Dr Amit Kumar Tyagi

Department of Experimental Therapeutics,
The University of Texas, M.D. Anderson Cancer Center,
Houston, Texas, U.S.A.

Biography

Dr Amit Kumar Tyagi received his PhD degree in Applied Microbiology from Indian Institute of Technology Delhi, New Delhi, India where he studied the antimicrobial potential of different phytochemicals against food spoiling and disease causing microorganisms in in-vivo and in-vitro food models. During his PhD, he was awarded for European grant 'Erasmus Mundus Corporation Window' for doing part of his thesis work in University of Bologna, Italy. His work at The university of Texas MD Anderson Cancer Center revealed that TNF exhibit pro-inflammatory activities and may mediate carcinogenesis through the activation of a transcription factor NF-κB. The gene products regulated by NF-κB have now been linked to cellular transformation, tumor cell survival, proliferation, invasion, angiogenesis, metastasis, chemoresistance, and radioresistance. Mostly carcinogens, tumor promoters, growth factors, inflammatory agents, chemotherapeutic agents, radiation, viruses, bacteria, cigarette smoke, alcohol and other life style factors activate NF-κB and another transcription factor STAT3. Dr Tyagi's research group is working on safe and multi-targeting chemopreventive agents derived from natural resources suppress NF-κB and STAT3 pathway and suppress tumorigenesis.

Research Interest

Study of transcription factors NF-kappaB and STAT3 signaling pathway, death receptor pathway, extrinsic and intrinsic pathway of apoptosis, anticancer properties of natural compounds in both in vitro and nude mouse models, study of cell cycle by flow cytometry, study of oxidative stress in animal models, antioxidants, study of genotoxicity by chromosomal aberration and micronuclei assay, study of gene expression by using western blotting and RT-PCR, DNA binding assay by EMSA, reporter gene expression, Immunohistochemical analysis, studies on both in vivo and in vitro experimental models, SEM, TEM, AFM, Food Microbiology and Food Chemistry, SPME-GCMS.

Multi-targeting of Multigenic Cancer Prevention and Treatment by Nutraceuticals

Working Hypothesis:

Dysregulated chronic inflammation caused by life style factors mediate chronic diseases including cancer!

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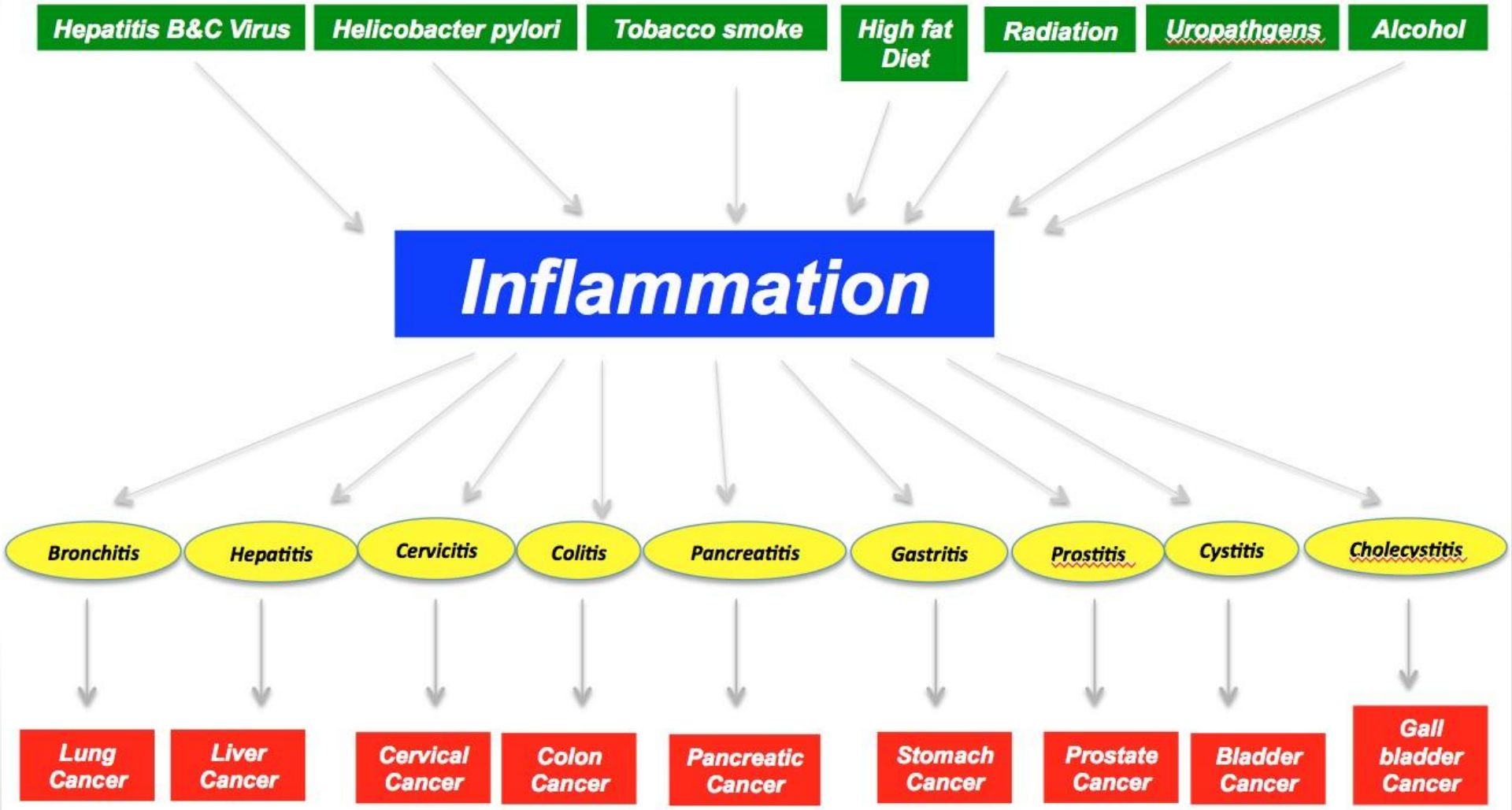
Origin of inflammation and its role in various cancers



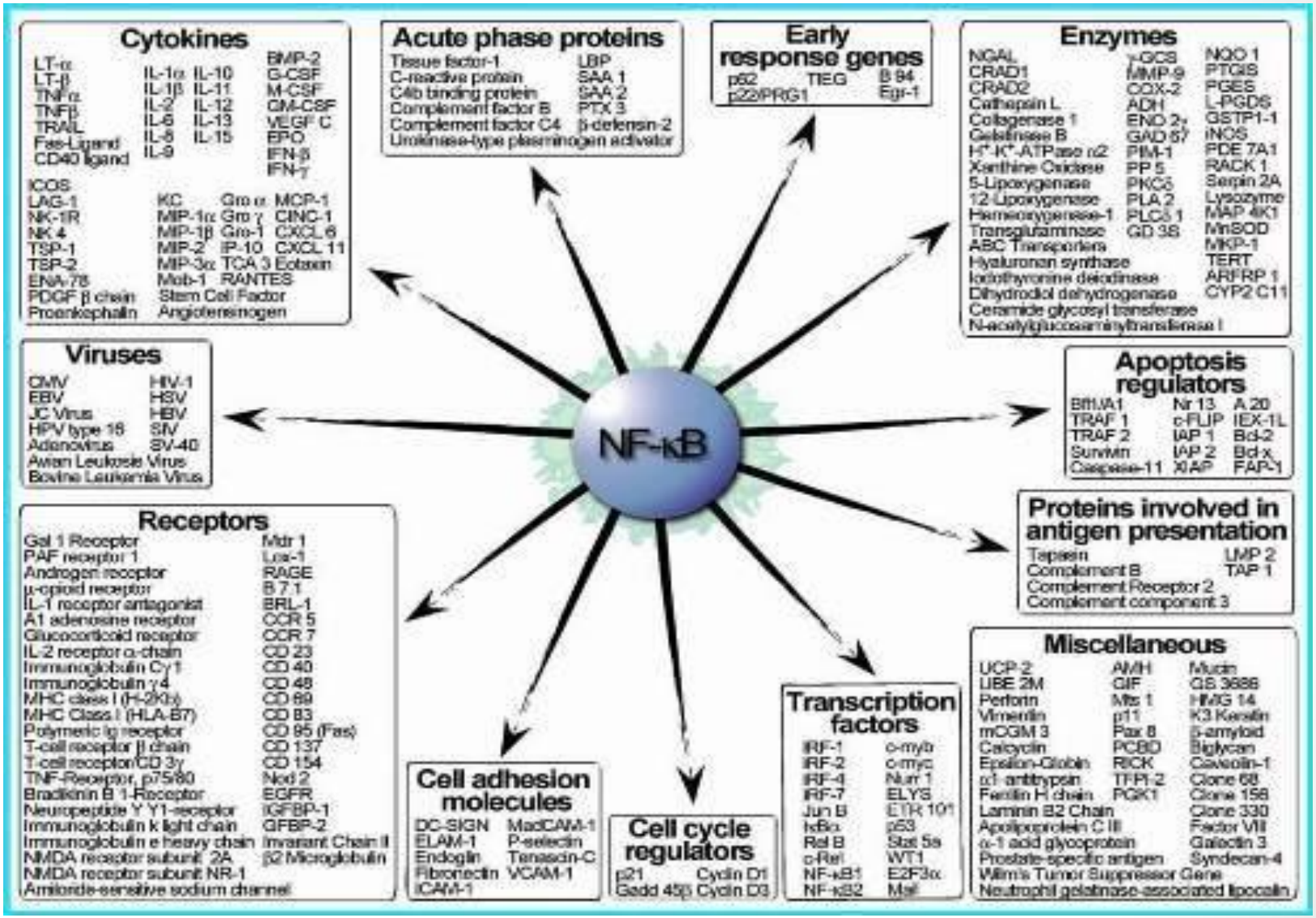
Hypothesis!

NF-κB activation is a major mediator of inflammation in most chronic diseases (including cancer)

&

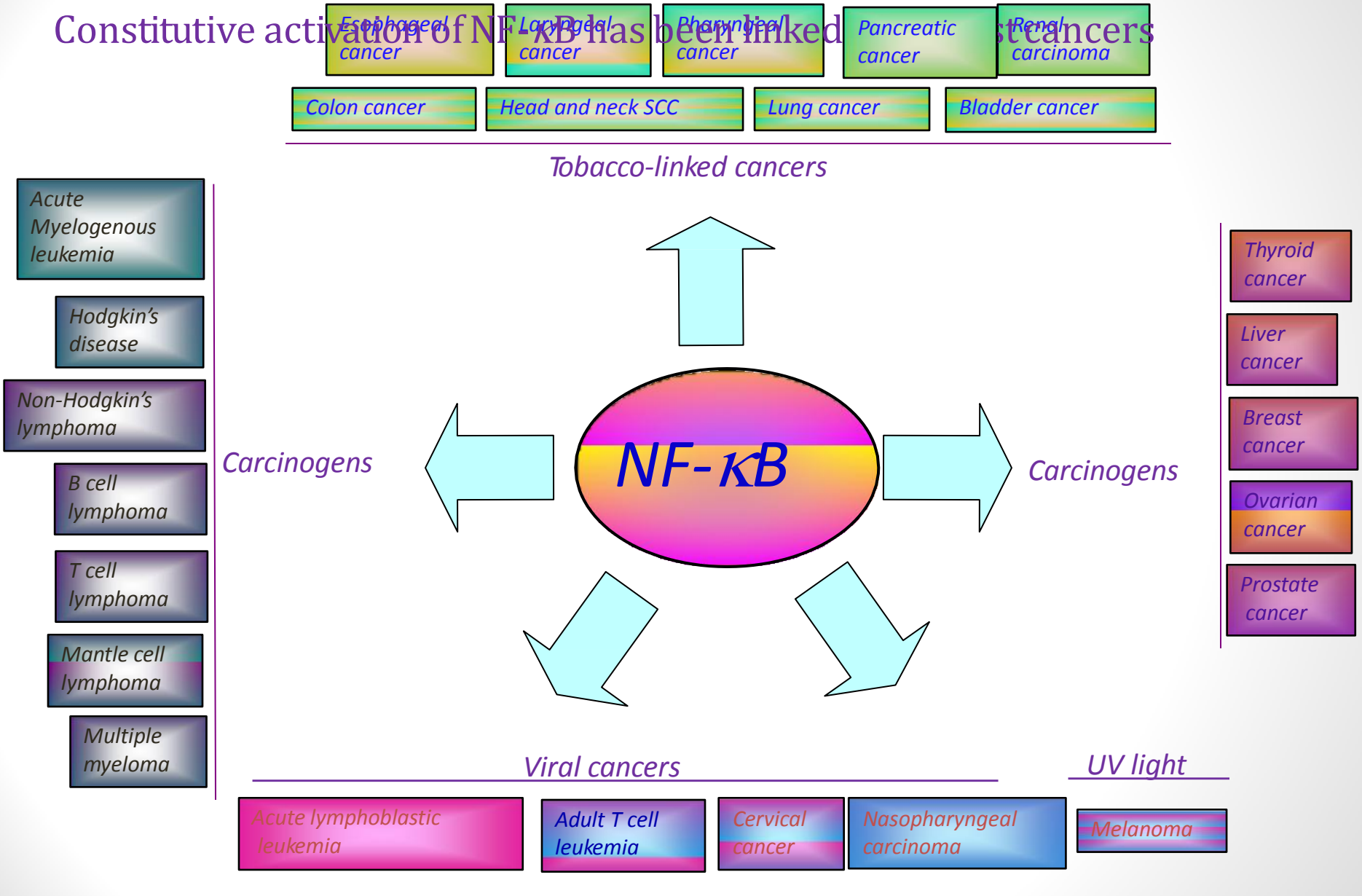
inhibition of NF-κB can prevent/delay the onset of the chronic diseases!

NF-κB -regulated genes



Aggarwal BB. *Journal of Molecular Medicine* 2004;82:434-48

Constitutive activation of NF-κB has been linked to most cancers



Shishodia and Aggarwal, Biochemical Pharmacology, 2004

Role of inflammation in tumorigenesis

NF-κB

DNA damage
Oncogenes

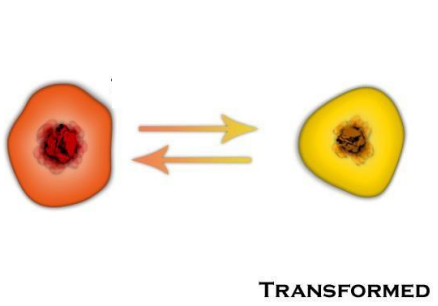
Bcl-xl
Bcl-2
Survivin
C-FLIP
cIAP-1
cIAP-2
XIAP

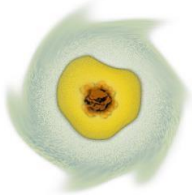
Cyclin D1
C-myc
TNF
IL-1
IL-6
COX2

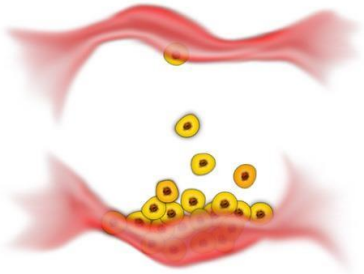
MMP-9
uPA
ICAM-1
ELAM-1
VCAM-1

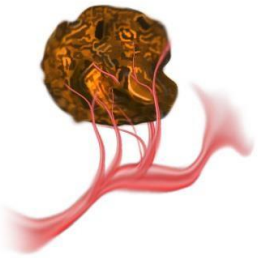
VEGF

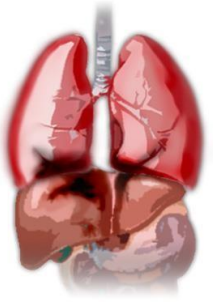
CXCR4
TWIST





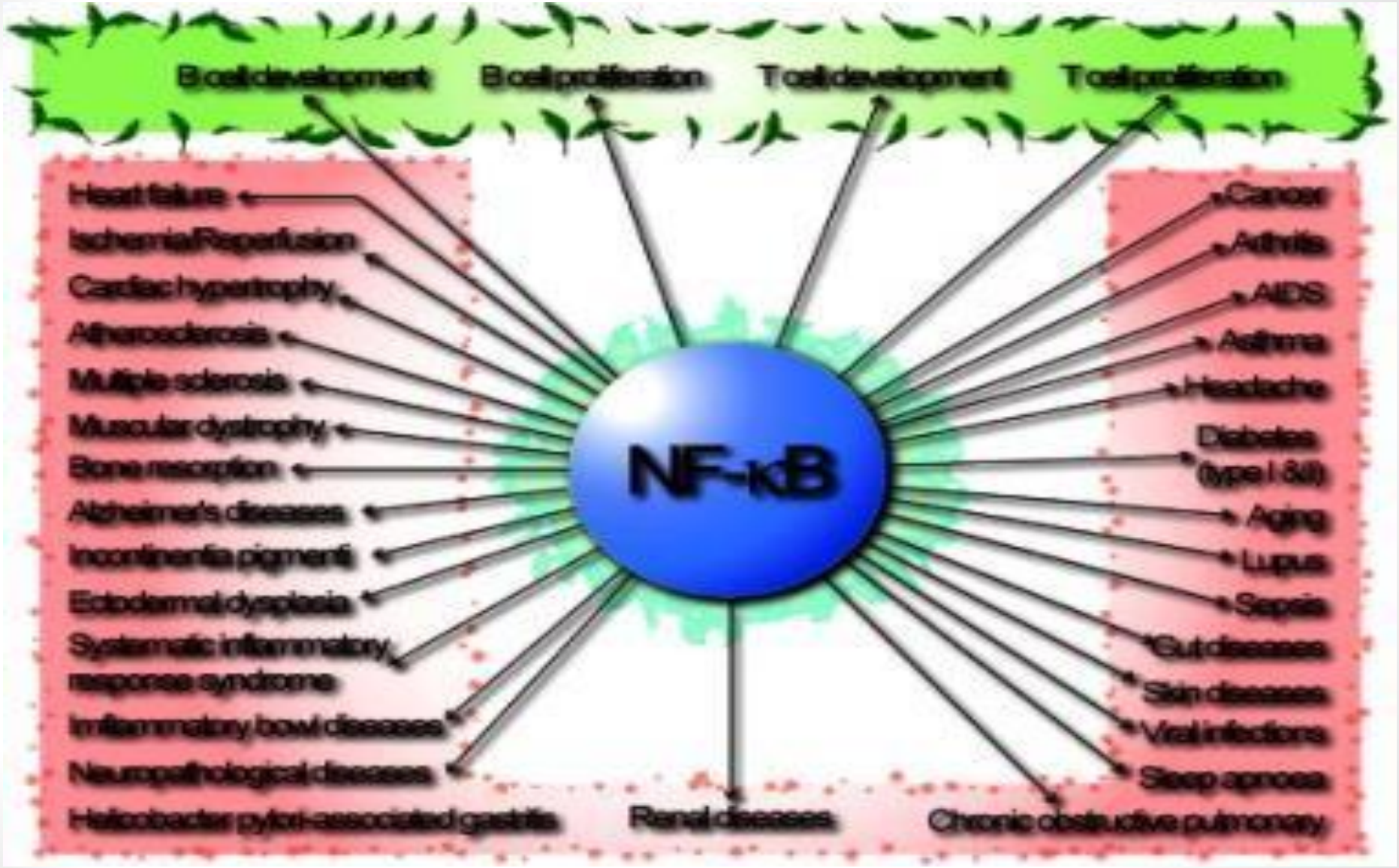






Aggarwal etal, CCR, 2010

NF-kappa B activation has been linked to most major diseases



Journal of Molecular Medicine 2004;82:434-48

A Fire Extinguisher!

How to suppress NF-κB activation safely?

Natural products have played a significant role in the discovery of cancer drugs over the years;

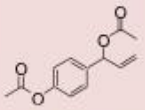
more than 70% of drugs have their roots in natural products

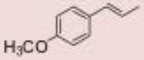
Newman, D. J., and Cragg, G. M. (2012)
Natural products as sources of new drugs over the 30 years from 198 to 2010.
Journal Natural Products 75, 311–335

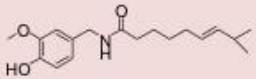
Anti-Inflammatory life style :Natural

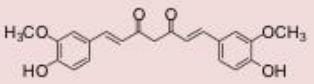
NF-κB Inhibitors

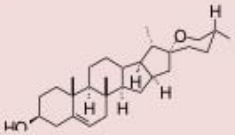
Spices

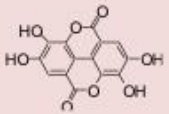

1'-Actoxychav-icolacetate

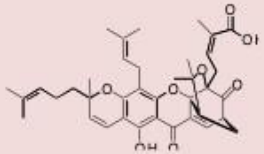

Anethole

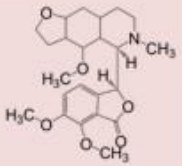

Capsaicin

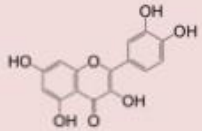

Curcumin

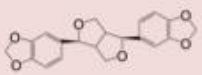

Diosgenin

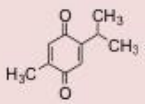

Ellagicacid

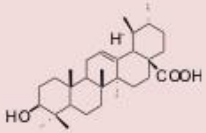

Gambogic acid


Noscapine

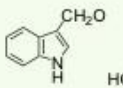

Quercetin

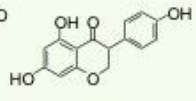

Sesamin

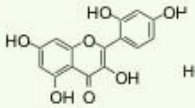

Thymoquinone

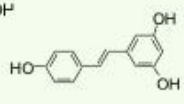

Ursolicacid

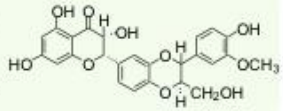
Fruits & Vegetables


Indole 3-carbinol

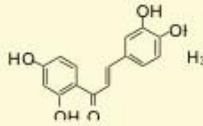

Genistein

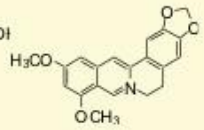

Morin

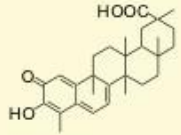

Resveratrol

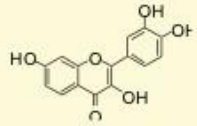

Silymarin

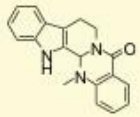
Traditional Chinese Medicine

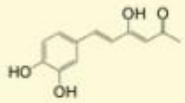

Butein

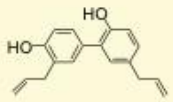

Berberin

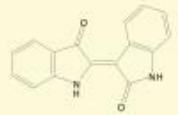

Celastrol


Fisetin

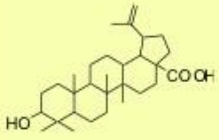

Evodiamine

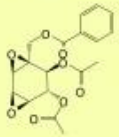

Hispolon


Honokiol


Indirubin

Ayurvedic Medicine


Betulinicacid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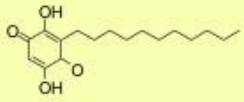
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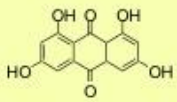
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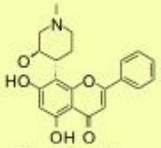
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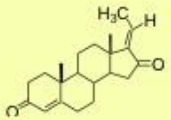
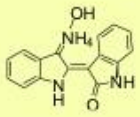
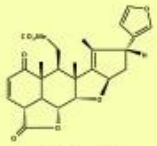
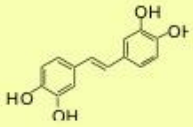
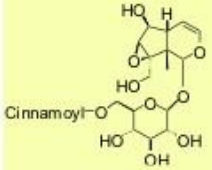
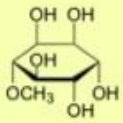

Guggulusterone


Indirubin 3'-monoxime


Nimbolide


Piceatannol


Picroliv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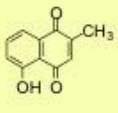
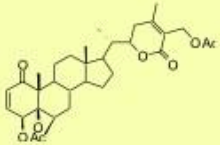
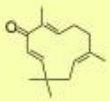
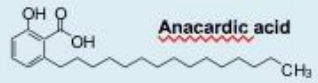

Plumbagin


Withanolide


Zerumbone

Others


Anacardic acid

Coronarin-D

Deguelin

Gossypin

Gossypol

Isodeoxyelephantopin

Pentamethoxyflavone

Oleandrin

Thiocolchicoside

γ-Tocotrienol

Xanthohumol

Inflammation as a risk factor for most cancers

Inducer	Inflammation	Cancers	% predisposed progress to cancer
Tobacco smoke	Bronchitis	Lung Cancer	11-24
Helicobacter pylori	Gastritis	Gastric Cancer	1 - 3
Human papilloma virus	Cervicitis	Cervical cancer	<1
Hepatitis B & C virus	Hepatitis HCC	10	
Bacteria, GBS	Cholecystitis	Gall bladder cancer	1 – 2%
Gram- uropathogens	Cystitis	Bladder cancer	<1
Tobacco, genetics	Pancreatitis	Pancreatic cancer	≤10%
GA, alcohol, tobacco	Esophagitis	Esophageal cancer 15	
Asbestos fibers	Asbestosis	Mesothelioma	10–15
Epstein-Barr virus	Mononucleosis	Burkitt's lymphoma	<1
	Hodgkin's disease		
Gut pathogens	IBD	Colorectal cancer	1*
Ultraviolet light	Sunburn	Melanoma	≤9%
Infections, STD	PIA	Prostate cancer	?

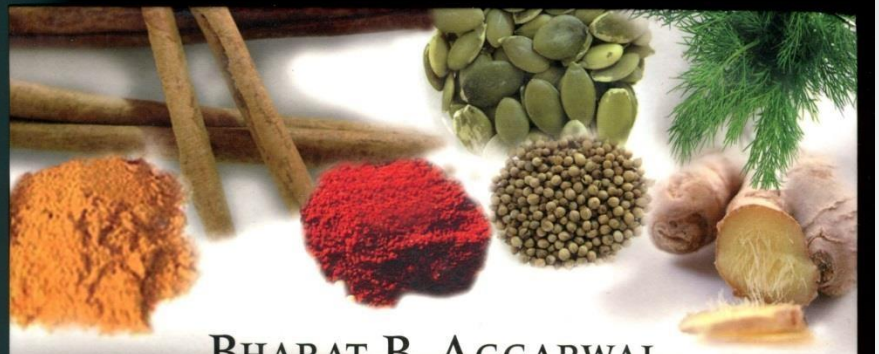
GA, gastric acid; GBS, gall bladder stones; HCC, hepatocellular carcinoma; STD, sexually transmitted diseases; PIA, prostate inflammatory atrophy.

Aggarwal BB, et al. Biochemical Pharmacology, 72, 2006, 1605-21

HEALING Spices

USE SPICES TO BOOST HEALTH AND BEAT DISEASE

BHARAT B. AGGARWAL, PHD



BHARAT B. AGGARWAL

Le SPEZIE che salvano la vita

Prevenire le malattie cardiache, il cancro e il diabete grazie all'uso di questi aromi naturali

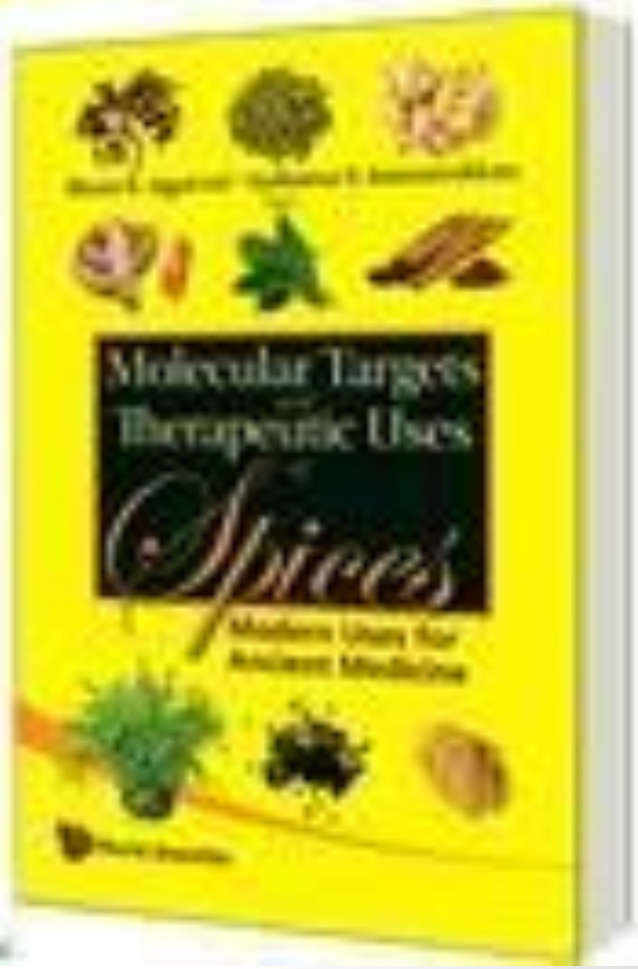
ARMENIA

Connecting Great Minds

MOLECULAR TARGETS AND THERAPEUTIC USES OF SPICES

Modern Uses for Ancient Medicine

edited by Bharat B Aggarwal (The University of Texas M D Anderson Cancer Center, Houston, Texas, USA) & Ajaikumar B Kunnumakkara (National Institute of Health, Bethesda, MD, USA)



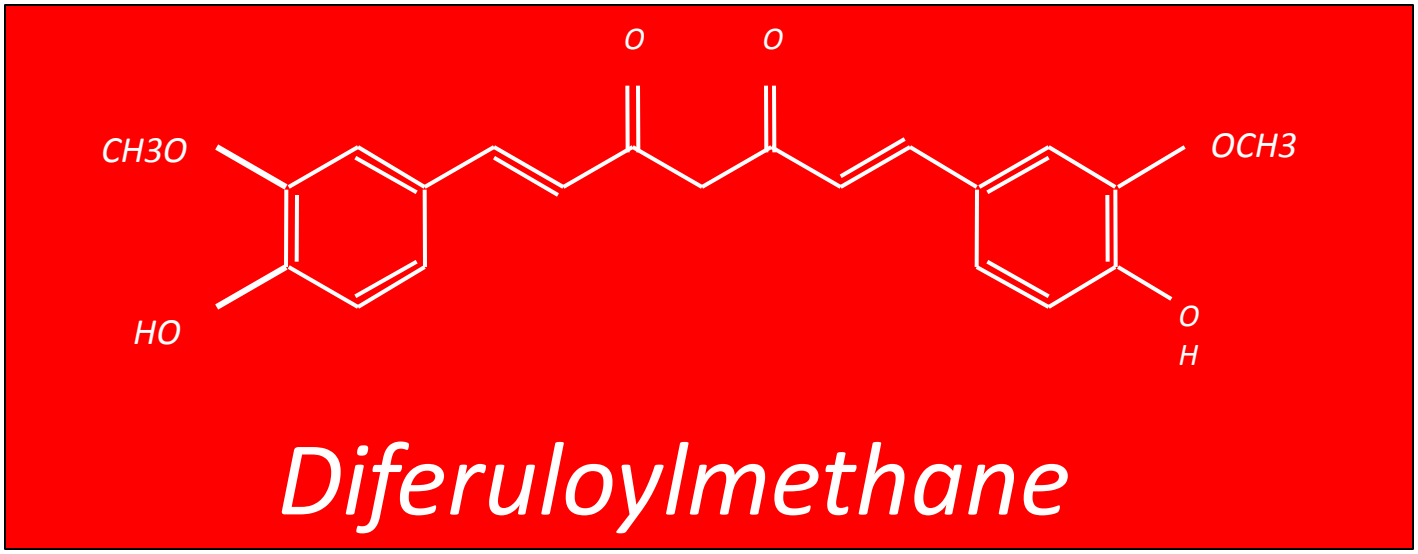
Most therapeutics available today are highly toxic.

Contents

Add spices to your diet and life!

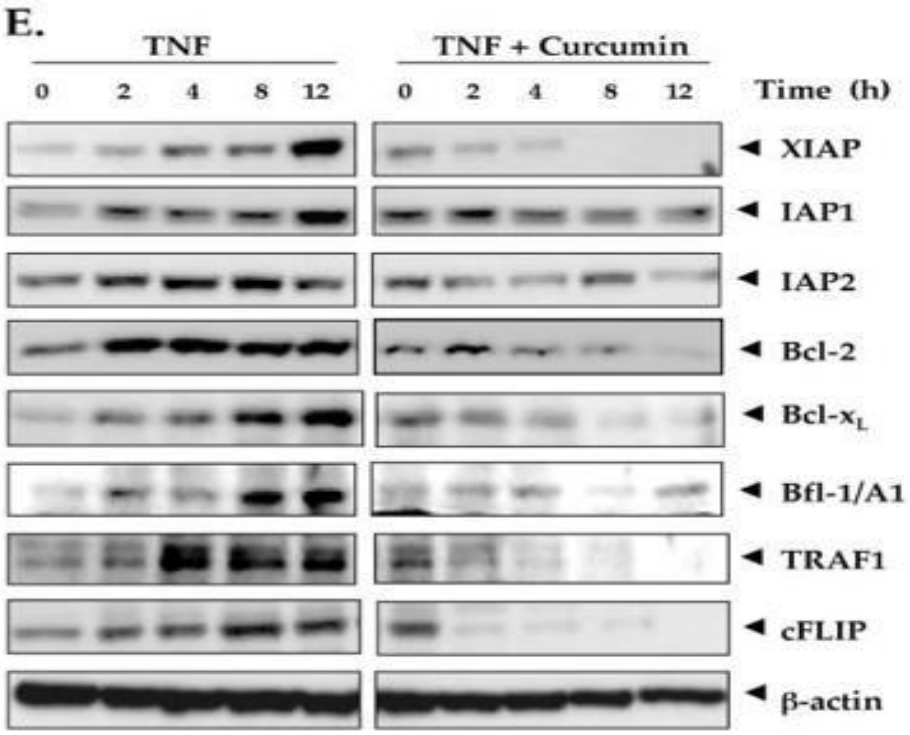
Structure of Curcumin

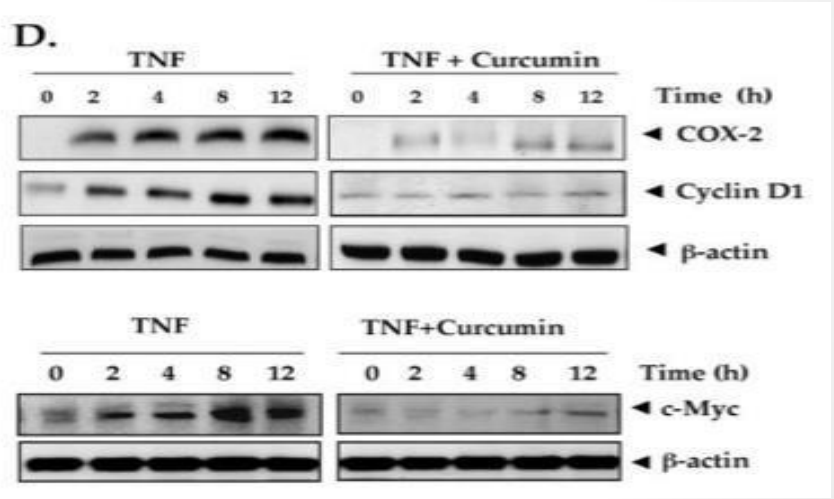
From turmeric (curry powder)

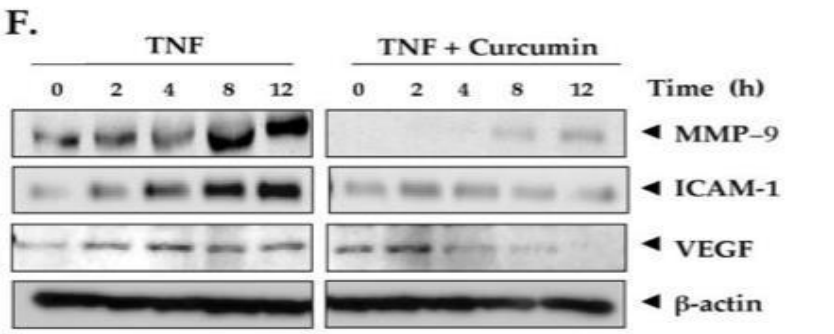


Curcumin Downregulates Expression of Cell Proliferation, Antiapoptotic and Metastatic Gene Products Through Suppression of IκBα Kinase and AKT Activation

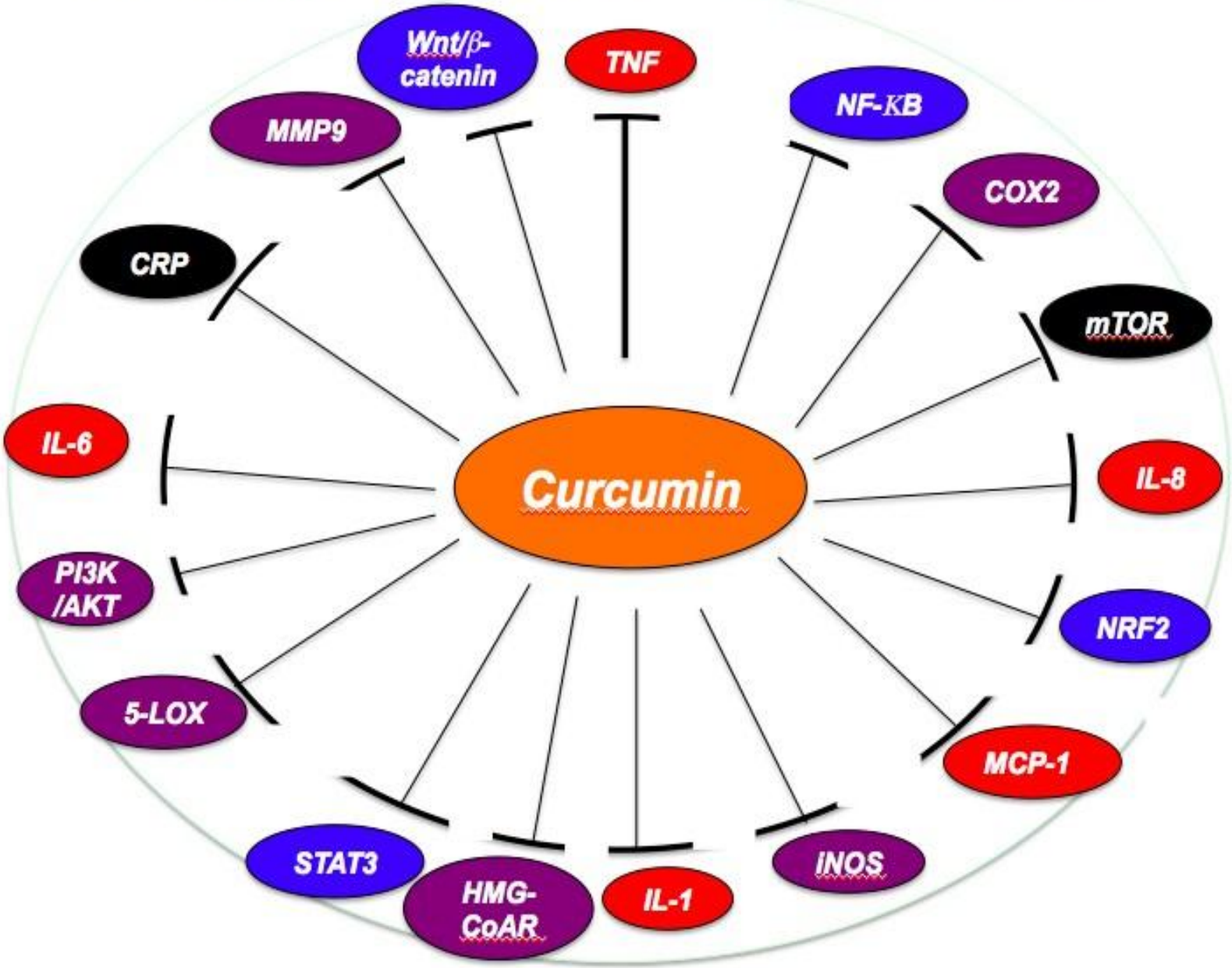
Aggarwal, et al., Molecular Pharmacology, 2006; 69(1):195-206



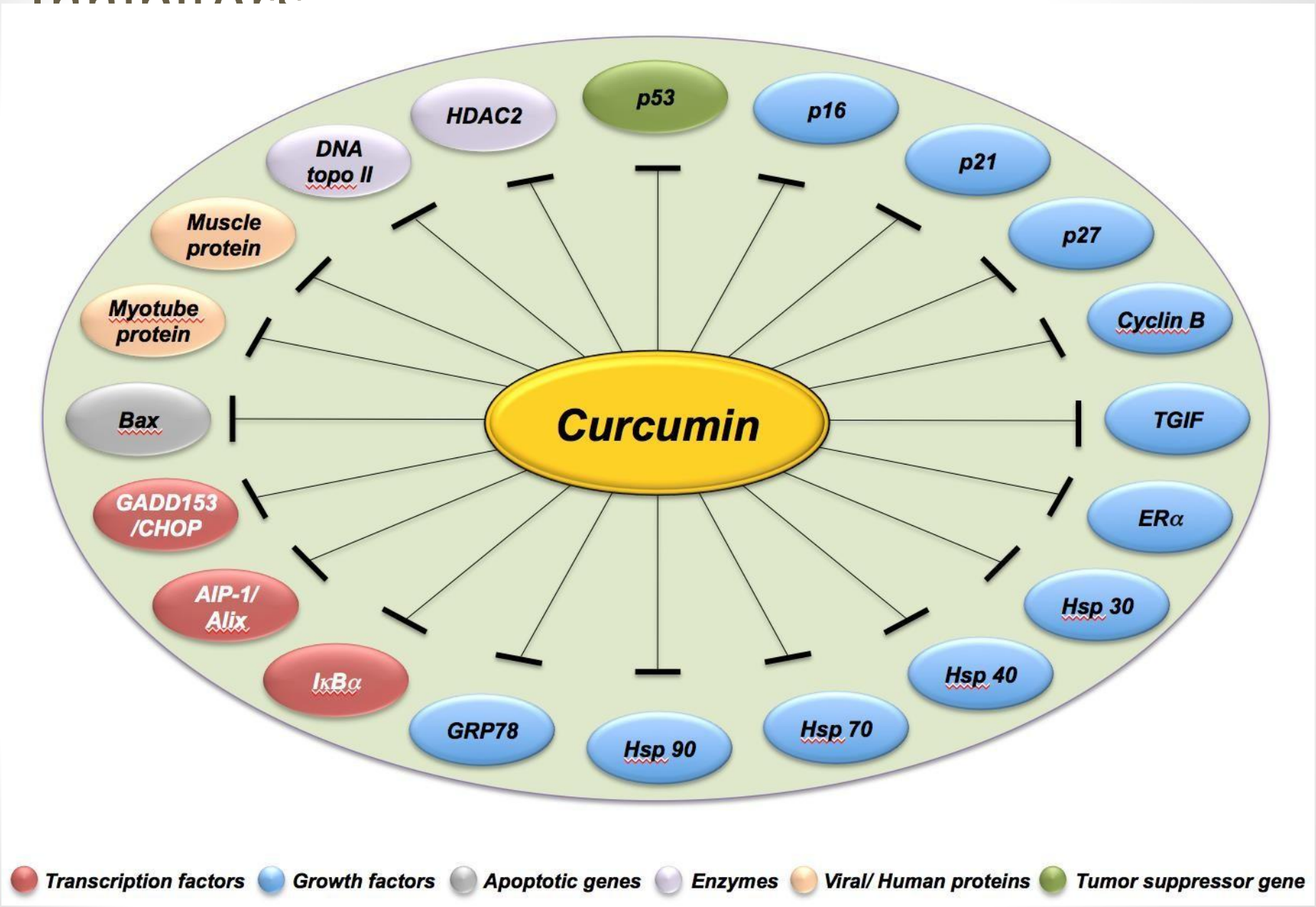




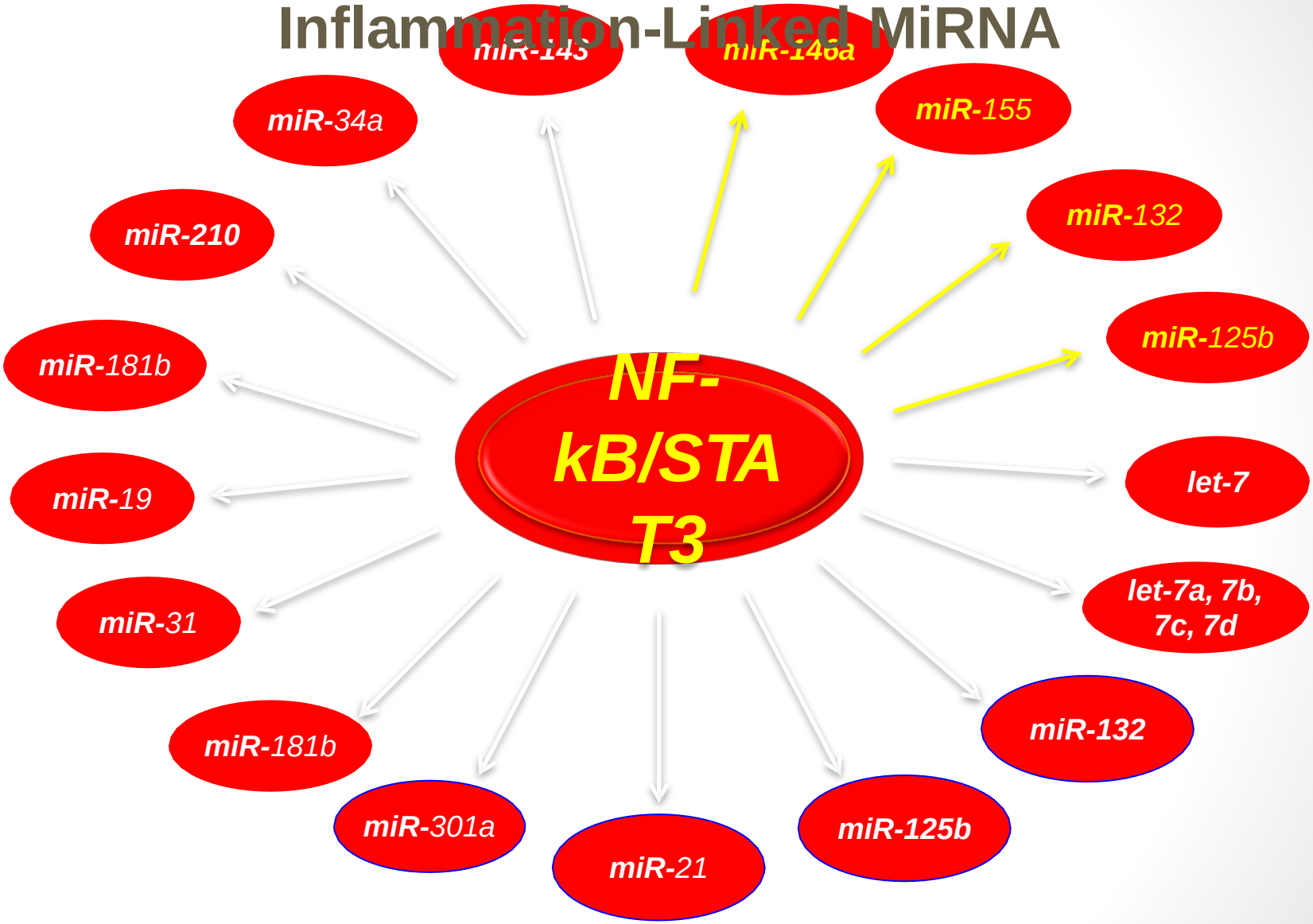
Inflammatory Targets of Curcumin



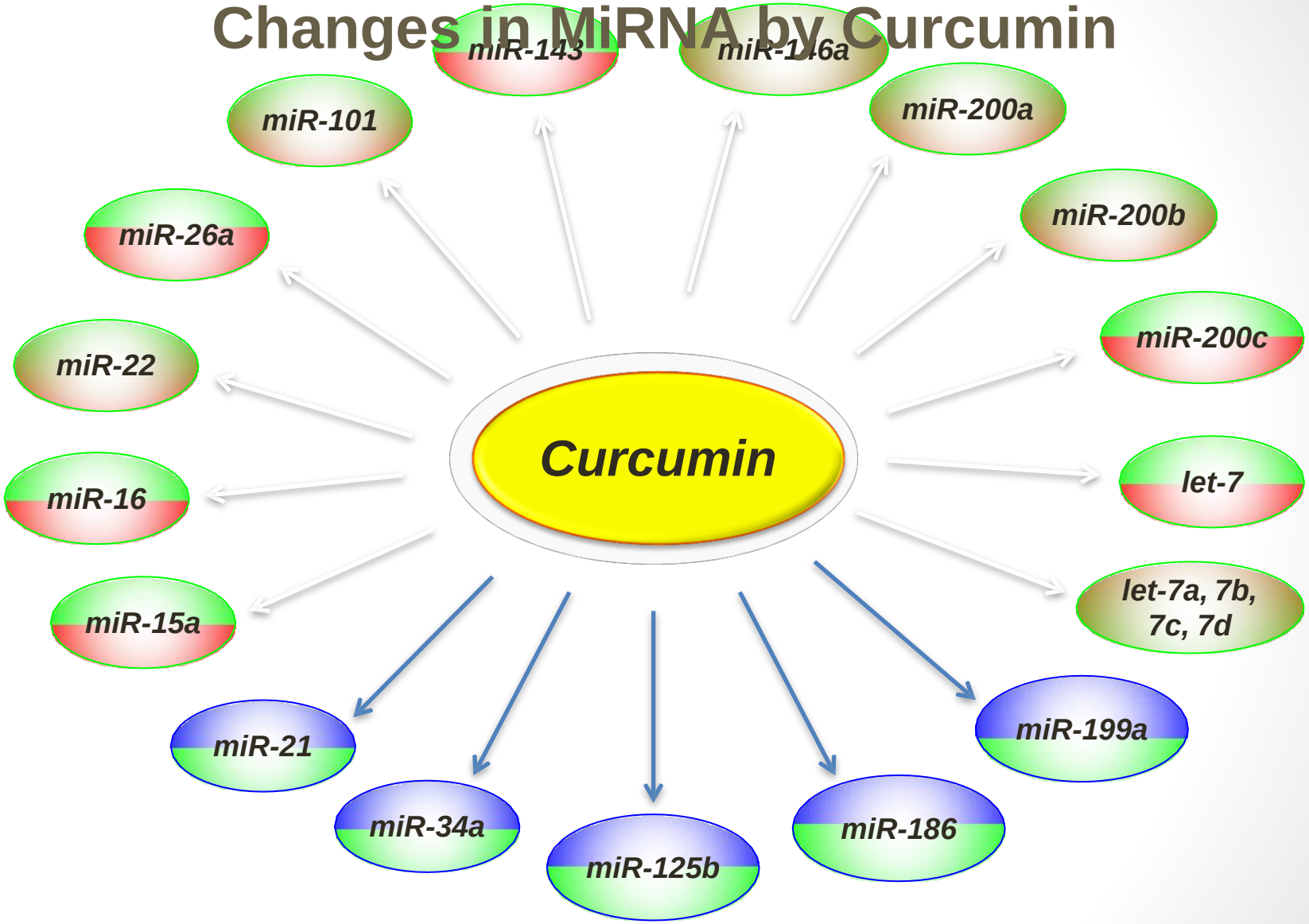
Curcumin as a Proteasome Inhibitors



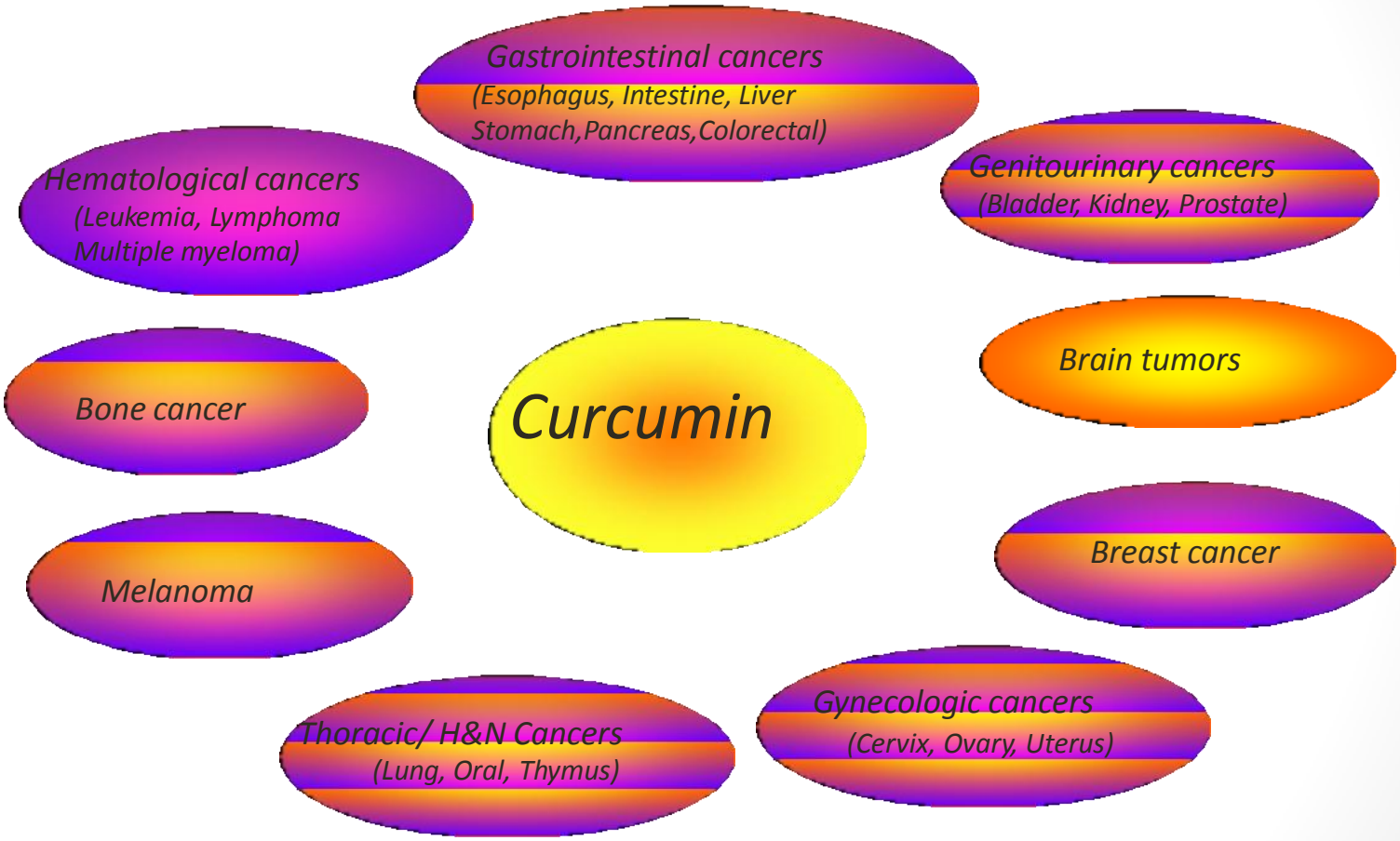
Inflammation-Linked MiRNA



Changes in MiRNA by Curcumin

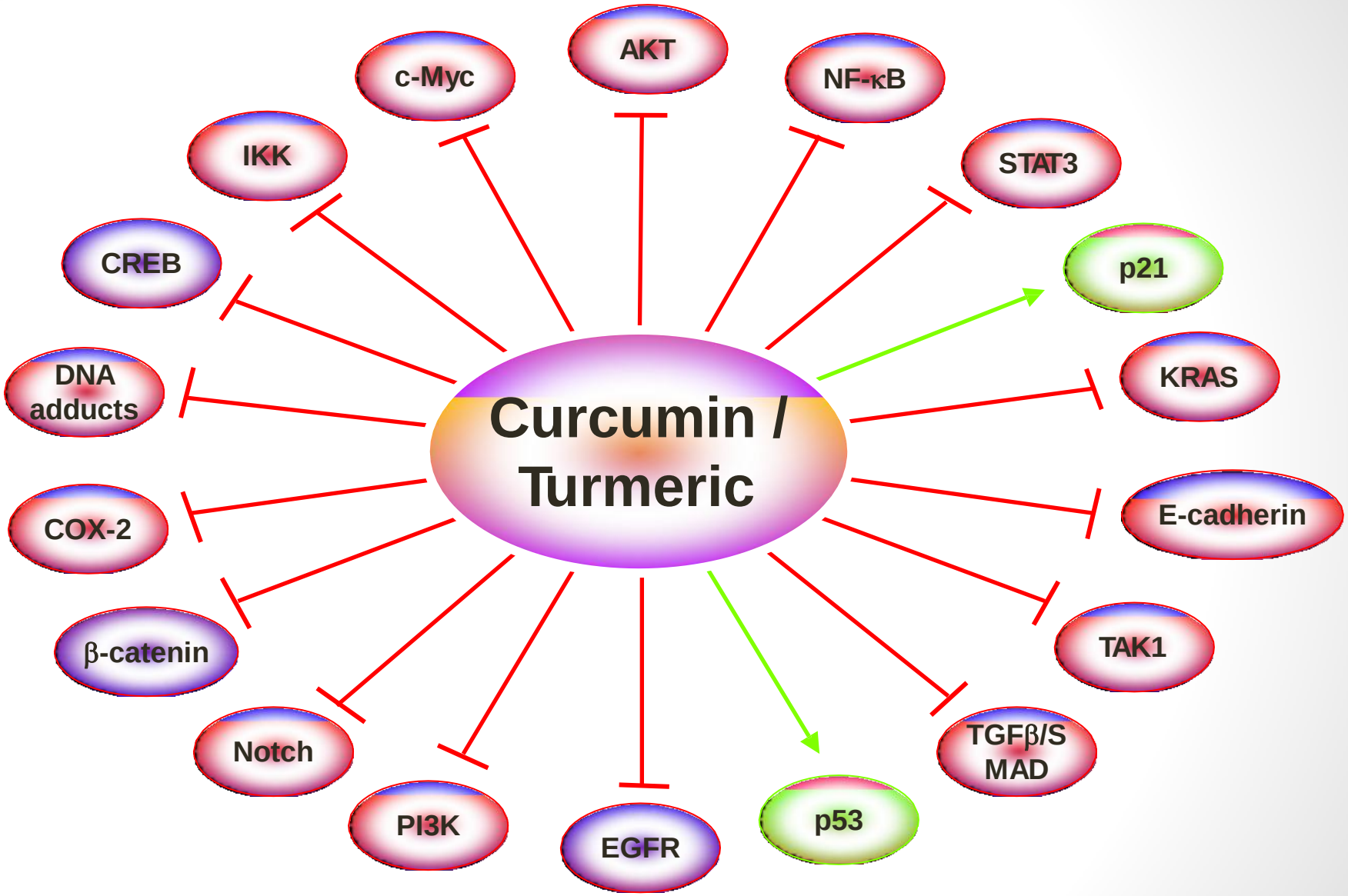


Preclinical data with curcumin against various cancers



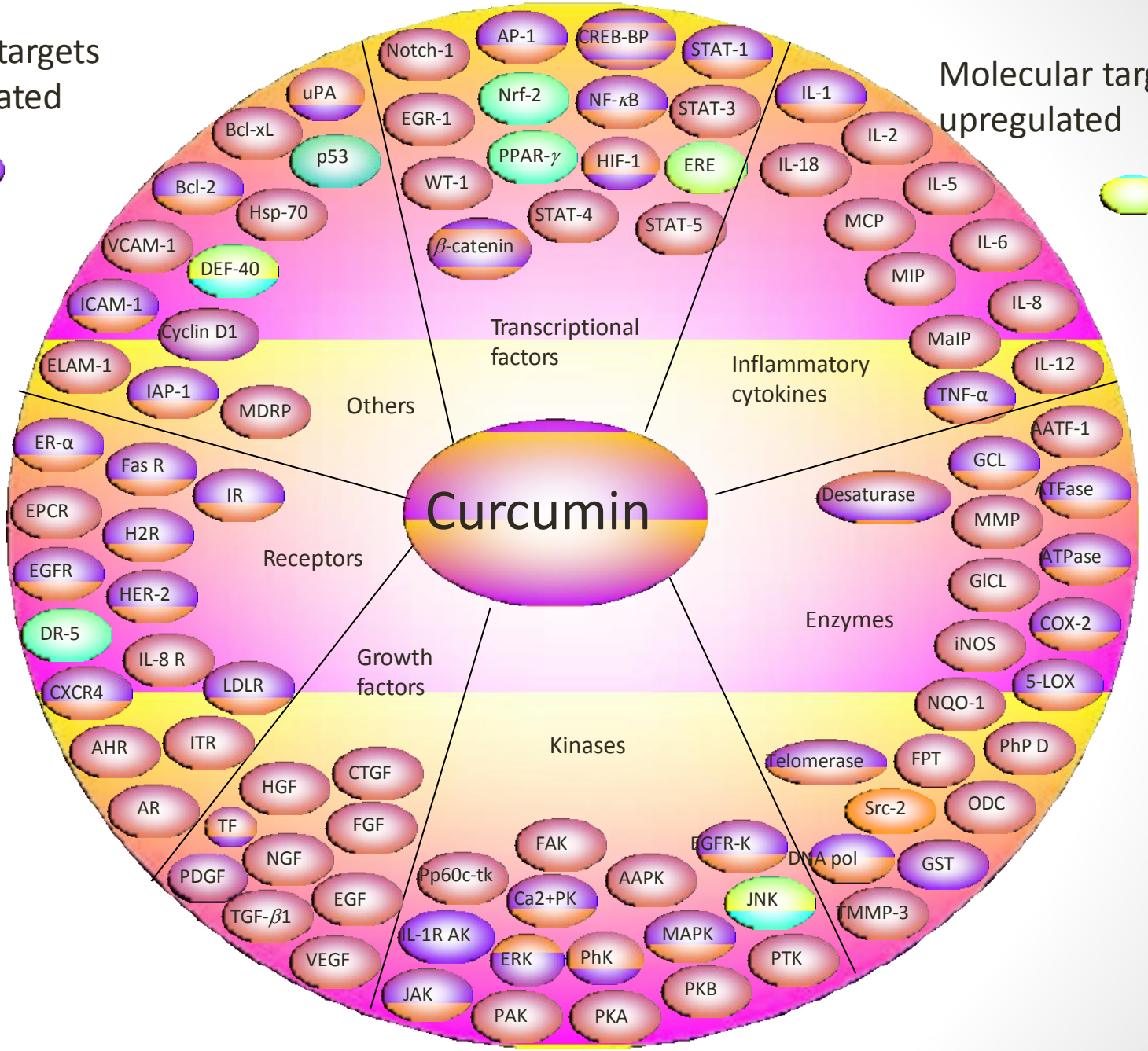
Anand etal, Cancer Letters, 2008

Multi-targeted Approach to Prevention of Colorectal Cancer by Curcumin/Turmeric

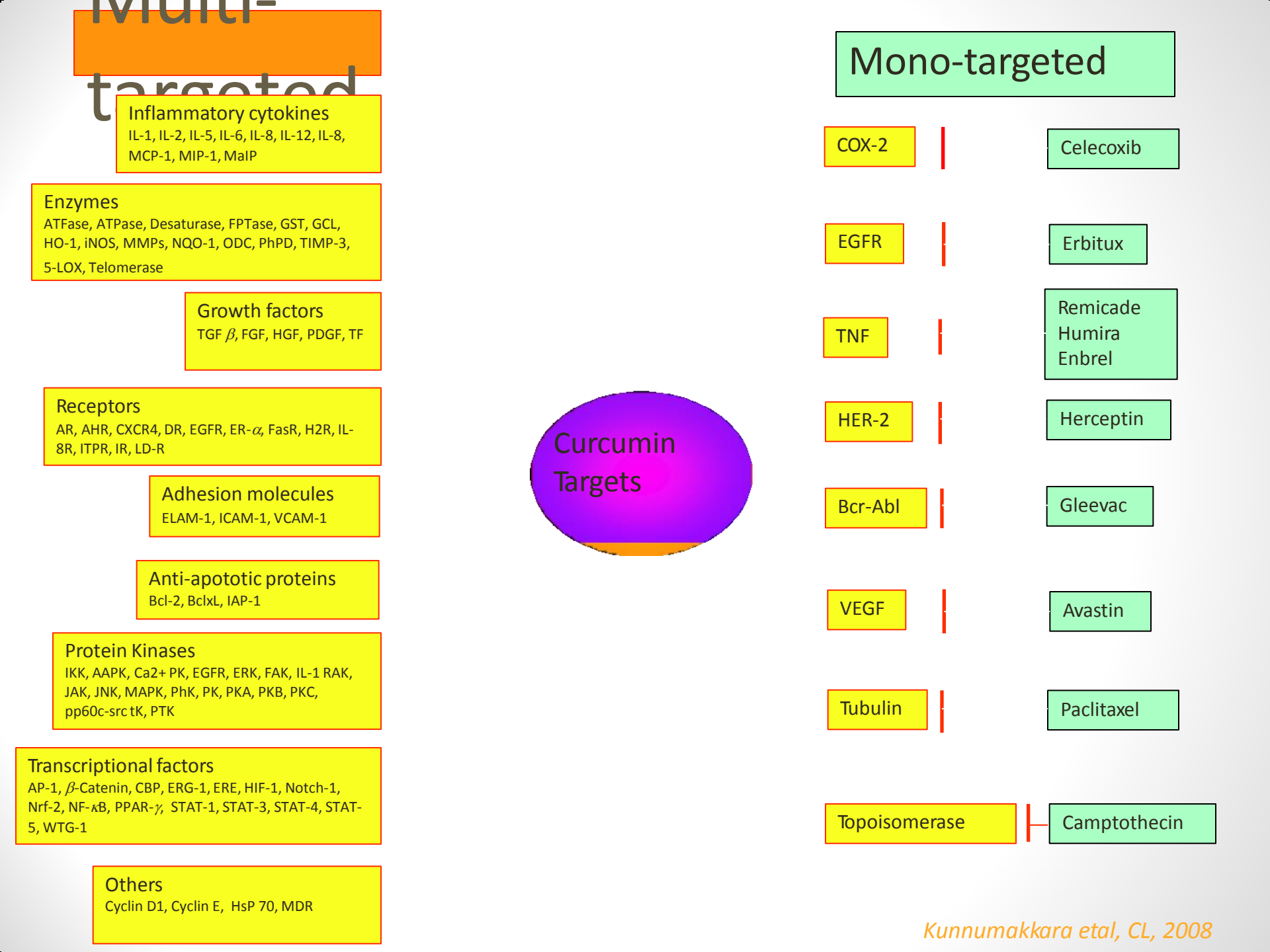


Molecular targets downregulated

Molecular targets upregulated



Anand etal, CL, 2008

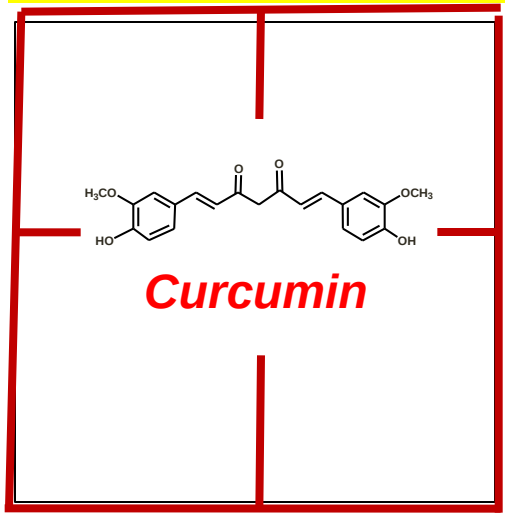


Kunnumakkara etal, CL, 2008

Curcu Trials?

Cancer
- Colorectal cancer
- Pancreatic cancer
- Breast cancer
- Prostate cancer
- Multiple myeloma
- Lung cancer
- Cancer lesions
- Head and neck cancer

Inflammatory diseases
- Crohn disease
- Ulcerative proctitis
- Ulcerative colitis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Rheumatoid arthritis
- Osteoarthritis
- Chronic anterior uveitis
- Recurrent anterior uveitis
- Post operative Inflammation
- Gastric ulcer
- Peptic ulcer
- H. pylori infection
- Idiopathic orbital inflammatory Pseudotumor



Skin diseases
- Vitiligo
- Psoriasis

Neurodegenerative diseases
- Dejerine-Sottas disease
- Alzheimer's disease

Cardiovascular diseases
- Acute coronary syndrome
- Atherosclerosis

Metabolic diseases
- Diabetes
- Diabetic nephropathy
- Diabetic microangiopathy
- Lupus nephritis

Renal diseases
- Renal transplantation

Viral diseases
- Acquired immunodeficiency syndrome

OTHERS
- β-Thalassemia
- Biliary dyskinesia
- Gallbladder contraction
- Recurrent respiratory tract infections
- Cholecystitis
- Hepatoprotection
- Chronic arsenic exposure
- Alcohol intoxication
- Chronic bacterial prostatitis

Curcumin downregulates NF-ĸB and related genes in patients with multiple myeloma:

Results of a phase 1/2 study.

Vadhan-Raj, et al., *Blood, 2007;110(11):357a.*

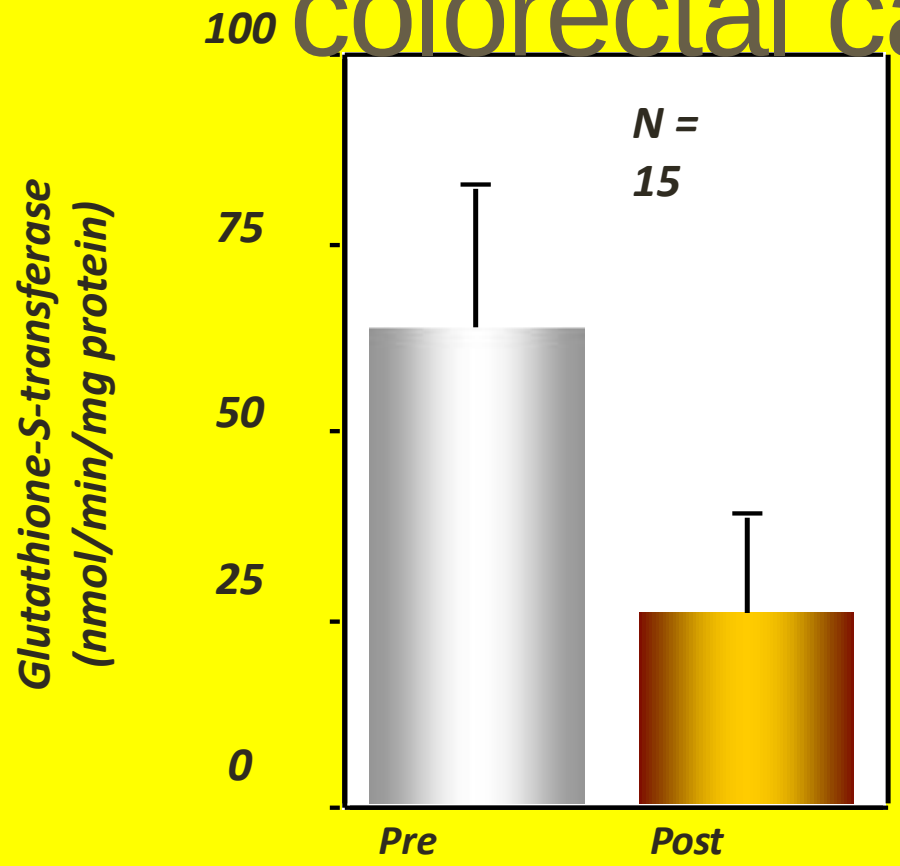
patients with asymptomatic, relapsed, or plateau phase multiple myeloma.

Curcumin was given either alone (orally at 2, 4, 6, 8, or 12 g/d in two divided doses) or in combination with bioperine (10 mg in two divided doses) for 12 weeks.

Peripheral blood mononuclear cells from 28 patients examined at baseline showed constitutively active NF-κB, COX-2, and STAT3.

Furthermore, oral administration of curcumin was associated with significant down-regulation in the constitutive activation of NF-κB and STAT3, and it suppressed COX-2 expression in most of the patients. These observations suggest the potential of curcumin against multiple myeloma.

glutathione S-transferase in lymphocytes from patients with colorectal cancer

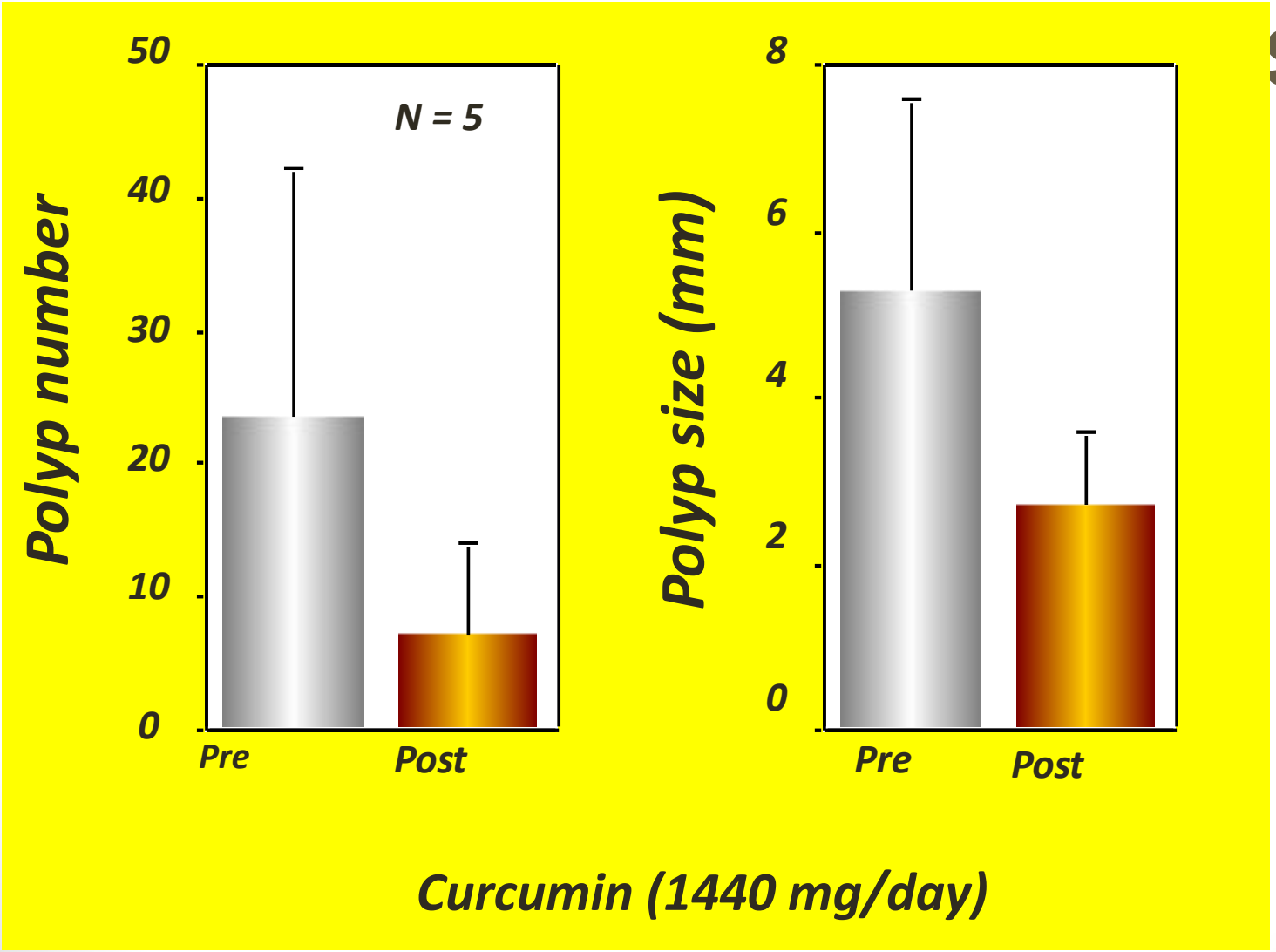


Ingestion of 440 mg of Curcuma extract (36 mg curcumin) for 29 days was accompanied by a 59% decrease in lymphocytic glutathione S-transferase activity.

At higher dose levels, this effect was not observed.

Sharma et al., 2001, Clinical Cancer Research

curcumin and quercetin of adenomas in familial sis

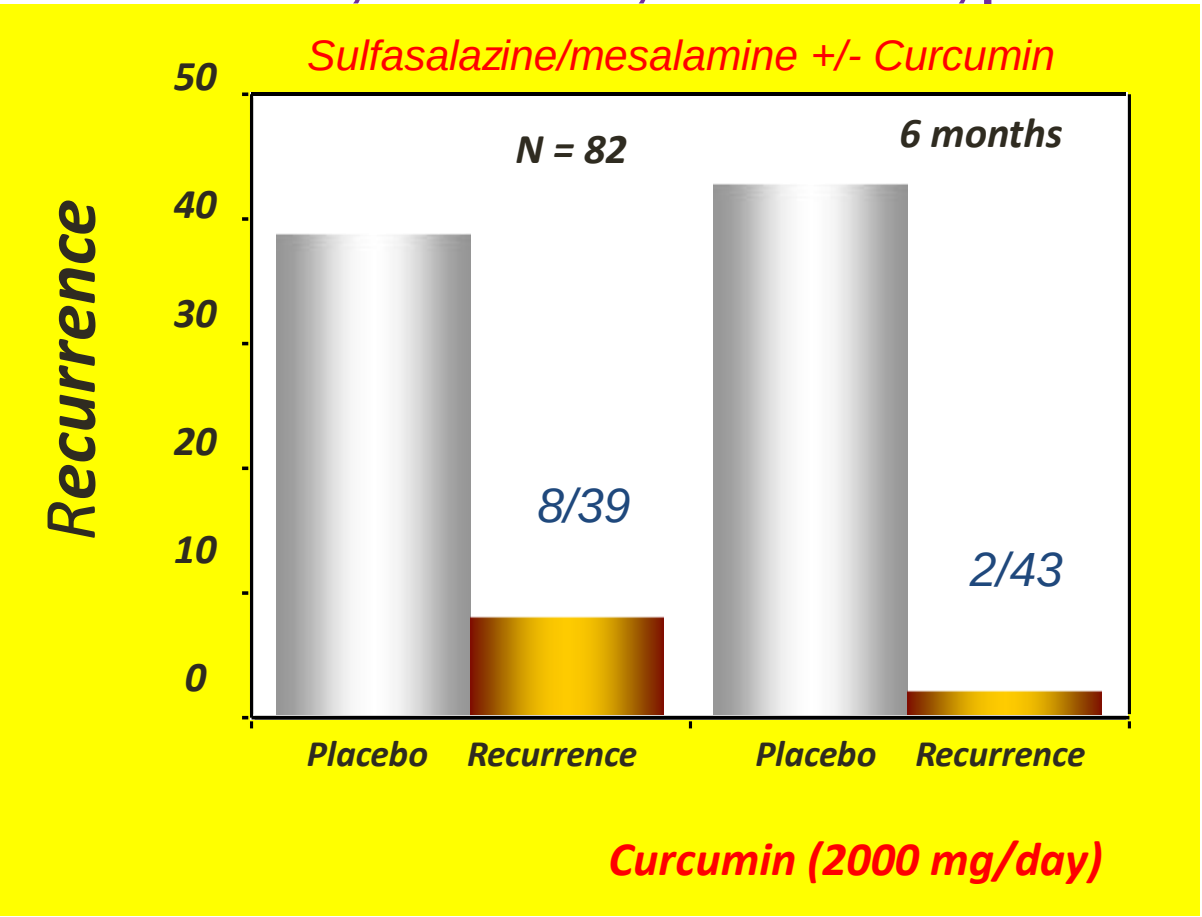


After six months, the mean percent decrease in the number and size of polyps from baseline was 60.4%

and 50.9%, respectively.

Curcumin maintenance therapy for ulcerative colitis:

randomized, multicenter, double-blind, placebo-controlled trial.



Eighty-nine patients with quiescent UC were recruited.

Forty-five patients received curcumin, 1g after breakfast and 1g after the evening meal, plus sulfasalazine (SZ) or mesalamine, and 44 patients received placebo plus SZ or mesalamine for 6 months.

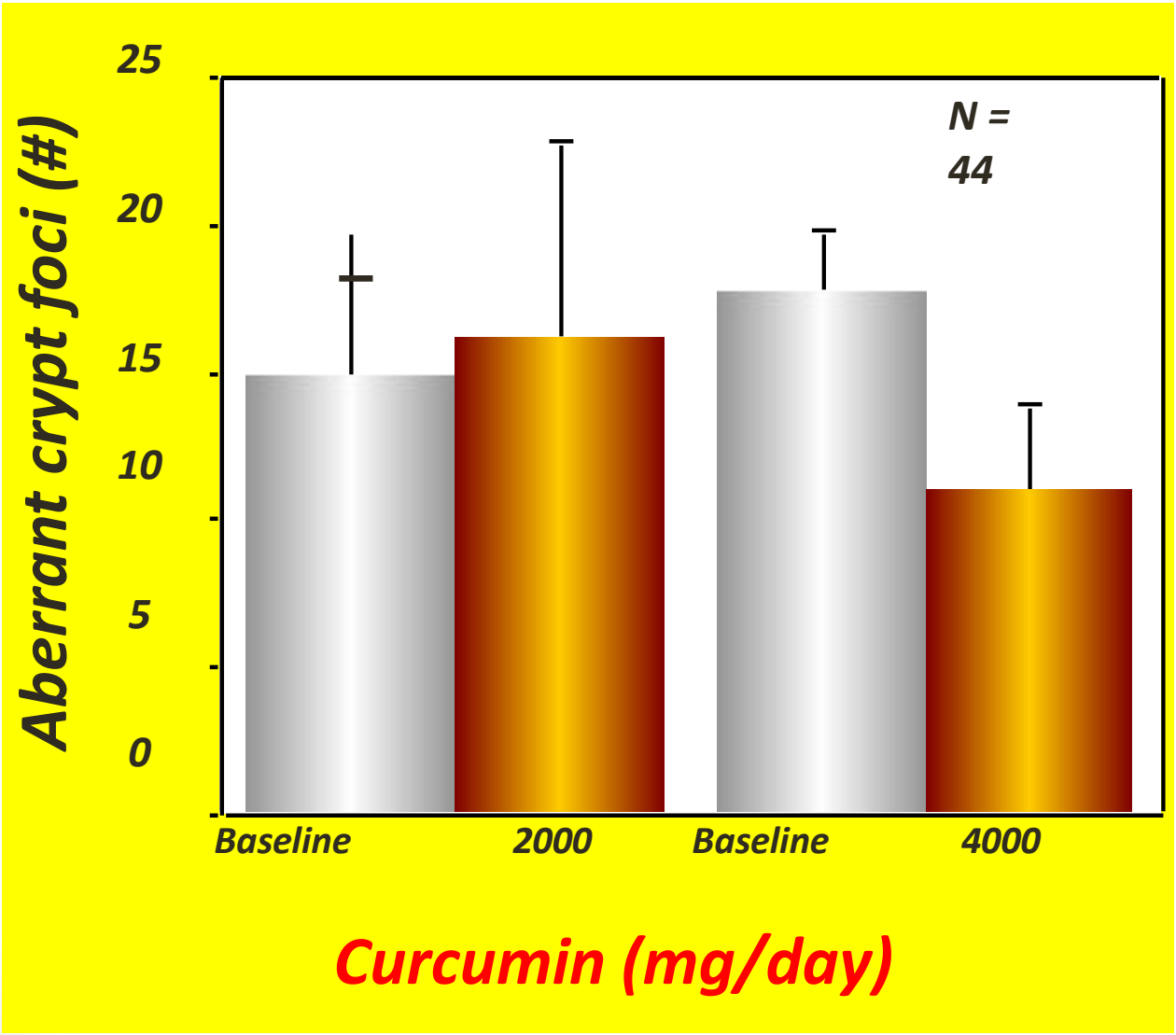
Of 43 patients who received curcumin, 2 relapsed during 6 months of therapy , whereas 8 of 39 patients in the placebo group relapsed.

Furthermore, curcumin improved both CAI (P=.038) and EI (P=.0001), thus suppressing the morbidity associated with UC.

A 6-month follow-up was done during which patients in both groups were on SZ or mesalamine.

Hanai et al., 2006, Clinical Gastroenterology Hepatology

Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia



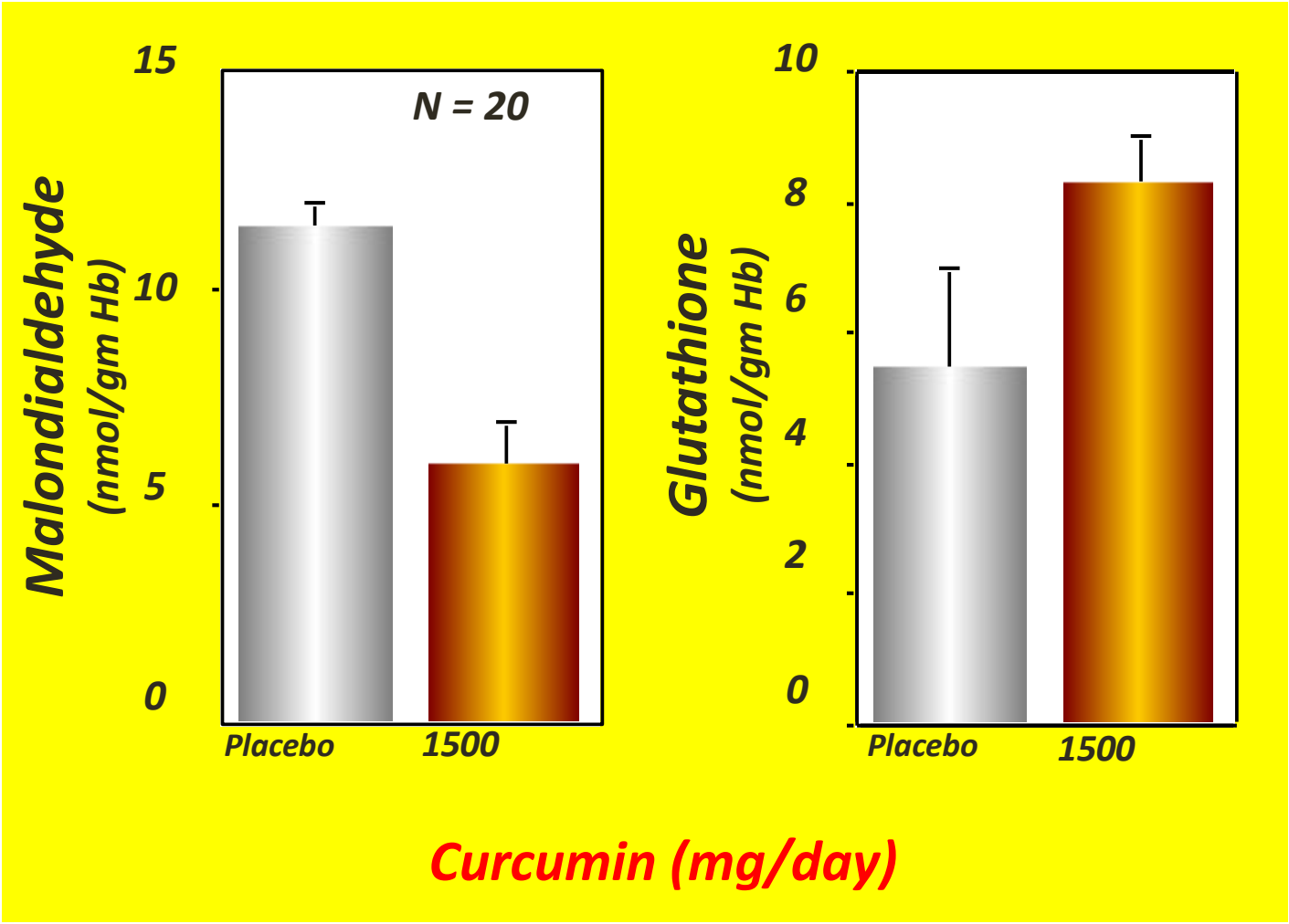
Forty-one subjects completed the study (30 days).

Neither dose of curcumin reduced PGE_2 or 5-HETE within ACF or normal mucosa or reduced Ki-67 in normal mucosa.

A significant 40% reduction in ACF number occurred with the 4-g dose, whereas ACF were not reduced in the 2-g group

Carroll et al., 2011, Cancer Prevention Research

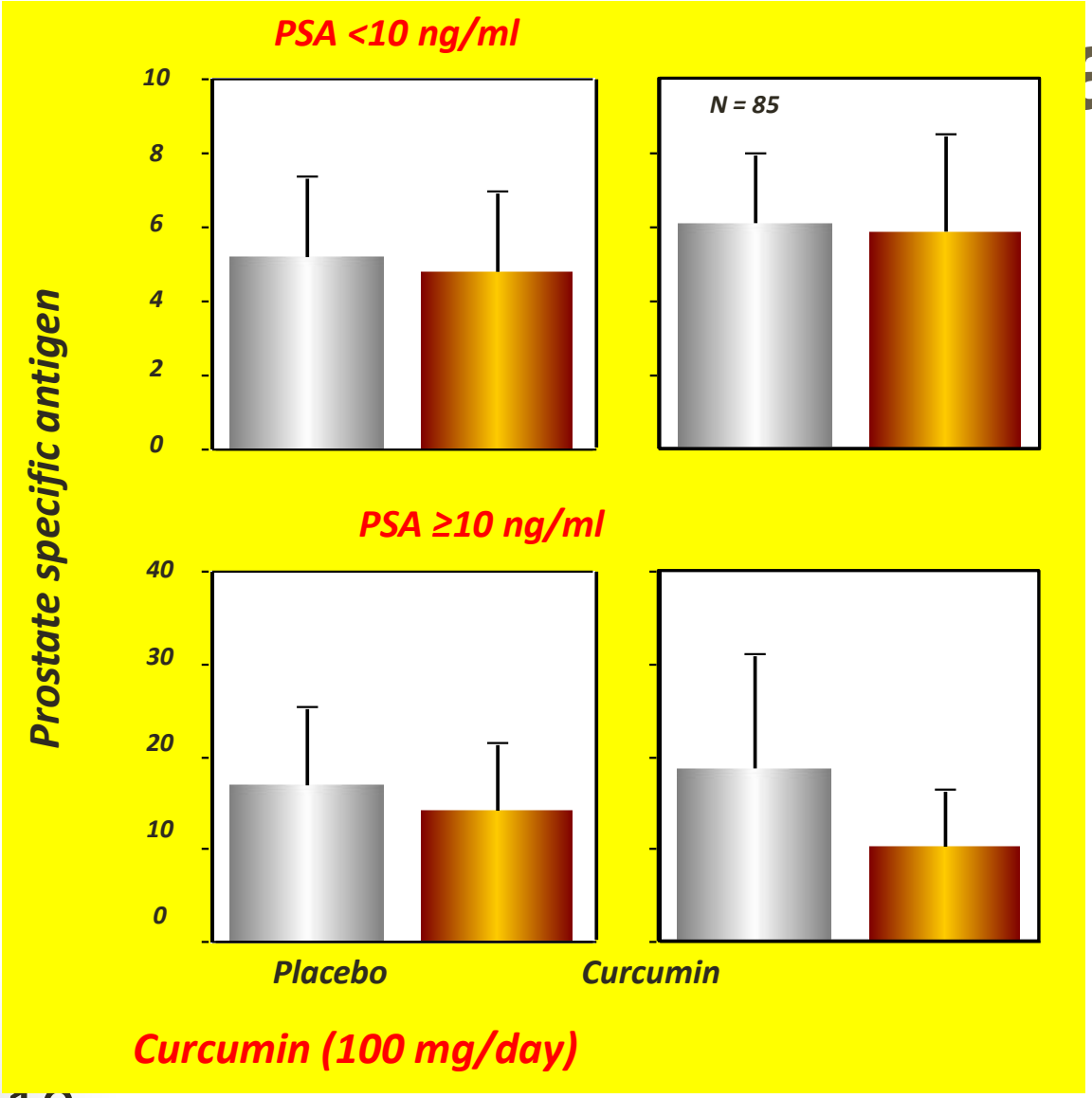
A pilot study of the antioxidant effect of curcumin in tropical pancreatitis.



MDA and GSH levels in patients with tropical pancreatitis after oral administration of curcumin for 6 weeks

Durgaprasad et al., 2005, Indian Journal Medical Research

# of soy isoflavones and curcumin on the production antigen



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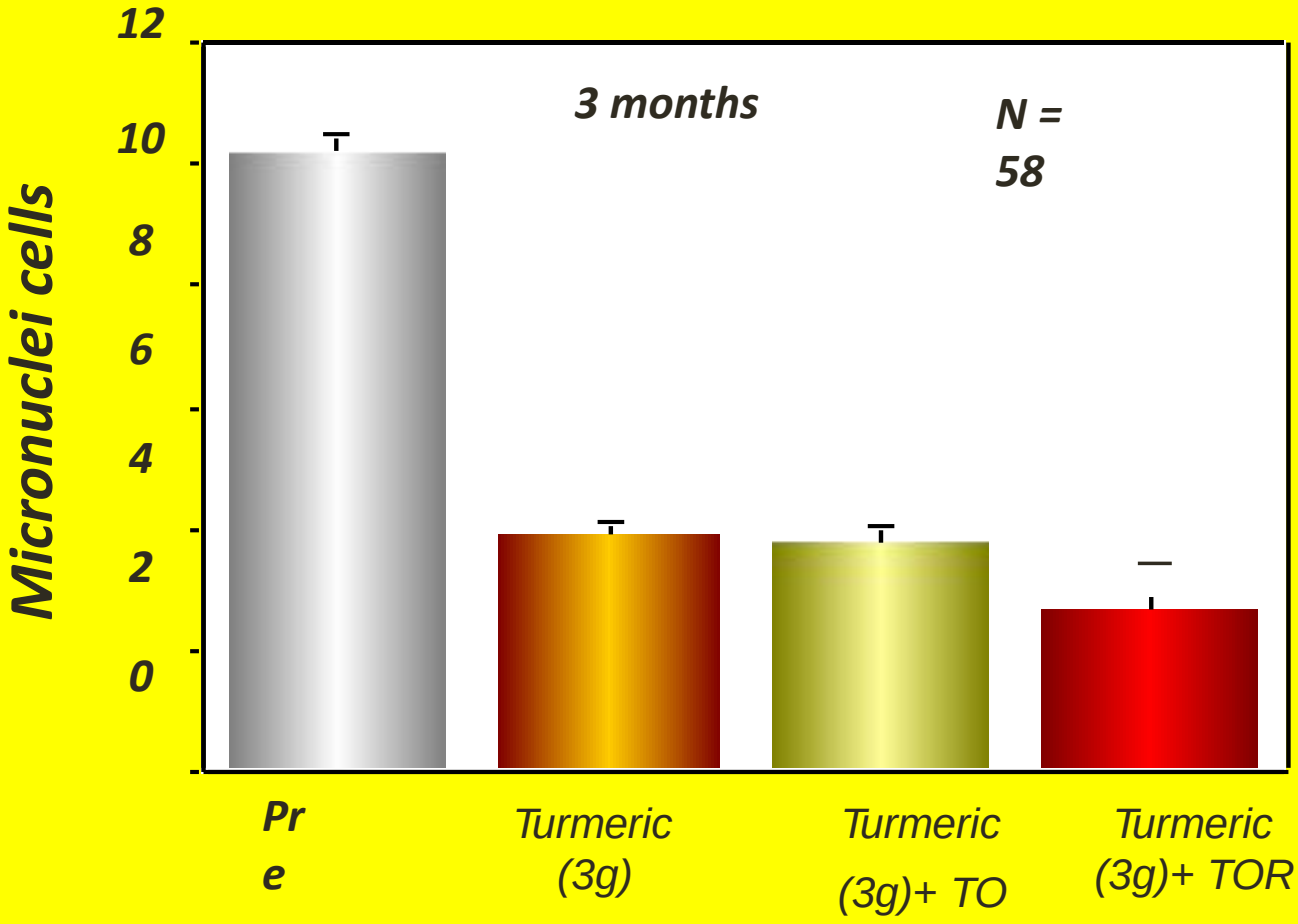
Ide et al., 2010, Prostate.

Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis.



Patients suffering from submucous fibrosis were given a total oral dose of turmeric oil (600 mg TO mixed with 3 g turmeric/day).

Turmeric oleoresin (600 mg + 3 g turmeric/day) and 3 g turmeric/day as a control for 3 months.

It was observed that all three treatment modalities decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes.

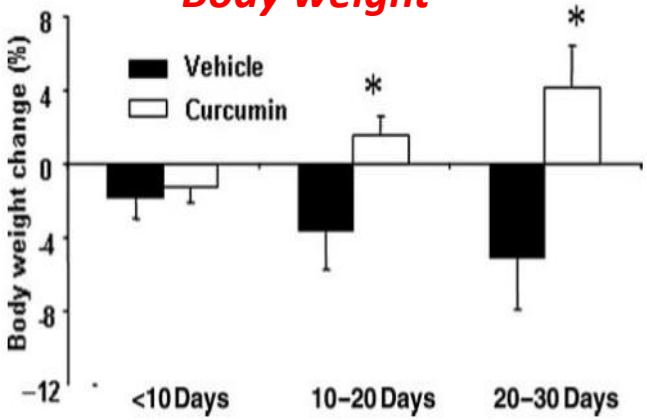
Turmeric oleoresin was found to be more effective in reducing the number of Mn in oral mucosal cells, but in circulating lymphocytes the decrease in Mn was comparable in all three groups.

Hastak et al., 1997, Cancer Lett .

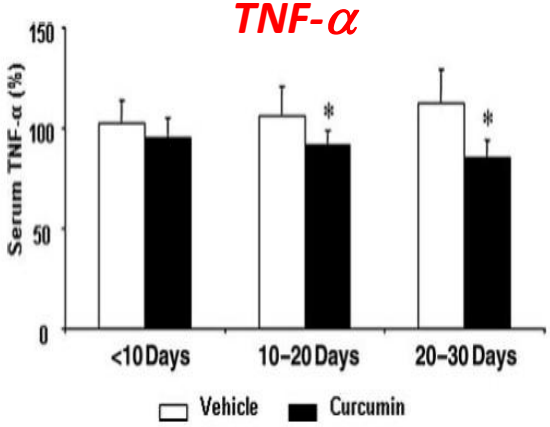
Curcumin & CRC patients

126 pts; 360 mg curcumin; thrice/day

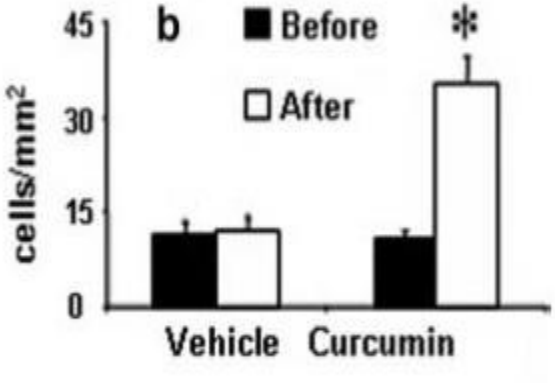
Body weight



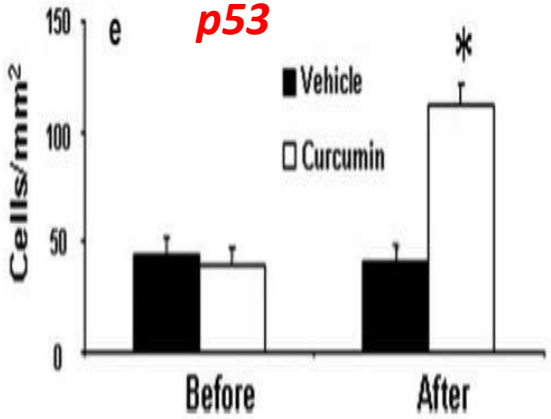
TNF-α

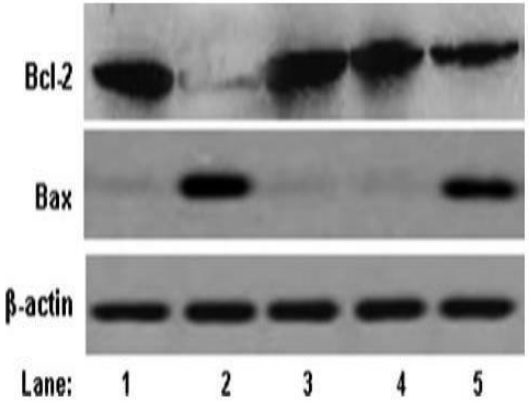


Apoptosis



p53





(He et al, 2011)

Cancer incidence is less in spice consuming countries:

Comparison of Cancer Incidence in USA and India

Cancer	USA		India	
	Cases	Deaths	Cases	Deaths
Breast	660	160	79	41
Prostate	690	130	20	9
Colon/Rectum	530	220	30	18
Lung	660	580	3 8	37
Head & Neck SCC	140	44	153	103
Liver	41	44	12	13
Pancreas	108	103	8	8
Stomach	81	50	33	30
Melanoma	145	27	1.8	1
Testis	21	1	3	1
Bladder	202	43	15	11
Kidney	115	44	6	4
Brain, Nervous system	65	47	19	14
Thyroid	55	5	12	3
Endometrial Cancers	163	41	132	72
Ovary	76	50	20	12
Multiple myeloma	50	40	6	5
Leukemia	100	70	19	17
Non-Hodgkin lymphoma	180	90	17	15
Hodgkin's disease	20	5	7	4

Showing cases per 1 million persons calculated on the basis of current consensus: Endometrial cancers include Cervix uteri and Corpus uteri.

GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5. Lyon, IARC Press, 2001.

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