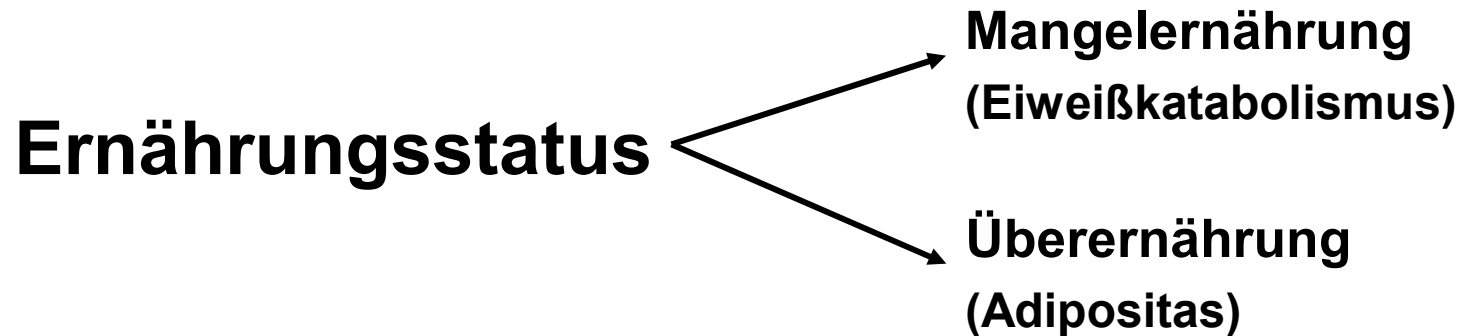


Was ist Immunonutrition?

***Erich Roth,
Chirurgische Forschungslaboratorien,
Medizinische Universität Wien***



Ernährung - Immunkompetenz



Makro-Mikronährstoffe

Zufuhrweg

1. Warum Immunonutrition

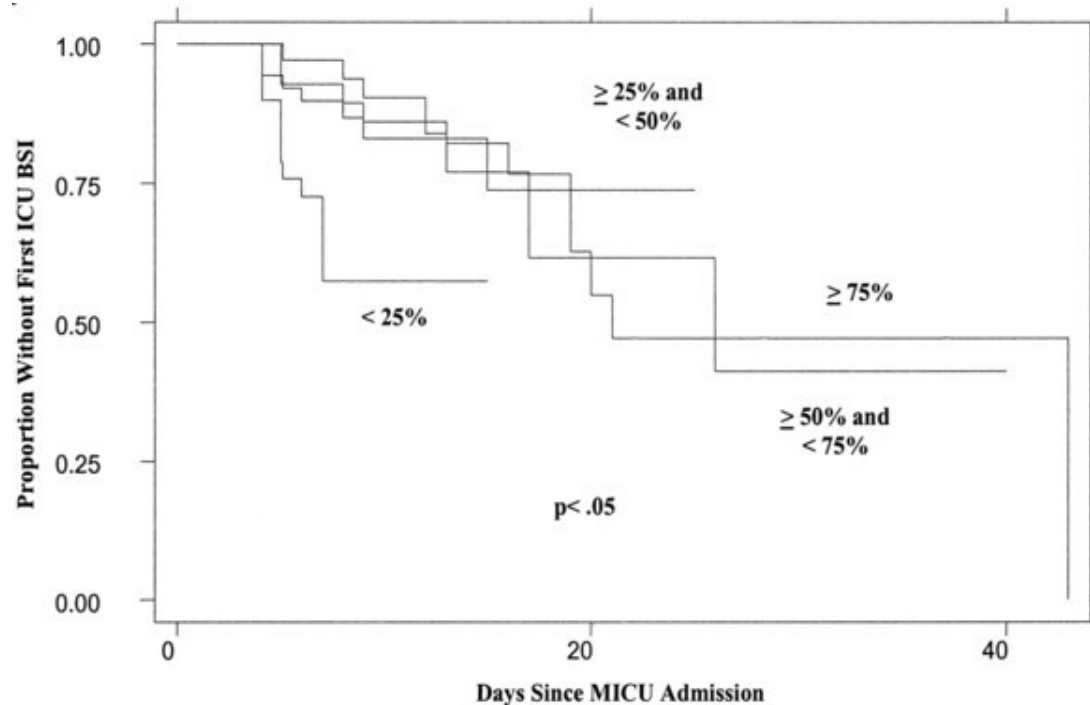
The Delayed Hypersensitivity Response and Host Resistance in Surgical Patients. 20 years later

- **4292 patients**
- **mortality of DTH reactive patients: 2.9 %**
- **Anergic patients: 20.9 % (p<0.0000001)**
- **Lack of T cells**
- **Only a mild malnutrition in anergic patients**
- **PN failed to correct the DTH response**

N.V. Christou et al, *Ann Surg* 1995: 222; 534

Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit

- 138 adult patients not taking food by mouth for more than 96 h after medical ICU admission



Nutrient deprivation

↓ Energy charge – ↑ AMP:ATP

cell survival
mitochondrial biogenesis
glycolysis
fatty acid oxidation



AMPK*



protein synthesis
fatty acid synthesis
cholesterol synthesis

growth factors
thyroid hormones

Nutrient-rich conditions
amino acids, leucine
insulin

m-TOR^o

cell size

proliferation

Immune-stimulation

translation

S6 kinase 1

eIF4E

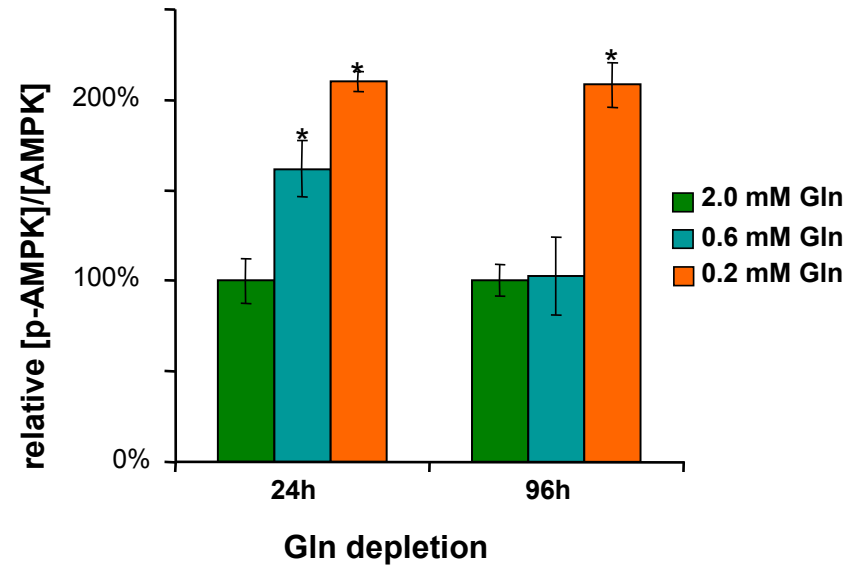
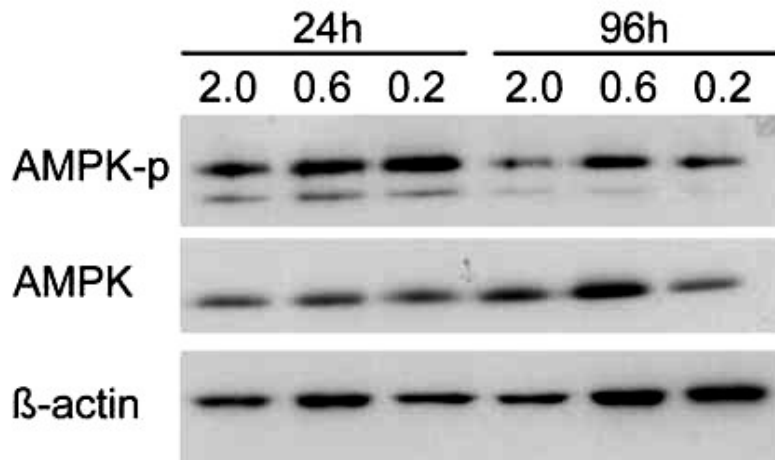
*AMP-activated kinase

^omammalian target of rapamycin

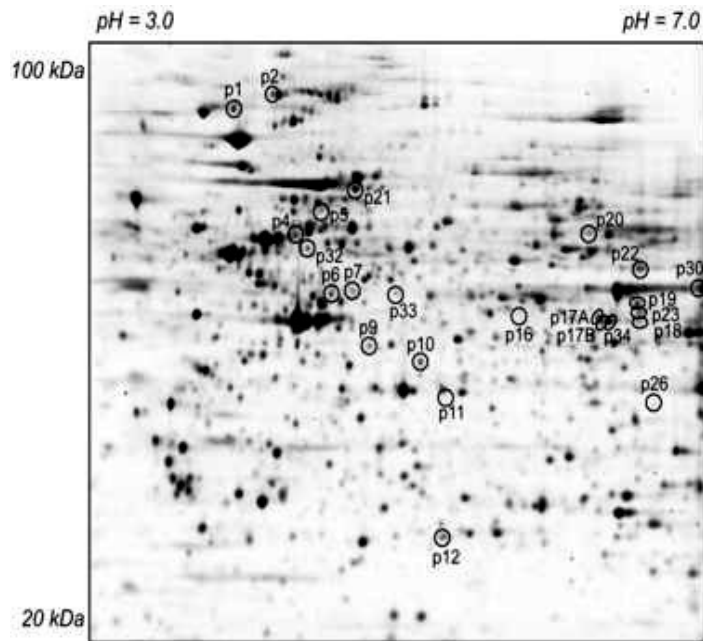
4 days of Gln depletion



AMPK phosphorylation



Altered protein expression after 4 days of Gln depletion



Spot ID	SwissProt Acc. Nr.	Protein Name	spot position	
			MW [kDa]	pI
p1	-			
p2	P34932	Heat shock 70 kDa protein 4 (Hsp-4)	100	5.2
p4	Q12874	Splicing factor 3A subunit 3 (SAP 61)	60	5.3
p5	-			
p6	P52597	Heterogeneous nuclear ribonucleoprotein F (hnRNP F)	45	5.5
p7	-			
p11	Q96C86	Scavenger mRNA decapping enzyme (DcpS)	35	6.0
p12	-			
p14	P40925	Malate dehydrogenase (MDH)	35	6.5
p16	-			
p17A	P49411	Elongation factor Tu, (EF-Tu)	42	6.5
p17B	P49411	Elongation factor Tu, (EF-Tu)	42	6.5
p18	-			
p19	P52209	6-phosphogluconate dehydrogenase (PGDH)	45	6.8
p20	-			
p21	P08133	Annexin 6 (A6)	70	5.5
p22	P00367 P25705	Glutamate dehydrogenase 1 (GDH) ATP Synthase α -chain (ATP-S α)	55 55	6.6 6.6
p23	P62195	26S protease regulatory subunit 8 (p45/SUG)	42	6.6
p26	-			
p30	-			
p32	-			
p33	-			
p34	P22234	Phospho ribosyl amino imidazole-succino carboxamide synthase (PUR6)	42	6.5

Reduced lymphocyte proliferation

Declined function of monocytes

Decreased intestinal immune response

Increased cell apoptosis

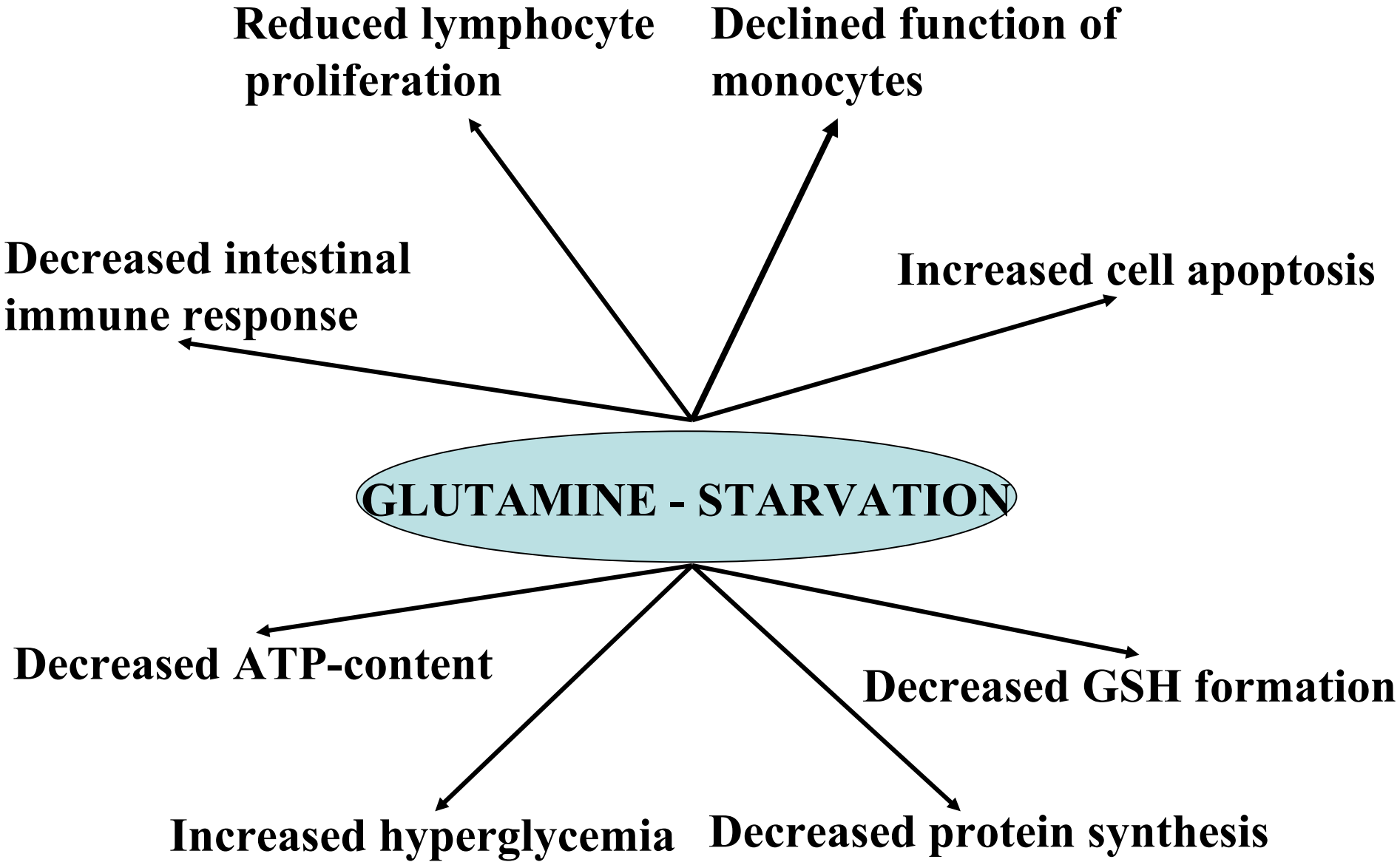
GLUTAMINE - STARVATION

Decreased ATP-content

Decreased GSH formation

Increased hyperglycemia

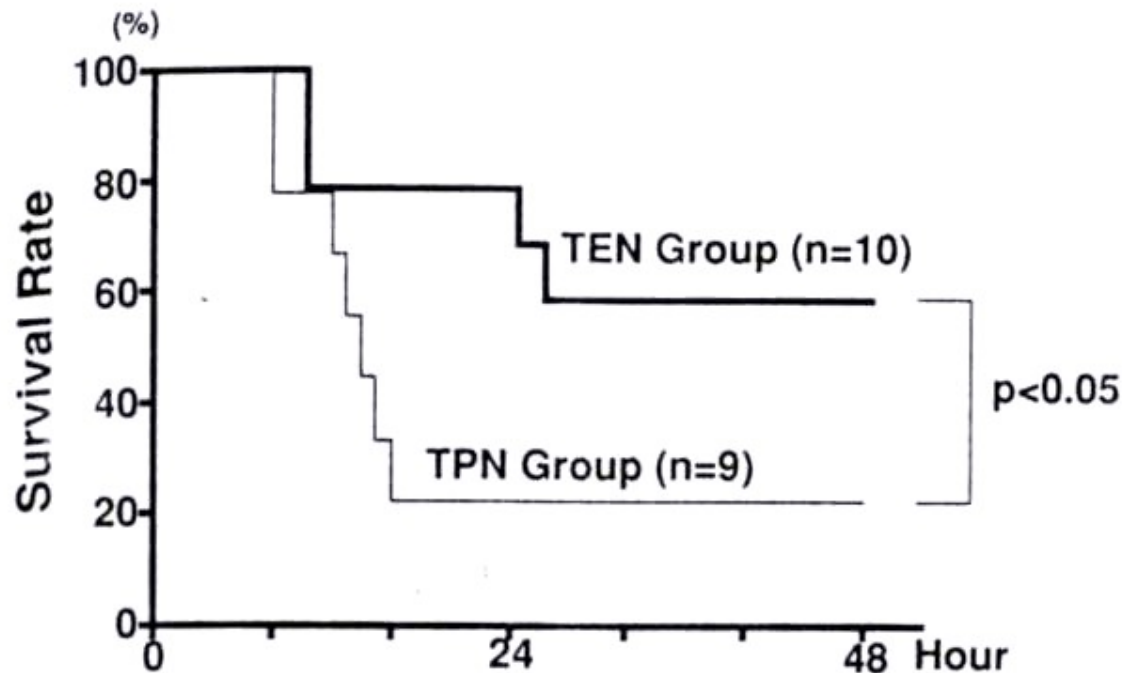
Decreased protein synthesis



2. Immunantwort in Abhängigkeit vom Zufuhrweg

Route of Nutritional Supply Influences Local, Systemic, and Remote Organ Responses to Intraperitoneal Bacterial Challenge

Ming-Tsan Lin et al., Ann Surg 223: 84; 1996



Survival rate after *E. coli* peritoneal challenge

Cytokine Production in Dependence on Route of Nutritional Supply

Peritoneal Fluid:

TPN ↑ TNF
EN ↑ IFN- γ

Bronchoalveolar Lavage Fluid:

EN ↑ IFN- γ

Blood:

EN ↑ IFN- γ

3. Was ist ein “Immunonutrient” ?

- **Ein Nutrient, das in einer Menge einer parenteralen oder oral/enteralen Diät zugesetzt ist, die immunmodulierend wirkt.**
- **Die Immunmodulation kann immun-stimulierend oder -supprimierend sein**

Welche immunmodulierenden Nährstoffe werden in der klinischen Ernährung eingesetzt?

- **Glutamin**
- **Arginin**
- **schwefel- hältige Aminosäuren**
- **Verzweigt-kettige Aminosäuren**
- **ω -3 Fettsäuren**
- **Nukleotide**
- **Antioxidative Vitamine**
- **Mikronährstoffe**
- **(Proteine, Glukose)**

Glucose and immunological reactions

Cytokines

The presence of glucose leads to a **higher resting cytokine** production; **after stimulation**, this **cytokine production is impaired** compared to the situation without glucose.

M Morohoshi et al. *Ann NY Acad Sci* 1995; 748:562
D Reinhold et al. *Horm Metab Res* 1996; 28:267

Phagocytosis

Impairment of phagocytosis is found in PMNs isolated from poorly regulated patients and **better regulation** of the DM leads to an **improved function**.

M Delamaire et al. *Diabetic Met* 1997; 14:29
JD Bagdade et al. *Diabetes Care* 1997; 20:392

Oxidative burst

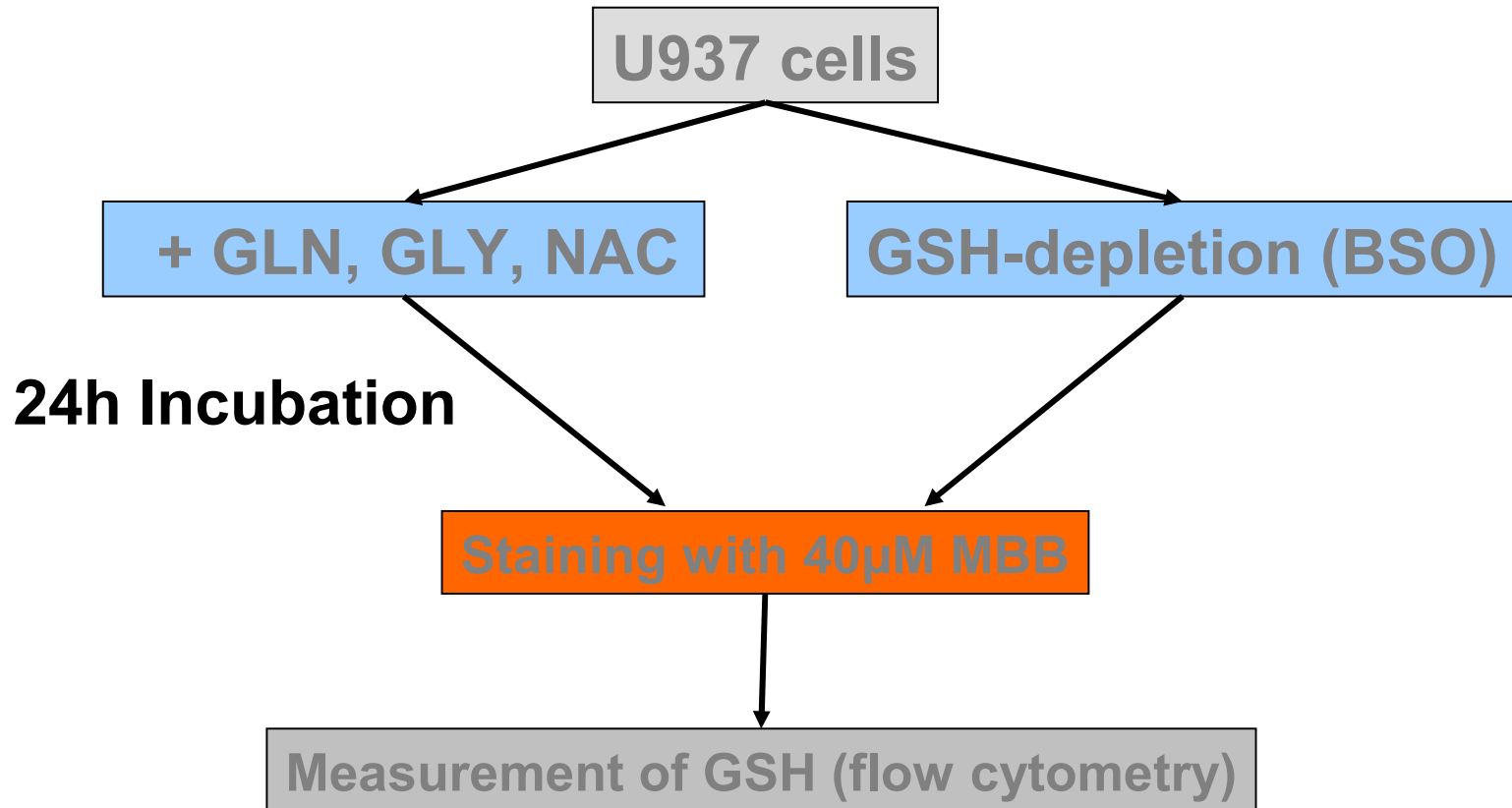
Oxidative burst is higher or the same in PBMC of diabetic patients; **after stimulation, oxidative burst in PBMC is lower** than that of control patients.

W Marhoffer et al. *Diabetes Care* 1992; 15:256
SV Shah et al. *J Clin Endocrinol Metab* 1983; 57:740

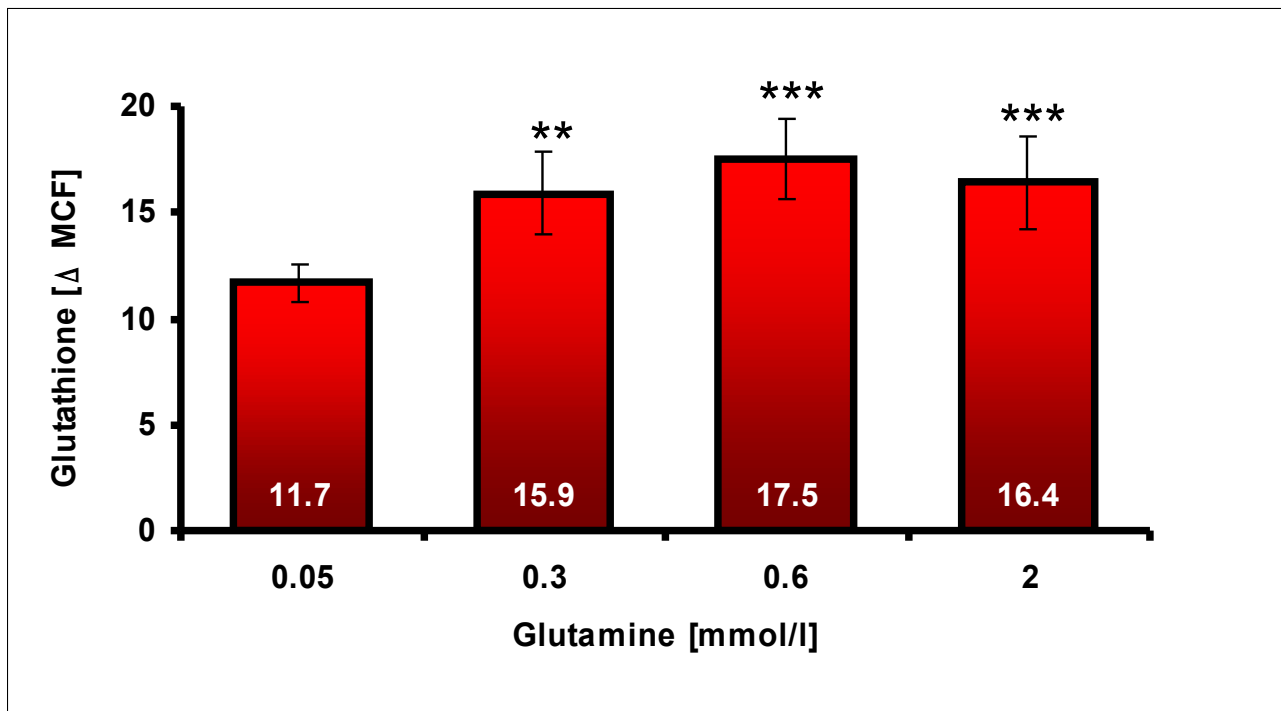
4. Verhalten sich Immunonutrients wie Pharmaka?

**Kinetik von Immunonutrients am
Beispiel von Glutamin und Glyzin in
einem Zellkultursystem**

Experimental design



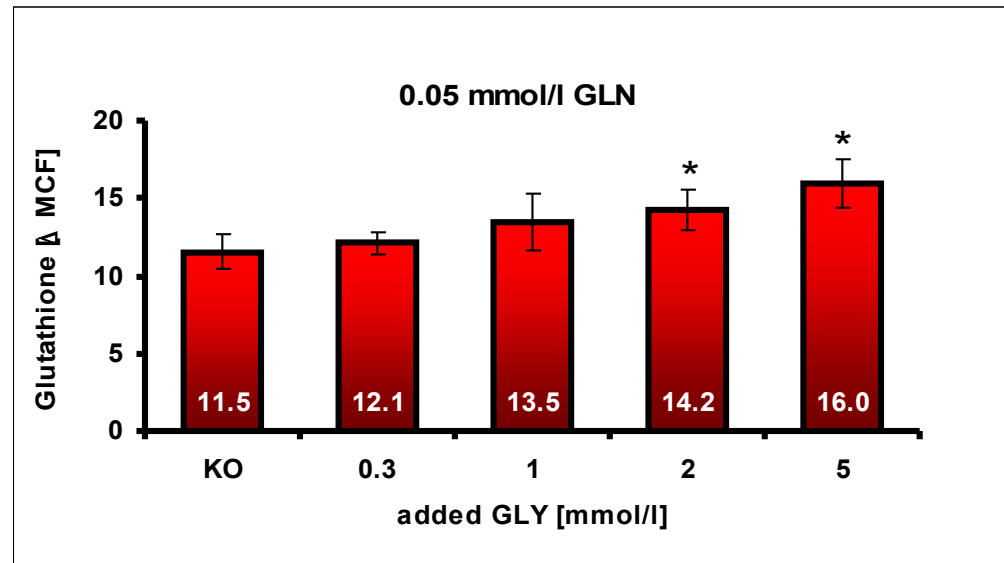
Influence of Glutamine on GSH-content of U937 cells



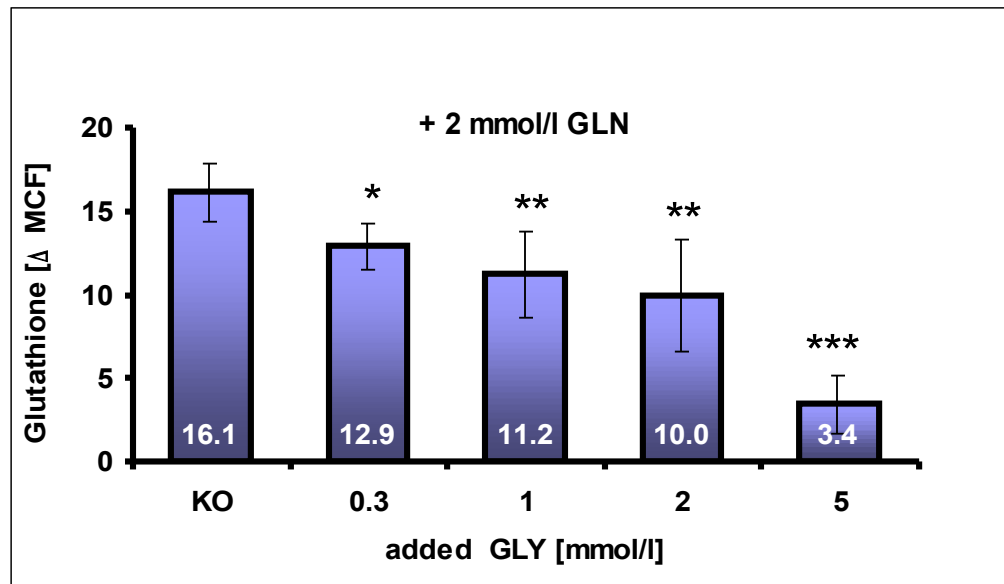
B Wessner, E Roth et al, *Clin Nutr*, 2003

** p < 0.01 vs 0.05mM GLN
*** p < 0.001 vs 0.05mM GLN

Glycine + Glutamine



Low GLN

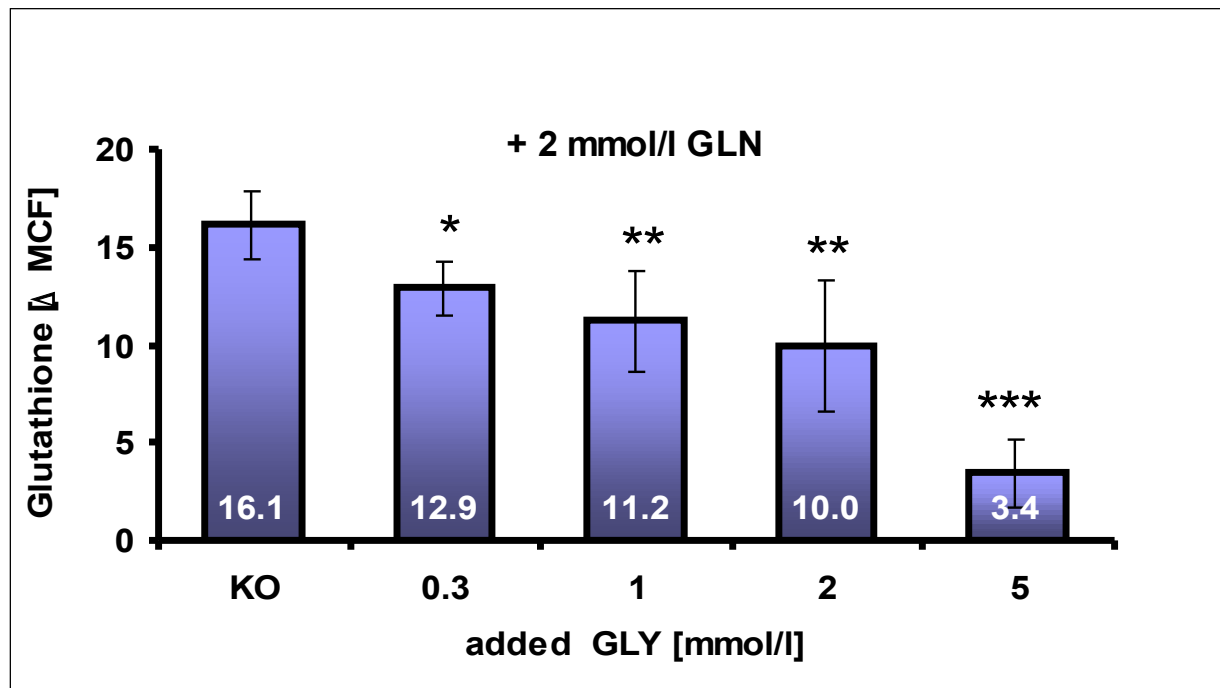


High GLN

0.02 vs KO

- * p < 0.05 vs KO
- ** p < 0.01 vs KO
- *** p < 0.001 vs KO

Glycine + high Glutamine: decreases ic glutamine concentration



B Wessner, E Roth et al, *Clin Nutr*, 2003

* $p < 0.05$ vs KO
** $p < 0.01$ vs KO
*** $p < 0.001$ vs KO

Effect of Different Combinations of Dietary Additives on Bacterial Translocation and Survival in Gut-Derived Sepsis

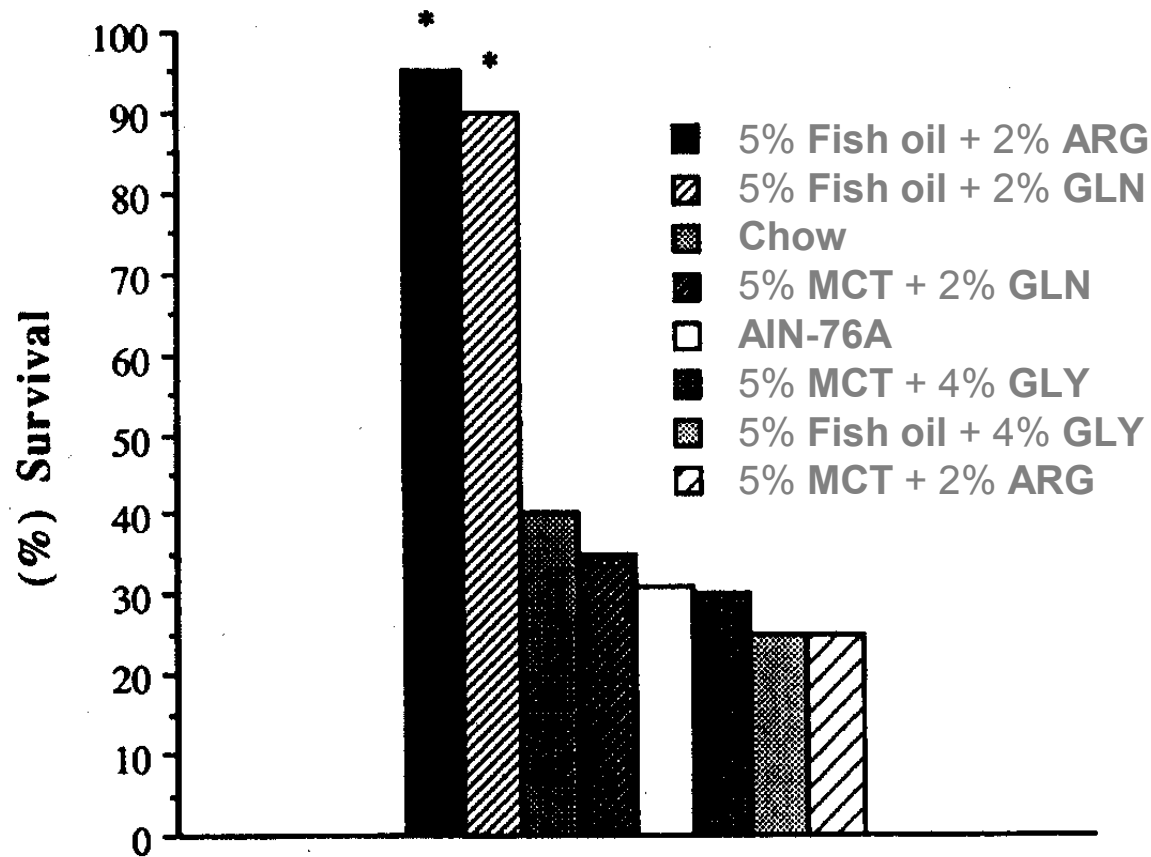


FIG. 3. Survival rate of transfused, gavaged, and burned mice fed with different pellet diets. * $p < .0001$ vs all other groups.

R Gennari, W Alexander
et al, *JPEN* 1995

Zusammenfassung-Pharmakokinetik

- **Der Effekt von Immunonutrients ist dosisabhängig**
- **Die Kombination von Immunonutrients muss sorgfältig sowohl auf synergistische als auch antagonistische Wirkung untersucht werden**

D.K. Heyland:

... We included studies that compared enteral nutrition with some combination of arginine, glutamine, nucleotides, ω - 3 fatty acids

	IMPACT	Optimential
Arginine (g/L)	12.5 (14)	5.5
Nucleic acids (g/L)	1.23	0
ω - 3 PUFAs (g/L)	1.7	4.83
ω - 6 : ω - 3 ratio	1.5 : 1	0.86 : 1
Osmolarity	375	560
Vitamin E	60	250
Vitamin C	80	215
Selenium (μg/L)	100	50

**Aus Metaanalysen, die unterschiedlich
zusammengesetzte Therapielösungen
vergleichen, sind keine
Schlussfolgerungen zulässig**

5. Immunmodulatoren – Experimentelle Substrate

Lipoic acid

Curcumin

Green Tea Extract

Thymoquinone

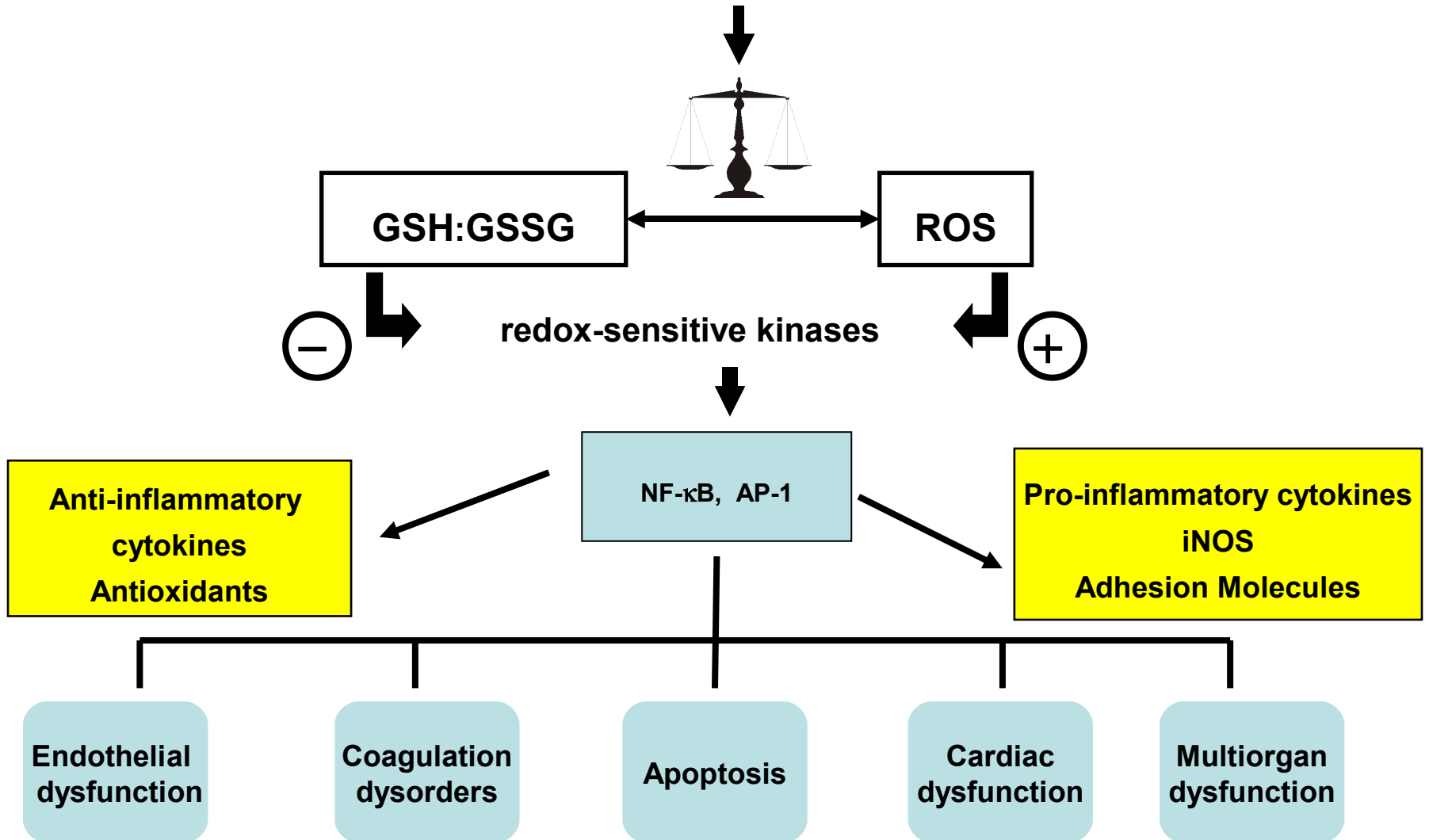
Sesamin

Kahweol

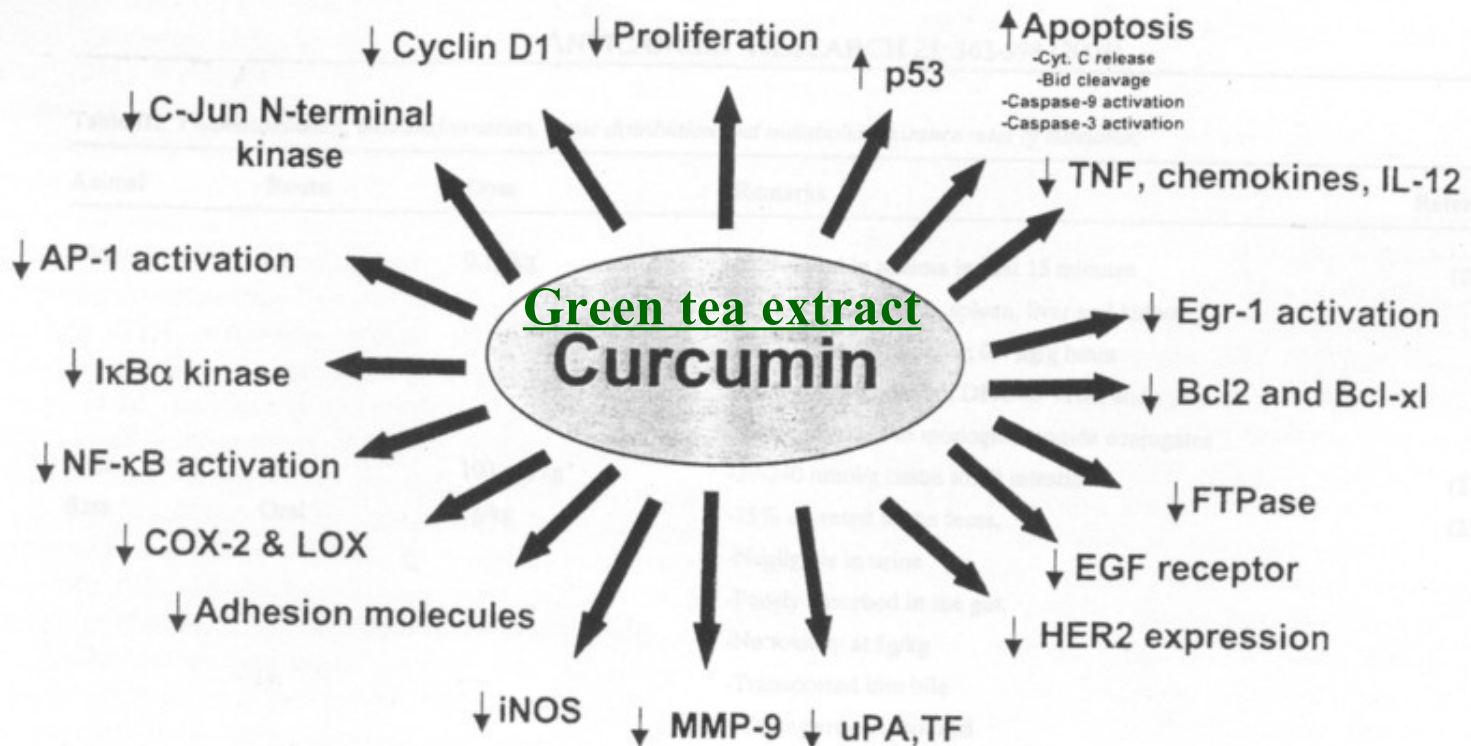
Cafestol

S-adenosyl-L-methionine (SAM)

Nutrients:
e.g. glutamine, glutamate, cysteine,
glycine, N-acetylcysteine, lipoic acid
vitamine E, C, β -carotene, phytochemicals

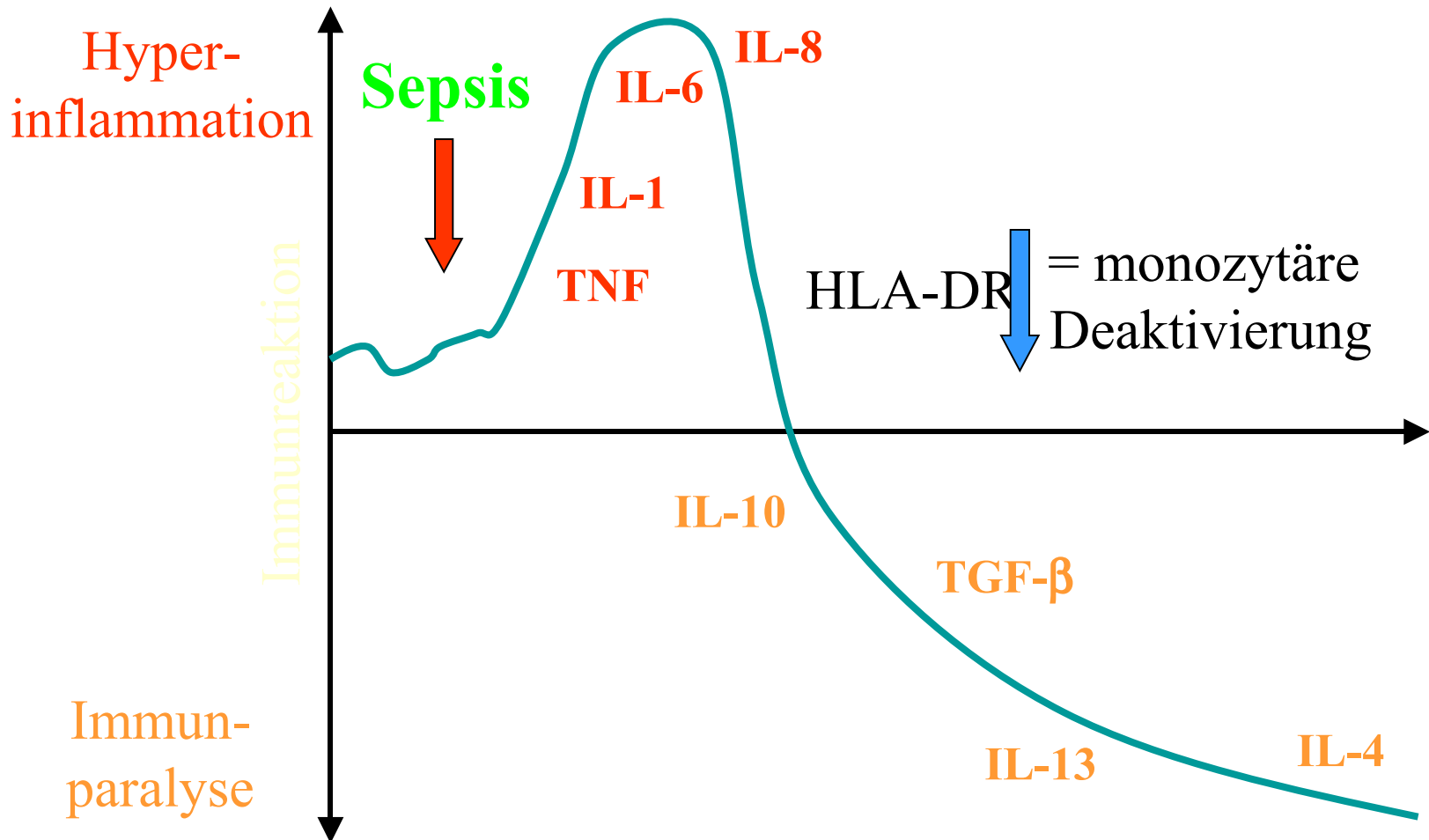


Influence of curcumin on signal transduction



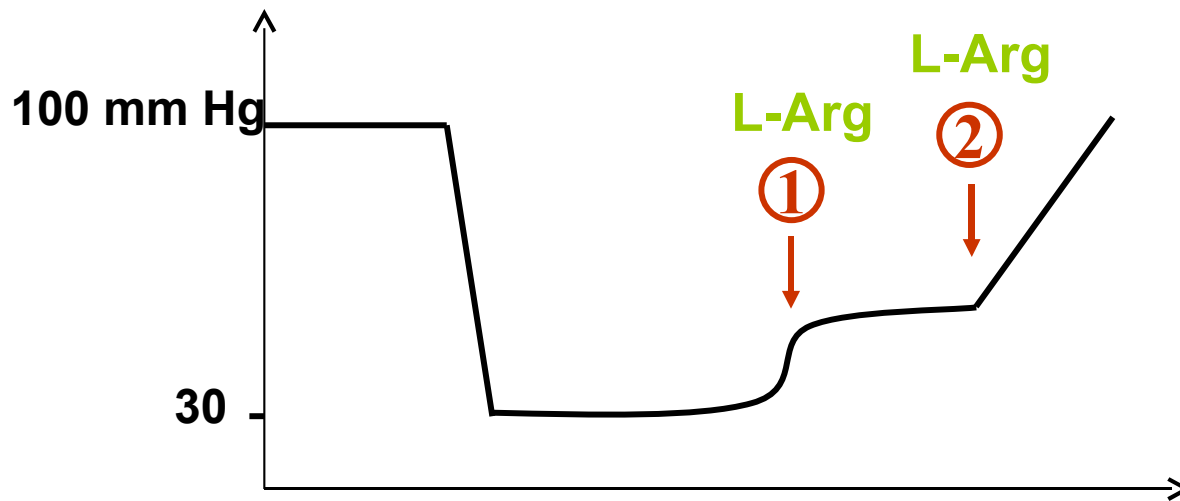
6. Gabe von Immunonutrients in Abhängigkeit vom pathophysiologischen Zustand

Zwei-Phasen-Modell der Sepsis



- **Modulation of hemorrhagic shock by intestinal mucosal N^G-nitro-L-arginine and L-arginine in the anesthetized rat** (D Mailman, *Shock* 1999;12:155)
 - **reduced survival by arginine analogs**
 - **improved survival by L-arginine**
- **Significance of NO in hemorrhage-induced hemodynamic alterations, organ injury and mortality in rats** (YM Yao et al., *Am J Phys* 1996;270: H1616)
 - **improved survival by arginine analogs**

NO and formation of peroxynitrite: Dichotomy of Arginine in Hemorrhagic Shock



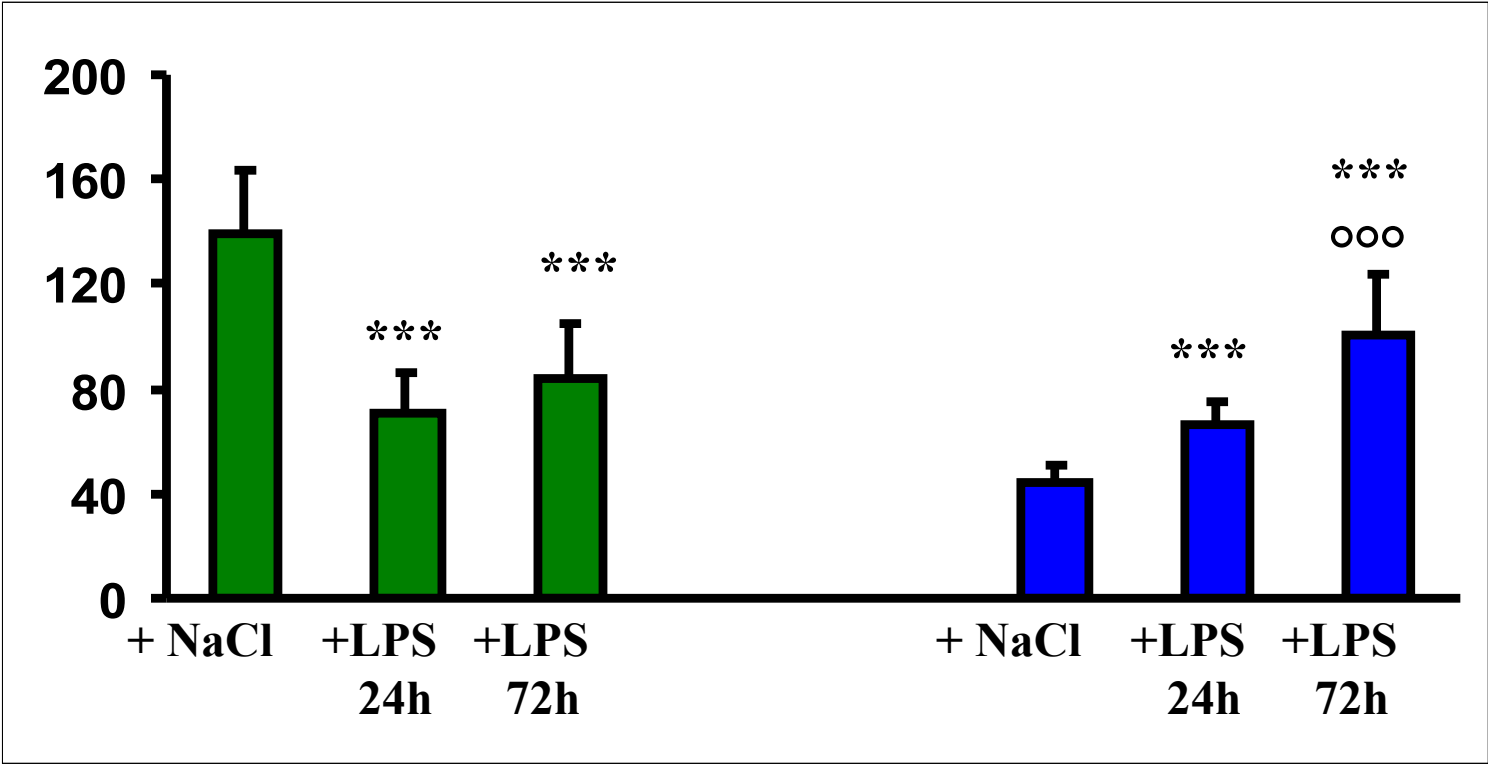
peroxynitrite = cytotoxic



7. Organspezifische Immunmodulation

Lipopolysaccharide causes atrophy of Peyer's Patches

TCY in spleen (10^6)



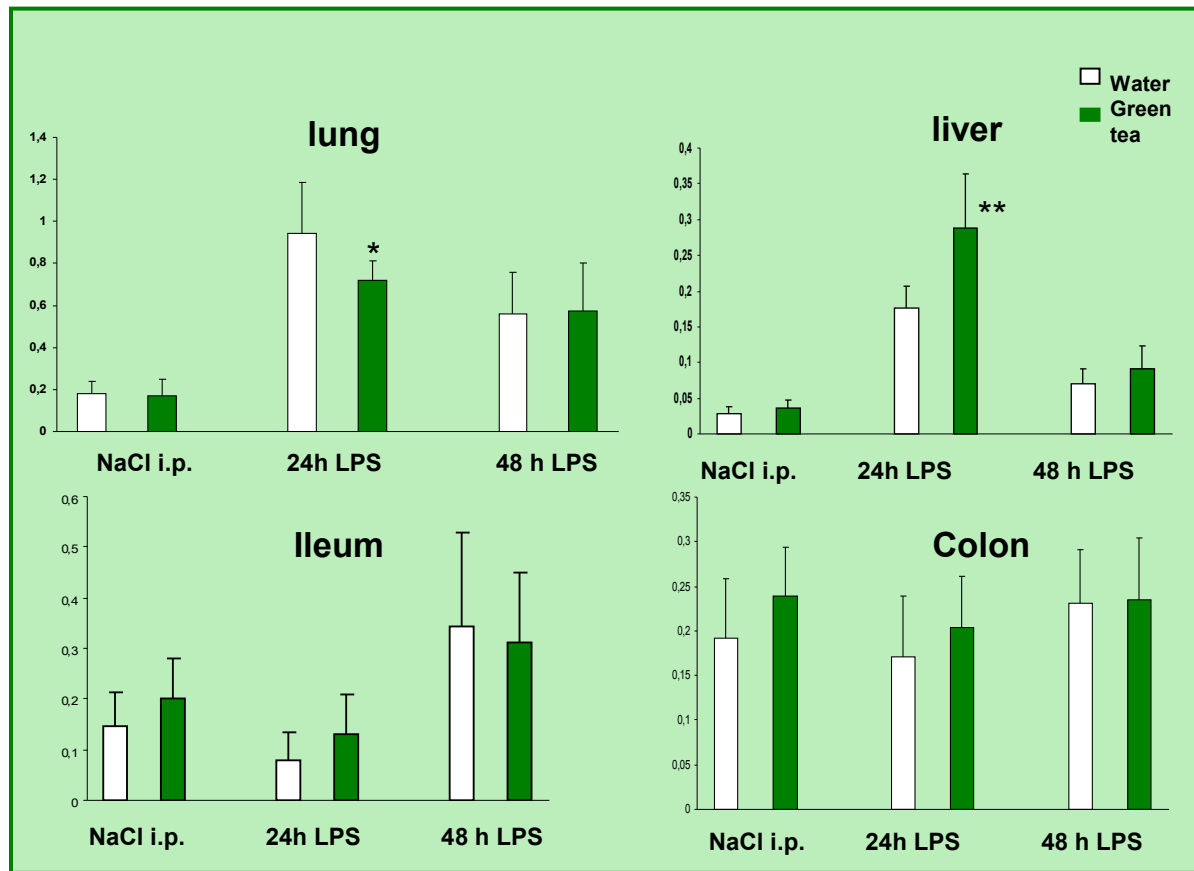
Green tea polyphenol administration partly ameliorates chemotherapy-induced side effects in the small intestine of mice

Wessner B, Manhart N, Roth E et al. J. Nutr 2007;137:634

Green tea polyphenols increase lymphocyte numbers and diminish oxidative stress in the Peyers patches of endotoxemic mice

Manhart N, Wessner B, Roth E et al.

Myeloperoxidase activity



Antioxidativ ist nicht gleich anti-inflammatorisch

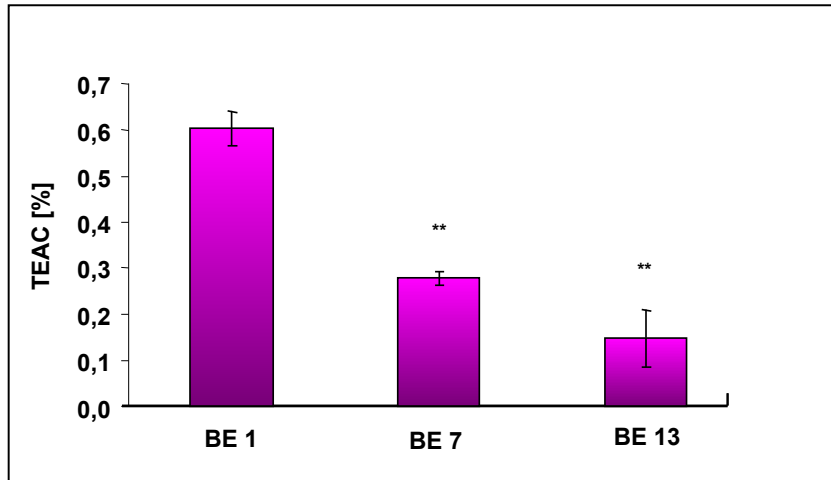


Abbildung 1

Anti-oxidative Kapazität der Basilikumextrakte

** $p < 0.01$

Daten aus 3 unabhängigen Experimenten

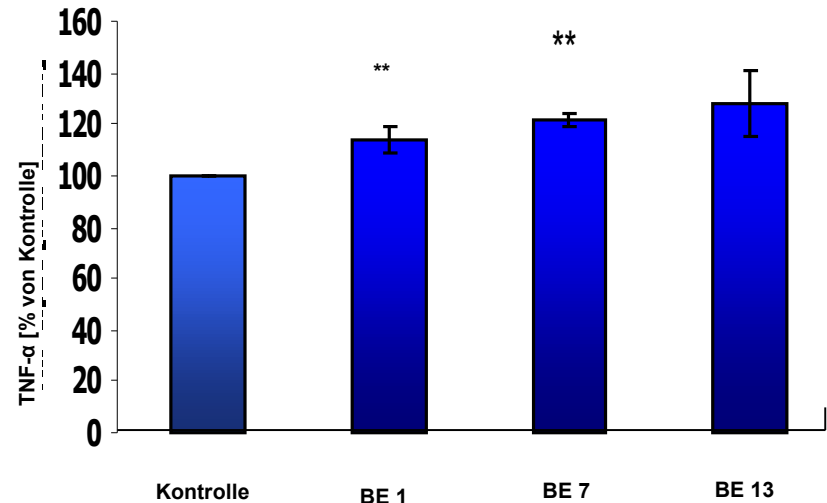


Abbildung 2

Einfluss der Basilikumextrakte auf die TNF- α Sekretion von LPS stimulierten U937 Zellen

** $p < 0.01$ vs. Kontrolle

Daten aus 4 unabhängigen Experimenten

Zusammenfassung

- **Hohe Korrelation zwischen Anergie und Mortalität bei Intensivpatienten**
- **Mangelernährung –Substratmangel führt zu einer Immunsuppression**
- **Immunonutrients folgen den Gesetzen der Pharmakokinetik**
- **Einsatz von Immunonutrients in Abhängigkeit der Immunlage**
- **Immunonutrients wirken organspezifisch**
- **Zentrale Angriffspunkte der Immunonutrients sind**
 - **das Redoxpotential +Transkriptionsfaktor NfkB**
 - **das AMPK/m-TOR System**
 - **die Signalkaskade**