Drug-Herb/Drug-Nutrient Interactions & Depletions

Mario Roxas, ND

ACHS 2010

Portland, OR

144 million

Source: Health, United States, 2009, table 95
http://www.cdc.gov/nchs/data/hus/hus09.pdf#095

$287

billion

Source: Consumer Reports
http://www.consumerreports.org/health/prescription-drugs/best-drugs-for-less/overview/best-drugs-for-less.htm

$9.4 billion

Source: Nutritional Supplements in the U.S., 4th Edition
http://www.packagedfacts.com/Nutritional-Supplements-Edition-2642045/

Top 20 Prescription Drugs in 2009

in units sold

1. Lipitor
2. Nexium
3. Plavix
4. Singulair
5. Lexapro
6. Pro-Air HFA
7. Synthroid
8. Crestor
9. Advair Diskus
10. Diovan
11. Cymbalta
12. Effexor XR
13. Klor-Con
14. Prevacid
15. Diovan HCT
16. Actos
17. Flomax
18. Seroquel
19. Levaquin
20. Tricor

(http://www.drugs.com/top200_units.html)

Lipitor (atorvastatin)/ **Crestor** (rosuvastatin)

Clinical Indication:

- Cholesterol-lowering medication

Action:

- Inhibits HMG CoA Reductase

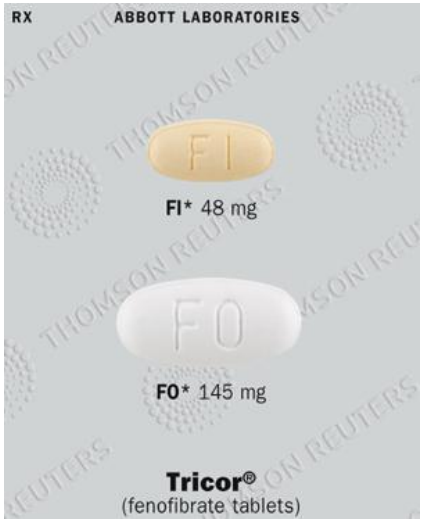
Tricor
(fenofibrate)

Clinical Indication:

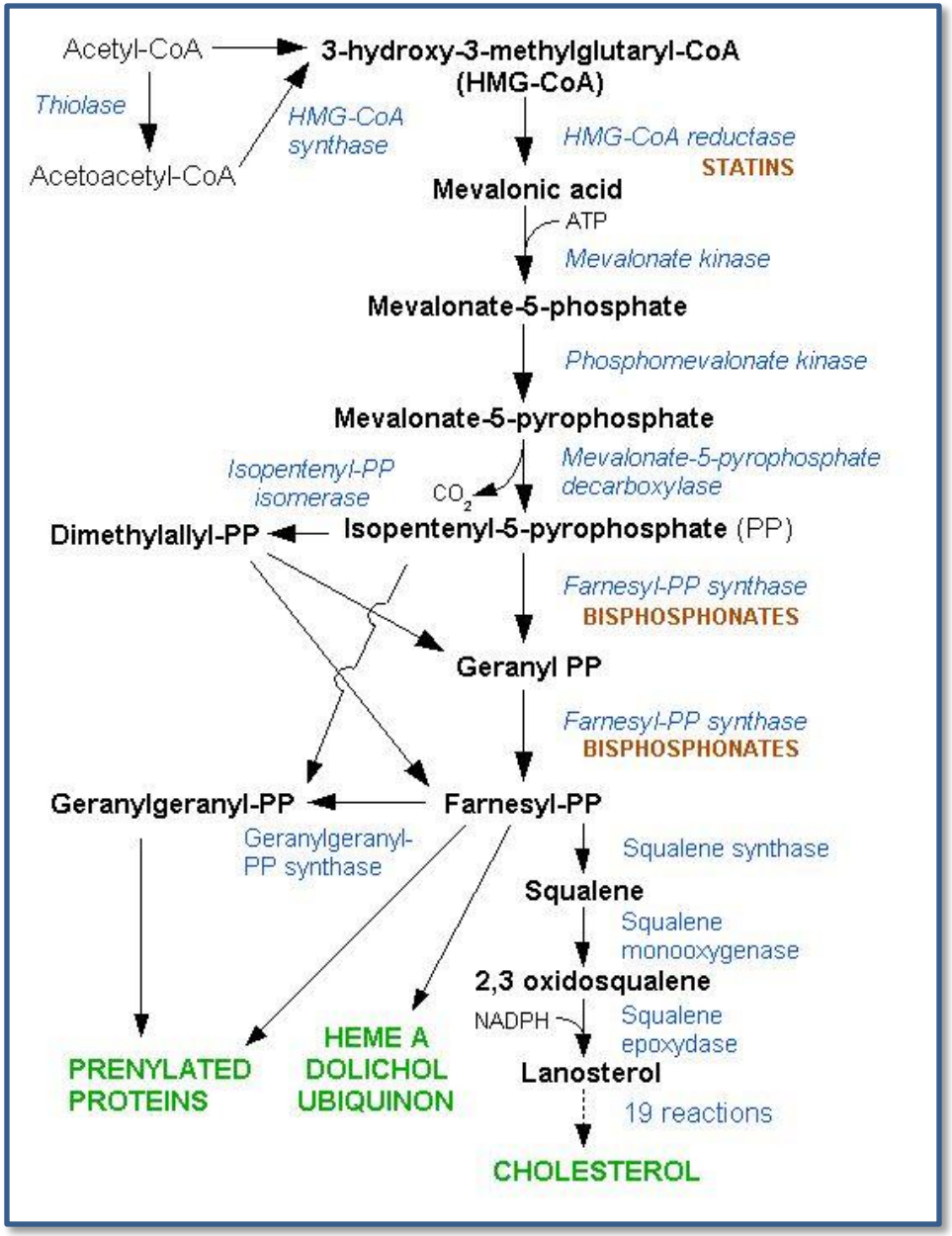
- Cholesterol-lowering medication

Action:

- Fibrate – Peroxisome proliferator-activated receptor alpha (PPAR-α) agonist

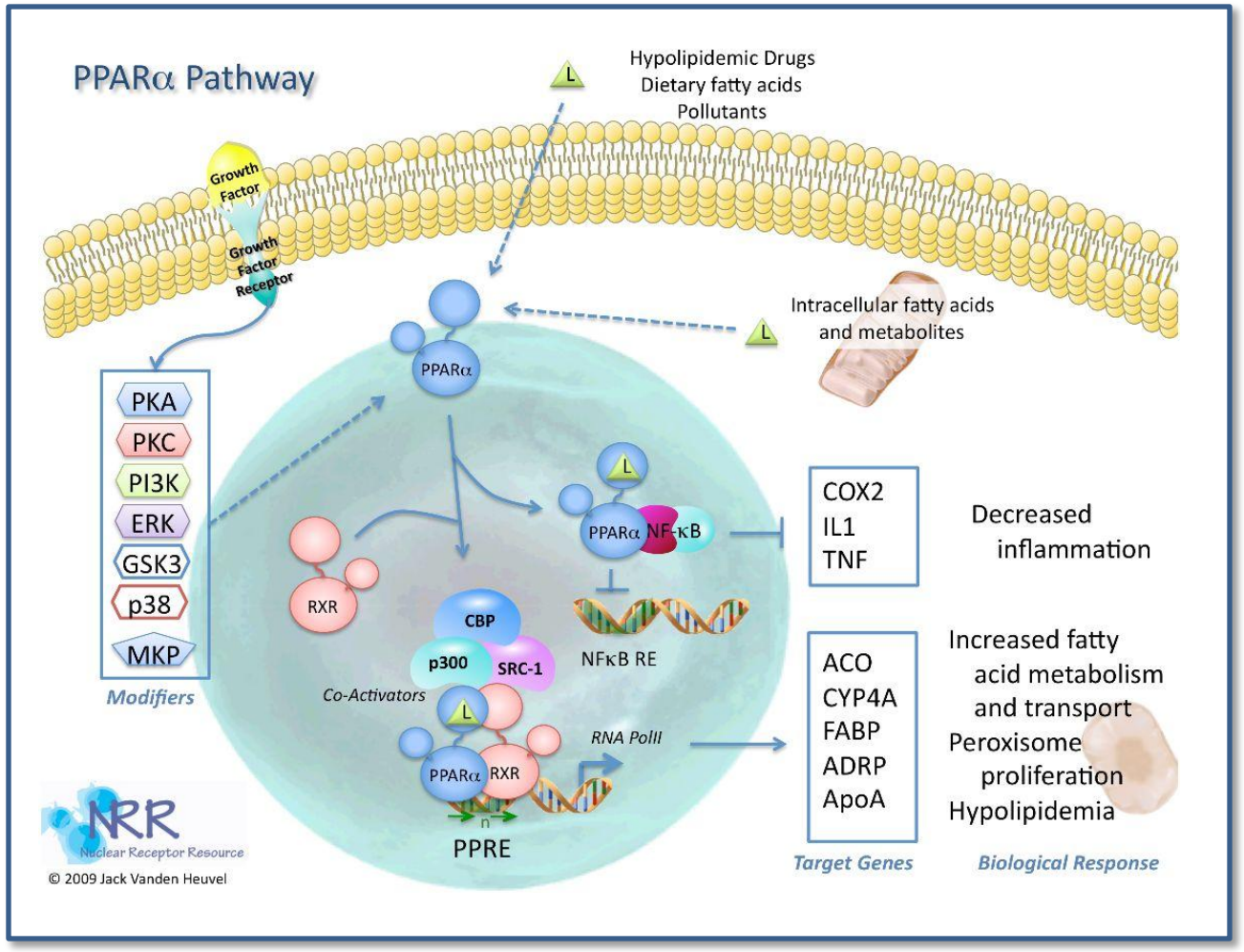


HMG-CoA Reductase Pathway



Source: [en:Image:HMG-CoA_reductase_pathway.png]

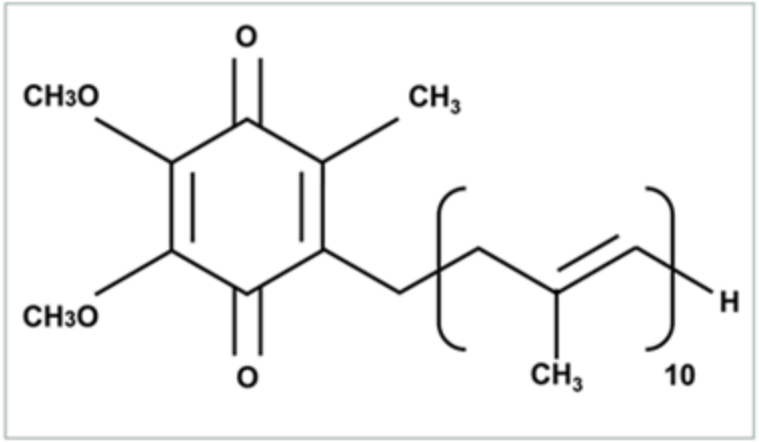
PPAR-alpha Pathway



CoQ10

Nutrient Depletion:

- **Coenzyme Q10**
  - Decreases CoQ10 serum levels
  - Consider supplementation w/ CoQ10
  - 100 mg/day prevented Q10 drop



Structure of CoQ10

Statins can reduce serum levels of coenzyme Q_{10} by up to 40%.

J Clin Pharmacol. 1993 Mar;33(3):226-9.

Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study.

Ghirlanda G, Oradei A, Manto A, Lippa S, Uccioli L, Caputo S, Greco AV, Littarru GP.

Institute of Internal Medicine, Catholic University Medical School, Rome, Italy.

Abstract

Inhibitors of HMG-CoA reductase are new safe and effective cholesterol-lowering agents. Elevation of alanine-amino transferase (ALT) and aspartate-amino transferase (AST) has been described in a few cases and a myopathy with elevation of creatinine kinase (CK) has been reported rarely. The inhibition of HMG-CoA reductase affects also the biosynthesis of ubiquinone (CoQ10). We studied two groups of five healthy volunteers treated with 20 mg/day of pravastatin (Squibb, Italy) or simvastatin (MSD) for a month. Then we treated 30 hypercholesterolemic patients in a double-blind controlled study with pravastatin, simvastatin (20 mg/day), or placebo for 3 months. At the beginning, and 3 months thereafter we measured plasma total cholesterol, CoQ10, ALT, AST, CK, and other parameters (urea, creatinine, uric acid, total bilirubin, gamma GT, total protein). Significant changes in the healthy volunteer group were detected for total cholesterol and CoQ10 levels, which underwent about a 40% reduction after the treatment. The same extent of reduction, compared with placebo was measured in hypercholesterolemic patients treated with pravastatin or simvastatin. Our data show that the treatment with HMG-CoA reductase inhibitors lowers both total cholesterol and CoQ10 plasma levels in normal volunteers and in hypercholesterolemic patients. CoQ10 is essential for the production of energy and also has antioxidative properties. A diminution of CoQ10 availability may be the cause of membrane alteration with consequent cellular damage.

PMID: 8463436 [PubMed - indexed for MEDLINE]

Lipitor (atorvastatin)/ **Crestor** (rosuvastatin)

Nutrient Interaction:

- **Niacin:**
  - Concomitant use may increase potential for myopathies
- **L-Arginine:**
  - Coadministration may enhance triglyceride-lowering effect
- **Vitamin A:**
  - Higher blood vitamin A levels found in individuals taking HMG CoA reductase inhibitors for 2 years
  - Unknown mechanism (hepatic storage?)
- **Vitamin D:**
  - Deficiency may increase risk of myalgia

Statins and Niacin

Am J Cardiol. 2010 Feb 15;105(4):487-94. Epub 2009 Nov 13.

Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia.

Fazio S, Guyton JR, Polis AB, Adewale AJ, Tomassini JE, Ryan NW, Tershakovec AM.

Division of Cardiovascular Medicine, Vanderbilt University, Nashville, Tennessee, USA.
sergio.fazio@vanderbilt.edu

Abstract

The safety and efficacy of combination ezetimibe/simvastatin (E/S) plus extended-release niacin was assessed in 942 patients with type IIa/IIb hyperlipidemia for 64 weeks in a randomized, double-blind study. Patients received E/S (10/20 mg) plus niacin (to 2 g) or E/S (10/20 mg) for 64 weeks, or niacin (to 2 g) for 24 weeks and then E/S (10/20 mg) plus niacin (2 g) or E/S (10/20 mg) for an additional 40 weeks. The primary end point, the safety of E/S plus niacin, included prespecified adverse events (ie, liver, muscle, discontinuations due to flushing, gallbladder-related, cholecystectomy, fasting glucose changes, new-onset diabetes). The secondary end points included the percentage of change from baseline in high-density lipoprotein (HDL) cholesterol, triglycerides, non-HDL cholesterol, and low-density lipoprotein cholesterol, other lipids, lipoprotein ratios and high-sensitivity C-reactive protein. The anticipated niacin-associated flushing led to a greater rate of study discontinuations with the E/S plus niacin regimen than with E/S alone (0.7%, p <0.001). The rate of liver and muscle adverse events was low (<1%) in both groups. Four patients had gallbladder-related adverse events; 1 patient in the E/S and 1 in the E/S plus niacin group underwent cholecystectomy. The occurrence of new-onset diabetes was 3.1% for the E/S and 4.9% for the E/S plus niacin group. The fasting glucose levels increased to greater than baseline during the first 12 weeks (E/S, 3.2 mg/dl; E/S plus niacin, 7.7 mg/dl) and gradually decreased to pretreatment levels by 64 weeks in both groups. E/S plus niacin significantly improved HDL cholesterol, triglycerides, non-HDL cholesterol, low-density lipoprotein cholesterol, apolipoprotein B and A-I, and lipoprotein ratios compared with E/S (p <or=0.004). The changes in high-sensitivity C-reactive protein were comparable for both groups. In

Statins and Niacin

J Neurol Sci. 2010 Jul 15;294(1-2):107-11. Epub 2010 May 7.

Combination treatment of experimental stroke with Niaspan and Simvastatin, reduces axonal damage and improves functional outcome.

Shehadah A, Chen J, Cui X, Roberts C, Lu M, Chopp M.

Department of Neurology, Henry Ford Health Sciences Center, Detroit, MI, 48202, USA.

Abstract

In this study we examined the effect of combination treatment of experimental stroke with Niaspan, a prolonged-release formulation of Niacin (vitamin B3), and Simvastatin, a cholesterol-lowering drug, on functional outcome, axonal damage, axonal density and the of Iba-1 immunoreactive microglia expression in the ischemic brain of rats. Adult male rats were subjected to 2 h middle cerebral artery occlusion (MCAo) and treated with or without Niaspan alone, Simvastatin alone and combination Niaspan and Simvastatin starting 24 h after MCAo and daily for 14 days. Neurological functional tests were performed. Axonal damage and density were evaluated by Amyloid Precursor Protein (APP) and Bielschowsky silver, respectively. Nogo66 Receptor (NgR) expression and immunoreactive microglia (Iba-1) were also measured in the ischemic brain. Niaspan and Simvastatin monotherapy and combination treatment significantly promote functional outcome after stroke ($p<0.05$) compared to MCAo control animals. Combination treatment with Niaspan and Simvastatin induces additive but not synergetic effects when compared to Niaspan or Simvastatin monotherapy groups. Combination treatment significantly decreased APP expression and increased Bielschowsky silver expression. NGR and Iba-1 expression were significantly decreased in the ischemic brain. These data suggest that treatment of experimental stroke with combination of Niaspan and Simvastatin significantly improves functional outcome, reduces axonal damage and increases axonal density. Decreased expression of the NGR and reduced activated microglia may contribute to functional recovery after stroke.

PMID: 20451219 [PubMed - in process] PMCID: PMC2885546 [Available on 2011/7/15]

Statins and L-Arginine

L-Arginine enhances the triglyceride-lowering effect of simvastatin in patients with elevated plasma triglycerides

Friedrich Schulze[a], Sabrina Glos[b], Dörte Petruschka[a], Christiane Altenburg[b], Renke Maas[c], Ralf Benndorf[a], Edzard Schwedhelm[a], Ulrich Beil[b], Rainer H. Böger[a,*]

[a]*Center for Experimental Medicine, Institute for Experimental and Clinical Pharmacology, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany*

[b]*Department of Internal Medicine III, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany*

[c]*Institute for Experimental and Clinical Pharmacology and Toxicology, University Erlangen-Nuremberg, 91054 Erlangen, Germany*

Received 1 April 2009; revised 29 April 2009; accepted 30 April 2009

Low Vitamin D a Cause of Statin-induced Myositis-Myalgia?

Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients

WAQAS AHMED, NASEER KHAN, CHARLES J. GLUECK, SUMAN PANDEY, PING WANG, NAILA GOLDENBERG, MUHAMMAD UPPAL, and SURAJ KHANAL

CINCINNATI, OHIO

AT A GLANCE COMMENTARY

Background

Low serum 25 (OH) vitamin D has been associated with myositis. Myositis is common in statin-treated subjects to promote statin intolerance.

Translational Significance

The current report revealed that patients with statin-induced myalgias had lower serum vitamin D levels than statin-treated patients without myalgias. Low serum 25 (OH) vitamin D (D2 + D3) (<32 ng/mL) is associated with myalgia in statin-treated patients; while continuing statins, this myalgia can largely be reversed by vitamin D supplementation that normalizes serum vitamin D levels. We speculate that vitamin D deficiency reversibly augments statin-induced myalgias.

erum 25 (OH) vitamin D (D2 + D3)
treated patients and whether the
entation while continuing statins.
r supplemental vitamin D, serum
ents, which consisted of 128 pa-
patients. The 128 myalgic patients
itamin D than the 493 asymptom-
< 0.0001), but they did not differ
abetes, or creatine kinase levels.
e, sex, and age, the least square
ower in the 128 patients with my-
8.7 ± 1.2 vs 34.3 ± 0.6 ng/mL,
4%) patients with myalgia versus
, $P < 0.0001$). Of the 82 vitamin-
tatins, 38 were given vitamin D
ncrease in serum vitamin D from
esolution of myalgia in 35 (92%).
treated patients with concurrent
raction between vitamin D defi-
al Research 2009;153:11–16)

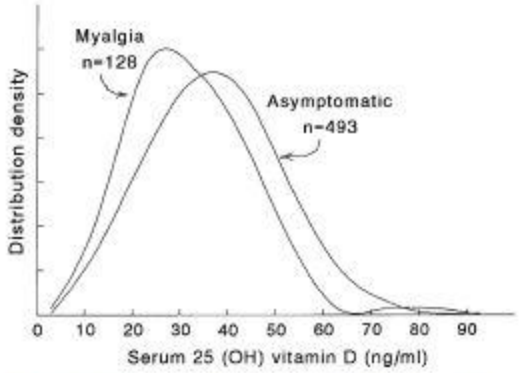


Fig 2. Distributions of serum 25 OH vitamin D in 128 statin-treated patients with myalgia at study entry and in 493 statin-treated asymptomatic patients.

Tricor
(fenofibrate)

Nutrient Interaction:

- CoQ10
  - May deplete natural stores
  - Concurrent supplementation may be beneficial
- Vitamin E
  - May deplete natural stores in liver

Tricor (fenofibrate) and CoQ10

European Journal of Clinical Nutrition (2002) 56, 1137–1142

0954–3007/02 $25.00
www.nature.com/ejcn

ORIGINAL COMMUNICATION

Coenzyme Q_{10} improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes

JM Hodgson[1], GF Watts[1]*, DA Playford[2], V Burke[1] and KD Croft[1]

[1]*University of Western Australia Department of Medicine and HeartSearch, Royal Perth Hospital, Perth, Western Australia, Australia; and* [2]*Department of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia*

Objective: Our objective was to assess effects of dietary supplementation with coenzyme Q_{10} (CoQ) on blood pressure and glycaemic control in subjects with type 2 diabetes, and to consider oxidative stress as a potential mechanism for any effects.
Subjects and design: Seventy-four subjects with uncomplicated type 2 diabetes and dyslipidaemia were involved in a randomised double blind placebo-controlled 2×2 factorial intervention.
Setting: The study was performed at the University of Western Australia, Department of Medicine at Royal Perth Hospital, Australia.
Interventions: Subjects were randomly assigned to receive an oral dose of 100 mg CoQ twice daily (200 mg/day), 200 mg fenofibrate each morning, both or neither for 12 weeks.
Main outcome measures: We report an analysis and discussion of the effects of CoQ on blood pressure, on long-term glycaemic control measured by glycated haemoglobin (HbA_{1c}), and on oxidative stress assessed by measurement of plasma F_2-isoprostanes.
Results: Fenofibrate did not alter blood pressure, HbA_{1c}, or plasma F_2-isoprostanes. There was a 3-fold increase in plasma CoQ concentration ($3.4 \pm 0.3\,\mu mol/l$, $P < 0.001$) as a result of CoQ supplementation. The main effect of CoQ was to significantly decrease systolic (-6.1 ± 2.6 mmHg, $P = 0.021$) and diastolic (-2.9 ± 1.4 mmHg, $P = 0.048$) blood pressure and HbA_{1c} ($-0.37 \pm 0.17\%$, $P = 0.032$). Plasma F_2-isoprostane concentrations were not altered by CoQ (0.14 ± 0.15 nmol/l, $P = 0.345$).
Conclusions: These results show that CoQ supplementation may improve blood pressure and long-term glycaemic control in

Tricor (fenofibrate) and vitamin E

Biochim Biophys Acta. 1997 May 24;1360(3):222-8.

Chemiluminescence and antioxidant levels during peroxisome proliferation by fenofibrate.

Lores Arnaiz S, Travacio M, Monserrat AJ, Cutrín JC, Llesuy S, Boveris A.

National Laboratory of Free Radical Biology, School of Pharmacy and Biochemistry, University of Buenos Aires, Argentina.

Abstract

Fenofibrate, the hypolipidemic drug and peroxisome proli
diet) during 1-3 weeks and H2O2 and TBARS steady state
and antioxidant levels were measured. Administration of f
increase of 89% in H2O2 steady state concentration. Spo
decreased by 57% during fenofibrate treatment, while no
concentration. Hydroperoxide-initiated chemiluminescenc
fenofibrate treatment, probably due to an increase in endo
glutathione increased gradually after fenofibrate administ
and 58% respectively, after 22 days of treatment. An increa
treated mice, as compared with the controls. alpha-tocopl
liver of fenofibrate-treated mice. According to our findings,
with peroxisome proliferation, would not lead to an increa
explained by the presence of high levels of ubiquinols, wh
production of H2O2, would lead to DNA damage directly, a

Photodermatol Photoimmunol Photomed. 1997 Oct-Dec;13(5-6):173-7.

Phototoxic lysis of erythrocytes from humans is reduced after oral intake of ascorbic acid and d-alpha-tocopherol.

Eberlein-König B, Placzek M, Przybilla B.

Dermatologische Klinik und Poliklinik, Ludwig-Maximilians-Universität München, Germany.

Abstract

Ultraviolet (UV) radiation causes hemolysis of human erythrocytes in the presence of photosensitizers. This can be used as an in vitro model for evaluating photosensitizing properties of substances. Antioxidants such as ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E) have been found to be photoprotective in such test systems. We assessed the effect of combined systemic intake of both ascorbic acid and d-alpha-tocopherol by human volunteers on phototoxic in vitro lysis of their erythrocytes. In a double-blind placebo-controlled study, 10 subjects took daily 2 g ascorbic acid combined with 1000 IU d-alpha-tocopherol, and 10 took a placebo. Blood was taken before and after 7 days of treatment, erythrocytes were prepared and then incubated with 10(-3) mol/l fenofibrate, a photosensitizer acting in the UVA and UVB region. The suspensions were exposed to radiation rich in UVA (up to 40 J/cm2 UVA) or to radiation rich in UVB (up to 1.6 J/cm2). Photohemolysis of the samples was calculated as a percentage of complete hemolysis. At the end of the treatment phase, in the placebo group photohemolysis was not significantly reduced compared with the initial values at all irradiation doses except for 1.6 J/cm2 UVB (96% vs 79%; $P < 0.01$). In the group taking vitamins, photohemolysis was significantly reduced at nearly all UV doses, most impressively after moderate UVA irradiation (20 J/cm2 UVA: 86.5% vs 14.5%; $P < 0.01$). It is concluded that the results of the photohemolysis test are influenced by the antioxidative status of the cell donor and that ascorbic acid and d-alpha-tocopherol also may protect against phototoxic damage in vivo.

Red Yeast Rice

(*Monascus purpureus*)

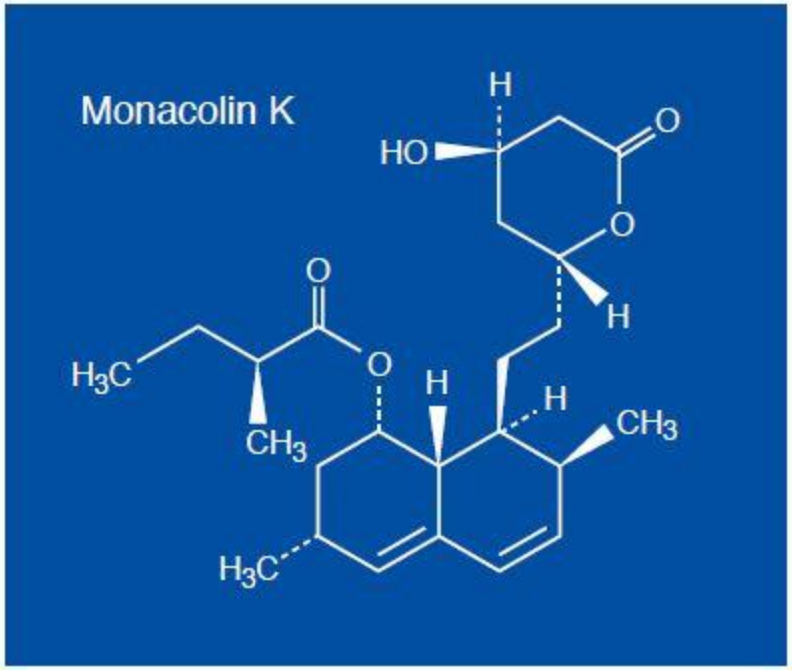
Monacolin K (aka mevinolin)**:**

The HMG-CoA reductase activity of red yeast rice comes from a family of naturally occurring substances called monacolins.

Monacolin K is the ingredient in red yeast rice that Merck & Co., pharmaceutical manufacturer of Mevacor, (lovastatin), asserts is a patented pharmaceutical.

However, red yeast rice contains a family of nine different monacolins, all of which have the ability to inhibit HMG-CoA reductase.

Other active ingredients in red yeast rice include sterols (betasitosterol, campesterol, stigmasterol, sapogenin), isoflavones, and monounsaturated fatty acids.



Simvastatin vs Therapeutic Lifestyle Changes and Supplements: Randomized Primary Prevention Trial

David J. Becker, MD; Ram Y. Gordon, MD; Patti B. Morris, RD; Jacqueline Yorko, MEd; Y. Jerold Gordon, MD; Mingyao Li, PhD; and Nayyar Iqbal, MD, MSCE

CONCLUSION: **Lifestyle changes combined with ingestion of red yeast rice and fish oil reduced LDL-C in proportions similar to standard therapy with simvastatin. Pending confirmation in larger trials, this multifactorial, alternative approach to lipid lowering has promise for a subset of patients unwilling or unable to take statins.**

Lipid-Lowering Efficacy of Red Yeast Rice in a Population Intolerant to Statins

Carmelo V. Venero, MD[a], Jose V. Venero, MD[b], Dale C. Wortham, MD[a], and Paul D. Thompson, MD[c,d,*]

Chinese red yeast rice is a dietary supplement containing monacolins, unsaturated fatty acids, and phytosterols capable of lowering low-density lipoprotein (LDL) cholesterol. Few studies have reported on its use in clinical practice or in statin-intolerant patients. We reviewed approximately 1,400 clinical charts and identified 25 patients treated with red yeast rice for ≥4 weeks. The patients were included if they had pre- and post-treatment lipid levels without simultaneous changes in other lipid-lowering medications. These patients had experienced myalgias (68%), gastrointestinal intolerance (16%), and/or elevated alanine aminotransferase levels (8%) with previous use of other lipid-lowering agents. The total cholesterol decreased 15% (−37 ± 26 mg/dl, $p < 0.001$) and LDL cholesterol decreased 21% (−35 ± 25 mg/dl, $p < 0.001$) during 74 ± 39 days of treatment. Most (92%) patients tolerated the treatment, and many (56%) achieved their LDL cholesterol goal. In patients unable to tolerate daily statin use, the total cholesterol level decreased 13% (−33 ± 10 mg/dl, $p < 0.001$) and LDL cholesterol decreased 19% (−31 ± 4 mg/dl, $p < 0.001$). In conclusion, red yeast rice modestly decreased total and LDL cholesterol, was well-tolerated, and was an acceptable alternative in patients intolerant of other lipid-lowering medications. (Am J Cardiol 2010; 105:664–666)

Tolerability of Red Yeast Rice (2,400 mg Twice Daily) Versus Pravastatin (20 mg Twice Daily) in Patients With Previous Statin Intolerance

Steven C. Halbert, MD[a,e], Benjamin French, PhD[a,b], Ram Y. Gordon, MD[f], John T. Farrar, MD[a], Kathryn Schmitz, PhD[a], Patti B. Morris, RD[f], Paul D. Thompson, MD[g], Daniel J. Rader, MD[c,d], and David J. Becker, MD[f,*]

Currently, no consensus has been reached regarding the management of hyperlipidemia in patients who develop statin-associated myalgia (SAM). Many statin-intolerant patients use alternative lipid-lowering therapies, including red yeast rice. The present trial evaluated the tolerability of red yeast rice versus pravastatin in patients unable to tolerate other statins because of myalgia. The study was conducted in a community-based setting in Philadelphia, Pennsylvania. A total of 43 adults with dyslipidemia and a history of statin discontinuation because of myalgia were randomly assigned to red yeast rice 2,400 mg twice daily or pravastatin 20 mg twice daily for 12 weeks. All subjects were concomitantly enrolled in a 12-week therapeutic lifestyle change program. The primary outcomes included the incidence of treatment discontinuation because of myalgia and a daily pain severity score. The secondary outcomes were muscle strength and plasma lipids. The incidence of withdrawal from medication owing to myalgia was 5% (1 of 21) in the red yeast rice group and 9% (2 of 22) in the pravastatin group ($p = 0.99$). The mean pain severity did not differ significantly between the 2 groups. No difference was found in muscle strength between the 2 groups at week 4 ($p = 0.61$), week 8 ($p = 0.81$), or week 12 ($p = 0.82$). The low-density lipoprotein cholesterol level decreased 30% in the red yeast rice group and 27% in the pravastatin group. In conclusion, red yeast rice was tolerated as well as pravastatin and achieved a comparable reduction of low-density lipoprotein cholesterol in a population previously intolerant to statins.
(Am J Cardiol 2010;105:198–204)

Nexium (esomeprazole)/ Prevacid (lansoprazole)

Clinical Indication:

- Hyperchlorhydria, GERD

Action:

- Proton Pump Inhibitors

Nexium (esomeprazole)/ Prevacid (lansoprazole)

Nutrient Depletion:

- Beta Carotene
- Vitamin B12
- Folates
- Calcium
- Chromium
- Copper
- Iron
- Selenium
- Zinc

Plavix
(clopidrogrel)

Clinical Indication:

- Stroke/MI Prevention

Action:

- Anti-platelet agent - Specifically inhibits $P2Y_{12}$ ADP receptors involved in platelet aggregation

Plavix
(clopidrogrel)

Nutrient Interaction/

Depletion:

- No established cases

Warfarin-induced Atherosclerosis

HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats

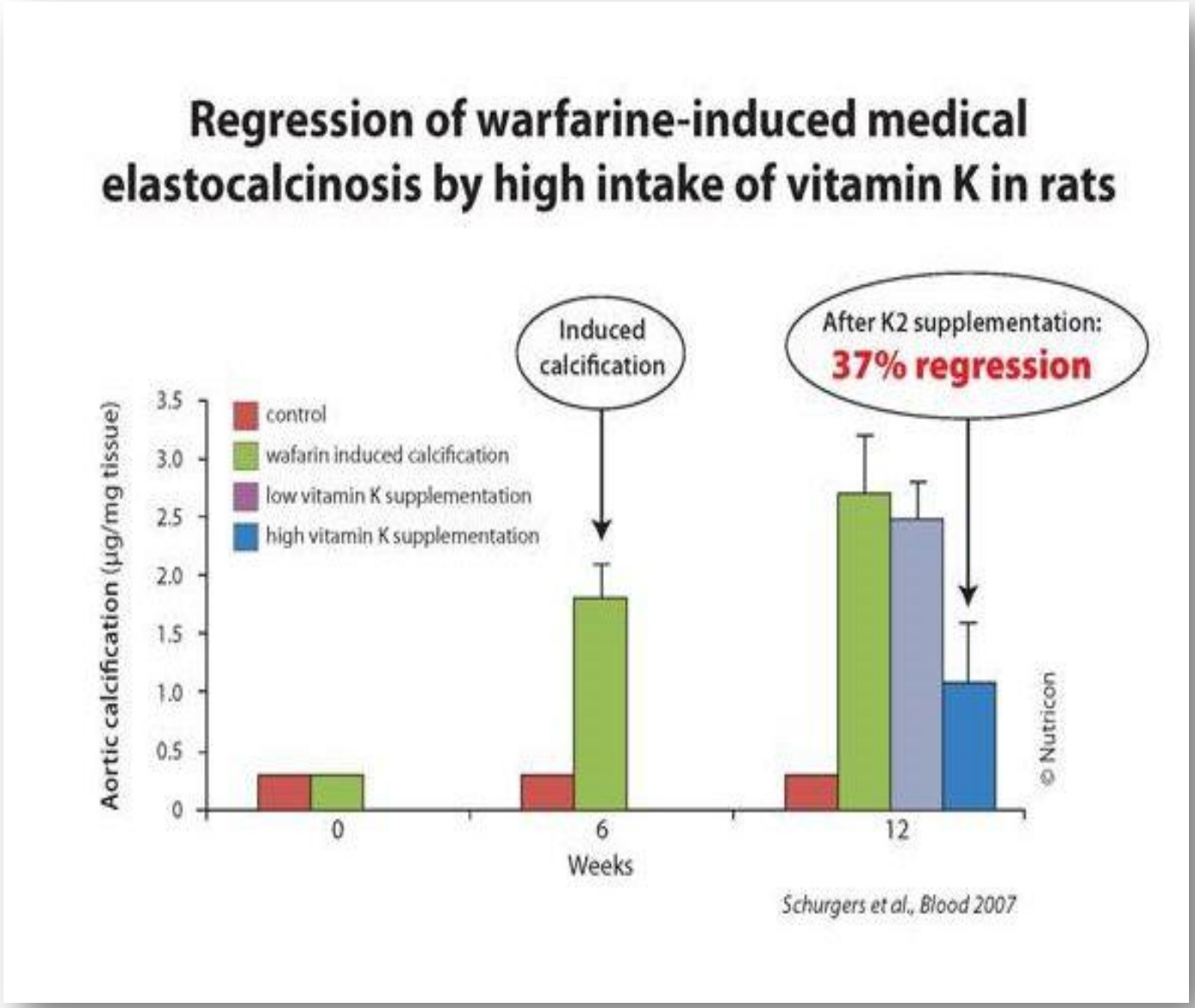
Leon J. Schurgers,[1,2] Henri M. H. Spronk,[3] Berry A. M. Soute,[1] Paul M. Schiffers,[4] Jo G. R. DeMey,[4] and Cees Vermeer[1,2]

[1]Cardiovascular Research Institute (CARIM), Maastricht University, The Netherlands; [2]VitaK, Maastricht University, The Netherlands; [3]Department of Internal Medicine, Cardiovascular Research Institute (CARIM), Maastricht University, The Netherlands; [4]Department of Pharmacology and Toxicology, Cardiovascular Research Institute (CARIM), Maastricht University, The Netherlands

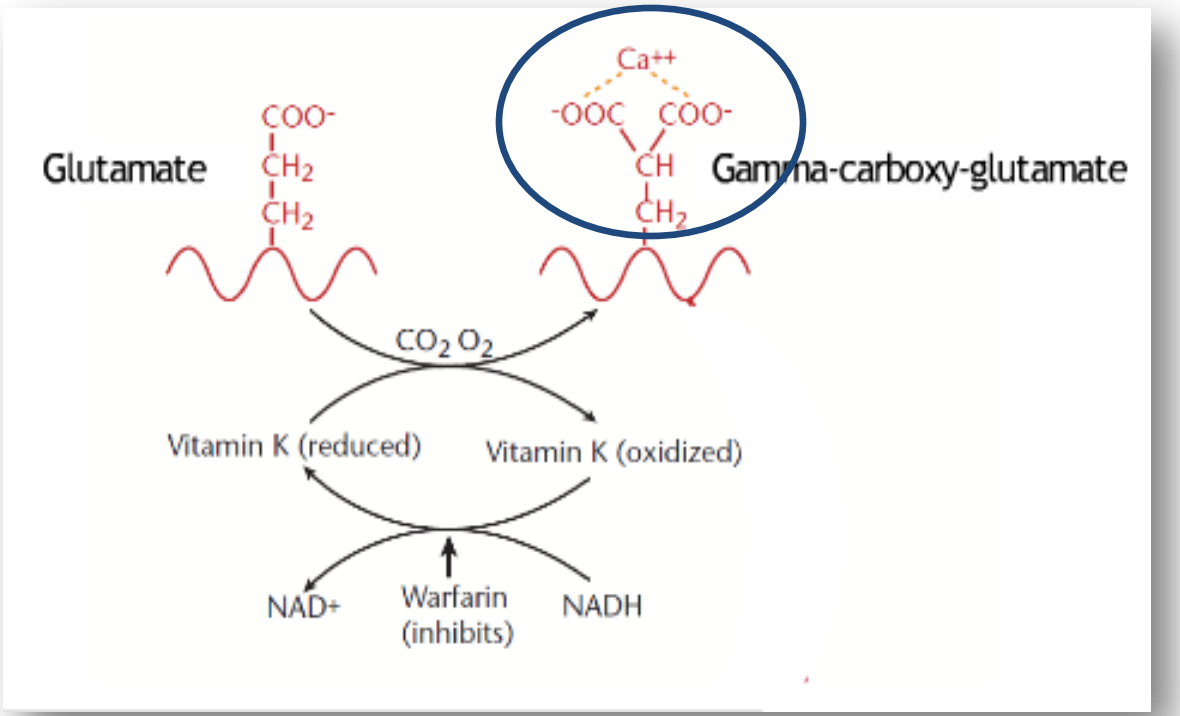
Arterial calcification (AC) is generally regarded as an independent risk factor for cardiovascular morbidity and mortality. Matrix Gla protein (MGP) is a potent inhibitor of AC, and its activity depends on vitamin K (VK). In rats, inactivation of MGP by treatment with the vitamin K antagonist warfarin leads to rapid calcification of the arteries. Here, we investigated whether preformed AC can be regressed by a VK-rich diet. Rats received a calcification-inducing diet containing both VK and warfarin (W&K). During a second 6-week period, animals were randomly assigned to receive either W&K (3.0 mg/g and 1.5 mg/g, subsequently), a diet containing a normal (5 μg/g) or high (100 μg/g) amount of VK (either K_1 or K_2). Increased aortic calcium concentration was observed in the group that continued to receive W&K and also in the group changed to the normal dose of VK and AC progressed. Both the VK-rich diets decreased the arterial calcium content by some 50%. In addition, arterial distensibility was restored by the VK-rich diet. Using MGP antibodies, local VK deficiency was demonstrated at sites of calcification. This is the first study in rats demonstrating that AC and the resulting decreased arterial distensibility are reversible by high-VK intake. (Blood. 2007; 109:2823-2831)

In rats arterial calcification was induced by warfarin and reversed by vitamin K

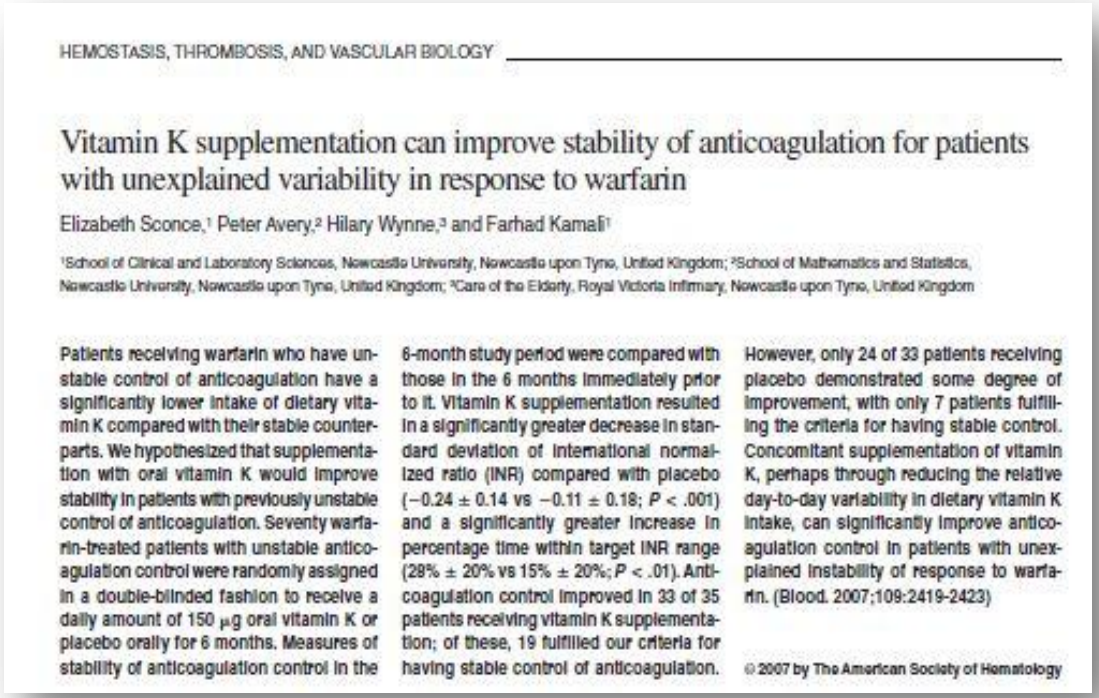
Warfarin-induced Atherosclerosis



Is Vitamin K Really Contraindicated with Warfarin?



Is Conventional Wisdom Really Wise?



HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin

Elizabeth Sconce,[1] Peter Avery,[2] Hilary Wynne,[3] and Farhad Kamali[1]

[1]School of Clinical and Laboratory Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; [2]School of Mathematics and Statistics, Newcastle University, Newcastle upon Tyne, United Kingdom; [3]Care of the Elderly, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

Patients receiving warfarin who have unstable control of anticoagulation have a significantly lower intake of dietary vitamin K compared with their stable counterparts. We hypothesized that supplementation with oral vitamin K would improve stability in patients with previously unstable control of anticoagulation. Seventy warfarin-treated patients with unstable anticoagulation control were randomly assigned in a double-blinded fashion to receive a daily amount of 150 μg oral vitamin K or placebo orally for 6 months. Measures of stability of anticoagulation control in the 6-month study period were compared with those in the 6 months immediately prior to it. Vitamin K supplementation resulted in a significantly greater decrease in standard deviation of international normalized ratio (INR) compared with placebo (−0.24 ± 0.14 vs −0.11 ± 0.18; $P < .001$) and a significantly greater increase in percentage time within target INR range (28% ± 20% vs 15% ± 20%; $P < .01$). Anticoagulation control improved in 33 of 35 patients receiving vitamin K supplementation; of these, 19 fulfilled our criteria for having stable control of anticoagulation. However, only 24 of 33 patients receiving placebo demonstrated some degree of improvement, with only 7 patients fulfilling the criteria for having stable control. Concomitant supplementation of vitamin K, perhaps through reducing the relative day-to-day variability in dietary vitamin K intake, can significantly improve anticoagulation control in patients with unexplained instability of response to warfarin. (Blood. 2007;109:2419-2423)

- **double-blind, 6-month RCT**
- **n=70 patients on warfarin with unstable anticoagulation**
- **150 mcg/day vit K or placebo**
- **K supplementation resulted in significant decrease in variation of INR**
- **K supplementation also resulted in sig. increase in % of time within target INR range**

Is Conventional Wisdom Really Wise?

Pharmacotherapy. 2005 Dec;25(12):1746-51.

Low-dose vitamin K to augment anticoagulation control.

Reese AM, Farnett LE, Lyons RM, Patel B, Morgan L, Bussey HI.

College of Pharmacy, University of Texas, Austin, and the Anticagulation Clinics of North America, San Antonio, Texas, USA. a.reese@usip.edu

STUDY OBJECTIVES: To determine the effect of daily low-dose oral vitamin K supplementation on reducing variations in the international normalized ratios (INRs) in patients taking warfarin. DESIGN: Retrospective analysis. SETTING: Anticoagulation clinic in a large, private-practice hematology group. PATIENTS: Eight motivated patients (three men, five women), aged 45-79 years, receiving anticoagulant therapy with warfarin, whose INRs had been fluctuating for reasons not associated with identifiable changes in diet, warfarin dosage, activity level, illness, or changes in drug therapy. INTERVENTION: Daily supplementation with oral vitamin K, starting with 100 microg/day MEASUREMENTS AND MAIN RESULTS: Anticoagulation providers monitored INR responses; all documented INR values were included in the analysis, even those intentionally allowed outside the therapeutic range when dosages were adjusted for procedures. After dietary vitamin K supplementation, INR fluctuations diminished in nearly all patients. Overall, a significant decrease was noted in the INR standard deviation ($p<0.05$), and more INRs were in the therapeutic range after the start of supplementation. Allowing for small fluctuations on either side of the target range, the number of INRs within 0.2 units of the target range increased from 32% to 57% (relative increase 76%). Time in range also increased by a similar degree. CONCLUSION: Supplementation with daily low-dose oral vitamin K significantly increased the number of INRs in range as well as the time in range, and decreased INR fluctuation in this small series of selected patients.

Conclusion: Small series of 8 patients poorly controlled on warfarin: 100 mcg K daily "significantly increased the number of INRs in range as well as the time in range, and decreased INR fluctuation in this small series of selected patients."

Bottom line on Vitamin K and Anticoagulants

- Wise to avoid high doses of vitamin K in patients on anticoagulant therapy.

- Low-dose – 100-150 mcg – may actually benefit patients on warfarin

- Need to do in conjunction with prescribing doctor as would need to adjust warfarin dose accordingly

Seroquel (quetiapine)

Clinical Indication:

- Schizophrenia, Bipolar Disorder, Depression

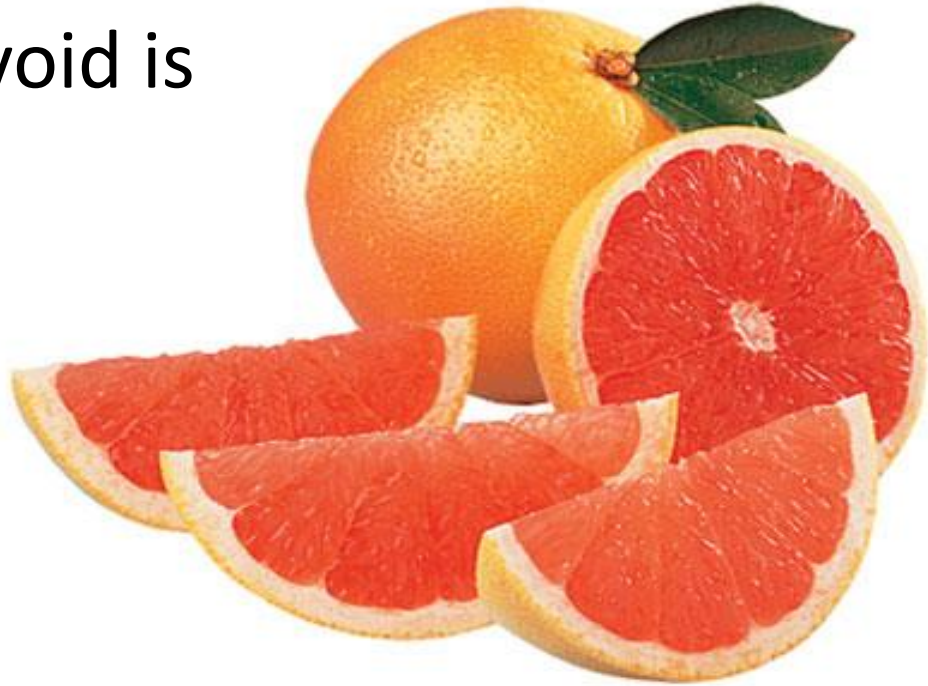
Action:

- Atypical antipsychotic

Seroquel
(quetiapine)

Nutrient Interaction/Depletion:

- No established cases
- But one food to avoid is grapefruit



Lexapro (escitalopram)/Cymbalta (duloxetine)/Effexor XR (venlafaxine)

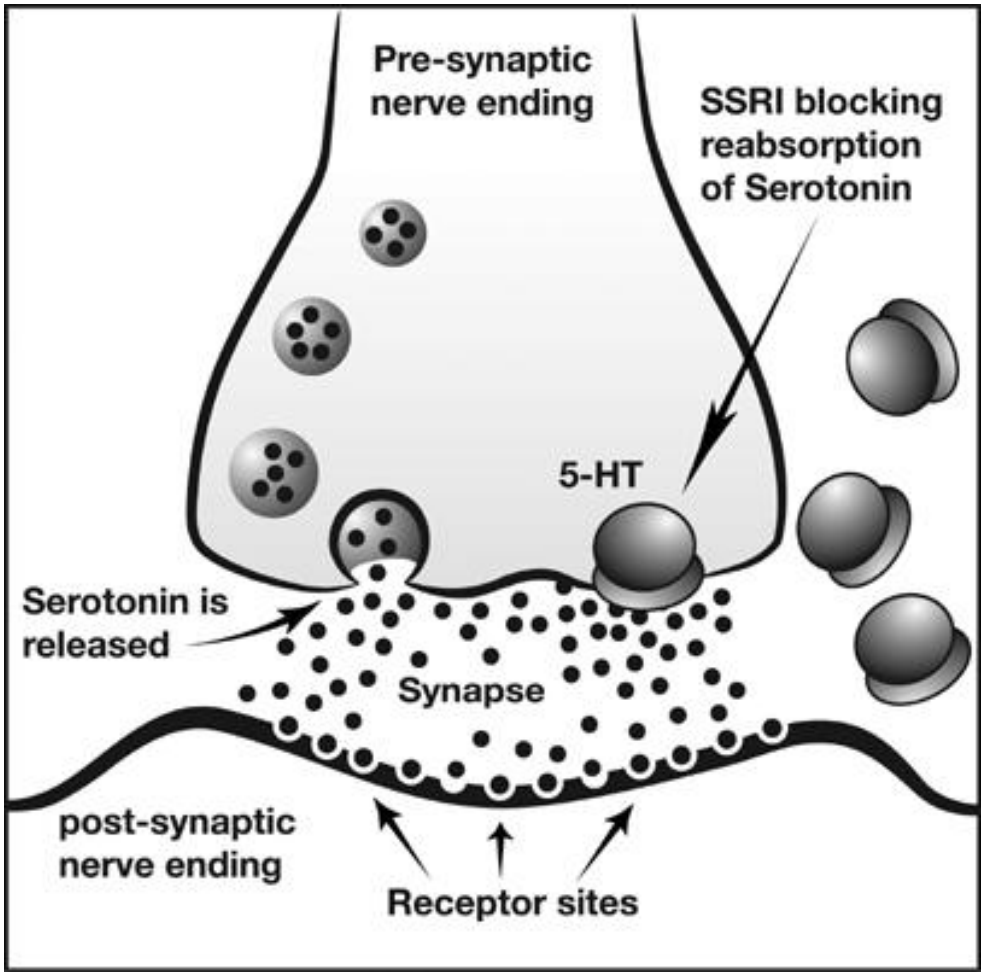
Indication:

- Depression
- Anxiety
- Peripheral neuropathy (Cymbalta)

Lexapro (escitalopram)/Cymbalta (duloxetine)/Effexor XR (venlafaxine)

Action:

- Selective Serotonin Reuptake Inhibitor (SSRI)/ Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI)



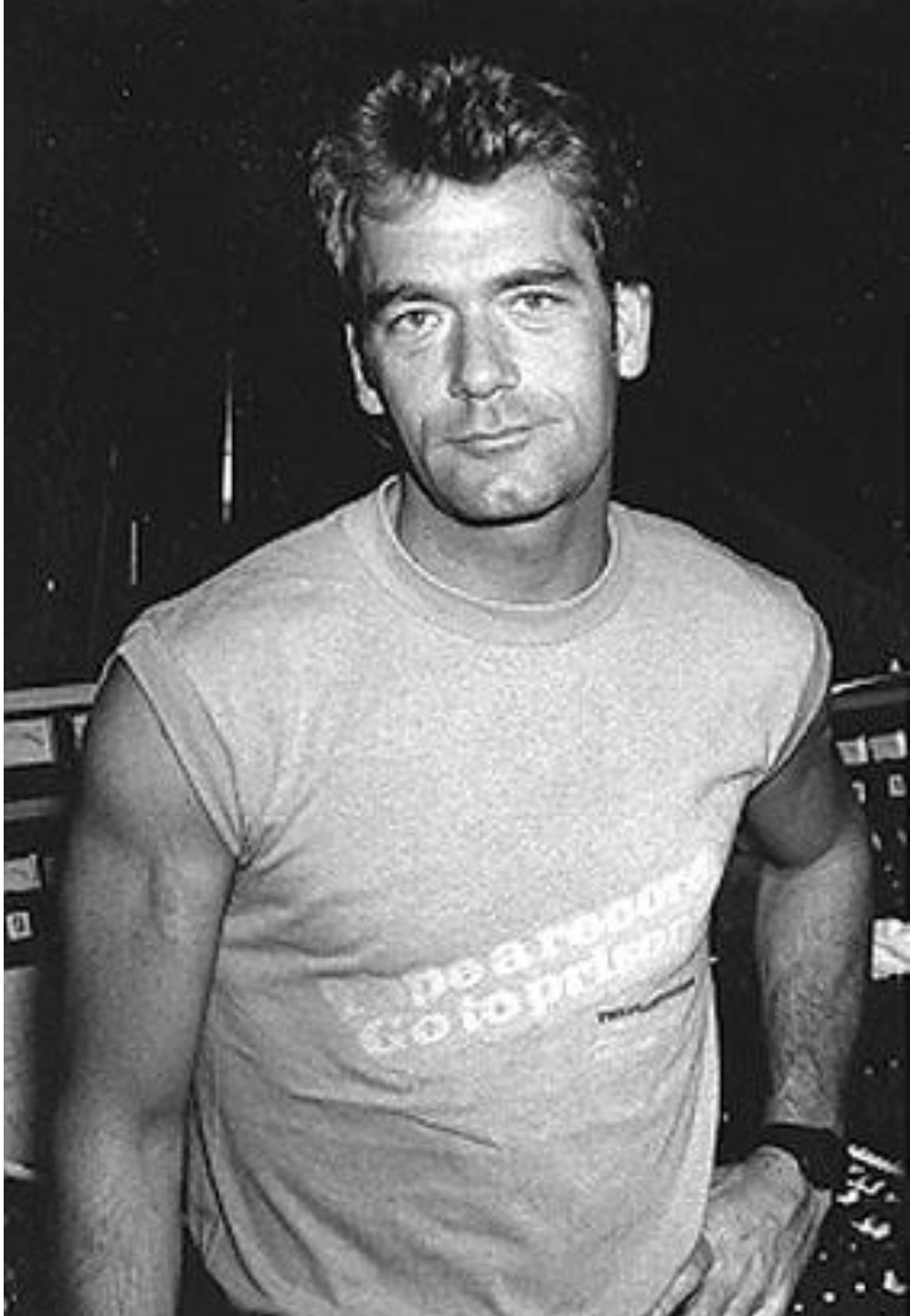
Lexapro (escitalopram)/Cymbalta (duloxetine)/Effexor XR (venlafaxine)

Herb/Nutrient Interactions:

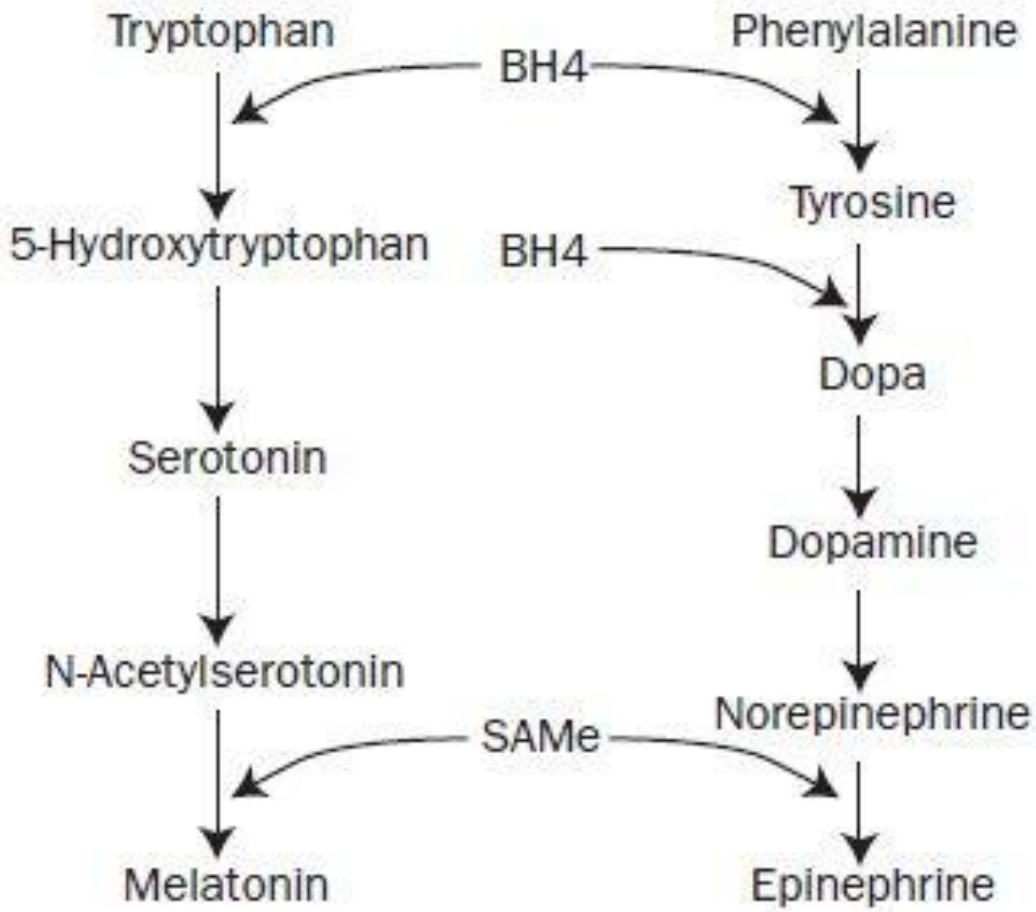
- St Johns wort
- 5-HTP/L-tryptophan
- Chromium
- Zinc
- Folate

“I want a new drug...”

- Huey Lewis



5-MTHF
(5-methyltetrahydrofolate)


Tryptophan
BH4
Phenylalanine
Tyrosine
5-Hydroxytryptophan
BH4
Dopa
Serotonin
Dopamine
N-Acetylserotonin
Norepinephrine
SAMe
Melatonin
Epinephrine

5-MTHF (5-methyltetrahydrofolate)

- J Clin Psychopharmacol. 2003 Jun;23(3):309-13.
- **Prediction of treatment response in geriatric depression from baseline folate level: interaction with an SSRI or a tricyclic antidepressant.**
- Alpert M, Silva RR, Pouget ER.
- Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, NY 10016, USA.
- **Abstract**
- Depressed geriatric patients have lower levels of folate (FOL) than controls. Also, FOL supplement can reduce depressive morbidity. One hypothesis consistent with this is that FOL deficiency causes a lowering of CNS serotonin that contributes to depression. The present report is from one site of a multicenter study that compared an SSRI (sertraline) with a nonspecific tricyclic antidepressant (nortriptyline) in geriatric depressed patients. We added measures of FOL at baseline and outcome for 22 depressed patients older than 60 years. Both treatments were effective. At baseline, FOL levels were within the normal range. Higher FOL levels at baseline predicted greater improvement. Further study of FOL interaction with SSRI is warranted. For the group treated with the SSRI, baseline FOL level was a more efficient predictor of improvement, especially for results on a self-rating depression scale (POMS).

5-MTHF (5-methyltetrahydrofolate)

Ann Clin Psychiatry. 2002 Mar;14(1):33-8.

Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression.

Alpert JE, Mischoulon D, Rubenstein GE, Bottonari K, Nierenberg AA, Fava M.
Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston 02114, USA. jalpert@partners.org

Abstract

Low folate is associated with poorer response to selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder (MDD). Folate supplementation in MDD has been studied in other settings with promising results. The objective of this study was to assess the efficacy of methylfolate as an adjunctive treatment among adults with MDD and inadequate response to an SSRI. Twenty-two adults (59% female; mean age 45.2 +/- 11.0 years) with DSM-IV MDD, partial or nonresponse to an SSRI after at least 4 weeks of treatment, and a 17-item Hamilton Depression Rating Scale (HAM-D-17) score > or = 12 were enrolled in this 8-week prospective open trial. Exclusion criteria included current use of anticonvulsants or psychotropics other than an SSRI, or B12 deficiency. Leucovorin (folinic acid), which is metabolized to methylfolate, was added to SSRIs at 15-30 mg/day. Folate levels rose from 28 +/- 19 ng/mL to 301 +/- 203 ng/mL ($p < 0.001$). HAM-D-17 scores among the 16 completers decreased from 19.1 +/- 3.9 to 12.8 +/- 7.0 ($p < 0.01$). However only 31% of completers and 27% of the intent-to-treat (ITT) sample achieved response (>

Singulair (montelukast)

Indication:

- Asthma
- Seasonal Allergies

Action:

- Leukotriene inhibitor

Singulair
(montelukast)

Nutrient Interaction/ Depletion:

- No established cases

ProAir HFA

(albuterol inhalation)

Indication:

- Asthma/COPD

Action:

- Beta-II-adrenoceptor agonist; bronchodilator

Nutrient Interaction/Depletion:

- Calcium
- Magnesium
- Potassium

Advair Diskus

(fluticasone and salmenterol)

Indication:

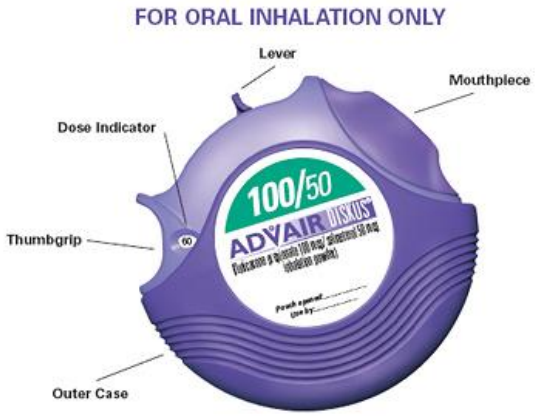
- Asthma/COPD

Action:

- Corticosteroid/beta-agonist combination inhaler for bronchodilation and anti-inflammatory support.

Nutrient Depletion:

- Calcium



Advair Diskus
(fluticasone and salmenterol)

Nutrient Depletion (cont.)**:**

- Magnseium
- Potassium
- Selenium
- Zinc
- Folate
- Vitamin C
- Vitamin D

Synthroid
(levothyroxine)

Indication:

- Hypothryoidism

Action:

- Synthetic thyroid hormone

Nutrient Interaction/Depletion:

- Iron
- Soy
- Bugleweed (*Lycopus spp.*)
- Lemon Balm (*Melissa officinalis*)

Diovan/Diovan HCT
(valsartan and hydrochlorothiazide)

Indication:

- Hypertension, CHF, post-MI

Action:

- Angiotensin II receptor agonist/ thiazide diuretic combination

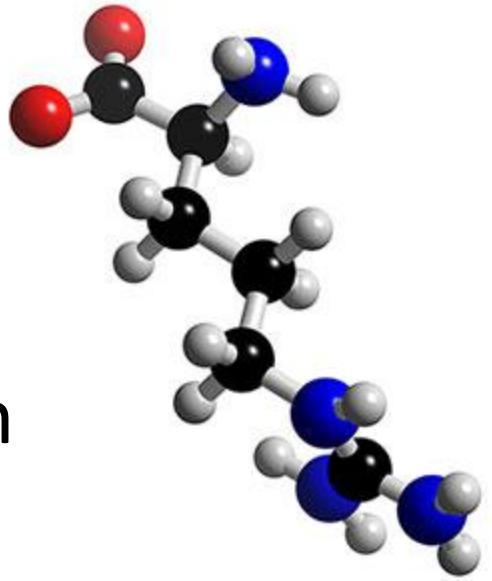
Nutrient Depletion:

- Magnesium
- Phosphorous
- Potassium
- Sodium
- Zinc

Diovan/Diovan HCT (valsartan and hydrochlorothiazide)

Nutrient Interaction:

- **L-Arginine:**
  - Co-administration may improve blood pressure in essential hypertension



Pezza V, Bernardini F, Pezza E, et al. *Am J Hypertens* 1998;11:1267-1270.

Klor-Con
(potassium hydrochloride)

Indication:

- Hypokalemia

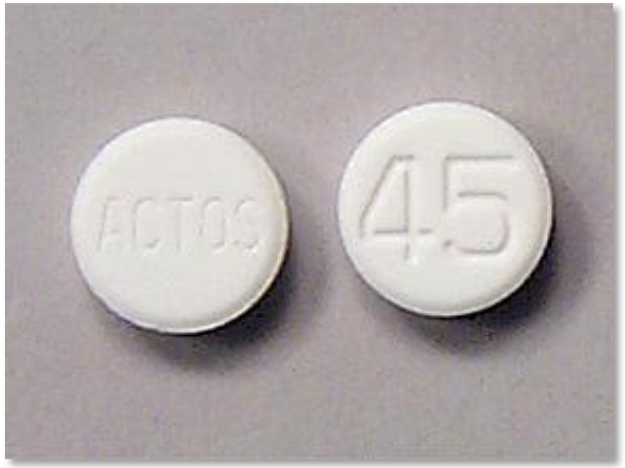
Action:

- Prevention of hypo-kalemia

Nutrient Interaction/Depletion:

- No established cases

Actos
(pioglitazone)



Indication:

- Anti-diabetic agent

Action:

- Thiazolidinedione

Nutrient Interaction/Depletion:

- No established cases

Flomax
(tamsulosin)

Indication:

- BPH

Action:

- Alpha-adrenergic blocker

Nutrient Interaction/Depletion:

- No established cases

Levaquin
(levofloxacin)

Clinical Indication:

- Antibiotic for bacterial infections of the skin, sinuses, kidneys, bladder, or prostate; also used for bronchitis, pneumonia, and anthrax

Action:

- Fluoroquinolone antibiotic

Levaquin
(levofloxacin)

Nutrient Depletion/Interactions:

- *Bifidobacterium bifidum*
- *Lactobacillus acidophilus*
- Biotin
- B Vitamins
- Calcium
- Iron
- Vitamin K
- Magnesium
- Quercetin

Levaquin (levofloxacin)

Adv Exp Med Biol. 1995;390:59-69.

A comparison of active site binding of 4-quinolones and novel flavone gyrase inhibitors to DNA gyrase.

Hilliard JJ, Krause HM, Bernstein JI, Fernandez JA, Nguyen V, Ohemeng KA, Barrett JF.

R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA.

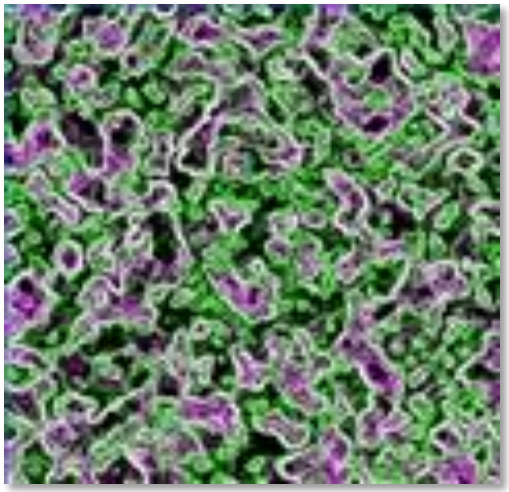
Abstract

The activity of 4-quinolone antibacterials at the enzyme target level is based on the well known and reported observations that 4-quinolone antibacterials target the Gyr A subunit of the DNA gyrase holoenzyme, inhibiting supercoiling while facilitating the "cleavable complex". Such inhibition can be observed by running the in vitro DNA gyrase supercoiling inhibition assay or the "cleavable complex" DNA gyrase assay. Although potency of the gyrase inhibitor is dependent on many factors including permeability and pharmacokinetics, the inherent potency of a gyrase inhibitor lies in its activity against the target enzyme. We have examined the binding activity of novel flavones [Bioorganic & Med. Chem. Letters 3:225-230, 1993] to Escherichia coli DNA gyrase and have found differences in binding consistent with inhibition of DNA gyrase supercoiling and ability to facilitate the cleavable complex, but of different rank order. [3H]norfloxacin was used in vitro competition studies with test compounds, pBR322 and E. coli DNA gyrase. Binding affinity results indicate the rank order of greatest to weakest binding (ability to compete with [3H]norfloxacin) of test compounds: Levofloxacin = ciprofloxacin > ofloxacin > norfloxacin > flavone compounds (including ellagic acid, quercetin, and compounds 5a through 5n [Bioorganic & Med. Chem. Letters 3:225-230, 1993]). Such differences in binding ability of the 4-quinolones and flavones to the ternary complex of DNA.DNA gyrase.drug, as compared to the catalytic inhibition and "cleavable complex" data, suggests a more complex binding of flavones than the previously hypothesized models for 4-quinolone binding.

PMID: 8718602 [PubMed - indexed for MEDLINE]

Lactobacillus sporogenes

- Spore-forming, highly stable Bacillus organism
- Also known as *Bacillus coagulans*



Saccharomyces boulardii

- a subspecies of *Saccharomyces cervesiae*
- Beneficial yeast for the GI tract

Celebrex
(celecoxib)

Indication:

- Osteoarthritis/Rheumatoid arthritis

Action:

- Sulfa non-steroidal anti-inflammatory drug (NSAID); COX-2 Inhibitor

Nutrient Depletion:

- Folate

Curcumin Complex

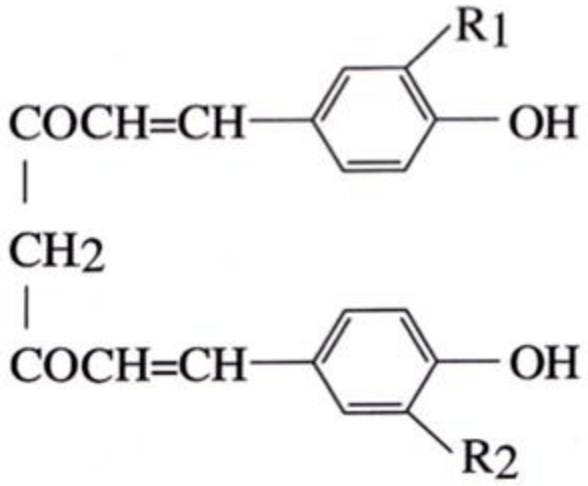
The main polyphenols in turmeric root (*Curcuma longa, Family Zingiberaceae*).

All are lipophilic, sparingly water-soluble.

THE CURCUMIN COMPLEX

Three main polyphenols:

- Curcumin I
- Demethoxy-curcumin (Curcumin II)
- Bis-demethoxy-curcumin (Curcumin III)



THE CURCUMIN COMPLEX

Over 3,000 scientific articles

- Antioxidant
- Anti-inflammatory
- Joint Protective
- GI Protective
- Modulates cholesterol
- Improves blood vessel function

Review

Cell PRESS

Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets

Bharat B. Aggarwal and Bokyung Sung

Cytokine Research Laboratory, Department of Experimental Therapeutics, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA

Extensive research within the past two decades has shown that curcumin mediates its anti-inflammatory effects through the down regulation of inflammatory transcription factors (such as nuclear factor Kappa B), enzymes (such as cyclooxygenase 2 and 5 lipoxygenase) and cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6).

inflammatory transcription factors (such as nuclear factor κB), enzymes (such as cyclooxygenase 2 and 5 lipoxygenase) and cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6). Because of the crucial role of inflammation in most chronic diseases, the potential of curcumin has been examined in neoplastic, neurological, cardiovascular, pulmonary and metabolic diseases. The pharmacodynamics and pharmacokinetics of curcumin have been examined in animals and in humans. Various pharmacological aspects of curcumin *in vitro* and *in vivo* are discussed in detail here.

ovascular, pulmonary, metabolic and psychological diseases. How curcumin manifests these pharmacological effects *in vitro* and *in vivo* is discussed here.

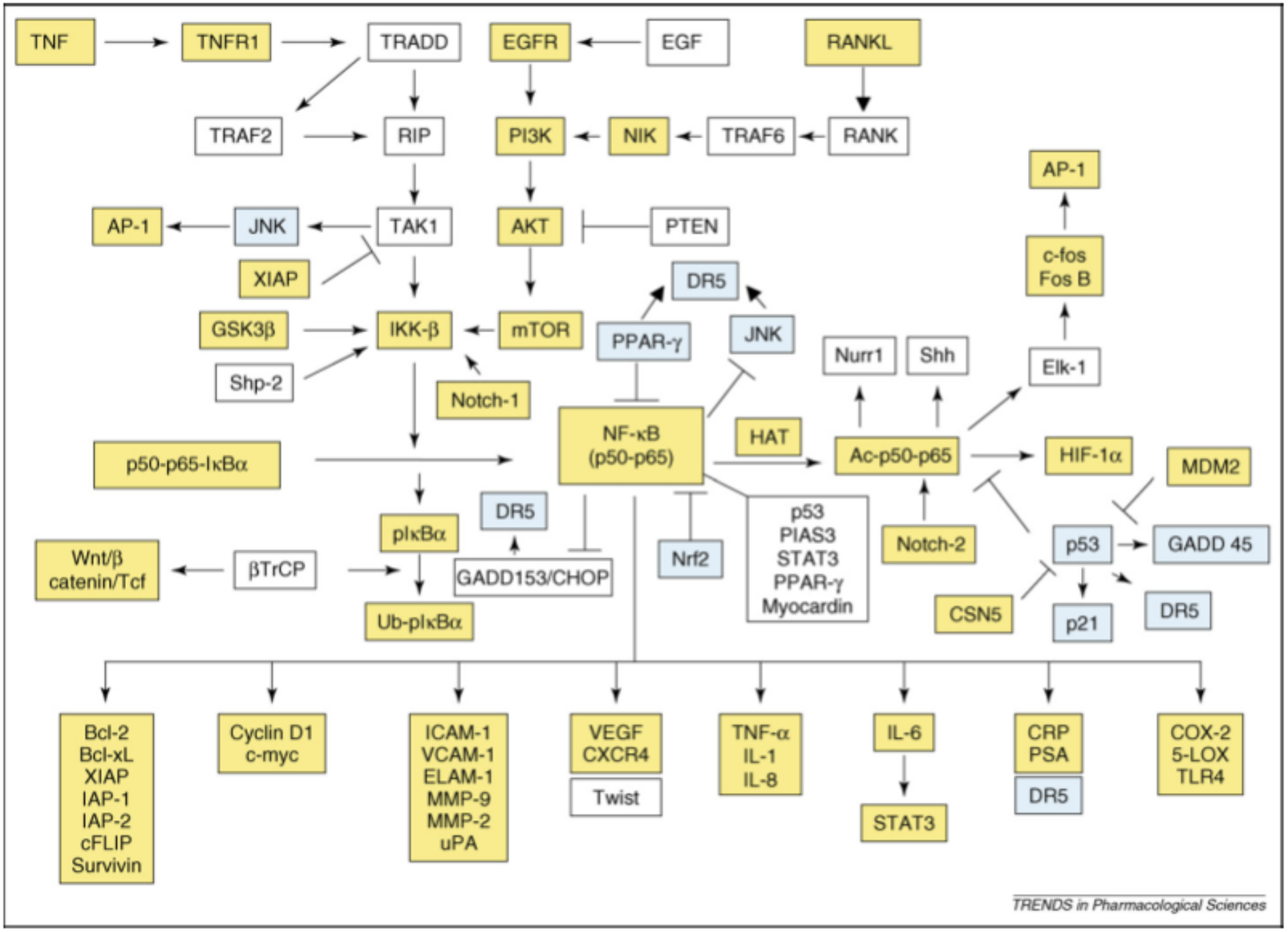
Molecular targets

Our gain in knowledge about curcumin has been exponential over recent years. Since the first article on curcumin published in *Nature* in 1949, only 17 articles were published until 1980, 65 in the next 10 years, and 452 in the next 10. Since 2000, almost 2000 more publications have appeared in the National Institutes of Health PubMed database (www.ncbi.nlm.nih.gov/sites/entrez). These studies have revealed that curcumin has antioxidant, anti-

CURCUMIN

Anti-Inflammatory Mechanisms of Action

- Inhibition of NF-kB
- Downregulation of COX-2
- Inhibition of lipoxygenase
- Inhibition of inducible nitric oxide synthase


TNF
TNFR1
TRADD
EGFR
EGF
RANKL
TRAF2
RIP
PI3K
NIK
TRAF6
RANK
AP-1
JNK
TAK1
AKT
PTEN
AP-1
c-fos
Fos B
XIAP
DR5
GSK3β
IKK-β
mTOR
PPAR-γ
JNK
Nurr1
Shh
Elk-1
Shp-2
Notch-1
NF-κB
(p50-p65)
HAT
p50-p65-IκBα
Ac-p50-p65
HIF-1α
MDM2
DR5
pIκBα
p53
PIAS3
STAT3
PPAR-γ
Myocardin
Nrf2
Notch-2
p53
GADD 45
Wnt/β
catenin/Tcf
βTrCP
GADD153/CHOP
CSN5
p21
DR5
Ub-pIκBα
Bcl-2
Bcl-xL
XIAP
IAP-1
IAP-2
cFLIP
Survivin
Cyclin D1
c-myc
ICAM-1
VCAM-1
ELAM-1
MMP-9
MMP-2
uPA
VEGF
CXCR4
Twist
TNF-α
IL-1
IL-8
IL-6
STAT3
CRP
PSA
DR5
COX-2
5-LOX
TLR4
TRENDS in Pharmacological Sciences

Product-evaluation registry of Meriva®, a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis

G. BELCARO [1], M. R. CESARONE [1], M. DUGALL [1], L. PELLEGRINI [1], A. LEDDA [1], M. G. GROSSI [1], S. TOGNI [2], G. APPENDINO [3]

Aim. A proprietary complex of curcumin with soy phosphatidylcholine **(Meriva®, Indena SpA) was evaluated in a registry study to define its efficacy in 50 patients with osteoarthritis (OA) at dosages corresponding to 200 mg curcumin per diem.**

Methods.OA signs/symptoms were evaluated by the WOMAC **scores. Mobility was studied by walking performance (treadmill), and inflammatory status was assessed by measurements of C-reactive**

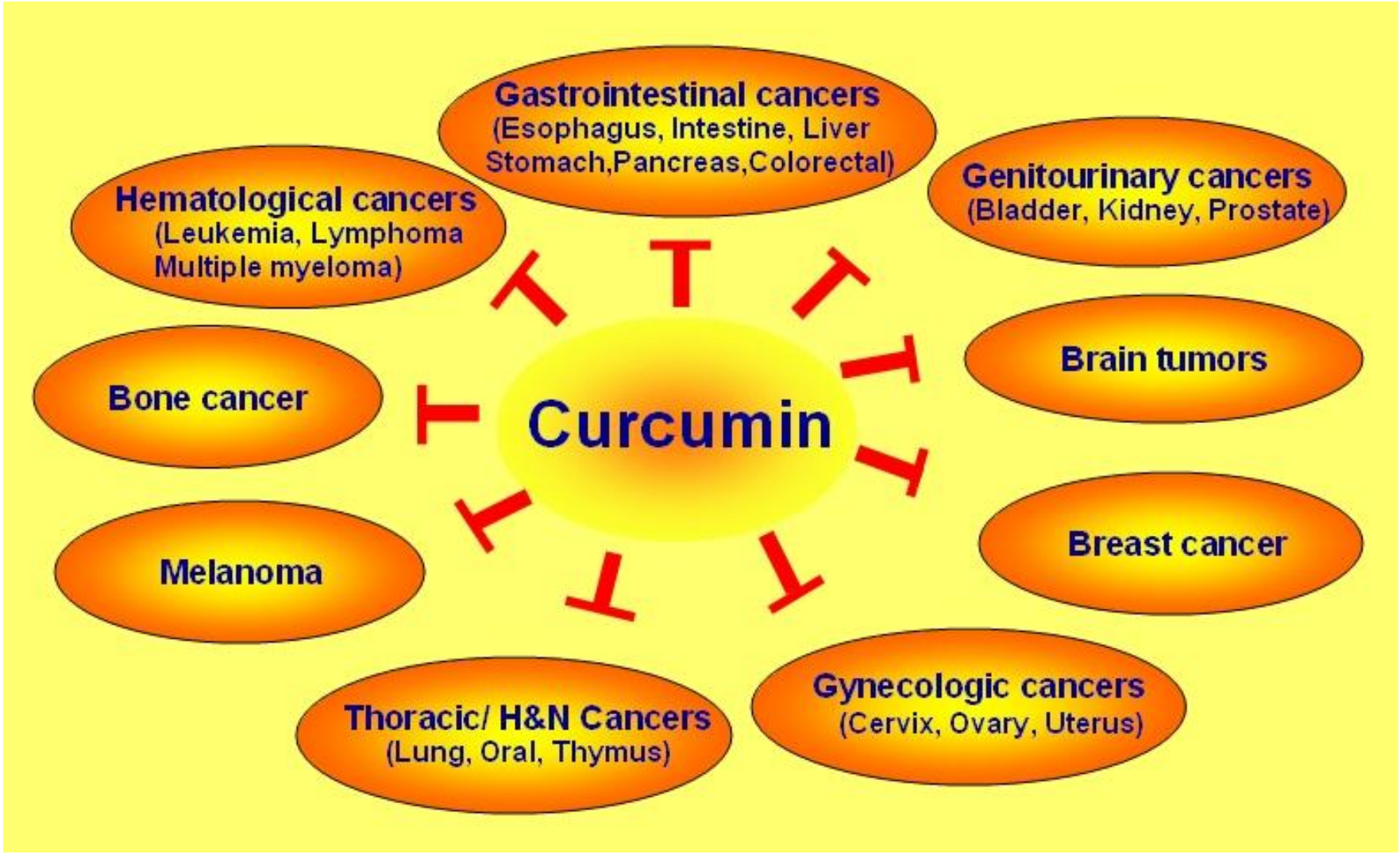
- 50 patients
- 250 mg bid of curcumin/phospholipid combo (200 mg curcumin/day)
- Significant improvement in CRP
- Significant improvement in walking distance

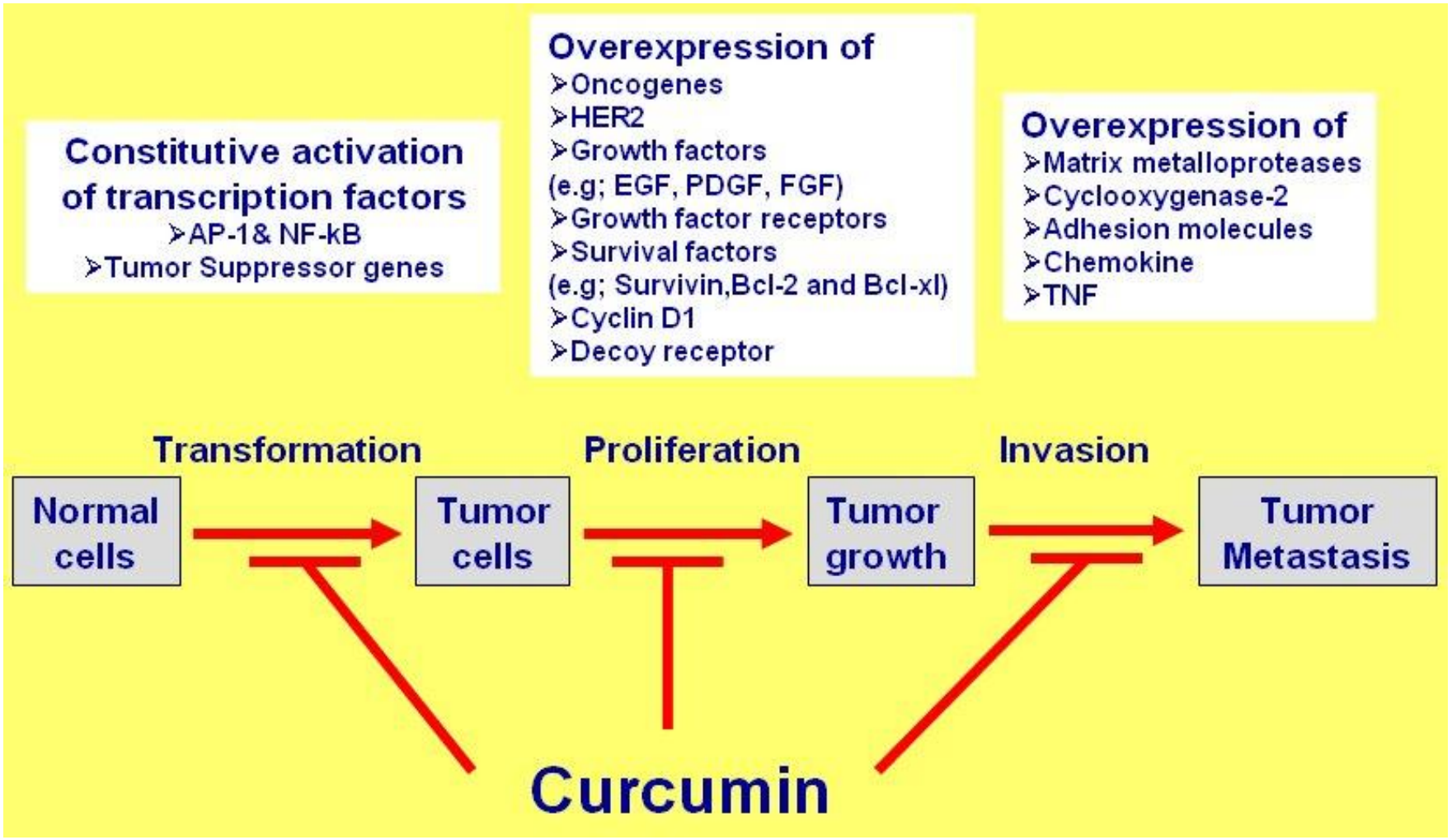
Results. Afte **05), walking distance in t** **ecreased from 168 ± 18 to 1** **group experienced** **m 82 m to 129 m in the treadr** **test, and fro** **eatment costs (use of anti-inflammatory drugs, treatment and hospitalization) were reduced significantly in the treatment group.**

Conclusion. These results show that Meriva® is clinically effective **in the management and treatment of osteoarthritis and suggests that the increased stability and better absorption of curcumin induced by complexation with phospholipids has clinical relevance and sets the stage for larger and more prolonged studies.**

PANMINERVA MED 2010;52

CURCUMIN & CANCER


Gastrointestinal cancers
(Esophagus, Intestine, Liver
Stomach,Pancreas,Colorectal)
Genitourinary cancers
(Bladder, Kidney, Prostate)
Hematological cancers
(Leukemia, Lymphoma
Multiple myeloma)
Brain tumors
Bone cancer
Curcumin
Breast cancer
Melanoma
Gynecologic cancers
(Cervix, Ovary, Uterus)
Thoracic/ H&N Cancers
(Lung, Oral, Thymus)


Constitutive activation of transcription factors
➢AP-1& NF-kB
➢Tumor Suppressor genes
Overexpression of
➢Oncogenes
➢HER2
➢Growth factors
(e.g; EGF, PDGF, FGF)
➢Growth factor receptors
➢Survival factors
(e.g; Survivin,Bcl-2 and Bcl-xl)
➢Cyclin D1
➢Decoy receptor
Overexpression of
➢Matrix metalloproteases
➢Cyclooxygenase-2
➢Adhesion molecules
➢Chemokine
➢TNF
Transformation
Proliferation
Invasion
Normal cells
Tumor cells
Tumor growth
Tumor Metastasis
Curcumin

Conclusions


Thank you!