innate immune system. Cancer immunotherapies, in particular immune checkpoint inhibitors, are becoming a highly promising cancer therapeutic approach that has remarkable increased progress in combating various cancer types. Unfortunately, their mechanisms of action induce some complications, such as inflammatory reactions and immune-related adverse events. In the management of side effects during anticancer therapy, complementary and integrative therapy approaches are becoming of growing interest. Particularly, mistletoe, *Viscum album* L. (VA), has a long traditional history of about 100 years as an add-on therapy of cancer treatment in German-speaking countries. Besides antitumoral and quality of life-promoting activities, VA applications reduce side effects of modern conventional anticancer therapies and exert immunomodulatory characteristics. As these properties may provide a good basis for a combination with modern oncological therapies, the biological activities of VA applications and mechanisms involved have to be understood. In this review, the impact of VA compounds on different cellular pathways and immunological reactions in the fight against cancerous cells is discussed.

Immunological Effects of mistletoe products



Measurable Effects

Body temperature	NK-Activity Phagocytosis	Leukocytes (neutrophils, eosinophils, lymphocytes, NK-cells)	Sister chromatid exchange rate in lymphocytes ↓ (immune protection)	Endorphins
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Clinical Efficacy: A possible result of mistletoe-induced immunomodulation

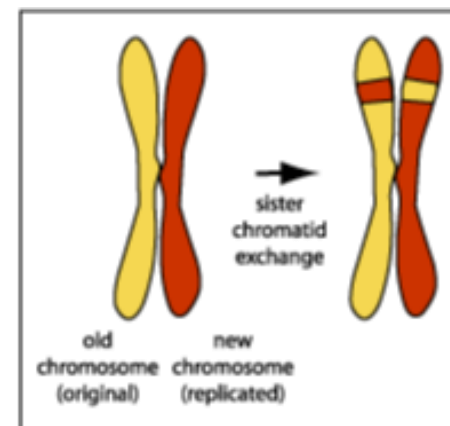
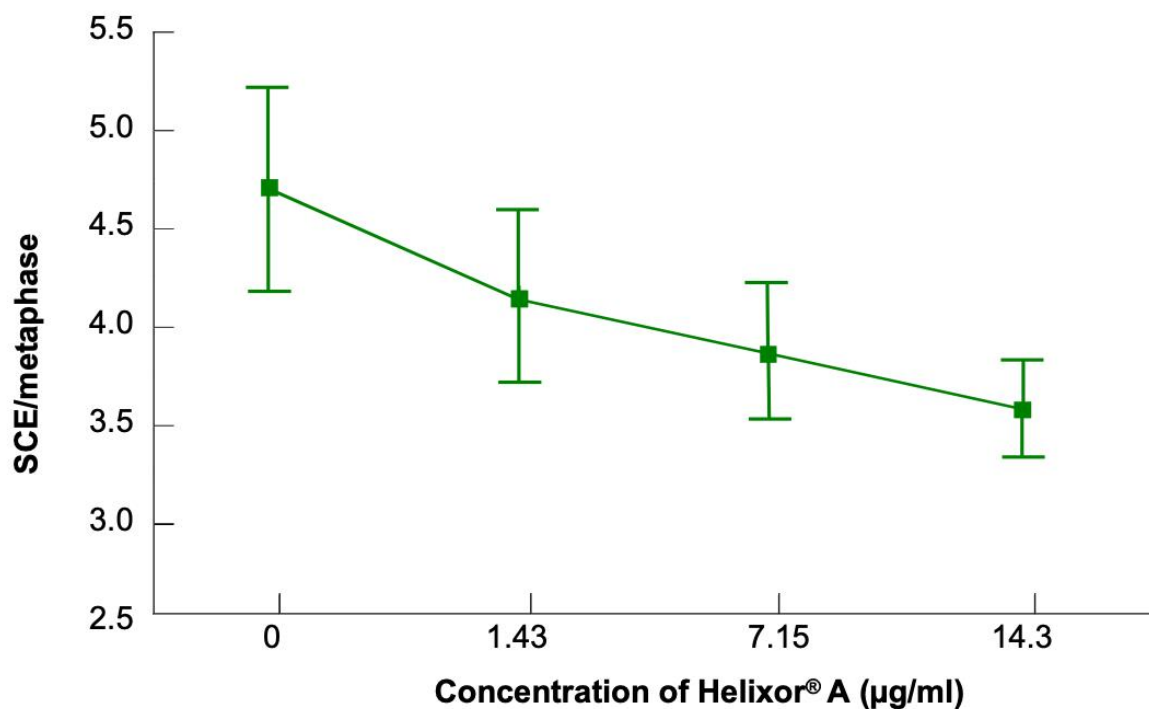
General condition Quality of life	Infections ↓	Tolerance of radio-/ chemotherapy	Pain ↓
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Pharmacological Effects of Mistletoe Products Relevant for Cancer Patients

**Immunoprotection
(only in normal cells)**

DNA-Stabilization and Antimutagenic Effect of *Viscum album* L. Extracts

Significant decrease in sister chromatid exchanges (SCE) of phytohemagglutinin-stimulated peripheral blood mononuclear cells after treatment with Helixor® A ($p < 0.0001$).



Büssing, A. et al.: European Journal of Cancer 1994, 30A (12), 1836-1841

The *in vitro* Effect of *Viscum album* (VA) Extract on DNA Repair of Peripheral Blood Mononuclear Cells (PBMC) in Cancer Patients

Eva Kovacs*

Society of Cancer Research, CH-4144 Arlesheim, Switzerland

Viscum album (VA) extract as an immunomodulator was tested in an *in vitro* model to investigate DNA repair in damaged peripheral blood mononuclear cells (PBMC) of ten breast cancer patients. The cells were exposed by gamma rays or 4-hydroxycyclophosphamide (4-HCy). Two hours after exposure the following were measured, without or with VA extract (1) DNA repair using the alkaline sucrose gradient for the sedimentation of DNA strand breaks, (2) DNA-gamma-production in the supernatant of the cultured cells. The VA extract led to an improvement of DNA repair in gamma-ray or 4-HCy damaged PBMC and to a significant increase of the IFN-gamma-production both in undamaged and in damaged cells.

RESEARCH ARTICLE

Open Access

Interaction of standardized mistletoe (*Viscum album*) extracts with chemotherapeutic drugs regarding cytostatic and cytotoxic effects *in vitro*

Ulrike Weissenstein^{1*}, Matthias Kunz¹, Konrad Urech¹ and Stephan Baumgartner^{1,2}

Abstract

Background: Given the importance of complementary and alternative medicine (CAM) to cancer patients, there is an increasing need to learn more about possible interactions between CAM and anticancer drugs. Mistletoe (*Viscum album* L.) belongs to the medicinal herbs that are used as supportive care during chemotherapy. In the *in vitro* study presented here the effect of standardized mistletoe preparations on the cytostatic and cytotoxic activity of several common conventional chemotherapeutic drugs was investigated using different cancer cell lines.

Methods: Human breast carcinoma cell lines HCC1937 and HCC1143 were treated with doxorubicin hydrochloride, pancreas adenocarcinoma cell line PA-TU-8902 with gemcitabine hydrochloride, prostate carcinoma cell line DU145 with docetaxel and mitoxantrone hydrochloride and lung carcinoma cell line NCI-H460 was treated with docetaxel and cisplatin. Each dose of the respective chemotherapeutic drug was combined with *Viscum album* extract (VAE) in clinically relevant concentrations and proliferation and apoptosis were measured.

Results: VAE did not inhibit chemotherapy induced cytostasis and cytotoxicity in any of our experimental settings. At higher concentrations VAE showed an additive inhibitory effect.

Conclusions: Our *in vitro* results suggest that no risk of safety by herb drug interactions has to be expected from the exposition of cancer cells to chemotherapeutic drugs and VAE simultaneously.

Keywords: Mistletoe (*Viscum album* L.), Iscador, Chemotherapy, Drug interactions, Cytostasis, Cytotoxicity



HELIXOR EN CALIDAD DE VIDA

Impact of Complementary Mistletoe Extract Treatment on Quality of Life in Breast, Ovarian and Non-small Cell Lung Cancer Patients. A Prospective Randomized Controlled Clinical Trial

B. K. PIAO¹, Y. X. WANG², G. R. XIE³, U. MANSMANN⁴, H. MATTHES⁵, J. BEUTH⁶ and H. S. LIN¹

¹Guang An Men Hospital, Beijing; ²Liaoning Tumor Hospital, Shenyang;

³Tianjin Tumor Hospital, Tianjin, China; ⁴Universität Heidelberg, Institut für

Medizinische Biometrie und Informatik, Heidelberg; ⁵Gemeinschaftskrankenhaus Havelhöhe, Berlin;

⁶Institut zur wissenschaftlichen Evaluation naturheilkundlicher Verfahren Universität zu Köln, Köln, Germany

Abstract. *Standardized aqueous mistletoe extracts have been applied to cancer patients for several decades as complementary medicine. A multicentric, randomized, open, prospective clinical trial was conducted in three oncological centers in the People's Republic of China in Beijing, Shenyang and Tianjin. Following the guidelines of "Good Clinical Practice" (GCP) this study was performed to get information on efficacy, safety and side-effects of the standardized mistletoe extract (sME). Two hundred and thirty-three patients with breast (n=68), ovarian (n=71) and non-small cell lung cancer (NSCLC; n=94) were enrolled into this study. Two hundred and twenty-four patients fulfilled the requirements for final analysis (n=115 treated with sME HELIXOR® A; n=109 comprising the control group being treated with the approved immunomodulating phytopharmakon Lentinan). All patients were provided with standard tumor-*

control group. Additionally, the occurrence of adverse events (AEs) was less frequent in the sME than in the control group (total number of AEs 52 versus 90 and number of serious AEs 5 versus 10 in study and control group, most of them due to chemotherapy). Only one serious AE was allocated to complementary treatment in each group (1 angioedema in sME group). All other side-effects of the sME (7 harmless local inflammatory reactions at subcutaneous injection site, 4 cases with fever) were self-limiting and did not demand therapeutic intervention. This study showed that complementary treatment with sME can beneficially reduce the side-effects of chemotherapy in cancer patients and thus improve quality of life.

Aqueous extracts from mistletoe are widely used in complementary cancer treatment as immunomodulating

Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer

- prospective-randomised multicenter study

Patients and method:

- 233 patients treated with standard chemotherapy
- Verum group: additionally Helixor® A 3x/week s.c.
progressive dose increase 1 mg → 200 mg
- Control group: additionally Lentinan® 4 mg daily i.m.
- Recording of quality of life through 3 different measuring systems:
 - Karnofsky Performance Index = KPI
 - Functional Living Index Cancer = FLIC
 - Traditional Chinese Medicine (= TCM) Index
- Recording of adverse events and analysis of causality
- Statistical analysis: Institute for Biometrics and Informatics of the Heidelberg University

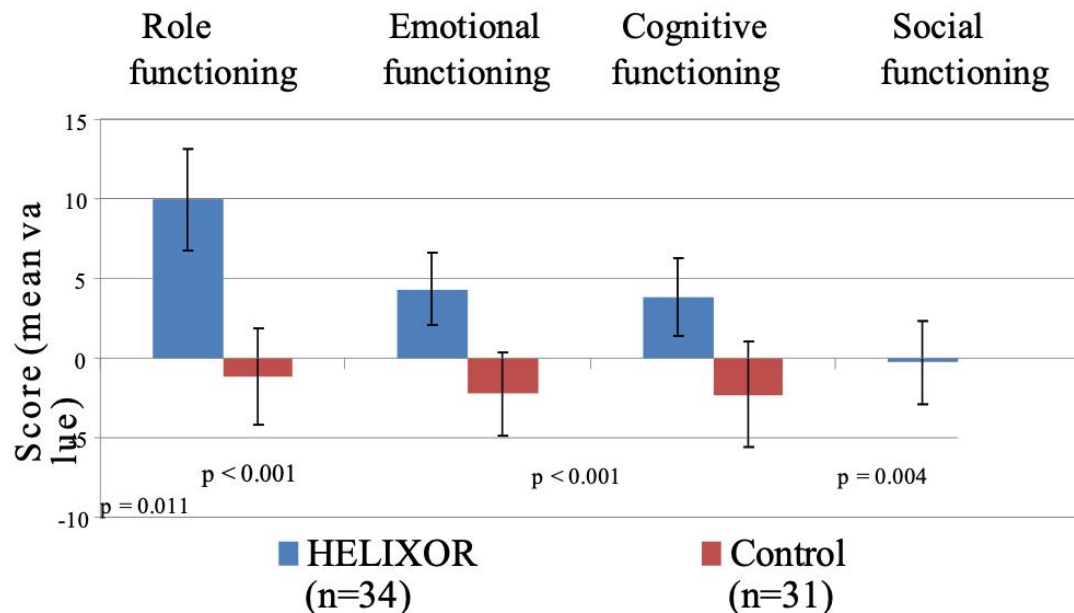
Improved Quality of Life during Chemotherapy in Breast Cancer Patients Receiving an Adjunctive Treatment with Helixor® A

- Diagnosis:** Breast cancer patients (pT₁₋₃ pN₀₋₂ M₀) during chemotherapy (6 cycles of CAF)
- Objectives:** Influence of an adjunctive Helixor® A therapy on quality of life and neutropenia
- Design:** Prospective randomized open label pilot study (phase III)
- Number of patients:** 65 patients (34 Helixor®, 31 controls)
- Study groups:** *Treatment group:* CAF plus Helixor® A
- 3 times weekly 1 ampoule s.c.
 - dose escalation 1 mg max. 200 mg
- Control group:* CAF alone

Tröger, W. Helixor® therapy during chemotherapy. Results of a randomized clinical trial. Onkologie 33(suppl 2), 34 (2010)

Improved Quality of Life during Chemotherapy in Breast Cancer Patients Receiving an Adjunctive Treatment with Helixor® A

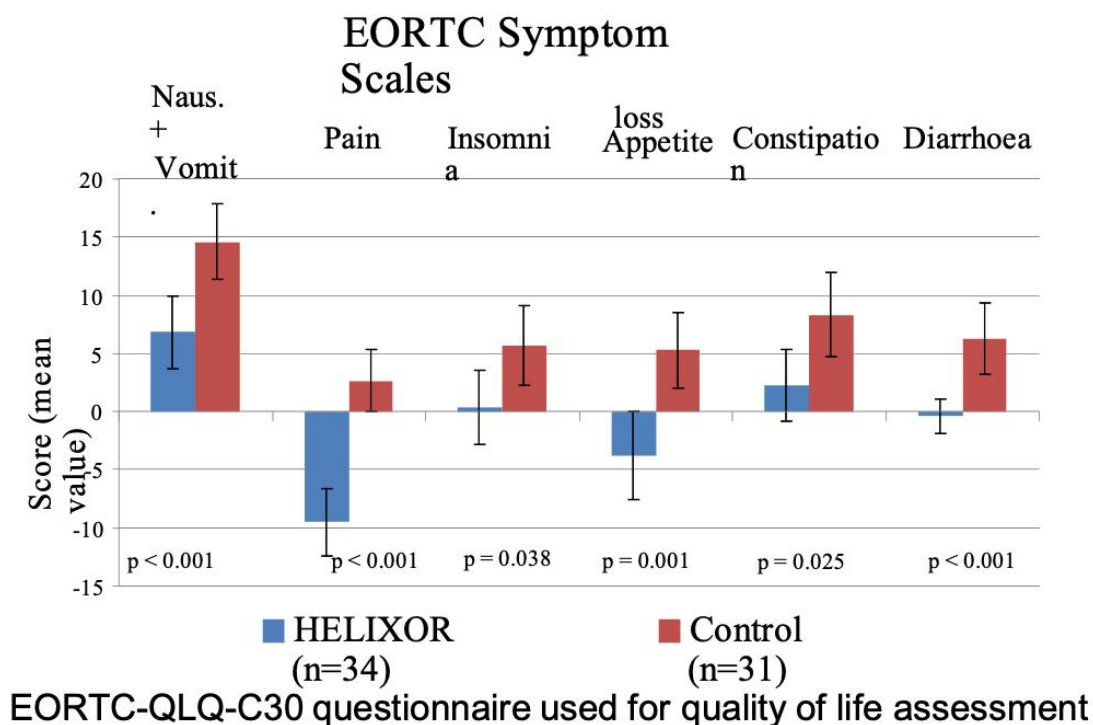
EORTC Functional Scales



EORTC-QLQ-C30 questionnaire used for quality of life assessment

Tröger, W. Helixor® therapy during chemotherapy. Results of a randomized clinical trial. Onkologie 33(suppl 2), 34 (2010)

Improved Quality of Life during Chemotherapy in Breast Cancer Patients Receiving an Adjunctive Treatment with Helixor® A

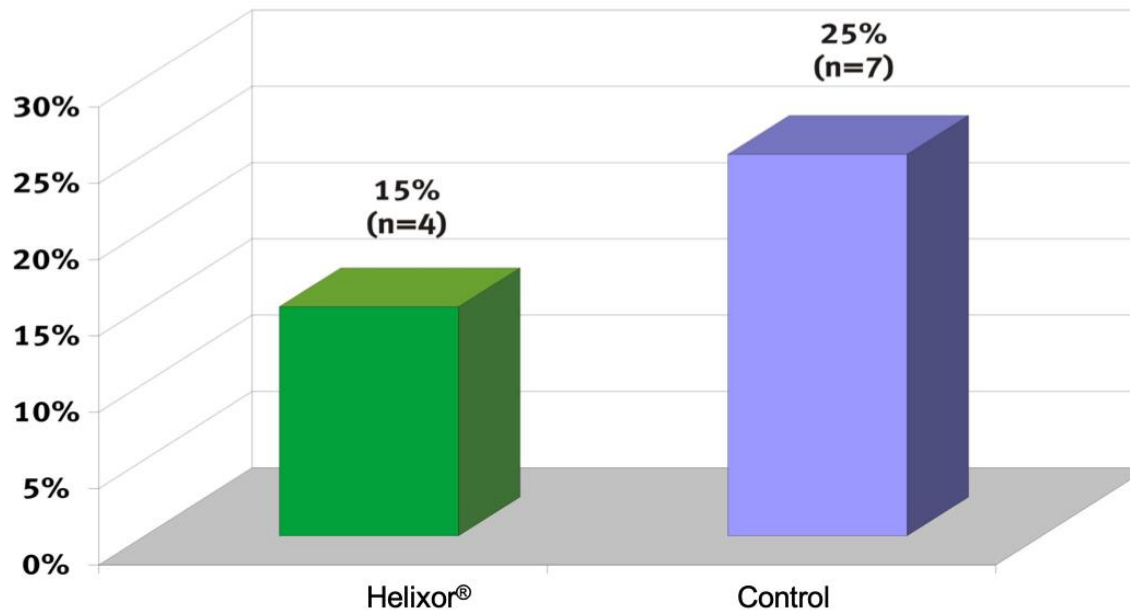


Tröger, W. Helixor® therapy during chemotherapy. Results of a randomized clinical trial. Onkologie 33(suppl 2), 34 (2010)

Improved Quality of Life during Chemotherapy in Breast Cancer Patients Receiving an Adjunctive Treatment with Helixor® A

Frequency of neutropenia ($< 1,000/\mu\text{l}$)

$p = 0.505$ (Fisher's exact test)



Tröger, W. Helixor® therapy during chemotherapy. Results of a randomized clinical trial. Onkologie 33(suppl 2), 34 (2010)

Complementary Treatment with Mistletoe Extracts During Chemotherapy: Safety, Neutropenia, Fever, and Quality of Life Assessed in a Randomized Study

Florian Pelzer, MSc,¹ and Wilfried Tröger, Dr rer nat²

Abstract

Objectives: Evaluate the safety and clinical response of complementary treatment with European mistletoe extracts during chemotherapy.

Design: Monocentric controlled trial with 95 patients randomized into three groups.

Settings/Location: National Cancer Research Center of Serbia.

Subjects: Breast cancer patients (stage T₁₋₃N₀₋₂M₀) undergoing surgery and adjuvant chemotherapy with six cycles of cyclophosphamide, adriamycin, and 5-fluorouracil.

Interventions: Two different European mistletoe extracts (Helixor A, Iscador M Spez) were injected three times per week during 18 weeks of chemotherapy in the mistletoe group. Five-year follow-up of routine visits was documented in case report forms.

Outcome measures: Safety was assessed by measuring adverse events, body temperature during chemotherapy, and probability of relapse or metastasis in a 5-year follow-up. During chemotherapy, the neutrophil count and quality of life according to EORTC QLQ-C30 were assessed.

Results: The two patient groups receiving different complementary mistletoe treatments were integrated into one mistletoe group for this safety analysis. Patients in the mistletoe group did not develop more fever symptoms than patients in the control group (two short-term events in each group). No significant differences in probability of relapse or metastasis were measured between the groups ($p=0.7637$). The mistletoe group showed a trend toward less neutropenia ($p=0.178$) and improved pain and appetite loss scores ($p<0.0001$ and $p=0.047$, respectively) while having positive, but not significant, impact on other EORTC QLQ-C30 scores.

Conclusions: Mistletoe extracts were safe in this clinical study. Neither did subcutaneous injections induce fever, nor did they influence the frequency of relapse and metastasis within 5 years. This result suggests that mistletoe extracts had no adverse interactions with the anticancer agents used in this study. Furthermore, certain side effects of chemotherapy decreased under this complementary treatment in breast cancer patients.

Quality of Life of Patients With Advanced Pancreatic Cancer During Treatment With Mistletoe

A randomized controlled trial

Wilfried Tröger, Danijel Galun, Marcus Reif, Agnes Schumann, Nikola Stanković, Miroslav Miličević

SUMMARY

Background: The treatment of cancer patients with mistletoe extract is said to prolong their survival and, above all, improve their quality of life. We studied whether the quality of life of patients with advanced pancreatic cancer could be improved by mistletoe extract.

Method: An open, single-center, group-sequential, randomized phase III trial (ISRCTN70760582) was conducted. From January 2009 to December 2010, 220 patients with locally advanced or metastatic pancreatic cancer who were receiving no further treatment for pancreatic cancer other than best supportive care were included in this trial. They were stratified by prognosis and randomly allocated either to a group that received mistletoe treatment or to one that did not. Mistletoe extract was given in escalating doses by subcutaneous injection three times a week. The planned interim evaluation of data from 220 patients indicated that mistletoe treatment was associated with longer overall survival, and the trial was terminated prematurely. After termination of the study, the results with respect to quality of life (assessed with the QOL-C30 scales of the European Organisation for Research and Treatment of Cancer) and trends in body weight were evaluated.

Results: Data on quality of life and body weight were obtained from 96 patients treated with mistletoe and 72 control patients. Those treated with mistletoe did better on all 6 functional scales and on 7 of 9 symptom scales, including pain (95% confidence interval [CI] -29 to -17), fatigue (95% CI -36.1 to -25.0), appetite loss (95% CI -51 to -36.7), and insomnia (95% CI -45.8 to -28.6). This is reflected by the trend in body weight during the trial.

Conclusion: In patients with locally advanced or metastatic pancreatic carcinoma, mistletoe treatment significantly improves the quality of life in comparison to best supportive care alone. Mistletoe is an effective second-line treatment for this disease.

► Cite this as:

Tröger W, Galun D, Reif M, Schumann A, Stanković N, Miličević M: Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe—a randomized controlled trial. *Dtsch Arztebl Int* 2014; 111: 493–502. DOI: 10.3238/arztebl.2014.0493

Clinical Research Dr. Tröger, Freiburg; Dr. rer. nat. Tröger

First Surgical Clinic of the Clinical Centers of Serbia (Belgrade); Prof. Dr. med. Galun, Prof. Dr. med. Miličević

Institute for Clinical Research, Berlin; Dr. rer. nat. Reif, A. Schumann Dipl.-mat.

CLINICOBSS, NIS, Serbia; Dr. med. Stanković

Faculty of Medicine, University of Belgrade, Serbia; Prof. Dr. med. Miličević

For patients with pancreatic carcinoma who cannot tolerate first-line treatment as specified in the S3 guideline recommendations (1) or who decline to undergo such treatment, best supportive care is often the only available therapeutic option (2–5). Second-line treatment for these patients must be very well tolerated and should not only prolong survival, but also improve the quality of life (6).

Prolongation of survival and improvement of the quality of life are the two goals of mistletoe treatment. Mistletoe is well tolerated, even in high doses (7), but a Cochrane Review found inadequate evidence to document its efficacy (8). In a critical evaluation of this review, however, it was pointed out that the review ignored 14 previously published studies providing grade I and II evidence on survival, tumor behavior, and quality of life (Kienle, G. S. and Kienle, H. Comment on “Mistletoe therapy in oncology” [Cochrane-Review 2008]; Web/URL: www.ifaemm.de/Abstract/PDFs/GK08_2.pdf). A later retrospective study of mistletoe treatment for pancreatic carcinoma yielded further evidence of its efficacy (9).

In this prospective, randomized trial, we investigated the efficacy of mistletoe monotherapy on the survival and quality of life (QoL) of patients with locally advanced or metastatic pancreatic carcinoma.

Such trials, if conducted in countries where mistletoe extracts are approved or registered, are bound to meet with difficulties in recruitment and compliance (10), because the physicians and patients already have a clear preference. In Serbia, however, mistletoe extracts are unknown and unavailable, and we were able to carry out this trial there without any problem with respect to recruitment.

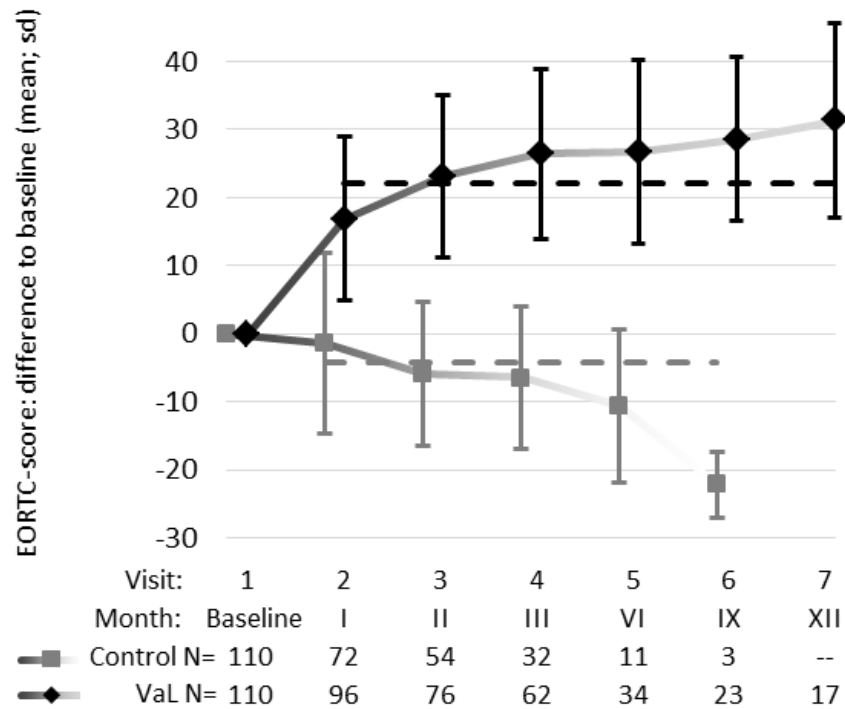
The analysis of overall survival (the primary endpoint of the trial), undesired events, and disease-related symptoms has been published elsewhere (11).

Methods

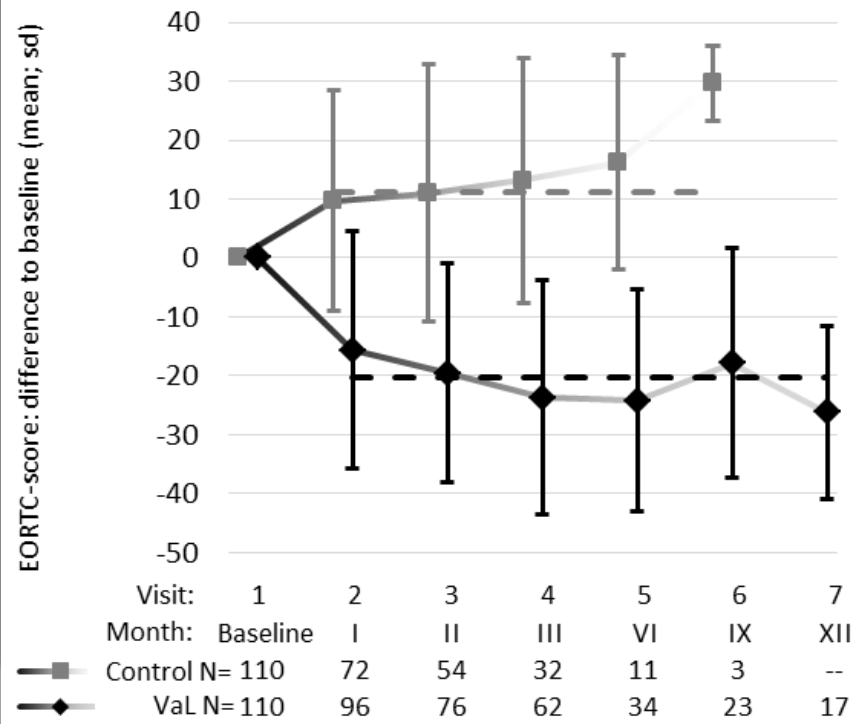
This randomized, prospective, open phase III trial was conducted in accordance with the Declaration of

Quality of life

Global Health Status / QoL

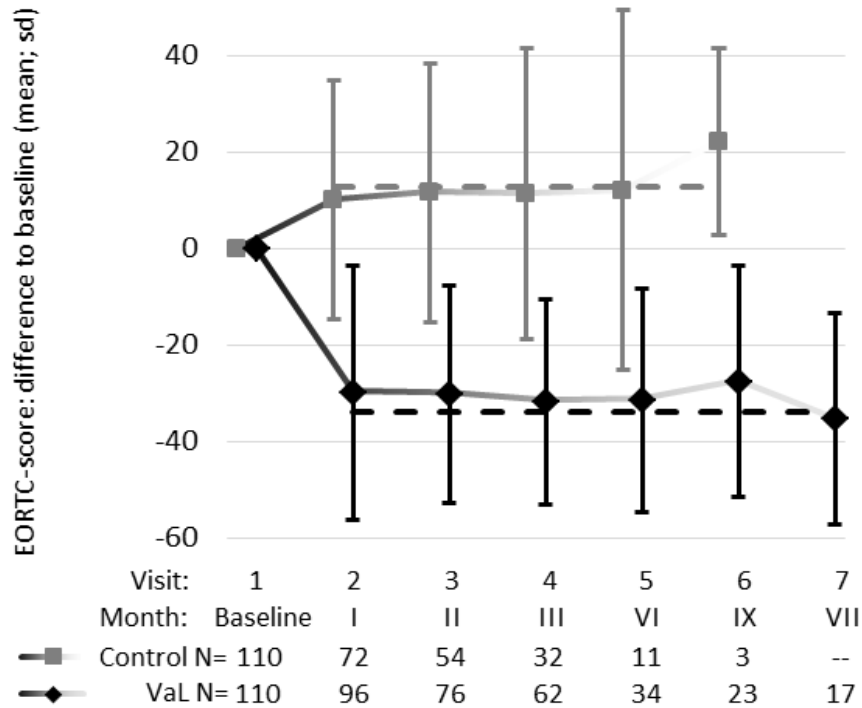


Fatigue

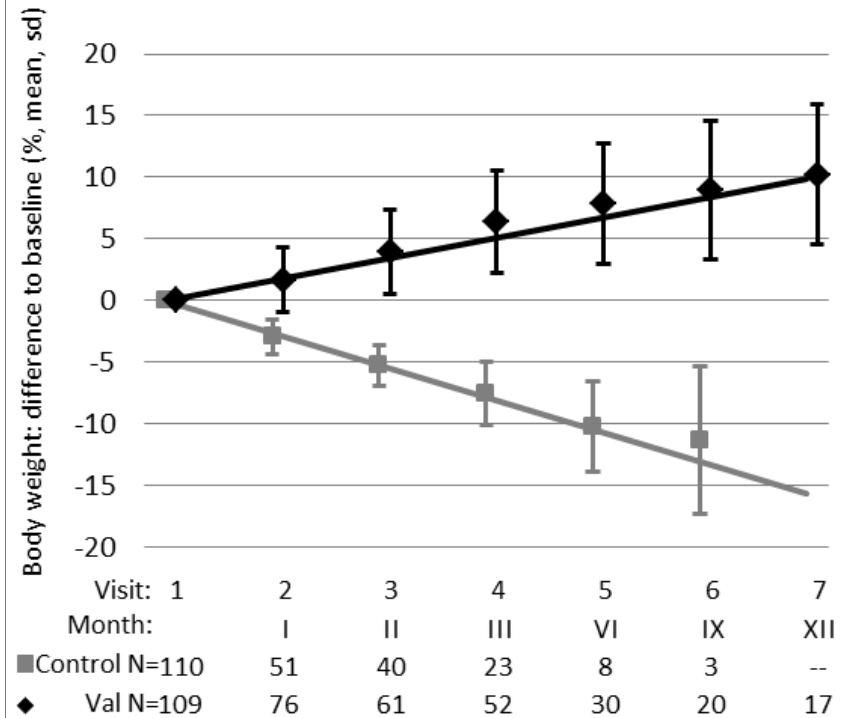


Quality of life

Appetite Loss

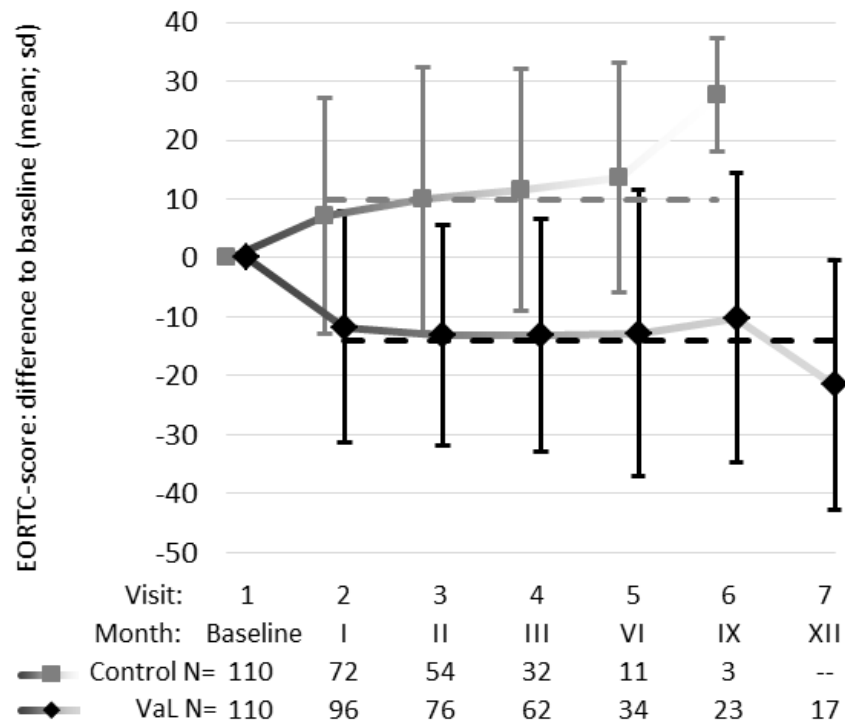


Body weight

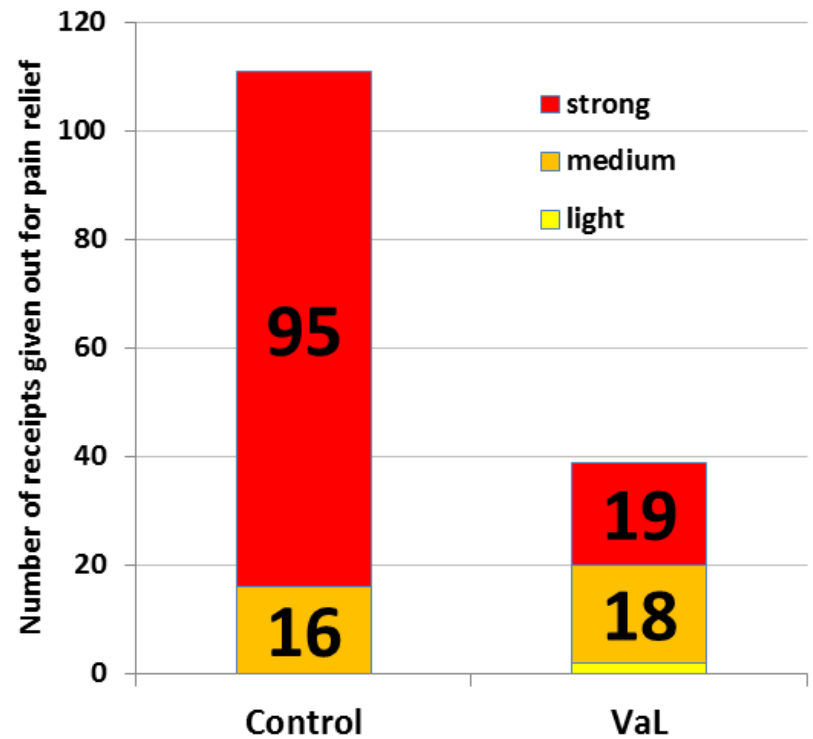


Quality of Life

Pain



Consumption of analgesics





Viscum album [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: A randomised clinical trial on overall survival

W. Tröger^{a,*}, D. Galun^b, M. Reif^c, A. Schumann^c, N. Stanković^d, M. Milićević^{b,e}

^a Clinical Research Dr. Tröger, Freiburg, Germany

^b The First Surgical Clinic of the Clinical Centre of Serbia, Belgrade, Serbia

^c Institute for Clinical Research, Berlin, Germany

^d CLINICOBSS, Niš, Serbia

^e Belgrade School of Medicine, University of Belgrade, Belgrade, Serbia

Available online 24 July 2013

KEYWORDS

Mistletoe
Pancreatic neoplasm
Randomised controlled trial
Survival analysis

Abstract Background: The unfavourable side-effects of late-stage pancreatic cancer treatments call for non-toxic and effective therapeutic approaches. We compared the overall survival (OS) of patients receiving an extract of *Viscum album* [L.] (VaL) or no antineoplastic therapy.

Methods: This is a prospective, parallel, open label, monocentre, group-sequential, randomised phase III study. Patients with locally advanced or metastatic cancer of the pancreas were stratified according to a binary prognosis index, composed of tumour stage, age and performance status; and were evenly randomised to subcutaneous injections of VaL extracts or no antineoplastic therapy (control). VaL was applied in a dose-escalating manner from 0.01 mg up to 10 mg three times per week. Patients in both groups received best supportive care. The primary end-point was 12-month OS, assessed in a group-sequential analysis.

Findings: We present the first interim analysis, including data from 220 patients. Baseline characteristics were well balanced between the study arms. Median OS was 4.8 for VaL and

* Corresponding author. Address: Zachenweg 6, 79111 Freiburg, Germany. Tel.: +49 761 1561309; fax: +49 761 1560309.

E-mail addresses: troeger@cdt.de (W. Tröger), galun@eunet.rs (D. Galun), marcus.reif@ikf-berlin.de (M. Reif), micikas@eunet.rs (N. Stanković), machak@sbb.rs (M. Milićević).

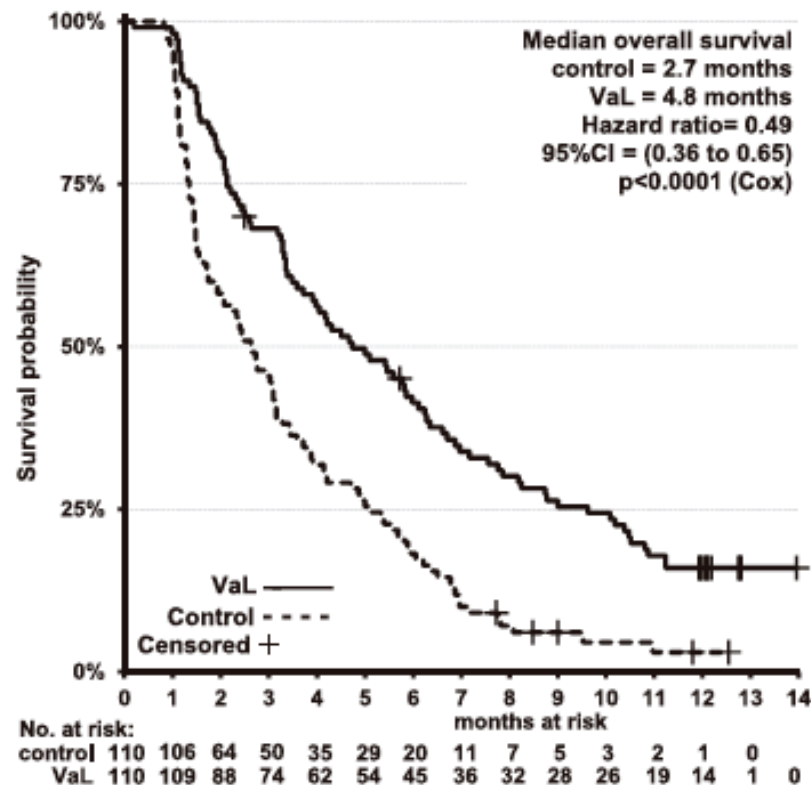


Fig. 2. Kaplan-Meier estimates of 12-month overall survival of 220 patients with advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control). Abbreviations: Cox, Cox regression adjusted for prognosis state; VaL, *Viscum album* [L.]. Note: All patients surviving for more than 12 months are censored and therefore not at risk any more.

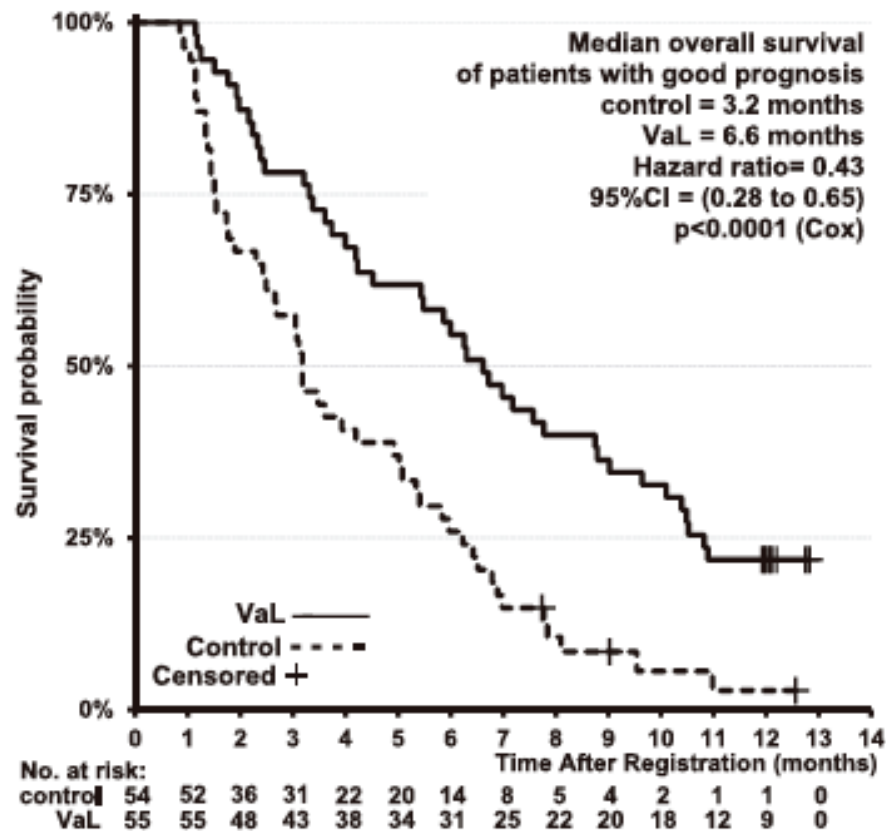


Fig. 3. Kaplan–Meier estimates of 12-month overall survival of 109 patients with advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control) and good prognosis. *Abbreviations:* Cox, Cox regression; VaL, *Viscum album* [L.].

ALTERNATIVE MEDICINE

Are mistletoe extract injections the next big thing in cancer therapy?

Joe Sugarman / Spring 2014

In September 2008, Ivelisse Page, a 37-year-old mother of four, was diagnosed with colon cancer. Several weeks later, she had 15 inches of her colon and 28 lymph nodes removed. But in December of that same year, Page's doctor, Luis Diaz, an associate professor of oncology in the School of Medicine, had to deliver the devastating news that the cancer had spread to her liver. He told her that she had just an 8 percent chance of surviving for more than two years.

Page had more surgery to remove 20 percent of her liver, but instead of undergoing conventional chemotherapy, she pondered the suggestion of another of her doctors, Peter Hinderberger of Baltimore's Ruscombe Mansion Community Health Center. A specialist in using complementary therapies, Hinderberger had seen positive effects from injections of mistletoe extract. The liquid, derived from the poisonous, semiparasitic mistletoe plant, has been a popular natural remedy in treating cancer in Europe for years, but Hinderberger is one of the few physicians nationwide who regularly use the therapy.

Page and Diaz had never heard of the treatment. Diaz, who is also the director of translational medicine at the Ludwig Center for Cancer Genetics and Therapeutics at the Johns Hopkins Kimmel Cancer Center, reviewed several European studies on the extract and somewhat reluctantly gave Page the green light. "I'm an oncologist who treats with chemotherapy— and I'm really good at it—and here's somebody who says not only do I not want chemotherapy, but I still want you to be my

28 comments



MORE FROM THE SPRING 2014 ISSUE





You are here: [Helixor](#) / [Healthcare professionals](#) / [Issue 1](#) / [2016](#) / [Believe Big: New US study](#)

Believe Big: New clinical trial for intravenous mistletoe therapy with Helixor in the US



Mistletoe therapy is the most widely used treatment of complementary oncology in Germany. The treatment is gaining importance in the US as well. To offer a therapy as "standard-of-care" in the US, a clinical trial has to be completed first.

With regards to mistletoe therapy, Believe Big took charge of this task: in cooperation with Johns Hopkins Hospital in Baltimore, Maryland (US) the 2011-founded non-profit organization leads the first US-American clinical trial for intravenous mistletoe therapy. The study shall build a bridge between conventional and complementary medicine.

Current Status

In December 2015 the Food and Drug Administration (FDA) officially approved the study protocol of the clinical trial. The final planning and preparation phase supervised by Johns Hopkins Hospital will soon be completed and the trial can begin. Study participants are patients of stadium IV cancer with solid tumors, who were undergoing at least one row of conventional therapy.

The study is financed exclusively by private funds. The so-called crowdfunding project could already raise \$395,000 of the needed \$500,000. Study medication is the German mistletoe preparation Helixor® M. Believe Big informs about the current status of the clinical trial on a regular basis via an e-newsletter. Interested people can register on the [organization's website](#).

In collaboration with Johns Hopkins Hospital in.. USA, Believe Big developed the first intravenous mistletoe clinical trial in the United States. This trial is a huge step forward, bringing together the conventional and complementary medicine communities. Tremendous benefits of mistletoe treatment with all types of cancer have been observed at Believe Big. Current Status of the trial:

In December 2015, the FDA confirmed that the intravenous mistletoe clinical trial has been approved to begin. However, before patients can be enrolled, Johns Hopkins Internal Review Board has to look over all aspects of the trial in order to give the green light to proceed. This process can take several months.

All stage IV, solid tumor types who have undergone at least one line of conventional therapy can enroll. Those interested in participating in the trial can subscribe to the [Believe Big eNewsletter HERE](#). As soon as Johns Hopkins confirms that patients can enroll in the trial, an email will be sent to all subscribers.

Founding Because mistletoe is a natural substance and there is not a patent possibility, pharmaceutical companies will not fund this trial. Therefore, all funding has been raised through philanthropic and private donations. The crowdfunding project can be supported via donations here. This way, \$395,000 of the \$500,000 needed were already raised

Memorial Sloan Kettering Cancer Center



Location Information

Main Entrance - Inpatient Hospital

1275 York Avenue
New York, NY 10065

[Parking](#) | [Get Directions](#) 
212-639-2000

Other Entrances

Haupt Entrance - Outpatient & Urgent Care
425 E. 67th Street | [Get Directions](#) 

Schwartz Entrance - Blood Donation Center
1250 First Avenue | [Get Directions](#) 

Bobst Entrance - Pediatric Day Hospital
444 E. 68th Street | [Get Directions](#) 

New Patient Appointments

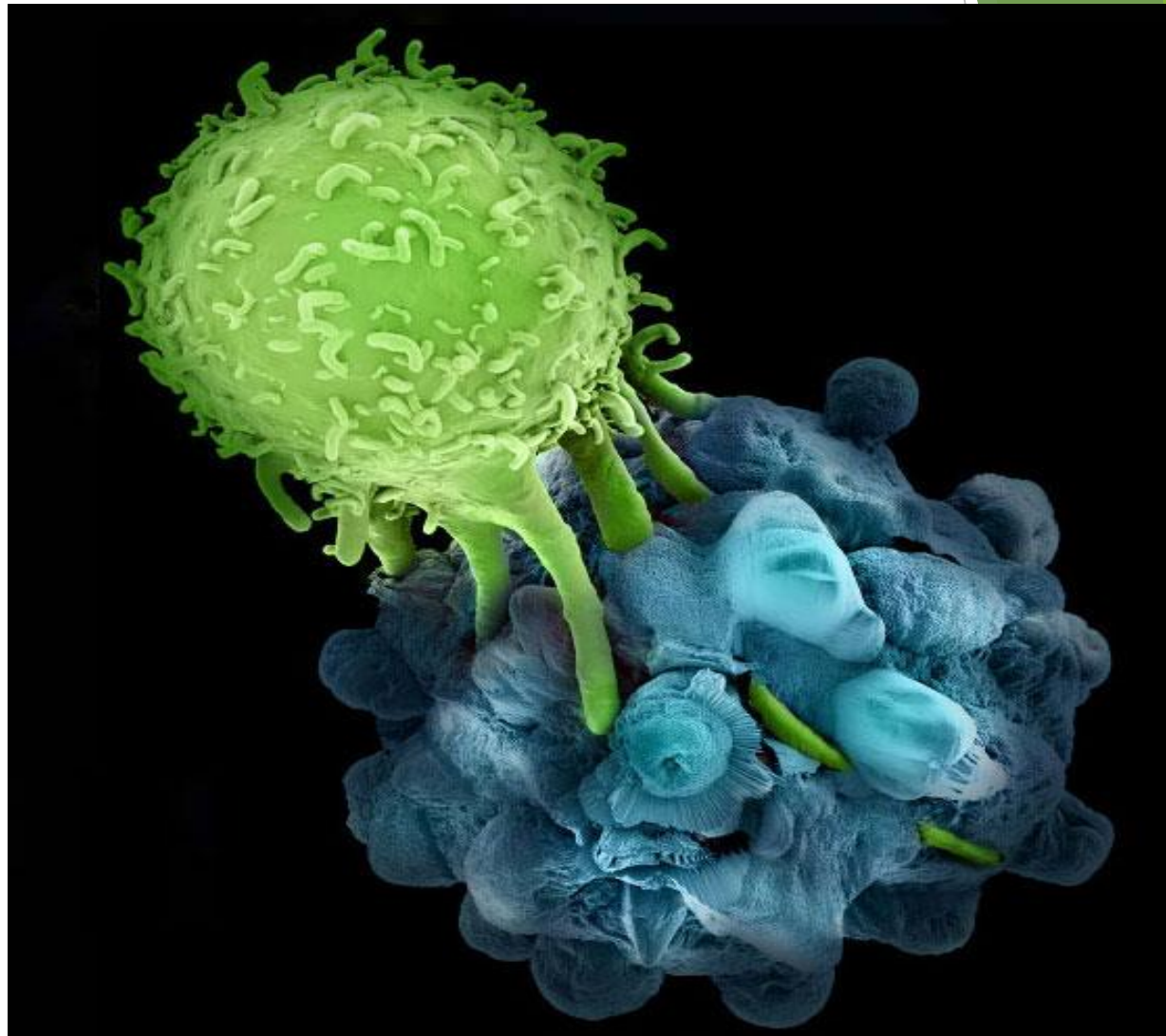
Phone

800-525-2225



Imagen
Icónica
Del
S. XXI

La
Benignidad
Triunfando
Sobre la
Malignidad





Starting Mistletoe with Helixor®

Subcutaneous application:



Location:

- if possible close to tumor
- otherwise:
 - abdominal wall
 - thigh
 - (upper arm)
- alternate location

avoid:

- radiated/inflamed area
- breast/arm post surgery (lymphedema)
- area of proposed surgery

Time of day:

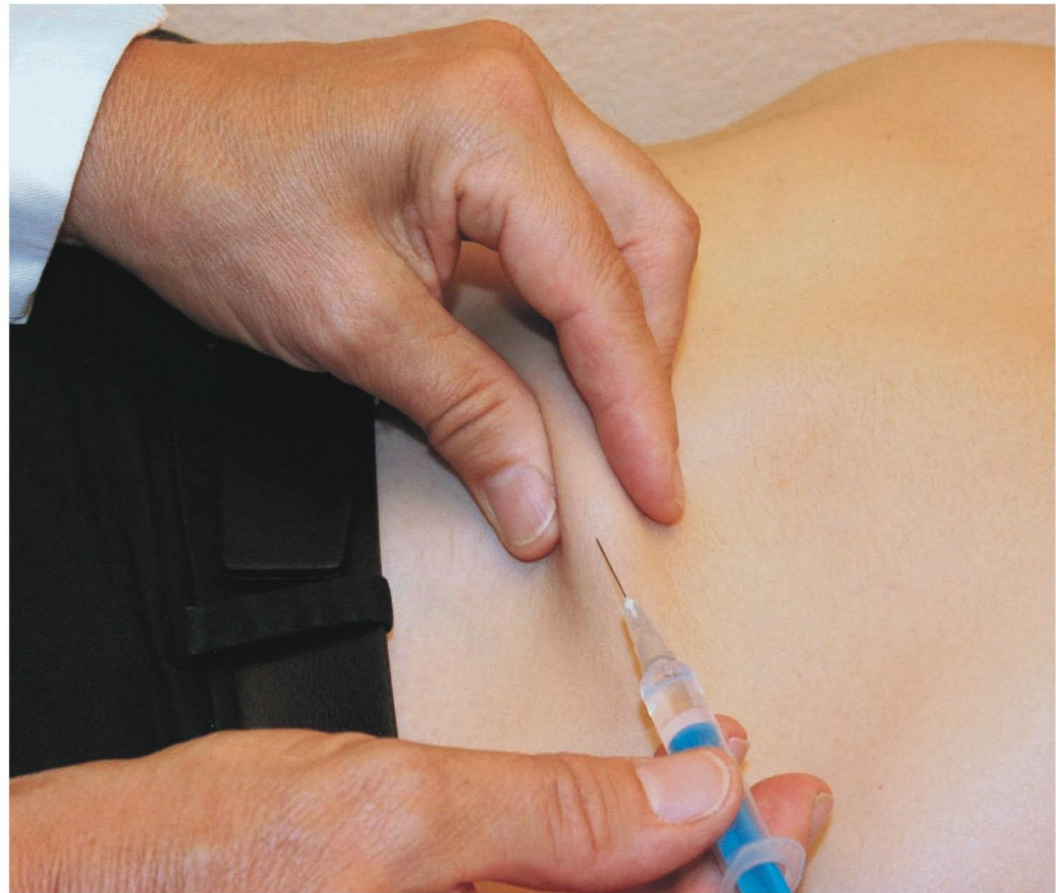
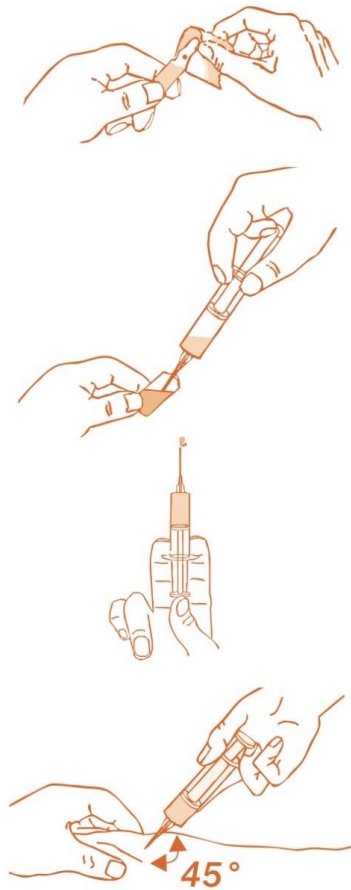
- any time of the day
- preferable always at same time
- after injection: rest for 30-60 min.

Subcutaneous Injection of Helixor®

Preferred injection site:

- 1) after cancer surgery or in metastasizing cancer:
 - first choice: abdominal wall
 - if not possible: upper thighs
 - if not possible: upper arms
- 2) inoperable primary tumour or metastasis:
 - as close as possible to the tumour

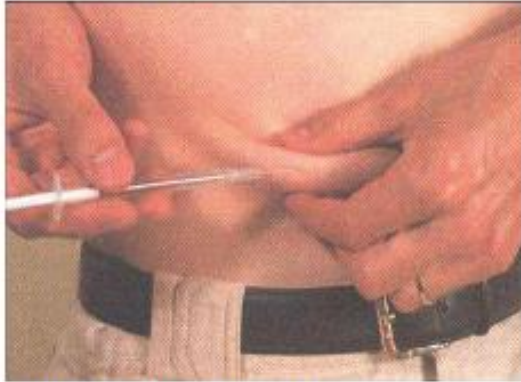
Helixor® – Subkutane Injektion



Local Skin Reaction at Subcutaneous Injection Site

- redness, swelling, subcutaneous induration (infiltration by activated T-helper cells)
- maximum size 48 – 72 hours after injection (delayed-type immune reaction), strictly dose-dependent
- important indicator reaction during induction therapy showing an immunologically effective dosage

Local Inflammatory Reaction to Subcutaneous Helixor® Injection



Typical site of injection



Local erythema, appr. 3 x 5 cm, 6 h p.i.



Local erythema, appr. 12 h p.i.



Slight induration, appr. 24 h p.i.

Reaction of Body Temperature to SC Helixor[®] Injection



56 years old female breast cancer patient with rigid body temperature. From mistletoe injections (Helixor M) 3 times a week arose a distinct circadian temperature rhythm with an amplitude of 1 °C

Matthes, H.: Onkologische Misteltherapie, in Scheer, R. et al. (Hrsg.): Die Mistel in der Tumorthherapie. KVC Verlag Essen 2001

Possible Adverse Drug Reactions (ADRs) to Helixor®

1) *Desired immunological reactions*

These reactions are regarded as ADRs only when exceeding the desirable level

ADRs	Frequency	Measures
Local inflammatory reaction > 5 cm diameter at the s.c. injection site	Frequently	Transitory break. After complete regression: dose reduction (2 steps). In case of pain or itching: local administration of an ointment.
Fever > 38 °C Flu-like symptoms (fatigue, feeling ill, rarely headache, dizziness, pain of extremities, arthralgia, shivering, chills)	Occasionally	Transitory break. After complete regression: dose reduction (1 step). If possible: physical fever reduction, no antipyretic drugs.
Swelling of regional lymph nodes (lymphadenopathy)	Rarely	Information of the patient. Changing of injection site.

Helixor: subcutaneous injections



Desired local reaction: diameter up to 5 cm (2 in)



Excessive local reaction: diameter over 5 cm (2 in)

Adverse Drug Reactions to Mistletoe Products

Adverse drug reactions	Measures
Inflammatory local reaction at sc injection site > 5 cm	→ Therapy pause until the symptoms subside → Dose reduction → No anti-inflammatory or antipyretic drugs
Fever > 38 °C, flu-like symptoms	
Swelling of regional lymph nodes	
Allergic reaction (urticaria/nettle rash > exanthema > angioneurotic edema > dyspnea > anaphylaxis)	→ Usual anti-allergic therapy → Discontinue mistletoe product
Activation of inflammation	→ Therapy pause until the symptoms subside → Removal of the focus of inflammation

Recomendación del tipo de Helixor® a usar en los tipos mas comunes de tumor

Por favor, asegúrese de observar en qué casos Helixor® A debe usarse preferentemente, independientemente del tipo de tumor.

Región Cabeza/cuello	Tipo	
Astrocitoma	A	
Tumores cerebrales	A	
Cáncer de ojo	A	
Glioblastoma	A	
Cáncer laríngeo	A	
Cáncer de labio	A	
Meningioma	A	
Cáncer oral	A	
Cáncer faríngeo (orofaringe e hipofaringe)	A	
Cáncer de glándula salival	A	
Tracto Respiratorio	Tipo	
Cáncer de pulmón	A	
Mesotelioma pleural	A	
Carcinoma de traquea	A	

Mamario		Tipo
Cáncer de mama (delgada/premenopáusica)	P	
Cáncer de mama (obesa/postmenopáusica)	M	
Tracto digestivo		Tipo
Cáncer ampolla de Vater	M	
Cáncer anal	M	
Cáncer de apéndice	M	
Colangiocarcinoma	M	
Cáncer de colon	M	
Cáncer de esófago	A	
Cáncer de vesícula biliar	M	
Carcinoma hepatocelular	M	
Cáncer de hígado	M	
Cáncer pancreático	M	



XENIUS PHARMA

Por favor, asegúrese de observar en qué casos Helixor* A debe usarse preferentemente, independientemente del tipo de tumor.

Tracto digestivo	Tipo	
Cáncer de intestino delgado	M	
Cáncer de estómago	M	
Tracto urogenital	Tipo	
Cáncer de vejiga	M	
Cáncer de cuello uterino	M	
Carcinoma coriónico	M	
Cáncer de endometrio	M	
Cáncer de ovario	M	
Cáncer de pene	P	
Cáncer de próstata	A	
Cáncer de recto	M	
Carcinoma de células renales	P	
Cáncer testicular	P	
Cáncer de células de transición de la pelvis renal y el uréter	M	
Cáncer de útero	M	
Cáncer vaginal	M	
Cáncer vulvar	M	

XENIUS PHARMA

Sistema endocrino	Tipo	
Cáncer adrenal	P	
Cáncer tiroideo	A	
Piel	Tipo	
Melanoma maligno	P	
Cáncer de piel	P	
Sarcoma	Tipo	
Osteosarcoma	P	
Sarcoma de partes blandas	P	

Different Modes of Helixor® Administration

	Helixor® Sort	Therapeutic Aims	Importance
Subcutaneous Injection	A, M, P	Immunomodulation	Usual administration in complementary cancer therapy
Intravenous Infusion	A, M, P	Stronger cancer inhibition and pain reduction in cases of ineffective standard therapy Strong cytoprotection during 5FU-chemotherapy	Longstanding clinical experience (not yet proven in clinical trials)
Intrapleural Instillation	M, P	Killing of cancer cells in the pleural cavity Pleurodesis	Proven in longstanding clinical experience and 2 clinical trials
Intraperitoneal Instillation	M	Killing of cancer cells in the abdominal cavity Inhibition of ascites production	Few clinical experience
Intralesional Injection	M, P	Tumour apoptosis/necrosis, followed by a strong immunologic reaction	Growing clinical experience, some animal studies and 2 pilot studies in inoperable cancer

High-Dose Helixor® Infusion Therapy

Authors	Journal	Patient Numbers	Results
Böcher et al.	Journal of Oncology 1996	21	good tolerance, no toxic effects on liver, kidney and bone marrow
Büssing et al.	Journal of Oncology 1996	12	juvenile granulocytes, monocytes ↑, activated T-helper-cells ↑
Salzer et al.	Journal of Oncology 1987	36	quality of life ↑
Kalden	Erfahrungsheilkunde 1994	1	case report: reproducible response of lung metastasis
Friedrichson	Erfahrungsheilkunde 1995	?	co-analgetic effects, quality of life ↑
Steinkellner	Lecture Oncological Conference Salzburg 1997	33	9 % response, 36 % no change, 27 % retardation of cancer growth
Sarkadi	Erfahrungsheilkunde 1995	60	23 % BSR ↓, 17 % tumor marker ↓
Maar	Forum of Complementary Oncology 2001	400	quality of life ↑, cancer pain ↓, mood ↑, in some cases: even cancer response
Zerm	Fortschritte in der Misteltherapie [Advances in Mistletoe Therapy] (eds. Scheer et al.), KVC Verlag Essen 2005	1	very good tolerance and efficacy of high-dose 5FU-chemotherapy

Maar, Forum Komplementäre Onkologie. 2001
High Dose Mistletoe Therapy

Results

- Excellent safety and tolerability
- Significant improvement in QoL
- Significant mood increase
- Cases with decline of tumor markers
- Cases with tumor regression or stable disease

High Dose Mistletoe Infusion Therapy with Helixor®

Listed in the Monograph *Viscum album*, Commission C 1984: „... in special cases for infusion treatment...”

Current Status: Not yet approved, Off-label use

- Tumor progression in case of absence or failure of oncological standard treatment
- Tumor pain in metastasising tumors
- In combination with chemotherapy to reduce toxicity (mucositis, nausea, emesis, weakness)
- Rapid deterioration of general condition

Helixor® Intravenous Infusion

Before the first administration

- i.c. test using 0.1 ml out of Helixor® 1 mg for exclusion of allergy

Frequency

- 1 - 3x/week with or without additional SC administration
- daily i.v. in case of rapid deterioration of general condition

Speed

- 26 drops/minute = 3 hours of infusion

Dosage

- 250 ml 0.9 % sodium chloride solution with 50 mg Helixor®
- ▼
- 100 mg
- ▼
- 200 mg
- ▼
- 400 mg
- ▼
- 600 mg

Stop of dose increase

- in case of
 - fever
 - eosinophilia
 - flu-like reaction

Duration

- long-term treatment over months
- in case of remission continue with SC administration only

Steele, Evid Based Complement Alternat Medicine 2014
Safety of Intravenous Application of Mistletoe
(Viscum album L.) Preparations in Oncology: An
Observational Study

Patients included: All consenting patients treated from 2003 – 2013 with known

- Birth date, gender
- Cancer Diagnosis Date, ICD-10 code
- Start and end date of i.v. therapy

n = 475 → 10-2 % of all treated cancer patients

→ 16.4 % of mistletoe patients

Used Mistletoe Preparations:

Helixor (1 – 3000 mg; median dose of 200 mg)

Abnoba (0.02 mg – 400 mg; median dose of 80 mg)

Iscador (0.1 mg – 100 mg; median dose of 10 mg)



Helixor[®] Mistletoe Therapy in Integrative Oncology

Intravenous Application



 Helixor

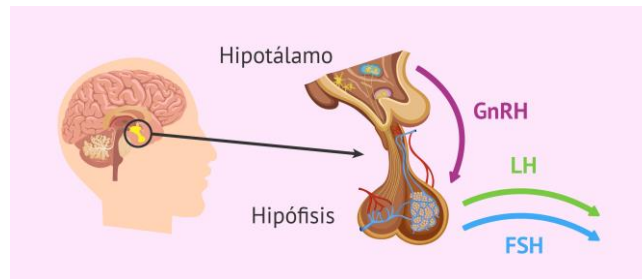
CAMBIOS CLAVES EN LA REMISION TOTAL

➤ CAMBIOS EMOCIONALES

➤ CAMBIOS MENTALES

➤ CAMBIOS ESPIRITUALES

- Tu energía espiritual está íntimamente conectada con tu cuerpo físico
- Al hacer un cambio por resonancia y como todo es uno cambia todo completamente
- Ayudar a equilibrar sistema inmunológico a través de la liberación de hormonas de tus glándulas maestras cerebrales



CAMBIOS CLAVES EN LA REMISION TOTAL

AUMENTAR LAS EMOCIONES POSITIVAS

- “La cura de la risa” que te hace sentir en paz con positivos efectos sobre la inmunidad
- Durante la aplicación de la quimioterapia viendo comedias mejora el recuento inmune al compararlo con pacientes control
- Recuperándose mas rápidamente
- Sentirse feliz permite iguales respuestas al distraer el circuito del miedo y la respuesta de lucha o de huida
- Entrar en modo de descanso y reparación es una oportunidad de reiniciación del sistema inmunológico



LIBERAR EMOCIONES SUPRIMIDAS RETENIDAS DEL PASADO

- Liberar todo lo que nos aleje del precioso momento presente
- Las emociones pueden quedar bloqueadas en el cuerpo físico impidiendo la circulación pránica adecuada
- Dejar ir la rabia, la pena, el dolor, los sentimientos negativos
- Buscando finalmente que la sangre, energía y Prana fluyan adecuadamente

CAMBIOS CLAVES EN LA REMISION TOTAL



SEGUIR SU INTUICION Y PERCEPCION

- Escuchar esa voz interior y dejar que haga parte de la mesa en la toma de sus decisiones
- No se puede ignorar esa voz “que ruge en su interior”
- La intuición es una parte nuestra que nos hace humanos y que no podemos negar
- Unificarnos con nuestro segundo cerebro intestinal
- Tu conoces el camino de antemano

CAMBIOS CLAVES EN LA REMISION TOTAL



CONFIAR EN LA SABIDURIA DE TU CUERPO Y DE SUS CONEXIONES ESPIRITUALES

- Tu cuerpo sabe que es lo que está pasando
- Cambiar drásticamente la forma en que tu mente cuerpo y espíritu están sintiendo silenciando tu mente y conectando tu respiración, sintiéndola, percibiendo los latidos cardíacos
- Estimulando la meditación que logra una mayor conexión espiritual
- Finalmente llegar a la profunda paz inquebrantable
- A nivel espiritual hay una esencia divina profunda sostenida por el amor

CAMBIOS CLAVES EN LA REMISION TOTAL



SENTIRSE AMADO POR SUS FAMILIARES AMIGOS Y MASCOTAS

- Tener en lo posible fuertes redes de apoyo social
- Percibir que las personas vienen a ayudarte, a abrazarte, a sanarte: Libera oxitocina asociada con la liberación de células NK, Glóbulos blancos
- Recibir frases vía correo electrónico y redes como “estoy pensando en ti”
- Actualmente tenemos mas poder sobre nuestra mente, cuerpo y salud
- De lo que pensábamos anteriormente
- Hacerles sentir que son amados generará un sistema inmunológico mas fuerte

CAMBIOS CLAVES EN LA REMISION TOTAL



ENCONTRAR UN PROPOSITO

- Encontrar razones que me den la fuerza suficiente para vivir y hacer los cambios necesarios
- Ponerse al frente de sus elecciones y de sus cambios hacen la diferencia en sus números
- Razones:
 - Estar cerca a la familia
 - Tener hijos y verlos crecer
 - Terminar de escribir el libro
 - Escalar la montaña....
 - Finalmente se busca elevar la fuerza vital que se percibe agotada
 - Según la MTC el Cáncer es el agotamiento del Chi

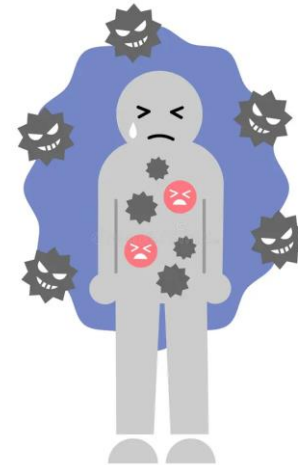
CAMBIOS CLAVES EN LA REMISION TOTAL



TOMAR EL CONTROL TOTAL DE TU SALUD

- El médico sabe que es lo que tienes, pero no sabe ni por que ni para que lo tienes
- No se conoce claramente la personalidad del cáncer, lo que si se conoce claramente es que si te sientes indefenso o deprimido tienes mayor riesgo de morir de ese cáncer
- El poder de la creencia es casi todo
- Debes ver el amanecer y disfrutarlo
- Tocar un instrumento musical
- Comer alimentos saludables
- El poder la creencia lo es todo

CAMBIOS CLAVES EN LA REMISION TOTAL



A tall glass of vibrant green juice with a thick white foam on top, sitting on a wooden surface. Fresh green vegetables, including spinach leaves and a cucumber, are arranged around the glass. The background is a blurred green, suggesting an outdoor setting. The image is framed by green geometric shapes on the left and right sides.

MUCHAS GRACIAS

Raw Food