

World of Drug Information

Volume 17 Issue 4

December 2006

DDIS

Division of
Drug Information Service

In this Issue...

1

LYCOPENE AND
TURMERIC: ANTI-
CANCER THERAPY
ALTERNATIVES?

7

CE ASSESSMENT
QUESTIONS

8

NEW MOLECULAR
ENTITIES &
BIOLOGICALS

11

SEARCH TIP: SEARCHING
HERBAL MEDICINES,
NATURAL PRODUCTS
AND VITAMINS

12

IMPORTANT NEW
ADDITIONS TO THE *IDIS*
DATABASE

Lycopene and Turmeric: Anti-Cancer Therapy Alternatives?

Learning Objectives

1. Describe lycopene's proposed mechanisms of action for decreasing the risk of cancer and other chronic diseases.
2. Discuss clinical studies in which lycopene supplementation was evaluated for the prevention or treatment of prostate cancer.
3. Summarize the evidence of the use of turmeric in cancer therapy.
4. Determine the safety profile of turmeric.

Introduction

The past few decades have seen an explosion of interest in herbal therapy. More recently, considerable attention has been focused on the use of herbals in the treatment of cancer, either as a chemopreventive agent or as a complementary agent to mainstream chemotherapy¹. It has been estimated that 20 to 55% of patients undergoing cancer treatment use nutritional supplements to decrease side effects and toxicity, to protect and stimulate their immune systems, or to prevent additional cancers or recurrences². This article reviews the evidence for two such interventions: lycopene and turmeric.

Lycopene

Lycopene is a red pigment found in tomatoes and tomato products, watermelon, papaya, pink grapefruit, and pink guava.³ In the American diet, more than 80% of lycopene intake comes from ketchup, tomato juice, and pizza sauce.³ Heat and processing results in increased absorption of lycopene, thus the bioavailability of lycopene is greater from processed and cooked tomato products than from raw tomatoes.^{3,4} Lycopene is also available in capsules, softgels, and tablets as an oral dietary supplement.⁵ A recent survey of 8,470 Americans found that lycopene was the 8th most commonly used dietary supplement in men aged 45-64.⁶

Epidemiological evidence has shown that dietary intake of lycopene from tomatoes and tomato products is associated with a lower risk of some chronic diseases, such as cardiovascular disease and several types of cancers; however, the evidence for the role of lycopene in disease prevention is mainly suggestive.⁷ Lycopene, a carotenoid and an acyclic isomer of beta-carotene, is one of the most potent antioxidants. As an antioxidant, it ultimately reduces oxidative stress, which may lead to decreased risk of cancer and heart disease. Additionally, it has been proposed that lycopene may lower the risk of chronic disease by regulating gene functions, improving gap-junction communication, modulating hormone and immune response, and regulating metabolism.⁷

Only a few human intervention studies have been performed to evaluate the effectiveness of lycopene in decreasing cancer risk, and most of these have utilized tomatoes or tomato products, not lycopene supplements.⁷ A number of clinical studies have used lycopene as a potential agent for the prevention or treatment of prostate cancer. This review will present some of the epidemiological evidence for the relationship between lycopene and prostate cancer and will primarily focus on studies in which lycopene supplements were used.

An association between high intake of tomato products and decreased risk of prostate cancer was noticed in a case-control study conducted between 1976 and 1979.⁸ Since that time, a number of studies examining the relationship between tomato consumption and risk of prostate cancer have been undertaken. Recently, Etminan and fellow researchers⁴ performed a meta-analysis of 11 case-control studies, 5 cohort studies, and 5 nested case-control studies. This meta-analysis showed that tomato products may play a role in preventing prostate cancer, although the effect is modest and requires a high intake. Based on the evidence from their meta-analysis, the authors did not recommend the use of lycopene supplements for the prevention of prostate cancer.

A case report by Matlaga and colleagues⁹ described dramatic improvement in a 62-year-old man with prostate cancer that had metastasized to the bone. After failing therapy with bicalutamide, ketoconazole, hydrocortisone, doxorubicin, vinorelbine, and prednisone and with a prostate specific antigen (PSA) of 365.0 ng/mL, the patient stopped formal treatment and began hospice care. He began lycopene 10 mg orally once daily and saw palmetto 300 mg orally three times daily. After two months, his PSA had decreased to 8.1 ng/mL, and ranged from 3 to 8 ng/mL for the next 18

months. At the time of writing, the patient was asymptomatic. Although causality cannot be determined in a case report like this, the authors attributed the decrease in PSA to lycopene rather than saw palmetto. Even though saw palmetto is used to treat benign prostate hyperplasia, they pointed out that saw palmetto does not affect PSA.

Ansari and Gupta¹⁰ used lycopene (Lycored softules) 10 mg/day for 3 months in the treatment of a series of 20 patients (median age 72 years; range 56-90 years) with metastatic prostate cancer who had undergone orchiectomy and flutamide treatment and did not respond to antiandrogen withdrawal. For at least 8 weeks, PSA returned to normal (< 4 ng/mL) in 1 patient (5%), decreased by at least 50% in 6 patients (30%), remained stable in 10 patients (50%), and progressed in 3 patients (15%). All 7 of the responders had a baseline PSA between 8.2 and 20 ng/mL and were in the lowest Gleason score group (the lower the Gleason score, the better the prognosis). Eastern Cooperative Oncology Group performance improved in half the patients and stayed the same or worsened in the other half at minimum follow-up of 24 weeks. Sixteen patients had bone pain. After therapy with lycopene, bone pain improved in 10 of these patients (62.5%) and stayed the same or worsened in 6 patients (37.5%). Ten patients were able to decrease their daily analgesic dose; these same patients also had a 25 ± 5% decrease in the quantity of metastatic lesions. Eighteen patients had lower urinary tract symptoms, which improved along with the flow rate in 11 patients (61.1%) and remained unchanged or worsened in 7 patients (38.9%). The median duration of response was 25 weeks (range 12-72 weeks). Median overall survival was 14 months (range 3-36). Adverse effects were not reported by any of the patients.

The authors concluded that lycopene should be tried first before more toxic substances are used. However, this was a non-randomized, non-controlled trial in only a handful of patients. Only 7 patients (35%) were judged to be responders, and these were the ones with the lower PSA levels and more favorable prognosis at baseline. The results provide no justification for the authors' recommendation that lycopene be tried before standard prostate cancer therapy.

Clark and contemporaries¹¹ performed a phase I-II dose-escalating trial of lycopene in patients with prostate cancer who relapsed after undergoing radiotherapy or surgery. Six cohorts of 6 patients received lycopene (Lyc-O-Mato[®]) at escalating doses of 15, 30, 45, 60, 90, or 120 mg/day given in divided doses twice daily. The median age was 74 years (range 56-83 years). The median baseline PSA level was 4.4 ng/mL (range 0.8 to 24.9). Thirty-four of the men were white and 2 were black. Patients were assessed for toxicity and compliance every month. Serum PSA levels were measured at baseline and every 4 weeks. At 12 weeks, those patients who had a PSA response, defined as a 50% decrease in PSA from baseline that was maintained for at least 1 month and confirmed after at least 2 PSA tests, or who had stable disease remained in the study for a total of 12 months, with regular assessments every 3 months. One patient discontinued lycopene because of grade 2 diarrhea that was thought to be related to lycopene. No patients had a PSA response, and 13 patients (37%) had PSA progression. All doses except 120 mg/day achieved similar plasma lycopene levels. There was a statistically significant elevation in plasma lycopene levels at 120 mg/day as compared to the lower doses ($p < 0.0001$). After 3 months of therapy at each dose level, a plateau in plasma lycopene level was observed. The authors concluded that lycopene supplementation in men with relapsed prostate cancer, after failed definitive local therapy, is safe and well tolerated but that it does not have any clinically significant effect on serum PSA.

Three randomized trials have investigated the effects of lycopene supplementation in men with prostate cancer (Table 1). Kucuk and co-investigators¹² evaluated the effect of lycopene supplements on clinical parameters of disease aggressiveness, biomarkers in cancerous and benign prostate tissue, prostate tissue levels of lycopene, and plasma levels of lycopene, PSA, insulin-like growth factor-1 (IGF-1), and IGF binding protein-3 (IGFBP-3).

Men in the treatment arm were given lycopene (Lyc-O-Mato[®]), while men in the control group received no intervention. Statistically significant differences observed in the lycopene group as compared to the control group are shown in Table 1. There were no statistically significant differences between the two groups in prostate tissue biomarkers or in plasma lycopene, IGF-1, and IGFBP-3 levels. Plasma PSA levels decreased by 18% in the lycopene group and increased by 14% in the

control group, but the changes were not statistically significant. The patients in the lycopene group appeared to be patients with a better prognosis at baseline as indicated by a lower clinical stage and lower Gleason score, although the authors reported no significant differences in the two groups. No adverse effects were reported. The authors concluded that lycopene supplements may decrease the growth of prostate cancer. The study population was small and the duration was brief, so it is difficult to draw any conclusions from this study.

Ansari and Gupta¹³ randomized men with metastatic prostate cancer to orchiectomy alone or orchiectomy plus lycopene beginning on the day of orchiectomy. Every three months serum PSA levels were measured and the patients underwent a bone scan and uroflowmetry. According to the authors, patients were followed up for a minimum of 2 years, and the mean follow-up of patients still alive was 25.5 (range 24-28) months; however, they also state in two places that patients entered the trial between March 2000 and June 2002. The article was accepted for publication on June 5, 2003, and it would not have been possible for all patients to have been followed for 2 years if the dates of trial entry are correct as stated. No patients receiving lycopene reported any adverse reactions. The authors concluded that orchiectomy plus lycopene produced a more reliable and consistent decrease in serum PSA level, that it shrunk the primary and secondary tumors, that it provided better relief from bone pain and decreased lower urinary tract symptoms, and that it improved survival compared to orchiectomy alone. While the results of this trial favored orchiectomy plus lycopene over orchiectomy alone for the treatment of prostate cancer (Table 1), the results should be interpreted with caution because of the small number of patients and unclear length of follow-up. In addition, since there was no mention of a placebo supplement given to the orchiectomy alone group, the absence of blinding to the intervention may have biased the results.

Mohanty and collaborators¹⁴ studied the role of lycopene in the prevention or delay of high-grade prostate intraepithelial neoplasia (HGPIN), a precursor to prostate cancer. Men undergoing transurethral resection of the prostate for benign prostatic hyperplasia (BPH) received lycopene (Lyc-O-Mato[®]) or no treatment for 1 year and were followed up for 1 additional year. The control group was advised to decrease its intake of tomato and melon. Serum PSA levels decreased in the group receiving lycopene and increased in the control group. Mean serum lycopene increased in the lycopene group and decreased in the control group. During the follow-up period, 6 patients (30%) in the lycopene group had increased PSA; biopsy showed BPH in 4 of these patients and adenocarcinoma in 2. In the control group, 9 patients (45%) had increased PSA; biopsy revealed BPH in 3 of these patients and adenocarcinoma in 6. Adverse effects were not observed in the lycopene group.

The authors concluded that lycopene can prevent or delay the development of prostate cancer in patients with HGPIN. They did not perform any statistical analysis, so statistical significance cannot be determined. No information was provided regarding the amount of lycopene the control group ingested from their diet, but advising them to decrease their intake of tomatoes and melons could have produced a biased control group.

Turmeric

Turmeric, a widely cultivated Asian plant belonging to the *Zingiberaceae* family (genus *curcumin*), recently has been the subject of extensive research. Turmeric's underground tuberous roots hold a long tradition in Chinese and Indian Ayurvedic medicine for the control or treatment of a wide variety of conditions, such as arthritis, sore throat, cough, anorexia, liver disease, biliary disorders, muscular conditions, tumors, and wound infections^{15,16}. Although primarily known as a spice in the West, turmeric has emerged as a potential anti-cancer agent¹⁵. Turmeric is listed in both the Food and Drug Administration's GRAS (Generally Recognized As Safe) list and the expanded German Commission E's list of approved herbs.

Chemical analysis of turmeric rhizomes identified two clinically important compounds: the sesquiterpenes volatile oils and the polyphenolic pigments curcuminoids¹⁷. Among the curcuminoids, curcumin (diferuloylmethane) is the most studied. It is a compound with minimal toxicities even when it is given at high dose (500-12,000 mg)¹⁸. It possesses multiple pharmacological activities, but curcumin's

Table 1. Randomized clinical trials using lycopene supplementation.

Citation	Population	Intervention	Duration	Statistically Significant Results (Lycopene group vs. control group, respectively)
Kucuk et al ¹² (2001)	26 men with newly diagnosed, localized prostate cancer Median age = 61 years	Lycopene 15 mg BID (n = 15) OR No supplementation (n = 11)	3 weeks (immediately prior to radical prostatectomy)	Prostate tissue lycopene levels 0.53 ± 0.03 vs. 0.36 ± 0.06 ng/g of prostate tissue; p = 0.02 Extent of involvement of the prostate gland with high-grade prostate intraepithelial neoplasia (HGPIN) Number of patients with focal involvement: 5 vs. 0; p = 0.05 Number of patients with multifocal/diffuse involvement: 10 vs. 11; p = 0.05 Microscopic extension of prostate cancer to surgical margins and/or to extraprostatic tissues Number of patients with surgical tumor stage confined to prostate: 11 vs. 2; p = 0.02 Number of patients with surgical tumor stage not confined to prostate: 4 vs. 9; p = 0.02
Ansari and Gupta ¹³ (2003)	54 men with metastatic prostate cancer and a World Health Organization performance status of 0 - 2	Lycopene 2 mg BID plus orchiectomy (n = 27) OR Orchiectomy alone (n = 27)	2 years minimum (beginning on the day of orchidectomy)	Decreased PSA at 24 months 3.0 ± 1.9 (range 0.7 – 13) vs. 9.0 ± 7.5 (range 1.3 – 25) ng/mL; p < 0.001 Number of patients (and percent) With complete PSA response (defined as PSA < 4 ng/mL): 21 (78%) vs. 11 (40%); p < 0.05 With complete bone scan response (defined normal bone scan): 8 (25%) vs. 4 (15%); p < 0.02 Who progressed: 2 (7%) vs. 7 (25%); p < 0.02 Who died: 7 (13%) vs. 12 (22%); p < 0.001 Peak flow rate after intervention 12.2 ± 2.7 (range 6.5-15.90) vs. 11.0 ± 2.6 (range 2.5-13.9) mL/s; p < 0.04 Overall survival Longer in the orchiectomy + lycopene (OL) group than in the control group alone; p < 0.01 (exact data not reported; based on Kaplan-Meier curve approximately 30 months in OL group and 27 months in control group) Improvement in voiding symptoms (frequency, urgency, and dysuria) 80% vs. 50% (authors report this as “significant,” but p-values were not provided)
Mohanty et al ¹⁴ (2005)	40 men with HPGIN	Lycopene 4 mg BID (n = 20) OR No supplementation (n = 20)	1 year	Statistical analysis not reported

mechanism of action is still incompletely understood. Research suggests that turmeric possesses immunomodulatory, antithrombotic, antimicrobial, anti-inflammatory, antioxidant and anti-tumor properties¹⁵. Its main anti-tumor promoter activity is thought to be through its ability to down-regulate the activity of epidermal growth factor receptor (EGFR) and expression of cyclo-oxygenase-2 (COX-2), inhibit angiogenesis, induce apoptosis in cancer cells, modulate the inflammatory cascade, regulate the activation of several signal transduction pathways, up-regulate glutathione-S-transferase (GST) activity, and suppress the adhesion of tumor cells to endothelial cells¹⁹⁻²².

Turmeric anti-tumor activity is observed at all three stages of carcinogenesis: it inhibits the initiation of cancer induced by reactive radicals, it blocks the transformation of normal cells into tumor cells, and it inhibits tumor growth and delays tumor invasion and metastasis.^{19,23} A number of studies^{15,19,24} — both in-vitro cancer cell lines and pre-clinical animal models — have reported turmeric’s ability to suppress tumor cell

growth; however, the question remains: Is there concrete evidence of turmeric effectiveness in human cancer?

In the late 1980s, Kuttan et al²⁵ reported the beneficial use of turmeric in 62 adult patients with locally recurrent cancerous lesions who had inadequate response to standard chemotherapy and radiation therapy (age 40-85 years; 37 oral cavity, 7 breast, 4 vulva, 3 skin, and 11 other cancer sites). A topical preparation of 0.5% curcumin in white vaseline or alcohol was applied 3 times daily to the lesions without any other anticancer drugs. Weekly evaluation for up to 4 weeks showed topical turmeric was well tolerated and its application was associated with a symptomatic relief in 42/62 cases (67.7%). Twenty four out of 37 oral cavity cancer patients achieved considerable decrease in foul smell and ulcer size, relief of itching and pain, and drying of exudates. The overall symptomatic improvement of the lesions in response to treatment was also observed in other cancers (breast cancer 71%, skin cancer 66%, vulva cancer 100%, and cancer at other sites 63%). No patients experienced any side effects

Table 2 . Curcumin trials being currently registered with Clinicaltrials.gov.

Site	Phase	Currently Recruiting	Cancer Type	Study Design	Regimen	Total Enrollment	Primary Outcomes
Israel	II	Yes	Advanced or metastatic pancreatic cancer	Non-randomized Active control	8,000 mg oral curcumin + Gemcitabine weekly	45	Time to tumor progression
Israel	I	No	Myelodysplastic syndrome	Non-randomized Historical	Curcumin + Coenzyme Q10	50	Major hematologic improvement
Israel	III	No	Advanced or metastatic colorectal cancer	Randomized Double-blind Placebo-controlled	Curcumin + Gemcitabine + Celecoxib	100	Time to tumor progression
U.S.	II	Yes	Advanced pancreatic cancer	Non-randomized Uncontrolled	Curcumin	50	Six-month survival
U.S.	II	Yes	Prevention of colon cancer in smokers with aberrant crypt foci	Non-randomized Uncontrolled	Curcumin	48	Mean percentage change in PGE ₂
U.S.	II	Yes	Familial adenomatous polyposis	Non-randomized Uncontrolled	Curcumin	Not listed	Polyps regression
U.S.	II	Yes	Previously resected adenomatous colonic polyps	Randomized Double-blind Placebo-controlled	Curcuminoids	68	Cellular proliferation and apoptosis in colonic mucosa

About the Authors:



ThaiBinh Ton-That, a registered pharmacist, joined the IDIS staff in 1984. She earned a “Diplome National De Pharmacien” from the “Faculte Mixte de Medecine et de Pharmacie” of Grenoble, France and a Doctor of Pharmacy degree from the University of Southern California.

Her responsibilities at IDIS include supervision of indexing for the database, indexing articles, providing assistance to subscribers, and maintaining the disease vocabulary.



Vicki Kee is a 1989 graduate of the University of Alabama at Birmingham (B.A. in English) and a 1999 graduate of Samford University School of Pharmacy (Pharm.D.). She completed a drug information residency at Idaho State University College of Pharmacy in 2003 and then joined IDIS. In 2005 she became a Board Certified Pharmacotherapy Specialist.

Vicki is a contributing author to the *World of Drug Information* newsletter, assists with answering drug information inquiries made to the Iowa Drug Information Network (IDIN), teaches drug information to pharmacy students and indexes journal articles for inclusion into the IDIS database.

except a possible allergic rash occurring in 1 patient. The results from this small non-randomized uncontrolled case series showed that curcumin was well tolerated and possessed possible benefits in cancerous lesions. Again, in a case series and no control, the causality of the results seen cannot be determined.

In a smaller clinical setting, ascending doses of curcumin (2, 4, 6, 8 and 10 capsules, each containing 18 mg of curcumin and 2 mg desmethoxycurcumin in 200 mg of curcuma oil) were given once a day for at least 29 days to 15 patients with advanced colorectal cancer to investigate its effect on COX-2 activity - measured as alteration of stimulated prostaglandin E2 (PGE2) production. Curcumin dose-dependently inhibited lipopolysaccharide (LPS)-induced PGE2 activity ($p < 0.005$), but there was no significant difference compared with values from pretreatment time points ($p = 0.075$).²⁶

Garcea et al²⁷, conducted a study to assess the uptake of curcumin and its metabolites in the intestinal mucosa of cancer patients and examine its potential anti-tumor activity. Twelve chemo- and radio-therapy naïve colorectal cancer patients (age 47-72 years) were given oral curcumin for 1 week before colectomy (450, 1,800, or 3,600 mg/day; 4 patients per dose level).

Curcumin was poorly available after oral administration; no measurable amount of the parent compound or its metabolites was found in the plasma even when high doses were given. Normal colorectal mucosa curcumin concentration ranged from 0 to 19.6 nmol/g. Concentration in colorectal cancerous tissue ranged from 0.9 ± 0.4 to 7.7 ± 1.8 nmol/g (7.7 ± 1.8 , 6.7 ± 1.6 , and 0.9 ± 0.4 nmol/g, respectively for 3,600, 1,800, and 450 mg doses). Curcumin sulfate and glucuronide were also detected in tumor tissue of patients receiving the highest dose. COX-2 protein was undetectable in normal colorectal tissue. COX-2 expression was higher in colorectal cancerous tissue, but its level stayed unaffected after one week of oral curcumin administration. The level of oxidative DNA adduct M1G was higher in malignant tissue compared to healthy tissue ($p < 0.05$). Curcumin treatment did not affect M1G level in normal tissue but induced a decrease in M1G level in malignant colorectal tissue. A borderline statistically significant decrease was observed only in biopsies taken from patients receiving the highest dose ($p < 0.05$). The authors recommended a phase II clinical trial of curcumin in patients at risk of colon or rectal cancer.

Cheng et al²⁸ conducted a phase I prospective non-randomized uncontrolled study to determine the safety, pharmacokinetics, and chemopreventive effects of curcumin in patients with cancer or pre-cancerous lesions. Twenty-five eligible patients (median age 60 years; range 36-77 years) with intraepithelial squamous cell carcinoma of the skin (6), cervical intraepithelial neoplasia (4), oral leukoplakia (7), intestinal metaplasia of gastric mucosa (6), and resected bladder cancer (2) were enrolled and received once daily oral administration of standardized curcumin at escalating doses of 500, 1,000, 2,000, 4,000, 8,000, and 12,000 mg for 3 months. A 500 mg dose was given on an empty stomach to the first cohort; an additional cohort was enrolled at a higher dose level if at least 3 consecutive patients from the previous cohort completed the 3 month treatment and no more than 1 patient experienced any toxicity \geq grade 2. No further dose escalation was conducted after 8,000 mg due to patients' refusal to ingest a bulky volume of curcumin.

Biopsy of the lesions taken at 3 months post-intervention showed a non-dose-dependent histological improvement in 7 patients (28%) with normalization of pre-cancerous lesions, decrease in hyperplasia, lesser inflammation, fewer goblet cells, less hyperkeratosis, and less parakeratosis when compared to pre-treatment assessment. Pharmacokinetic assessment showed that when given orally curcumin was undetected in the urine and was poorly absorbed. Measurable serum curcumin concentration was only detected in patients receiving more than 2,000 mg/day. The treatment was well tolerated with no side effects observed in any patient. All patients completed 3 months of treatment, except for 1 who withdrew due to disease progression. Oral curcumin at a dose up to 8,000 mg/day for 3 months was administered safely and seemed to induce histologically proven response in certain types of cancer. The authors recommended further phase II studies with 6,000-8,000 mg curcumin/day.

Sharma et al²⁹ conducted a pilot study to evaluate the pharmacodynamic and pharmacokinetic profiles of an oral standardized curcumin extract in patients with colorectal cancer. Five cohorts of 3 patients each received escalating oral doses of curcuma extract (440, 880, 1,320, 1,760, and 2,200 mg/day equivalent to 36–180 mg curcumin). Pharmacodynamic markers were assessed before and after intervention on days 1, 2, 8, 29 and monthly thereafter. Lymphocytic GST activity decreased over time in the 440 mg cohort ($p < 0.001$), whereas there were no noticeable activity changes in the other 4 cohorts. Ingestion of curcumin did not affect leucocytes M1G levels. Oral bioavailability was low; no measurable amount of curcumin or metabolites was detected in blood or urine samples. Oral curcumin was well tolerated. Three patients experienced mild gastrointestinal side effects (nausea and diarrhea), but no dose-limiting side effects were seen. A CT scan showed no progression of the disease during 3-4 months of treatment. No changes in cancer antigen 19-9 (CA 19-9) blood tumor marker level were observed. A decreased level of carcinoembryogenic antigen (CEA) tumor marker was observed in 1 patient.

Subsequent to this pilot study, Sharma et al³⁰ conducted a phase I dose-escalating study to evaluate the safety, pharmacokinetic parameters, and biologic activity of a standardized curcuma extract in cancer patients. Fifteen patients (age 50-74 years) with adenocarcinoma of the colon or rectum refractory to radiation therapy and conventional chemotherapeutic agents were given a 500 mg curcuma formulation containing 450 mg curcumin in combination with 50 mg of other curcuminoids. The starting dose was one capsule/day, with a 100% dose escalation for the next cohorts (900 mg, 1,800 mg, and 3,600 mg). Each cohort contained 3 patients, with the exception of the last cohort, which had 6 patients. Treatment was continued until time of disease progression or patient's withdrawal.^{29,30}

Pooled data showed that ingestion of 3,600 mg curcumin elicited a significant decrease in LPS-induced PGE2 levels. A 46% decrease between pre-dose and 1-hour post-dose levels was observed on days 1, 2, 8, and 29; ($p = 0.028$). No systemic activity of oral curcumin on leucocytes' M1G and GST levels was observed. Partial response, defined as at least 50% reduction in measurements of lesions before and after treatment and without development of new lesions, was not observed in any patient. Two patients had stable disease while on 900 mg and 1,800 mg oral curcumin. There was no lowering of blood levels of tumor markers CA 19-9 and CA 125 after curcumin treatment compared to pre-treatment. Curcumin up to 3,600 mg a day for a period up to 4 months was well tolerated; none of the 15 patients experienced dose-limiting toxicity. Three patients reported mild-to-moderate diarrhea or nausea. None of the patients experienced significant changes in the clinical laboratory tests. A mild-to-moderate rise in serum alkaline phosphatase was observed in 4 patients and an increase in serum lactate dehydrogenase in 3 patients.

The data from the above studies provide further rationale for the evaluation of oral curcuma in cancer. As of this writing, there are 7 trials (1 in Phase I, 5 in Phase II and 1 in Phase III) registered with ClinicalTrials.gov, a service of the U.S. National Institutes of Health³¹ (Table 2). A small study looking at the efficacy and safety of curcumin with or without bioperine in multiple myeloma patients (expected enrollment 24) is temporarily closed.³²

Conclusion

In studies performed thus far, lycopene and turmeric appear safe. Although some studies with design limitations have suggested that lycopene supplements may be useful in preventing or treating prostate cancer, not only is there is no conclusive evidence that lycopene supplements are effective, there is also no evidence that lycopene from tomato products has more than a modest effect. Patients should, however, be encouraged to eat tomato products and other lycopene-containing foods as part of a healthy diet since these are also good sources of other vitamins, minerals, and amino acids. Curcumin's pharmacokinetic and pharmacodynamic data in humans have been assessed, but it is not known if it has any clinical significance in any type of cancer. The roles of lycopene and turmeric in modifying cancer still remain to be elucidated. Sufficiently powered, well designed randomized

controlled trials are needed. The level of evidence is not sufficient at this point to recommend lycopene supplementation for the prevention or treatment of prostate cancer or to recommend turmeric for the prevention or treatment of any type of cancer.

Reference List

- Ben-Arye E, Frenkel M, Margalit RS. Approaching complementary and alternative medicine use in patients with cancer: questions and challenges. *J Ambul Care Manage.* 2004; 27:53-62.
- Frenkel M, Ben-Arye E, Baldwin CD et al. Approach to communicating with patients about the use of nutritional supplements in cancer care. *South Med J.* 2005; 98:289-94. (IDIS Article Number 531573)
- Lycopene. Monograph. *Altern Med Rev.* 2003; 8:336-42. (IDIS Article Number 503940)
- Etminan M, Takkouche B, Caamano-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:340-5.
- Lee CO. Complementary and alternative medicine patients are talking about: lycopene. *Clin J Oncol Nurs.* 2005; 9:245-6.
- Kelly JP, Kaufman DW, Kelley K et al. Recent trends in use of herbal and other natural products. *Arch Intern Med.* 2005; 165:281-6. (IDIS Article Number 529632)
- Agarwal S, Rao AV. Tomato lycopene and its role in human health and chronic diseases. *CMAJ.* 2000; 163:739-44. (IDIS Article Number 455207)
- Giovannucci E. A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. *Exp Biol Med (Maywood).* 2002; 227:852-9.
- Matlaga BR, Hall MC, Stindt D et al. Response of hormone refractory prostate cancer to lycopene. *J Urol.* 2001; 166:613. (IDIS Article Number 466644)
- Ansari MS, Gupta NP. Lycopene: a novel drug therapy in hormone refractory metastatic prostate cancer. *Urol Oncol.* 2004; 22:415-20.
- Clark PE, Hall MC, Borden LS et al. Phase I-II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. *Urology.* 2006; 67:1257-61.
- Kucuk O, Sarkar FH, Sakr W et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol Biomarkers Prev.* 2001; 10:861-8.
- Ansari MS, Gupta NP. A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. *BJU Int.* 2003; 92:375-8.
- Mohanty NK, Saxena S, Singh UP et al. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. *Urol Oncol.* 2005; 23:383-5.
- Turmeric. Natural Database Comprehensive Medicine; Cited: 7-21-2006; Available from: <http://naturaldatabase.com/> Last updated: 2006.
- HerbMed Database. Curcuma longa record. Alternative Medicine Foundation, Inc; Cited: 8-2-2006; Available from: <http://www.herbmed.org/herbs/herb9.htm>; Last updated: 2006.
- Turmeric Root. American Botanical Council; Cited: 10-31-2006; Available from: <http://www.herbalgram.org/iherb/expandedcommission/he096.asp>; Last updated: 2006.
- Lao CD, Ruffin MT, Normolle D et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med.* 2006; 6:10.
- Aggarwal BB, Kumar A, Aggarwal MS, Shishodia S. Curcumin derived from turmeric (*Curcuma longa*): a spice for all seasons. In: *Phytopharmaceuticals in Cancer Chemoprevention.* 2005: 349-387.
- Duvoix A, Blasius R, Delhalle S et al. Chemopreventive and therapeutic effects of curcumin. *Cancer Lett.* 2005; 223:181-90.
- Maheshwari RK, Singh AK, Gaddipati J et al. Multiple biological activities of curcumin: a short review. *Life Sci.* 2006; 78:2081-7.
- Sharma RA, Gescher AJ, Steward WP. Curcumin: the story so far. *Eur J Cancer.* 2005; 41:1955-68.
- Wallace JM. Modulation of the inflammatory cascade: an essential target in cancer therapy. *Int J Integ Med.* 2002; 4:6-29. (IDIS Article Number 490576)
- Conney AH. Enzyme induction and dietary chemicals as approaches to cancer chemoprevention: the Seventh DeWitt S. Goodman Lecture. *Cancer Res.* 2003; 63:7005-31. (IDIS Article Number 507218)
- Kuttan R, Sudheeran PC, Joseph CD. Turmeric and curcumin as topical agents in cancer therapy. *Tumori.* 1987; 73:29-31.
- Plummer SM, Hill KA, Festing MF et al. Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents. *Cancer Epidemiol Biomarkers Prev.* 2001; 10:1295-9.
- Garcea G, Berry DP, Jones DJ et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:120-5.
- Cheng AL, Hsu CH, Lin JK et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* 2001; 21:2895-900.
- Sharma RA, McLelland HR, Hill KA et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clin Cancer Res.* 2001; 7:1894-900. (IDIS Article Number 466531)
- Sharma RA, Euden SA, Platton SL et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res.* 2004; 10:6847-54. (IDIS Article Number 524323)
- National Institutes of Health Clinical Trials; Cited: 11-6-2006; Available from: <http://clinicaltrials.gov/>. Last updated: 2006.
- National Cancer Institute, U.S. National Institutes of Health; Cited: 11-6-2006; Available from: <http://www.cancer.gov/>. Last updated: 2006.



ACCREDITATION INFORMATION



The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 107-999-06-116-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation on page 11, and return to **Kristen K. Dearden, The Collaborative Education Institute, 8515 Douglas Avenue, Suite 16, Des Moines, IA 50322, with a \$7.50 check for the processing fee, made out to the College of Pharmacy.** A certificate will be awarded upon achieving a passing grade of 70% or better. Please allow up to 4 weeks for processing. Pharmacists must complete this program by December 29, 2009 to receive credit.

CE REGISTRATION

ACPE# 107-999-06-116-H01 (0.1 CEU/1 Hr.)

Volume: 17 Issue: 4 DECEMBER 2006

Title of Educational Activity (Article)

Lycopene and Turmeric: Anti-Cancer Therapy Alternatives?

Name _____

Address _____

City _____ State _____ Zip _____

Social Security Number (optional) _____

Pharmacy License Number(s) _____

I hereby certify that I have taken this test:

Signature/Date

(circle the correct answer)

1. The major source of lycopene in the American diet is:
 - a. raw tomatoes
 - b. processed tomato products such as ketchup, tomato juice, and pizza sauce
 - c. pink guava
 - d. papaya
2. Lycopene is an acyclic isomer of:
 - a. alpha-tocopherol
 - b. ascorbic acid
 - c. beta-carotene
 - d. vitamin B6
3. Lycopene is an:
 - a. antimetabolite
 - b. antitumor antibiotic
 - c. antimicrotubule agent
 - d. antioxidant
4. Daily doses of lycopene supplements used in prostate cancer randomized trials to date have ranged from:
 - a. 4 mg – 30 mg/day
 - b. 2 mg – 15 mg/day
 - c. 8 mg – 60 mg/day
 - d. 6 mg – 45 mg/day
5. In clinical studies in prostate cancer, lycopene-induced diarrhea occurred in approximately 5% of patients.
 - a. True
 - b. False
6. Turmeric has a good overall safety profile, even when given at high doses, but occasional side effects include:
 - a. arrhythmia
 - b. joint pain
 - c. weight gain
 - d. nausea and diarrhea
7. All of the following statements are true EXCEPT:
 - a. Turmeric has a long traditional use in Chinese and Ayurvedic medicines.
 - b. Turmeric is listed as an approved herb on the Expanded German Commission E list.
 - c. Turmeric is generally recognized safe for consumption by the Food and Drug Administration.
 - d. Turmeric is an FDA approved drug.

8. Which part of the turmeric plant is generally used in traditional medicine?
 - a. seed
 - b. leaves
 - c. underground roots
 - d. flowers
9. All of the following statements are true EXCEPT:
 - a. Curcumin possesses some antimicrobial and anti-inflammatory properties.
 - b. Curcumin possesses some antioxidant and anti-thrombotic properties.
 - c. Curcumin does not have immunomodulatory and anti-tumor properties.
 - d. Curcumin inhibits the initiation of cancer and blocks the transformation of normal cells into tumor cells.
10. Several studies are currently registered with the Clinicaltrials.gov, a service of the U.S. National Institutes of Health to evaluate curcumin as a potential therapeutic agent in:
 - a. gastrointestinal cancer
 - b. renal cancer
 - c. lung cancer
 - d. skin cancer

**Please Note: The CE processing fee has increased to \$7.50 USD. Forms should be mailed to: Kristen K. Dearden
Collaborative Education Institute,
8515 Douglas Avenue, Suite 16
Des Moines, IA 50322
Phone 515-270-0713
Fax: 515-270-2979
E/mail: kdearden@iarx.org**

PROGRAM EVALUATION

	Excellent			Poor	
	5	4	3	2	1
Overall quality					
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree			Disagree	
	5	4	3	2	1
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1
It took me _____ hours and _____ minutes to read this article and complete the assessment questions.					

New Molecular Entities & Biologicals

FDA Approvals
August 2006 – October 2006

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (FDA Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Ciclesonide <i>Omnaris</i> (S)	Altana Pharma (Oct. 20, 2006)	CICLESONIDE 84060030 (40 citations)	Seasonal and perennial allergic rhinitis (hayfever). Nasal Spray	Allergic Rhinitis, Pollen 477.0 Allergic Rhinitis NEC 477.
Kunecatechins <i>Veregen</i> (S)	Medigene (Oct. 31, 2006)	(0 citations) No published human studies have been found for entry into the <i>IDIS</i> database.	Genital and perianal warts. Topical Ointment	Wart, Viral 078.1
Panitumumab <i>Vectibix</i> (BIO)	Amgen (Sept. 27, 2006)	PANITUMUMAB 82000403 (4 citations)	Advanced colon cancer. IV Infusion	Neop, MGN-Intestine, LG NEC 153.
Posaconazole <i>Noxafil</i> (P)	Schering (Sept. 15, 2006)	POSACONAZOLE 8120522 (59 citations)	Fungal infections in patients with a suppressed immune system. Oral Suspension	Mycosis, NEC 117.
Sitagliptin Phosphate <i>Januvia</i> (S)	Merck (Oct. 16, 2006)	SITAGLIPTIN 68200002 (7 citations)	Type 2 diabetes. Oral Tablet	Diabetes Mellitus 250.
Telbivudine <i>Tyzeka</i> (S)	Idenix Pharma (Oct. 25, 2006)	TELBIVUDINE 8180069 (7 citations)	Chronic hepatitis B. Oral Tablet	Hepatitis, Viral B 070.2
Vorinostat <i>Zolinza</i> (P, O)	Merck (Oct. 6, 2006)	(0 citations) No published human studies have been found for entry into the <i>IDIS</i> database.	Cutaneous T-cell lymphoma. Oral Capsule	Neop, MGN-Lymph/Histio NEC 202.

Therapeutic Potentials:

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA= Accelerated Approval

FT=Fast Track

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL= Biological

O = Orphan drug



Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

Selected Bibliography

Ciclesonide

Schmidt BMW, Timmer W, Georgens AC, Hilt M, et al. The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis. *J Clin Pharmacol*. 1999; 39:1062-1069. (IDIS Article Number 434193)

Efficacy of ciclesonide was investigated in this randomized, placebo-controlled, double-blind crossover trial that included 24 symptom-free patients with a history of allergic rhinitis, who were given intranasal ciclesonide, 200 mcg per nostril once a day, or placebo, for 7 days. Provocation with allergen extracts was started 2 days before the start of treatment and on each treatment day. Ciclesonide significantly ($p < 0.05$) improved airflow from day 5 and significantly ($p < 0.05$) reduced the scores for itching, obstruction and rhinorrhea without side effects.

Posaconazole

Vazquez JA, Skiest DJ, Nieto L, Northland R, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. *Clin Infect Dis*. 2006; 42:1179-1186. (IDIS Article Number 552287)

This multicenter randomized study of 350 HIV patients with oropharyngeal candidiasis compared posaconazole and fluconazole at 200 mg oral suspension on day one, then 100 mg once daily for 13 days. Clinical success occurred in 155 (91.7%) of posaconazole and in 148 (92.5%) of those receiving fluconazole, however, fewer posaconazole patients relapsed (31.5% vs. 38.2%).

Ullman AJ, Cornely OA, Burchardt A, Hachem R, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agts Chemother*. 2006; 50:658-666. (IDIS Article Number 552985)

Different dosing schedules were used in this multicenter, open-label, randomized, parallel-group study of 66 patients with febrile neutropenia (FN) and 32 patients with refractory invasive fungal infection (rIFI) who were given posaconazole at doses of 200 mg 4 times a day for 9 doses, followed by 400 mg twice a day, or 400 mg 4 times a day for 9 doses, followed by 600 mg twice a day, or 800 mg twice a day for five doses, followed by 800 mg once a day. Patients were treated up to 6 months or until neutrophil recovery occurred. Posaconazole was well tolerated, and in evaluable patients, 43% of rIFI patients and 77% of FN patients had successful clinical responses.

Sitagliptin phosphate

Herman GA, Bergman A, Liu F Stevens C, et al. Pharmacokinetics and pharmacodynamic effects of the oral DPP-4 inhibitor sitagliptin in middle-aged obese subjects. *J Clin Pharmacol*. 2006; 46:876-886. (IDIS Article Number 560144)

Investigators conducted a multicenter, randomized, double-blind, placebo-controlled trial with 32 obese patients who were given either oral sitagliptin 200 mg or placebo twice daily for 28 days. Compared to placebo, treatment with sitagliptin resulted in ~90% inhibition of plasma dipeptidyl peptidase-IV activity, and a 2.7 fold increase in levels of active glucagon-like peptide-1 ($p < 0.001$).

Telbivudine

Lai CIL, Leung N, Teo EK, Tong M, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with Hepatitis B e antigen-positive chronic Hepatitis B. *Gastroenterology*. 2005; 129:528-536. (IDIS Article Number 538058)

A total of 104 hepatitis B e antigen positive adult patients with chronic hepatitis B participated in this multicenter, randomized, double-blind trial that assessed the safety and efficacy of telbivudine 400 mg or 600 mg/day and telbivudine 400 mg or 600 mg/day plus lamivudine 100 mg/day compared with lamivudine 100 mg/day. Investigators found that patients treated with telbivudine had significantly greater virologic and biochemical responses compared with those treated with lamivudine, and that results from the combination treatments were similar to those of telbivudine given alone.

Attention IDIS Database Subscribers

The 2007 subscription renewal materials for the IDIS Database were mailed to you in October. Please contact our office if you have not received the mailing or would like to make any changes to your current configuration; we can fax or e-mail the materials to you directly. To avoid any interruption in your service we should receive your subscription renewal order in our office by December 29th, 2006. Thank you in advance for your prompt attention to your subscription renewal and your continued support of the Iowa Drug Information Service.



*IDIS/*Web Advantages

Consider the advantages that *IDIS/*Web offers to you:

- The complete index database, 1966 to the most current update, is available to search all at once.
- PDF journal articles from 1997 to the current update are available without a requirement to load additional CD-ROM discs.
- No installation of software or copying of article files is required.
- No additional hardware (e.g. CD-ROM or extra hard drives) required for access to the index database and articles.
- The database and articles are available from any web-connected computer.
- Monthly updates are available several weeks earlier in *IDIS/*Web.
- Upon request, the number of concurrent users will be increased to accommodate teaching in classroom settings.
- *IDIS/*Web Training Tools are available on our web site <http://itsnt14.its.uiowa.edu/>.
- Search results can be sent to you or a colleague using Email.
- The *IDIN Answers* database (over 900 previously answered drug information questions) is available via your *IDIS/*Web subscription.
- Currently the *IowaTeach Case Database* is available through your *IDIS/*Web subscription on a trial basis.
- Indexed FDA Advisory Committee and AHRQ documents are available seamlessly within your *IDIS/*Web subscription. Hyperlink bookmarks are added to these documents for quick and easy navigation.
- Some future enhancements to the database will be available in *IDIS/*Web only.

If you would like to evaluate some of these new features, we have three easy ways for you to request a free trial:

idis@uiowa.edu

1-800-525-4347

<http://www.uiowa.edu/~idis/webtrial.htm>

Search Tip:

Searching Herbal Medicines, Natural Products and Vitamins

Nicola R. Sarrazin, R.Ph., Pharm.D.

The literature in herbal medicines, natural products, and vitamins, continues to grow at an increasing pace. Searching for literature in any subject area is more efficient and effective when you are well versed in the controlled terminology used to index that information.

As a group, these substances are often referred to in the literature as nutraceuticals, complimentary, and alternative medicines. The *IDIS* database organizes these substances into one major category, **VITAMINS 88000000**, and two subcategories, **HERBAL MEDICINES 92510000** and **NATURAL PRODUCTS-OTHER 92520000**. To find valid terms and numeric codes, you can use the Look Up button beside the Drug field on the Search page. If you would like to see the terms listed in each subcategory, use the Drug Hierarchy option. To find individual valid terms for vitamins, click the 'Drug Hierarchy' link on the left side of the search page, then enter 88*, and click submit. The result will provide a pick list of terms which you may select by clicking in the box next to the term. For herbal medicines follow the same procedure and enter 9251*, for natural products enter 9252*.

The screenshot shows the IDIS advanced search interface. It features a navigation bar with 'DIS advanced search', 'basic search preferences', and 'history help'. A left sidebar contains links such as 'IowaTeach', 'IDIN Answers', 'Thesaurus', 'Journal', 'Drug Hierarchy', 'Drug List - A to Z Search', 'Disease Hierarchy', 'Disease List - A to Z Search', 'Descriptor Definitions', and 'Index Notes'. The main search area includes fields for 'All Fields', 'Drug', 'Disease', 'Descriptor', 'Title', 'Author', 'Abstract', 'Journal', 'Volume', 'Issue', 'Page', and 'Year'. The 'Drug' field is pre-filled with '* or 8816* or 8820* or 8824* or 8828* or 8832*' and has a 'Look Up' button. There are also fields for 'Article Number', 'Sequence Number', and 'Number'. Search and clear buttons are present at the bottom of the search area.

If you wish to conduct a search in which ALL substances within a subcategory are retrieved, you may enter the truncated numeric code in the drug field. For instance, there are over 200 individual valid drug terms in the subcategory HERBAL MEDICINES. To retrieve all articles containing herbal medicines, enter 9251* in the 'Drug' field of the Search page. This search will currently retrieve over 3,880 citations. The subcategory, NATURAL PRODUCTS-OTHER, currently contains 15 individual substance terms and can be searched by truncation, 9252*. This search currently retrieves 370 citations.

The major drug category for vitamins, **VITAMINS 88000000**, contains several subcategories: **VITAMIN A DERIVATIVES 88040000**, **VITAMIN B COMPLEX 88080000**, **VITAMIN C DERIVATIVES 88120000**, **VITAMIN D & DERIVATIVES 88160000**, **VITAMIN E & DERIVATIVES 88200000**, **VITAMIN K & DERIVATIVES 88240000**, **MULTIVITAMIN PREPARATIONS 88280000**, and **BIO-FLAVONOIDS 88320000**.

If you wish to retrieve ALL articles containing any of the vitamin drug terms, you will get the best results by using truncation with the first four digits of each subcategory, as well as the first four digits of the main category. Therefore to search for all articles containing vitamin terms, enter the following in the Drug field: 8800* or 8804* or 8808* or 8812* or 8816* or 8820* or 8824* or 8828* or 8832*. Currently, this search retrieves more than of 19000 citations.

With the strategies described above, a search can be structured to retrieve articles for a single substance, a single category or subcategory, or any combination. For example, if you wish to search for articles with information about drug interactions involving any vitamin, herb, or natural product in the *IDIS* database, start with truncation in the drug field by entering: 9251* or 9252* or 8800* or 8804* or 8808* or 8812* or 8816* or 8820* or 8824* or 8828* or 8832* (this search would over retrieve 22,700 citations), then add the descriptor for drug interaction and you will find more than 1,700 articles.

You may use other descriptors to limit your search to controlled trials, or by any of the other descriptors available. You may also wish to utilize disease terms with the vitamin, herb or natural product terms to find specific information.

Using these truncated numeric drug codes, or individual drug terms, the correct Boolean operators "or" or "and" along with disease terms and/or descriptors to expand or limit the search will help you to retrieve the specific information you need.

IMPORTANT NEW ADDITIONS TO THE IDIS DATABASE

FDA Black Box Warnings

“Black Box” Warnings that prominently appear in the product information of some drugs are U.S. Food and Drug Administration (FDA) mandated alerts of potential serious drug adverse reactions and safety hazards. Over 350 of these warnings have been identified and entered into the *Iowa Drug Information Service (IDIS)* database. As new warnings are issued, they will be entered into the *IDIS* database creating a continuing comprehensive list of FDA Black Box Warnings.

FDA Black Box Warnings may be found in the IDIS database by searching with descriptor **FDA BLACK BOX WARNING 165**.

FDA Advisory Committee Meetings

The briefing documents and transcripts from FDA Advisory Committee meetings are valuable drug information resources because they contain studies and data on important and sometimes controversial issues related to new drug approvals, drug safety or drug monitoring. They also contain comprehensive analyses and views on this data from experts within the field, the FDA, the pharmaceutical industry, and consumers.

Documents from a FDA Advisory Committee meeting include the Notice of Meeting, Briefing Information from Drug Sponsor, Briefing Information from FDA, Questions to the Committee, Transcript and Slides, and Summary Minutes.

FDA Advisory Committee documents may be found in the IDIS database by searching with descriptor **FDA ADVISORY COMMITTEE 164**.

Agency for Healthcare Research and Quality (AHRQ)

AHRQ Evidence Reports and AHRQ Comparative Effectiveness Reviews are evidence-based, systematic reviews prepared at Evidence-based Practice Centers selected and sponsored by the AHRQ. The AHRQ is the lead federal agency charged with improving the quality, safety, efficiency, and effectiveness of healthcare for all Americans. As one of 12 agencies within the Department of Health and Human Services, AHRQ supports health services research that will improve the quality of healthcare and promote evidence-based decision making.

AHRQ Evidence Reports may be found in the IDIS database by searching with the journal title abbreviation: **AHRQ EVID REP**.

AHRQ Comparative Effectiveness Reviews may be found in the IDIS database by searching with the journal title abbreviation: **AHRQ COMP EFF REV**.

DDIS

Division of Drug Information Service

The University of Iowa
100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000 USA

World of Drug Information is published quarterly
(March, June, September, December) by the Division
of Drug Information Service.

Editor-in-Chief Dr. Kevin Moores
Editor Donna Brus
Production/Design Coordinator Julie Tomash
Photographer..... David Luck

IDIS

Iowa Drug Information Service

Telephone: 319-335-4800
US Toll-Free: 800-525-IDIS
Fax: 319-335-4440
E-mail: IDIS@uiowa.edu
Web Site: <http://www.uiowa.edu/~idis>

IDIN

Iowa Drug Information Network

Telephone: 319-335-4800
US Toll-Free: 800-525-4347
Fax: 319-335-4440
E-mail: IDIN@uiowa.edu
Web Site: <http://www.uiowa.edu/~idin>



The University of Iowa prohibits discrimination in employment, educational programs, and activities on the basis of race, national origin, color, creed, religion, sex, age, disability, veteran status, sexual orientation, gender identity, or associational preference. The University also affirms its commitment to providing equal opportunities and equal access to University facilities. For additional information contact the Office of Equal Opportunity and Diversity, (319) 335-0705.