

LE Magazine February 2002

ABSTRACTS

Policosanol

Efficacy and tolerability of policosanol in hypercholesterolemic postmenopausal women.

This randomized, double-blind, multicenter placebo-controlled study was conducted to investigate the efficacy and tolerability of policosanol, a cholesterol-lowering drug purified from sugar cane wax, in women who had experienced menopause and showed elevated serum total cholesterol and low density lipoprotein (LDL)-cholesterol levels despite a 6-week standard lipid-lowering diet. Thus, 56 eligible patients were randomized to receive placebo or policosanol 5 mg/day for 8 weeks and the dose was doubled to 10 mg/day during the next 8 weeks. Policosanol (5 and 10 mg/day) significantly decreased LDL-cholesterol (17.3% and 26.7%, respectively), total cholesterol (12.9% and 19.5%) as well as the ratios of LDL-cholesterol to high-density lipoprotein (HDL)-cholesterol (17.2% and 26.5%) and total cholesterol to HDL-cholesterol (16.3% and 21.0%) compared with baseline and placebo. HDL-cholesterol levels were significantly raised by 7.4% at study completion. No significant changes occurred in the lipid profile of the placebo group. The drug was safe and well tolerated. No drug-related adverse effects were observed. None of the patients administered policosanol but three of those administered placebo withdrew from the trial because of adverse effects: one due to a serious hypertensive status, one because of an allergic reaction (pruritus plus skin rash) and one due to gastrointestinal disturbances (nauseas plus vomiting). Eleven placebo patients reported 24 adverse effects compared with six policosanol patients who reported seven adverse effects ($p < 0.05$). In addition, five placebo (17.9%) and 13 policosanol patients (46.4%) ($p < 0.05$) reported improvements in habitual symptoms and health perception during the study. In conclusion, policosanol was effective and well tolerated in hypercholesterolemic postmenopausal women, showing additional benefits in the health perception of the study patients.

Int J Clin Pharmacol Res 2001;21(1):31-41

Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk.

BACKGROUND: The present study was undertaken to investigate the effects of policosanol in older patients with type II hypercholesterolemia and more than one concomitant atherosclerotic risk factor. **METHODS:** After 6 weeks on a lipid-lowering diet, 179 patients randomly received a placebo or policosanol at doses of 5 followed by 10 mg per day for successive 12-week periods of each dose. Policosanol (5 and 10 mg/d) significantly ($p < .001$) reduced low-density lipoprotein cholesterol (LDL-C; 16.9% and 24.4%, respectively) and total cholesterol (TC; 12.8% and 16.2%, respectively), while significantly ($p \leq .01$) increasing ($p < .001$) high-density lipoprotein cholesterol (HDL-C) by 14.6% and 29.1%, respectively. **RESULTS:** Policosanol significantly decreased ($p < .01$) the ratios of LDL-C to HDL-C (29.1%) and TC to HDL-C (28%) at study completion, although triglycerides remained unchanged. Policosanol, but not the placebo, significantly improved ($p .01$) cardiovascular capacity, which was assessed using the Specific Activity Scale. No serious adverse experiences occurred in policosanol patients ($p < .01$), compared with seven adverse experiences (7.9%) reported by placebo patients. **CONCLUSIONS:** This study shows that policosanol is effective, safe, and well tolerated in older hypercholesterolemic patients.

J Gerontol A Biol Sci Med Sci 2001 Mar;56(3):M186-92

A long-term study of policosanol in the treatment of intermittent claudication.

Policosanol is a cholesterol-lowering drug with concomitant antiplatelet effects. This study was undertaken to investigate the long-term effects of policosanol administered to patients with moderately severe intermittent claudication. The study consisted of a 6-week single-blind, placebo-controlled run in phase, followed by a 2-year double-blind, randomized treatment step. Fifty-six patients who met study entry criteria were randomized to receive placebo or policosanol 10 mg twice daily. Walking distances on a treadmill (constant speed 3.2 km/h, slope 10 degrees, temperature 25 degrees C) were assessed before and after 6, 12, 18, and 24 months of treatment. Both groups were similar at randomization. After 6 months of therapy, policosanol significantly increased ($p < 0.01$) the initial claudication distance from 125.9 +/- 8.7 m to 201.1 +/- 24.8 m and the absolute claudication distance from 219.5 +/- 14.1 m to 380.7 +/- 50.2 m. Both variables remained unchanged in the placebo group ($p < 0.01$). These effects did not wear off but improved after long-term therapy, so that final values were 333.5 +/- 28.6 m (initial claudication distance) and 648.9 +/- 54.1 m (absolute claudication distance); both significantly greater ($p < 0.0001$) than those obtained in the placebo group, which showed values of 137.9 +/- 21.8 m (initial claudication distance) and 237.7 +/- 28.1 m (absolute claudication distance),

respectively. At study completion, 21 policosanol and 5 placebo patients attained increases in claudication distance values > 50% ($p < 0.001$). Policosanol, but not placebo, significantly increased the ankle/arm pressure index. In addition, from month 6 up to study completion, the frequency of patients reporting improvement of lower limb symptoms was greater in the policosanol group than in the placebo group. The treatment was tolerated well. There were 16 withdrawals (12 placebo, 4 policosanol) from the study. Eight patients in the placebo group experienced a total of 10 serious adverse events, 8 of which were vascular events, compared with none in the policosanol group ($p < 0.01$). In addition, 3 patients in the policosanol group and 3 patients in the placebo group reported mild adverse events during the study. The present results demonstrate the long-term usefulness of policosanol therapy to treat patients with intermittent claudication.

Angiology 2001 Feb;52(2):115-25

Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors.

INTRODUCTION: This study was undertaken to evaluate the efficacy, safety, and tolerability of policosanol, a new cholesterol-lowering drug, in patients with type II hypercholesterolemia and additional coronary risk factors. **PATIENTS AND METHODS:** After 5 weeks of a standard step-1 lipid-lowering diet, 437 patients were randomized to receive, under double-blind conditions, 5 mg policosanol or placebo once a day with the evening meal for 12 weeks and 10 mg policosanol or placebo for the next 12 weeks. **RESULTS:** Both groups were similar at randomization. Policosanol (5 and 10 mg/day) significantly reduced ($P < .001$) serum low-density lipoprotein cholesterol (18.2% and 25.6%, respectively) and cholesterol (13.0% and 17.4%), and it significantly raised ($P < .01$) high-density lipoprotein cholesterol (15.5% and 28.4%). Triglycerides remained unchanged after the first 12 weeks and lowered significantly (5.2%; $P < .01$) at study completion. Policosanol was safe and well tolerated, and no drug-related disturbances were observed. Two male patients who received placebo died during the study—one because of a myocardial infarction and the other because of a cardiac arrest that occurred during a surgical intervention. There were 11 serious adverse events (5.1%) in 10 patients who received placebo (4.6%), 7 of which were vascular, compared with no serious adverse events reported in patients receiving policosanol ($P < .01$). **CONCLUSIONS:** Subjects in the group treated with policosanol did not have serious adverse events during the 24-week study. This study shows that policosanol is effective, safe, and well tolerated in patients with hypercholesterolemia and concomitant coronary risk factors.

Clin Pharmacol Ther 1999 Apr;65(4):439-47

Effect of policosanol on lipofundin-induced atherosclerotic lesions in rats.

Policosanol is a mixture of higher aliphatic alcohols isolated from sugar cane wax, showing cholesterol-lowering effects and preventing the development of lipofundin-induced lesions in New Zealand rabbits. This study was conducted to determine whether policosanol orally administered to rats also protects against the development of lipofundin-induced atherosclerotic lesions. Fifty four male Wistar rats were randomly distributed amongst a negative control group, a positive control group intravenously injected with lipofundin for eight days, and four experimental groups also injected with lipofundin, but orally receiving policosanol at 0.5, 2.5, 5 and 25 mg kg⁻¹, respectively. Policosanol treatment was orally administered once-a-day for eight days, while control groups similarly received equivalent amounts of vehicle. A significant reduction of the atherosclerotic lesions in the treated animals was observed. It is concluded that policosanol has a protective effect on lipofundin-induced aortic lesions in Wistar rats.

J Pharm Pharmacol 1995 Apr;47(4):289-91

Protective effect of policosanol on atherosclerotic lesions in rabbits with exogenous hypercholesterolemia.

Policosanol is a mixture of higher aliphatic alcohols purified from sugar cane wax, with cholesterol-lowering effects demonstrable in experimental models and in patients with type II hypercholesterolemia. The protective effects of policosanol on atherosclerotic lesions experimentally induced by lipofundin in rabbits and rats and spontaneously developed in stump-tail monkeys have been described. The present study was conducted to determine whether policosanol administered orally to rabbits with exogenous hypercholesterolemia also protects against the development of atherosclerotic lesions. Male New Zealand rabbits weighing 1.5 to 2 kg were randomly divided into three experimental groups which received 25 or 200 mg/kg policosanol ($N = 7$) orally for 60 days with acacia gum as vehicle or acacia gum alone (control group, $N = 9$). All animals received a cholesterol-rich diet (0.5%) during the entire period. Control animals developed marked hypercholesterolemia, macroscopic lesions and arterial intimal thickening. Intima thickness was significantly less (32.5 \pm 7 and 25.4 \pm 4 microm) in hypercholesterolemic rabbits treated with policosanol than in controls (57.6 \pm 9 microm). In most policosanol-treated animals, atherosclerotic lesions were not present, and in others, thickness of fatty streaks had less foam cell layers than in controls. We conclude that policosanol has a protective effect on the atherosclerotic lesions occurring in this experimental model.

Braz J Med Biol Res 2000 Jul;33(7):835-40

Oral administration of policosanol inhibits in vitro copper ion-induced rat lipoprotein peroxidation.

Policosanol, a new cholesterol-lowering agent, is a mixture of higher aliphatic primary alcohols isolated from sugar cane (*Saccharum officinarum* L.) wax, which prevents the onset of spontaneously and experimentally induced atherosclerotic lesions in experimental models. Because the oxidation of low-density lipoprotein (LDL) may play a role in the pathogenesis of atherosclerosis, we investigate the effect of policosanol on copper oxidative susceptibility of rat lipoprotein fractions (VLDL + LDL). Rats fed normal diet were treated with policosanol (250-500 mg/kg/day) for up to 4 weeks. EDTA-free lipoprotein particles were oxidized in a cell-free system by the addition of copper ions, and conjugated dienes generation was monitored by changes of optical density at 234 nm. Thiobarbituric acid-reactive substances (TBARS) content and lysine-amino group reactivity were investigated. After administration, there was no change in cholesterol, triglycerides, and phospholipid content of lipoprotein fractions; however, policosanol significantly prolongs the lag time and reduces the propagation rate of diene generation. Also, policosanol reduces TBARS content and increases lysine reactivity in lipoprotein fractions treated with Cu^{2+} . In conclusion, policosanol, in addition to its cholesterol-lowering effect, has other properties that enables it to reduce the potential of lipoprotein to undergo lipid peroxidation. Such effect can be considered of promissory value in the management of atherosclerosis.

Physiol Behav 1999 Aug 1;67(1):1-7

Effect of policosanol on foam-cell formation in carrageenan-induced granulomas in rats.

Policosanol is a new cholesterol-lowering drug isolated and purified from sugar-cane wax, which prevents the development of lipofundin-induced lesions and foam-cell formation in New Zealand rabbits and Wistar rats. This study was conducted to examine the effects of policosanol on foam-cell formation in carrageenan-induced granulomas in rats. Eighteen Wistar rats were randomly distributed in three experimental groups which received orally for 20 days Tween 20 H₂O as vehicle (control group) or policosanol at 2.5 or 25 mg kg⁻¹. At the 11th day, lipofundin was injected intraperitoneally for 8 days to induce formation of foam cells in the granuloma. At day 13, carrageenan was injected subcutaneously for granuloma induction and seven days later animals were killed. A significant reduction of the foam-cell formation in granulomas of policosanol-treated rats was observed. It is concluded that policosanol prevents the development of foam cells in carrageenan-induced granulomas (extravascular medium) in rats.

J Pharm Pharmacol 1996 Mar;48(3):306-9

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ABSTRACTS

Effect of policosanol on platelet aggregation and serum levels of arachidonic acid metabolites in healthy volunteers.

Policosanol is a cholesterol-lowering drug with hypocholesterolemic effects demonstrated in experimental models, healthy volunteers and patients with type II hypercholesterolemia. In addition, antiplatelet effects of policosanol have been shown in experimental models and healthy volunteers. This study reports the results of a 2-week, randomized, double-blind, placebo-controlled trial investigating the effects of policosanol on platelet aggregation and thromboxane B2 and prostacyclin (6 keto PGF1alpha) production after stimulation with collagen in healthy volunteers. The volunteers were on a placebo-baseline period for 7 days and thereafter they received randomly, under double-blind conditions, placebo or policosanol (10 mg/day) for 15 days. Platelet aggregation was determined at baseline and after 15 days of treatment. Significant reductions of arachidonic acid and collagen-induced platelet aggregation were observed. Thromboxane, but not prostacyclin, generation induced by collagen was also inhibited by policosanol.

Prostaglandins Leukot Essent Fatty Acids 1998 Jan;58(1):61-4

Comparative study of policosanol, aspirin and the combination therapy policosanol-aspirin on platelet aggregation in healthy volunteers.

A randomized, double-blind, placebo-controlled study was conducted in 43 healthy volunteers to compare the effects of policosanol (20 mg day⁻¹), aspirin (ASA) (100 mg day⁻¹) and combination therapy (policosanol 20 mg day⁻¹ plus ASA 100 mg day⁻¹) on platelet aggregation. The healthy volunteers were randomly treated for 7 days. Both, platelet aggregation and coagulation time were measured at baseline and after therapy. When policosanol was administered platelet aggregation induced by ADP (37.3%), epinephrine (32.6%) and collagen (40.5%) were significantly reduced. Meanwhile, aspirin significantly reduced platelet aggregation induced by collagen (61.4%) and epinephrine (21.9%) but not ADP-induced aggregation. Combined therapy significantly inhibited aggregation induced by all the agonists reaching the highest reductions of platelet aggregation induced by collagen (71.3%) and epinephrine (57.5%). Coagulation time did not change significantly in any group. No subject withdrew from the trial. Four volunteers reported mild adverse experiences during the study: three ASA-treated cases referred headache, epigastralgia and nose bleeding, meanwhile one patient receiving combination therapy reported gum bleeding. The present results demonstrate that policosanol (20 mg day⁻¹) is as effective as ASA (100 mg day⁻¹). Moreover, combination therapy shows some advantages compared with the respective monotherapies.

Pharmacol Res 1997 Oct;36(4):293-7

Safety of HMG-CoA reductase inhibitors: focus on atorvastatin.

Statins effectively lower LDL-cholesterol and some members of this class have been shown to reduce the risk of major cardiovascular events and total mortality in patients with or at risk for coronary heart disease. Statins are in general well tolerated. Withdrawal rates related to adverse events are low (< or =3%). The most common adverse events are mild gastrointestinal symptoms. Elevated serum transaminase levels occur infrequently (< or = 1.5%). These are generally asymptomatic, reversible and rarely require drug withdrawal. Statins do not cause adverse endocrine effects, do not alter glycemic control in diabetic patients, and do not increase cancer risk. Dose-related myopathy and/or rhabdomyolysis also occurs very rarely, although the risk is increased by concomitant administration of cyclosporine, niacin, fibrates, or by CYP3A4 isoenzyme inhibitors (e.g. erythromycin, systemic azole antifungal agents etc.) with statins metabolized by this isoenzyme. The pharmacokinetics of the individual statin should be considered in patients receiving polypharmacological treatments, to minimize the risk of unfavorable drug interactions. Atorvastatin is well tolerated in long-term treatment of dyslipidemia and is characterized by a safety profile similar to the other available statins.

Cardiovasc Drugs Ther 2001;15(3):211-8

Eye health

Oxidative damage and age-related macular degeneration.

This article provides current information on the potential role of oxidation in relation to age-related macular degeneration (AMD). The emphasis is placed on the generation of oxidants and free radicals and the protective effects of antioxidants in the outer retina, with specific emphasis on the photoreceptor cells, the retinal pigment epithelium and the choriocapillaris. The starting points include a discussion and a definition of what radicals are, their endogenous sources, how they react, and what damage they may cause.

The photoreceptor/pigment epithelium complex is exposed to sunlight, is bathed in a near-arterial level of oxygen, and membranes in this complex contain high concentrations of polyunsaturated fatty acids, all considered to be potential factors leading to oxidative damage. Actions of antioxidants such as glutathione, vitamin C, superoxide dismutase, catalase, vitamin E and the carotenoids are discussed in terms of their mechanisms of preventing oxidative damage. The phototoxicity of lipofuscin, a group of complex autofluorescent lipid/protein aggregates that accumulate in the retinal pigment epithelium, is described and evidence is presented suggesting that intracellular lipofuscin is toxic to these cells, thus supporting a role for lipofuscin in aging and AMD. The theory that AMD is primarily due to a photosensitizing injury to the choriocapillaris is evaluated. Results are presented showing that when protoporphyric mice are exposed to blue light there is an induction in the synthesis of Type IV collagen synthesis by the choriocapillary endothelium, which leads to a thickened Bruch's membrane and to the appearance of sub-retinal pigment epithelial fibrillogranular deposits, which are similar to basal laminar deposits. The hypothesis that AMD may result from oxidative injury to the retinal pigment epithelium is further evaluated in experiments designed to test the protective effects of glutathione in preventing damage to cultured human pigment epithelial cells exposed to an oxidant. Experiments designed to increase the concentration of glutathione in pigment epithelial cells using dimethylfumarate, a monofunctional inducer, are described in relation to the ability of these cells to survive an oxidative challenge. While all these models provide undisputed evidence of oxidative damage to the retinal pigment epithelium and the choriocapillaris that is both light- and oxygen-dependent, it nevertheless is still unclear at this time what the precise linkage is between oxidation-induced events and the onset and progression of AMD.

Mol Vis 1999 Nov 3;5:32

Oxidative damage and protection of the RPE.

This review provides a model for the role of oxidative stress in the etiology of age-related macular degeneration (AMD). Epidemiological studies of diet, environmental and behavioral risk factors suggest that oxidative stress is a contributing factor of AMD. Pathological studies indicate that damage to the retinal pigment epithelium (RPE) is an early event in AMD. In vitro studies show that oxidant treated RPE cells undergo apoptosis, a possible mechanism by which RPE cells are lost during early phase of AMD. The main target of oxidative injury seems to be mitochondria, an organelle known to accumulate genomic damages in other postmitotic tissues during aging. The thiol antioxidant GSH and its amino acid precursors protect RPE cells from oxidant-induced apoptosis. Similar protection occurs with dietary enzyme inducers which increase GSH synthesis. These results indicate that therapeutic or nutritional intervention to enhance the GSH antioxidant capacity of RPE may provide an effective way to prevent or treat AMD.

Prog Retin Eye Res 2000 Mar;19(2):205-21

Vitamin supplement use and incident cataracts in a population-based study.

OBJECTIVE: To determine the relationship between vitamin supplement use and the 5-year incidence of nuclear, cortical, and posterior subcapsular cataract in the Beaver Dam Eye Study cohort. **DESIGN:** The 5-year incidence of cataract, determined from slitlamp (nuclear cataract) and retroillumination (cortical and posterior subcapsular cataract) photographs, was assessed in a population-based cohort of persons participating in baseline (1988-1990) and follow-up (1993-1995) examinations. Detailed data regarding the type, dosage, and duration of supplement use were obtained by in-person interviews at follow-up. **PARTICIPANTS:** Residents of Beaver Dam, Wis, aged 43 to 86 years, were identified by private census. Of the 3684 participants in both baseline and follow-up examinations, 3089 were eligible for incident cataract analysis in the present study. **RESULTS:** Compared with nonusers, the 5-year risk for any cataract was 60% lower among persons who, at follow-up, reported the use of multivitamins or any supplement containing vitamin C or E for more than 10 years. Taking multivitamins for this duration lowered the risk for nuclear and cortical cataracts but not for posterior subcapsular cataracts (odds ratios [95% confidence intervals] = 0.6 [0.4-0.9], 0.4 [0.2-0.8], and 0.9 [0.5-1.9], respectively). Use of supplements for shorter periods was not associated with reduced risk for cataract. Measured differences in lifestyle between supplement users and nonusers did not influence these associations, nor did variations in diet as measured in a random subsample. **CONCLUSIONS:** These data add to a body of evidence suggesting lower risk for cataract among users of vitamin supplements and stronger associations with long-term use. However, the specific nutrients that are responsible cannot be ascertained at this time, and unmeasured lifestyle differences between supplement users and nonusers may explain these results.

Arch Ophthalmol 2000 Nov;118(11):1556-63

Aging affects the retrobulbar circulation differently in women and men.

BACKGROUND: While aging clearly has protean biological effects on every organ system, the differential effects of aging in women and men in the retrobulbar vasculature, to our knowledge, have never been investigated. Because glaucoma and age-related macular degeneration are closely linked to advanced age, we performed a cross-sectional study using color Doppler imaging of 4 retrobulbar vessels in both healthy women and men. **OBJECTIVE:** To define the influence of aging per se on ocular hemodynamics. **METHODS:** Women (n = 73) and men (n = 55), aged from 20 to 90 years, free of ocular and systemic disease, and with normal intraocular pressure, were recruited for this study. Postmenopausal women who were not receiving estrogen

replacement therapy were also recruited. Studies involved color Doppler imaging analysis of the ophthalmic, central retinal, and nasal and temporal posterior ciliary arteries. Ophthalmic arterial peak systolic and end-diastolic velocities and a Pourcelot resistance index were determined for each vessel. RESULTS: In both sexes, ophthalmic arterial end-diastolic velocity decreased and the Pourcelot resistance index rose with advancing age (each $P < .001$); peak systolic velocity in the ophthalmic vessel was age-independent. In contrast, central retinal arterial flow velocities were unaffected by age in both sexes. In the posterior ciliary arteries, in men, flow velocities and the Pourcelot resistance index were independent of age. However, in women, end-diastolic velocity decreased with age in both the nasal and temporal posterior ciliary vessel (each $P < .05$); peak systolic velocity was constant; the Pourcelot resistance index in each ciliary artery rose with advancing age (each $P < .05$). CONCLUSION: In healthy women and men, aging-induced changes in retrobulbar hemodynamics are comparable to alterations seen in patients with glaucoma or age-related macular degeneration, suggesting that vascular changes with senescence may contribute to increased risk for these diseases in older age.

Arch Ophthalmol 2000 Aug;118(8):1076-80

A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.

BACKGROUND: Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss. **OBJECTIVE:** To evaluate the effect of high-dose vitamins C and E, beta carotene and zinc supplements on AMD progression and visual acuity. **DESIGN:** The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo. **MAIN OUTCOME MEASURES:** (1) Photographic assessment of progression to or treatment for advanced AMD and (2) at least moderate visual acuity loss from baseline ($>$ or $=15$ letters). Primary analyses used repeated-measures logistic regression with a significance level of .01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring. **RESULTS:** Average follow-up of the 3640 enrolled study participants, aged 55-80 years, was 6.3 years, with 2.4% lost to follow-up. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47-0.91; zinc: OR, 0.71; 99% CI, 0.52-0.99; antioxidants: OR, 0.76; 99% CI, 0.55-1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc (OR, 0.73; 99% CI, 0.54-0.99). No statistically significant serious adverse effect was associated with any of the formulations. **CONCLUSIONS:** Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

Arch Ophthalmol 2001 Oct;119(10):1417-36

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ABSTRACTS

Neuroprotection: is it already applicable to glaucoma therapy?

Many categories of both natural and synthetic compounds have been reported to have neuroprotective activity. These include not only antioxidants, N-methyl-D-aspartate receptor antagonists, inhibitors of glutamate release, calcium channel blockers, polyamine antagonists, and nitric oxide synthase inhibitors, but cannabinoids, aspirin, melatonin and vitamin B12. The lack of availability of specific neuroprotectant compounds in the United States and the lack of clinical trials examining the benefits of neuroprotective agents for glaucoma currently limit the use of these agents. This article provides a short overview of the concept of neuroprotection as it applies to glaucoma and suggests the possibility of neuroprotective activity that might be provided by compounds that are presently easily available.

Curr Opin Ophthalmol 2000 Apr;11(2):78-84

N-Acetylcarnosine, a natural histidine-containing dipeptide, as a potent ophthalmic drug in treatment of human cataracts.

A study was designed to document and quantify the changes in lens clarity over 6 and 24 months in 2 groups of 49 volunteers (76 eyes) with an average age of 65.3 +/- 7.0 enrolled at the time of diagnosis of senile cataracts of minimal to advanced opacification. The patients received N-acetylcarnosine, 1% sol (NAC) (26 patients, 41 eyes = Group II), placebo composition (13 patients, 21 eyes) topically (two drops, twice daily) to the conjunctival sac, or were untreated (10 patients, 14 eyes); the placebo and untreated groups were combined into the control (reference) Group I. Patients were evaluated upon entry, at 2-month (Trial 1) and 6-month (Trial 2)-intervals for best corrected visual acuity (b/c VA), by ophthalmoscopy and the original techniques of glare test (for Trial 1), stereocinematographic slit-image and retro-illumination photography with subsequent scanning of the lens. The computerized interactive digital analysis of obtained images displayed the light scattering/absorbing centers of the lens into 2-D and 3-D scales. The intra-reader reproducibility of measuring techniques for cataractous changes was good, with the overall average of correlation coefficients for the image analytical data 0.830 and the glare test readings 0.998. Compared with the baseline examination, over 6 months 41.5% of the eyes treated with NAC presented a significant improvement of the gross transmissivity degree of lenses computed from the images, 90.0% of the eyes showed a gradual improvement in b/c VA to 7-100% and 88.9% of the eyes ranged a 27-100% improvement in glare sensitivity. Topographic studies demonstrated less density and corresponding areas of opacification in posterior subcapsular and cortical morphological regions of the lens consistent with VA up to 0.3. The total study period over 24 months revealed that the beneficial effect of NAC is sustainable. No cases resulted in a worsening of VA and image analytical readings of lenses in the NAC-treated group of patients. In most of the patients drug tolerance was good. Group I of patients demonstrated the variability in the densitometric readings of the lens cloudings, negative advance in glare sensitivity over 6 months and gradual deterioration of VA and gross transmissivity of lenses over 24 months compared with the baseline and 6-month follow-up examinations. Statistical analysis revealed the significant differences over 6 and 24 months in cumulative positive changes of overall characteristics of cataracts in the NAC-treated Group II from the control Group I. The N-acetylated form of natural dipeptide L-carnosine appears to be suitable and physiologically acceptable for nonsurgical treatment for senile cataracts.

Peptides 2001 Jun;22(6):979-94

Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes.

BACKGROUND: It has been suggested that eating green leafy vegetables, which are rich in lutein and zeaxanthin, may decrease the risk for age related macular degeneration. The goal of this study was to analyse various fruits and vegetables to establish which ones contain lutein and/or zeaxanthin and can serve as possible dietary supplements for these carotenoids. **METHODS:** Homogenates of 33 fruits and vegetables, two fruit juices and egg yolk were used for extraction of the carotenoids with hexane. Measurement of the different carotenoids and their isomers was carried out by high performance liquid chromatography using a single column with an isocratic run, and a diode array detector. **RESULTS:** Egg yolk and maize (corn) contained the highest mole percentage (% of total) of lutein and zeaxanthin (more than 85% of the total carotenoids). Maize was the vegetable with the highest quantity of lutein (60% of total) and orange pepper was the vegetable with the highest amount of zeaxanthin (37% of total). Substantial amounts of lutein and zeaxanthin (30-50%) were also present in kiwi fruit, grapes, spinach, orange juice, zucchini (or vegetable marrow) and different kinds of squash. The results show that there are fruits and vegetables of various colours with a relatively high content of lutein and zeaxanthin. **CONCLUSIONS:** Most of the dark green leafy vegetables, previously recommended for a higher intake of lutein and zeaxanthin, have 15-47% of lutein, but a very low content (0-3%) of zeaxanthin. Our study shows that fruits and vegetables of various colours can be consumed to increase dietary intake of lutein and zeaxanthin.

Br J Ophthalmol 1998 Aug;82(8):907-10

Glutathione: a vital lens antioxidant.

The reducing compound glutathione (GSH) exists in an unusually high concentration in the lens where it functions as an essential antioxidant vital for maintenance of the tissue's transparency. In conjunction with an active glutathione redox cycle located in the lens epithelium and superficial cortex, GSH detoxifies potentially damaging oxidants such as H₂O₂ and dehydroascorbic acid. Recent studies have indicated an important hydroxyl radical-scavenging function for GSH in lens epithelial cells, independent of the cells' ability to detoxify H₂O₂. Depletion of GSH or inhibition of the redox cycle allows low levels of oxidant to damage lens epithelial targets such as Na/K-ATPase, certain cytoskeletal proteins and proteins associated with normal membrane permeability. The level of GSH in the nucleus of the lens is relatively low, particularly in the aging lens, and exactly how the compound travels from the epithelium to the central region of the organ is not known. Recently, a cortical/nuclear barrier to GSH migration in older human lenses was demonstrated by Sweeney et al. The relatively low ratio of GSH to protein -SH in the nucleus of the lens, combined with low activity of the glutathione redox cycle in this region, makes the nucleus especially vulnerable to oxidative stress, as has been demonstrated with use of in vivo experimental animal models such as hyperbaric oxygen, UVA light and the glutathione peroxidase knockout mouse. Effects observed in these models, which are currently being utilized to investigate the mechanism of formation of human senile nuclear cataract, include an increase in lens nuclear disulfide, damage to nuclear membranes and an increase in nuclear light scattering. A need exists for development of therapeutic agents to slow age-related loss of antioxidant activity in the nucleus of the human lens to delay the onset of cataract.

J Ocul Pharmacol Ther 2000 Apr;16(2):121-35

Effect of photooxidation on the eye lens and role of nutrients in delaying cataract.

The function of the eye lens is to collect and focus light on the retina. To do so, it must remain clear during the decades of life. Upon aging, lens constituents are damaged and precipitate in opacities called senile cataracts. Laboratory and epidemiologic data indicate that the damage is due in part to light and active forms of oxygen. Antioxidant nutrients—ascorbate, carotenoids, and tocopherol—appear to offer protection against cataract. Fifty million persons worldwide are blind due to cataract, and, in the U.S., there are 1.2 million cataract surgeries performed at an annual cost (including physician visits) of over \$3.2 billion. It has been estimated that a 10-year delay in the development of cataract would eliminate the need for half the surgeries. Since it will not be possible to replace most of the damaged lenses, it is essential to determine the efficacy of supplying adequate levels of antioxidant nutrients early in life to preserve lens function.

EXS 1992;62:266-79

Carotenoids in the retina—a review of their possible role in preventing or limiting damage caused by light and oxygen.

Two of the circa 600 naturally occurring carotenoids, zeaxanthin and lutein, the major carotenoids of maize and melon respectively, are the constituents of the macula lutea, the yellow spot in the macula, the central part of the retina in primates and humans. Of the circa ten carotenoids found in the blood these two are specifically concentrated in this area, which is responsible for sharp and detailed vision. This paper reviews the ideas that this concentration of dietary carotenoids in the macula is not accidental, but that their presence may prevent or limit damage due to their physicochemical properties and their capability to quench oxygen free radicals and singlet oxygen, which are generated in the retina as a consequence of the simultaneous presence of light and oxygen. Additionally, in vitro and in vivo animal experiments are reviewed as well as observational and epidemiological data in humans. These show that there is enough circumstantial evidence for a protective role of carotenoids in the retina to justify further research. Some emphasis will be put on age-related macular degeneration (AMD), a multifactorial degenerative retinal disease for which the exposure to light and thus photochemical damage has been suggested as one of the etiological factors. Recent attempts at nutritional intervention in this condition will also be reviewed.

EXS 1992;62:280-98

Effects of policosanol 20 versus 40 mg/day in the treatment of patients with type II hypercholesterolemia: a 6-month double-blind study.

Policosanol is a well defined mixture of higher aliphatic primary alcohols isolated from sugar cane wax with cholesterol-lowering effects proven for a dose range from 5-20 mg/day in patients with type II hypercholesterolemia and dyslipidemia associated with noninsulin dependent diabetes mellitus. This randomized, double-blind study investigated the cholesterol-lowering efficacy and tolerability of policosanol 20 mg/day compared with 40 mg/day. Changes in low-density lipoprotein (LDL)-cholesterol levels were predefined as the primary efficacy endpoint. Patients with type II hypercholesterolemia were enrolled in the study and instructed to continue a step I cholesterol-lowering diet for 6 weeks and those eligible to be included (89) were randomly allocated to receive under double-blind conditions placebo (n = 30), policosanol 20 mg/day (n = 29) or 40 mg/day (n = 30). After 24 weeks, policosanol at 20 and 40 mg/day significantly (p < 0.00001) lowered LDL-cholesterol by 27.4% and 28.1%, total cholesterol (p < 0.00001) by 15.6% and 17.3%, and the LDL-cholesterol/high-density lipoprotein (HDL)-cholesterol ratio by 37.2% and 36.5%, respectively. The

ratio of total cholesterol/HDL-cholesterol was lowered by 27.1% and 27.5%, while HDL-cholesterol levels increased ($p < 0.001$) by 17.6% and 17.0%, respectively. Compared with baseline, policosanol 20 mg/day lowered triglycerides ($p < 0.05$) by 12.7%, while they were lowered ($p < 0.01$) by 15.6% at a dose of policosanol 40 mg/day. All the above-mentioned significant differences were also different from placebo and no significant changes occurred in any lipid profile parameters in the placebo group. Based on the mean values of LDL-cholesterol levels at study completion, the mean percent reductions from baseline were 27.4% and 28.1% for the 20 and 40 mg/day groups, respectively. Thus, the effects of both policosanol doses on the main efficacy variable were practically identical. Consistent with the data obtained for LDL-cholesterol, both doses were similarly effective in changing all the other lipid profile parameters. No unexpected adverse effects were observed and there were no significant between-group differences regarding safety indicator values or reported adverse effects. In conclusion, although the tolerability profile remains excellent, according to the present results policosanol at a dose of 40 mg/day does not offer significant additional cholesterol-lowering efficacy over the 20 mg/day dose.

Int J Clin Pharmacol Res 2001;21(1):43-57

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ABSTRACTS

Thymosin beta 4

Chemical characterization of thymosin beta 4.

As part of our ongoing investigations on the endocrine thymus, we have isolated and purified to homogeneity a hormone-like peptide which we have termed thymosin beta 4. Thymosin beta 4 has Mr = 4982 and an isoelectric point of 5.1. The complete amino acid sequence of this polypeptide has been established by automated Edman degradation as well as by manual sequence analysis. Thymosin beta 4 is composed of 43 amino acid residues with acetylserine at the NH₂ terminus. This molecule induces expression of terminal deoxynucleotidyl transferase in transferase-negative murine thymocytes *in vivo* and *in vitro*. It also exhibits ability to inhibit the migration of macrophages. Comparison of the sequence of thymosin beta 4 to other thymic hormones or other published protein sequences does not reveal any statistically significant relationship. Two helical regions were identified in the structure using data for prediction of protein conformation. It is proposed that thymosin beta 4 is one of the biologically active peptides present in thymosin fractions 5 and 5A which participate in the regulation, differentiation, and function of thymus-derived lymphocytes and may also act directly or indirectly on macrophages and perhaps other cells involved in cell-mediated immunity.

Biol Chem 1982 Jan 25;257(2):1000-6

Thymosin beta 4 sulfoxide is an anti-inflammatory agent generated by monocytes in the presence of glucocorticoids.

The possibility that glucocorticoids upregulate the expression of anti-inflammatory mediators is an exciting prospect for therapy in inflammatory diseases, because these molecules could give the therapeutic benefits of steroids without toxic side effects. Supernatants from monocytes and macrophages cultured in the presence of glucocorticoids increase the dispersion of neutrophils from a cell pellet in the capillary tube migration assay. This supernatant factor, unlike other neutrophil agonists, promotes dispersive locomotion of neutrophils at uniform concentration, lowers their adhesion to endothelial cells, inhibits their chemotactic response to fMLP and induces distinctive morphological changes. Here we show that thymosin beta 4 sulfoxide is generated by monocytes in the presence of glucocorticoids and acts as a signal to inhibit an inflammatory response. *In vitro*, thymosin beta 4 sulfoxide inhibited neutrophil chemotaxis, and *in vivo*, the oxidized peptide, but not the native form, was a potent inhibitor of carrageenin-induced edema in the mouse paw. Thymosin beta 4 is unique, because oxidation attenuates its intracellular G-actin sequestering activity, but greatly enhances its extracellular signaling properties. This description of methionine oxidation conferring extracellular function on a cytosolic protein may have far-reaching implications for future strategies of anti-inflammatory therapy.

Nat Med 1999 Dec;5(12):1424-7

Thymosin beta 4 accelerates wound healing.

Angiogenesis is an essential step in the repair process that occurs after injury. In this study, we investigated whether the angiogenic thymic peptide thymosin beta 4 (T beta 4) enhanced wound healing in a rat full thickness wound model. Addition of T beta 4 topically or intraperitoneally increased reepithelialization by 42% over saline controls at 4 d and by as much as 61% at 7 d post-wounding. Treated wounds also contracted at least 11% more than controls by day 7. Increased collagen deposition and angiogenesis were observed in the treated wounds. We also found that T beta 4 stimulated keratinocyte migration in the Boyden chamber assay. After 4-5 h, migration was stimulated 2-3-fold over migration with medium alone when as little as 10 pg of T beta 4 was added to the assay. These results suggest that T beta 4 is a potent wound healing factor with multiple activities that may be useful in the clinic.

J Invest Dermatol 1999 Sep;113(3):364-8

Thymosin beta 4 stimulates directional migration of human umbilical vein endothelial cells.

Thymosin beta 4 (T beta 4) is a 4.9 kDa polypeptide that interacts with G-actin and is thought to be an important mediator in cell proliferation, migration, and differentiation. T beta 4 has been identified as a factor involved in the differentiation of human umbilical vein endothelial cells (HUVECs) cultured on Matrigel. Here we have used various *in vitro* and *in vivo* migration assays to demonstrate the role of T beta 4 in endothelial cell migration. Our results demonstrate that T beta 4 acts as a chemoattractant for endothelial cells, stimulating the migration of HUVECs in Boyden chambers four- to sixfold over that observed with media alone. Of the primary cell types tested, only human coronary artery cells responded to T beta 4 treatment, suggesting that the migration activity of T beta 4 was endothelial cell-specific. T beta 4 significantly accelerated the rate of migration into the scratch wounded area of a HUVEC monolayer. T beta 4 treatment also increased the production of matrix metalloproteinases that may degrade the

basement membrane during angiogenesis. Additional experiments using subcutaneously implanted Matrigel showed that T beta 4 stimulated cell migration in vivo. These results provide the first direct evidence that T beta 4 has chemoattractive activity and promotes angiogenesis by stimulating the migration of endothelial cells.

FASEB J 1997 May;11(6):474-81

Thymosin beta 4 (T beta 4) in activated platelets.

When resting human blood platelets are stimulated with thrombin, 50 to 60% of the G-actin polymerizes to F-actin within 60 seconds. The increase in F-actin is correlated with a corresponding decrease in the complex of G-actin with T beta 4. Within 5 seconds after stimulation, nucleation sites for pyrene actin polymerization increase 1.5 times in Triton-lysed supernatants. Cytochalasin D, known to inhibit the increase in F-actin after thrombin, also inhibits the fall in T beta 4-actin complex and the increase in nucleation sites. Phosphorylation of T beta 4 could not be detected in either control or activated cells. Increased T beta 4 corresponding to that lost from the T beta 4-actin complex is present in lysates from activated platelets and retains the ability to complex with actin. The data, taken together with previous estimates for the dissociation constant of the T beta 4-actin complex, show that actin polymerization following platelet activation could be controlled primarily by the increased availability of free barbed ends of actin filaments which have a higher affinity for G-actin than does T beta 4 and suggest that the increased free T beta 4 may serve to limit the degree of polymerization.

Eur J Cell Biol 1993 Aug;61(2):314-20

Thymosin beta 4 (Fx peptide) is a potent regulator of actin polymerization in living cells.

Thymosin beta 4 (beta 4) is a 5-kDa polypeptide originally identified in calf thymus. Although numerous activities have been attributed to beta 4, its physiological role remains elusive. Recently, beta 4 was found to bind actin in human platelet extracts and to inhibit actin polymerization in vitro, raising the possibility that it may be a physiological regulator of actin assembly. To examine this potential function, we have increased the cellular beta 4 concentration by microinjecting synthetic beta 4 into living epithelial cells and fibroblasts. The injection induced a diminution of stress fibers and a dose-dependent depolymerization of actin filaments as indicated by quantitative image analysis of phalloidin binding. Our results show that beta 4 is a potent regulator of actin assembly in living cells.

Proc Natl Acad Sci U S A 1992 May 15;89(10):4678-82

The modern approach to wound treatment.

INTRODUCTION: Wound healing is a complex process involving interactions among a variety of different cell types. The normal wound repair process consists of three phases—*inflammation, proliferation and remodeling* that occur in a predictable series of cellular and biochemical events. Wounds are classified according to various criteria: *etiology, lasting, morphological characteristics, communications with solid or hollow organs, the degree of contamination.* In the last few years many authors use the *Color Code Concept*, which classifies wounds as *red, yellow and black wounds.* This paper presents conventional methods of local wound treatment (*mechanical cleansing, disinfection with antiseptic solutions, wound debridement—surgical, biological and autolytic; wound closure, topical antibiotic treatment, dressing*), as well as general measures (*sedation, antitetanus and antibiotic protection, preoperative evaluation and correction of malnutrition, vasoconstriction, hyperglycemia and steroid use, appropriate surgical technique, and postoperative prevention of vasoconstriction through pain relief, warming and adequate volume resuscitation*). The role of physiological factors and antimicrobial agents in wound healing. Growth factors play a role in cell division, migration, differentiation, protein expression, enzyme production and have a potential ability to heal wounds by stimulating angiogenesis and cellular proliferation, affecting the production and the degradation of the extracellular matrix, and by being chemotactic for inflammatory cells and fibroblasts. There are seven major families of growth factors: *epidermal growth factor (EGF), transforming growth factor-beta (TGF-beta), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), interleukins (ILs) and colony-stimulating factor (CSF).* Acute wounds contain many growth factors that play a crucial role in the initial phases of wound healing. The events of early wound healing reflect a finely balanced environment leading to uncomplicated and rapid wound healing. Chronic wounds, for many reasons, have lost this fine balance. Multiple studies have evaluated the effect that exogenously applied growth factors have on the healing of chronic wounds. In the study conducted by Knighton and colleagues, topical application of mixture of various growth factors (*PDGF, TGF-beta, PDAF, PF4, PDEGF*) demonstrated increased wound healing over controls. Brown and associates demonstrated a decrease in skin graft donor site healing time of 1 day using topically applied EGF. Herndon and ass. used systemic growth hormone in burned children and reduction in healing time made a significant clinical difference by allowing earlier wound coverage and decreasing the duration of hospitalization. The TGF family of growth factors is believed to be primarily responsible for excessive scar formation, especially the beta 1 and beta 2 isoforms. TGF-beta 3 isoform has recently been described and may have an inhibitory function on scar formation by being a natural antagonist to the TGF-beta 1 and TGF-beta 2 isoforms. Cytokines, especially *interferon-alpha (INF-alpha), INF-alpha, and INF-alpha 2b,* may also reduce scar formation. These cytokines decrease the proliferation rate of fibroblasts and reduce the rate of collagen and fibronectin synthesis by reducing the production of mRNA. Expression of nitric oxide synthase (NOS) and

heat shock proteins (HSP) have an important role in wound healing, as well as trace elements (zinc, copper, manganese). Applications of some drugs (antioxidants—asiaticoside, vitamin E and ascorbic acid; calcium D-pantothenate, exogenous fibronectin; antileprosy drugs—oil of hydnocarpus; alcoholic extract of yeast) accelerate wound healing. Thymic peptide thymosin beta 4 (T beta 4R) topically applied, increases collagen deposition and angiogenesis and stimulates keratinocyte migration. Thymosin alpha 1 (T alpha 1R), peptide isolated from the thymus, is a potent chemoattractant which accelerates angiogenesis and wound healing. On the contrary, steroid drugs, hemorrhage and denervation of wounds have negative effect on the healing process.

Med Pregl 2000 Jul-Aug;53(7-8):363-8

Thymosin beta 4 is a shared antigen between lymphoid cells and oligodendrocytes of normal human brain.

In the normal human brain, immunoreactive thymosin beta 4, a well-characterized thymic extract, was demonstrated specifically in the cell bodies and processes of a subset of interfascicular and satellite oligodendrocytes with their stained processes terminating around myelin sheaths. Antisera directed against two other thymic polypeptides, thymosin alpha 1 and alpha 7, did not react. In lymphoid tissues, thymosin beta 4 was present in macrophages, Langerhans' cells of the skin, and the interdigitating cells of the thymus. Thus, a subset of oligodendrocytes shares a common antigen of thymic origin with the reticular-dendritic and phagocytic lymphoid cells—all Ia+ immunocompetent cells that participate in the presentation of antigens to T cells. The subset of thymosin beta 4-positive oligodendrocytes is antigenically distinct and may play a role in the immune surveillance of the central nervous system or the demyelinating processes induced by antigen-presenting activated macrophages.

Ann Neurol 1986 Apr;19(4):349-55

Biochemical and antibacterial analysis of human wound and blister fluid.

Fluid from a post-operative wound, six leg ulcers and a large blister were collected and analysed by biochemical, microbiological and immunological techniques. The results were compared with those from sera. All samples were lyophilized and extracted twice with 60% aqueous acetonitrile containing 1% trifluoroacetic acid. The pooled supernatants were lyophilized, redissolved, and the fluid extracts were characterized by six techniques (the blister exudate only with three): reverse-phase HPLC, Edman degradation, mass spectrometry, Western blot analysis, inhibition zone assay on plates with *Bacillus megaterium* (anti-Bm activity) and zone clearing on plates with cell walls from *Micrococcus luteus* (a lysozyme assay). The material corresponding to HPLC peaks of the wound fluid extract was identified as: histone H2B fragments 1-11, 1-15 and 1-16, intact thymosin beta-4, defensins HNP1, 2 and 3, lysozyme and the peptide antibiotic FALL-39 and its precursor(s). The HPLC-separated blister fluid was extremely rich in anti-Bm activity (mainly defensins) and lysozyme. It may also contain factors not identified before. The plate assays scored 50-fold differences in anti-Bm activities and more than 10-fold differences in lysozyme, factors which together with thymosin could be active in wound healing. It is concluded that analysis of wound fluid yields peptide and activity patterns with novel fragments of important peptides, and quantitative differences, that can be useful to understand molecular mechanisms of wound healing further.

Eur J Biochem 1996 Apr 1;237(1):86-92

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