A New Way To Manage Depression Without Drugs

June 2014

By Michael Downey

One in 10 American adults suffers from depression.

Standard care is prescription drugs that are laden with side effects.2-7 For many patients, the effectiveness of these drugs can diminish over the course of treatment, forcing depressed individuals to learn to live with their mood disorder.

Researchers have found that a specialized complex of curcumin fights the crippling effects of depression by attacking multiple underlying targets.

A team of internationally recognized scientists has published an impressive clinical trial on the antidepressant benefits of a superior-absorbing curcumin that Life Extension® members have used for many years. 9

In this 2013 study of depressed human subjects, curcumin's effectiveness was similar to that of a standard antidepressant medication. However, curcumin contains none of the side effects associated with commonly used drug therapies 9 and provides additional health benefits as well.

These results are in keeping with earlier research showing that curcumin increases levels of "feel good" neurotransmitters such as serotonin and dopamine.10

Landmark Clinical Trial On Curcumin

A breakthrough clinical study recently published in Phytotherapy Research should be welcome news to anyone afflicted with depression, which by 2020 is expected to become the world's second-leading cause of disability.11

Depression continues to escalate despite "more than half a century of modern psychopharmacology, with billions of dollars spent on antidepressants annually world-wide."12 And about 63% of patients who take antidepressants experience at least one of the numerous potential side effects,2 which include anxiety, thoughts of suicide, insomnia, weight gain, and sexual dysfunction.2-7 And the payoff for all these risks? Many depressed patients do not respond at all to drug antidepressants and most patients fail to achieve complete remission!13 Some evidence indicates response rates as low as 17% after taking specific antidepressants.14

Scientists have been seeking safer and effective alternatives to pharmaceutical medications.

The antidepressant activity of curcumin was initially suggested by various animal models of depression.10,15-19 But no evidence had been found on the clinical effectiveness of curcumin against depression.

So researchers designed a clinical experiment that was randomized and observer-masked. This means the observers were not told what treatment had been allotted to the patients, and the patients were instructed not to discuss their treatment regimens with the observers.9

The researchers randomly divided volunteers diagnosed with major depressive disorder into three study groups of 20 patients each. The first group took 20 mg of the antidepressant Prozac® (fluoxetine) every morning. The second group took a total of 1,000 mg of absorption-enhanced curcumin in two divided doses of 500 mg each. And the third group took both the once-daily fluoxetine and the twice-daily curcumin.9

The results were measured using the Hamilton Rating Scale for Depression (HAM-D scale).20 This scale provides a way to rate the severity of depression by assessing mood, anxiety, feelings of guilt, suicidal ideation, insomnia, agitation or motor retardation, weight loss, and other body symptoms.9

Efficacy and safety were evaluated after two, four, and six weeks. The HAM-D scale showed that the proportion of patients responding well to treatment was 62.5% in the curcumin group of the study, 64.7% in the fluoxetine group, and 77.8% in the combination group.9

The study team concluded that there was no statistically significant difference in the improvements among the three treatment arms.9 In other words, there was no difference in the effectiveness of the enhanced curcumin formulation compared to the prescription antidepressant fluoxetine in improving symptoms of depression between baseline and six weeks of treatment.9

The study team concluded that this "is the first randomized clinical trial that clearly highlights that curcumin may be an effective and safe agent when used as a modality of treatment in patients of MDD [major depressive disorder]."9

The advantage of curcumin as an antidepressant is its benign profile of adverse events as compared to other antidepressants.9 Curcumin is known to be safe—even in a huge dose of 8 grams (8,000 mg) a day.9

This remarkable clinical trial used a unique formulation—as we'll learn next—one that overcomes a longstanding problem with curcumin: limited absorption.

What You Need To Know

Curcumin Safely Targets Depression As Effectively As Drugs

Depression now afflicts 1 in 10 US adults. Drug antidepressants are now taken regularly, and the majority of patients who take them suffer at least one of the numerous, serious adverse effects.

By employing a special curcumin formulation called BCM-95®—with nearly seven times greater bioavailability than that of a standard curcumin—

scientists conducted a clinical study demonstrating that it specifically targets the multiple underlying pathways of depression.

This newly published human trial found that this superior-absorbing curcumin complex has similar efficacy to standard antidepressant medication. These potent results were achieved without the side effects that consistently accompany drug therapy.

This high-absorption curcumin works against depression by promoting neuro-genesis, increasing serotonin, norepi-nephrine, and dopamine levels—and inhibiting inflammation.

Increasing Curcumin's Absorption

The form of curcumin used to achieve the impressive results in this human study was an enhanced-absorption formulation—known as BCM-95®—now considered the gold standard of curcumin. Its absorption in the body is far superior to that of other curcumin extracts.21

Development of curcumin as a human nutraceutical has been hampered by a major obstacle. As one study report put it, "The use of curcumin in clinics for the treatment of major depression is limited due to its poor gastrointestinal absorption."13 In addition, curcumin appears to be rapidly broken down both in the intestine and after absorption into the bloodstream.21-23

To overcome this problem, very large doses of curcumin have been needed—doses so large that in some cases, people have balked at the size and number of capsules required to achieve a good effect.21,24,25 Doses as high as 12,000 mg—that's 12 grams or more than a third of an ounce—have been used in efforts to get significant amounts of curcumin into the bloodstream.24 At such high doses, curcumin can produce uncomfortable symptoms such as abdominal fullness, although no true toxicity has been demonstrated.25

In 2008, researchers showed that curcumin's absorption (bioavailability) could be enhanced through a very simple process.21 Curcumin is first extracted from the turmeric root. Next, it is highly purified, and then reconstituted with certain other compounds from the original turmeric plant. These constituents are thought to increase intestinal absorption of curcumin in the body.21 The reconstituted curcumin mixture is called BCM-95®, which was the form of curcumin used in this study.

Clinical studies of BCM-95® in human volunteers have shown that its bioavailability is nearly seven times greater than that of a standard extract of curcumin.21,26 BCM-95® was also more than six times as bioavailable as a leading mixture of curcumin that was combined with two other natural products, lecithin and piperine.21 Not only is the BCM-95® formulation better absorbed, it achieves significant blood levels and remains in the blood longer26 so that the body reaps the beneficial effects of curcumin for considerably more time.

This enhanced-absorption advantage has been shown to apply to other conditions in the past, such as rheumatoid arthritis27—and now to depression.9

But how exactly is curcumin able to so effectively target depression? Let's take a look at the apparent mechanisms.

Promotes Neurogenesis

The progressive loss of the function of brain neurons—neurodegeneration—often occurs simultaneously with depression.28 This condition is more common in aging individuals.28 Neuroinflammation is considered a major contributing factor in both diseases.28 Sustained stress and elevated levels of a class of steroid hormones called glucocorticoids reduce the creation of new brain neurons (neurogenesis).29

Despite all their negative side effects, chronic treatment with antidepressants such as fluoxetine and imipramine may increase neurogenesis.13,29,30

Similarly, the curcumin molecule has been shown in animal studies to boost the neurogenesis process by increasing the number of newly generated cells in a particular area (dentate gyrus) in a brain region known as the hippocampus.19,31 Curcumin is believed to prevent—and even reverse—stress-induced decreases in levels of brain-derived neurotrophic factor (BDNF),a protein that supports the survival of existing neurons and encourages the growth and differentiation of new neurons.13

Modulates Neurotransmitter Levels

High-risk antidepressants called monoamine oxidase inhibitors (MAOIs) work by inhibiting the activity of monoamine oxidase, a family of enzymes that supports the breakdown of neurotransmitters such as serotonin, norepinephrine, and dopamine.32

Other antidepressants known as selective serotonin reuptake inhibitors (SSRIs) specifically increase the extracellular level of serotonin by inhibiting its reabsorption (reuptake) after it has been released in areas of the brain known as synapses.33 Altering serotonin levels is believed to assist brain cells in the sending and receiving of chemical messages—which in turn boosts mood.33

Safely mimicking the mechanisms of both of these types of antidepressants, curcumin has been shown to modestly inhibit two types of monoamine oxidase enzyme (MAO-A and MAO-B)13 and to also modulate the levels of norepinephrine, dopamine, and serotonin in the brain.10,13

By boosting norepinephrine, curcumin may improve attentiveness, emotions, sleeping, dreaming, and learning. Higher levels of dopamine may improve pleasure, emotion, and locomotion. And enhancement of serotonin can play a key role in mood, appetite, sleep, memory, learning, sexual behavior, temperature regulation, and other functions.13

Inhibits Inflammation

Inflammation plays a major role in depression. Chronic inflammation has been shown to influence almost every pathway involved in the development of depression, including neurotransmitter metabolism.34

Curcumin is a potent anti-inflammatory compound. It is known to inhibit multiple compounds that help produce inflammation in the body.13,35 Studies demonstrate that curcumin:13

Inhibits the enzyme cyclooxygenase-2 (COX-2), in turn reducing inflammation.

Inhibits nuclear factor-kappa B (NF-kappa B), a protein complex that controls many genes involved in inflammation.

Blocks the synthesis of an enzyme called inducible nitric oxide synthase (iNOS), in turn decreasing the release of inflammatory nitric oxide (NO).

Lowers, by about 60%, levels ofinterleukin-1, a group of cytokines that plays a central role in the regulation of inflammation.

Reduces the expression of inflammatory markers of astrocytes, cells that support and protect brain neurons.36

Scientists believe that these anti-inflammatory mechanisms contribute to curcumin's antidepressant activity.

It is curcumin's remarkable capacity to modulate all of these antidepressant pathways—neurogenesis, neurotransmitter levels, and inflammation—that explains the impressive results of the newly published clinical findings.

However, it is curcumin's anti-inflammatory activity that underlies a host of other health benefits that go far beyond curcumin's antidepressant impact. Let's review some of these broader effects.

Curcumin And Osteoarthritis

Osteoarthritis , long thought to be a purely "degenerative" disease, is now recognized to have multiple inflammatory components. The breakdown of joint-lining cartilage is triggered by pro-inflammatory signaling molecules.37

In the joint-lining membranes, curcumin suppresses the growth of the inflammatory cells that are responsible for cartilage destruction38,39 and even inhibits the "cartilage-eating" compounds that carry out the destructive process itself.40,41

Human studies show that joint pain decreased and joint function improved in patients taking an enhanced-bioavailability curcumin complex42 and they show improvements in blood tests measuring inflammation.42

Side Effects Of Pharmaceutical Antidepressants

There have been at least 119 published studies from 12 countries, as well as 99 drug regulatory agency warnings from 10 countries plus the European Union, together indicating that antidepressants are involved in the following adverse effects:3-7,98-102

Abnormal bleeding or bruising

Abnormal thoughts

Aggression

Agitation

Ak

athisia (severe restlessness)

Anxiety

Birth defects

Black tongue

Blurred vision or vision changes

Coma

Confusion

Constipation

Convulsions

Crushing chest pain

Death

Decreased memory or concentration

Delirium

Delusional thinking

Depression

Diabetes

Diarrhea

Difficulty breathing or swallowing

Dizziness or faintness

Dry mouth

Emotional numbing

Fainting

Hallucinations

Headaches

Heart attacks

Heart rate decreases

Homicidal ideation or action

Hostility

Hyperactivity

Hypomania

Impaired driving

Insomnia

Lethargy

Liver problems

Low white blood cell count

Mania or manic reactions

Memory lapses

Mood swings

Muscle spasms

Nausea

Nervousness

Neuroleptic malignant syndrome

Night sweats

Nightmares

Numbness in extremities

Panic attacks

Paranoia

Premature births

Priapism

Psychotic episodes

Restlessness

Risk of breast cancer

Risk of falls

Sedation

Seizures

Self-harm

Serotonin syndrome

Severe headache

Severe muscle stiffness

Sexual dysfunction

Shakiness

Shuffling walk

Slow or difficult speech

Spontaneous abortion

Stroke

Suicidal thoughts or behavior

Tremors

Violent behavior

Weight gain

Withdrawal symptoms

Yellowing of skin or eyes

Curcumin And Rheumatoid Arthritis

A team of scientists conducted a 2012 study of rheumatoid arthritis patients who suffered from high levels of inflammation.27

Superior-absorbing curcumin beat the standard arthritis drug diclofenac on most measures of effectiveness, but was free of the side effects that so often accompany drug therapy.27

Curcumin directly attacks the source of the problem—inflammation—rather than simply masking pain and other symptoms.27,42

Curcumin And Cancer

Inflammation can contribute to the proliferation, survival, and migration of cancer cells.43

Fortunately, curcumin has emerged as a potent cancer-preventing agent. It intervenes at each stage in the complex sequence of events that must occur in order for a cancer to develop and ultimately metastasize to healthy tissue.

The multi-targeted mechanisms of curcumin have yielded compelling results in combating a remarkably broad array of cancers—including cancers of the breast,44,45 uterus,46 cervix,47,48 prostate,49-55 and gastrointestinal tract.56-70

Rapidly accumulating research also demonstrates curcumin's potential to counter cancers of the blood,71-73 brain,74 lung,75,76 bladder,77-80 head,81-83 throat,84,85 and pancreas86-90 (one of the most lethal forms of cancer).

Also, curcumin may have special benefits for individuals undergoing radiation cancer treatment. Radiation therapy is often limited due to its side effects.91 For example, prostate cancer patients undergoing external beam radiotherapy suffer, among other effects, urinary tract problems such as painful urination.92 Since curcumin's radioprotective effects had earlier been suggested,93-95 scientists conducted a pilot clinical study on 40 prostate cancer patients undergoing external beam radiotherapy.96

They randomly assigned half of the patients to receive 3 grams daily of the enhanced curcumin formulation BCM-95® while the rest took a placebo. After three months of radiotherapy, the curcumin group experienced much milder urinary problems than the placebo patients, especially reduced urination frequency.96 It has been suggested these results stem partly from curcumin's ability to reduce radiation-induced inflammation.96

These results have implications for radiotherapy for other cancers. Similar results were found in a 2013 study finding that curcumin—using the non-enhanced extract, but in larger doses of 6 grams daily—reduced the severity of radiation dermatitis, or radiation-induced skin inflammation, in breast cancer patients.97

Summary

Depression afflicts one in 10 American adults.1 The majority of patients prescribed antidepressant drugs experience at least one of their serious side effects.2,8

A study published in 2013 showed remarkable outcomes in depressed individuals using curcumin and black pepper. Curcumin targets depression by promoting neurogenesis, increasing levels of key neurotransmitters—serotonin, norepinephrine, and dopamine—and inhibiting inflammation.

Source:

http://www.lifeextension.com/Magazine/2014/6/A-New-Way-To-Manage-Depression-Without-Drugs/Page-01

References

1. Available at: http://www.cdc.gov/features/dsdepression/. Accessed March 19, 2014.
2. Available at: http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/Antidepressants_update.pdf. Accessed March 19, 2014.
3. Available at: http://www.cchrint.org/psychiatric-drugs/antidepressantsideeffects/. Accessed March 19, 2014.
4. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ*. 2011 Aug 2;343:d4551.
5. Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment—pharmacological mechanisms. *Pharmacol Ther*. 2010 Jan;125(1):169-79.
6. Csoka A, Bahrick A, Mehtonen O-P. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *J Sex Med*. 2008;5:227-33.
7. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J Clin Psychiatry*. 2001;62 Suppl 3:10-21.
8. Freeman MP, Mischoulon D, Tedeschini E, et al. Complementary and alternative medicine for major depressive disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. *J Clin Psychiatry*. 2010 Jun;71(6):682-8.
9. Sanmukhani J, Satodia V, Trivedi J, et al. Efficacy and safety of curcumin in major depressive disorder: A randomized controlled trial. *Phytother Res*. 2013;doi:10.1002/ptr.5025.
10. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: involvement of serotonin and dopamine system. *Psychopharmacology (Berl).* 2008 Dec;201(3):435-42.
11. Swartz HA, Rollman BL. Managing the global burden of depression: lessons from the developing world. *World Psychiatry*. 2003 Oct;2(3):162-3.
12. Grundmann M, Kacirova I, Urinovska R. Therapeutic monitoring of psychoactive drugs—antidepressants: A review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. doi: 10.5507/bp.2013.020. Epub 2013 Mar 21.
13. Kulkarni SK, Dhir A, Akula KK. Potentials of curcumin as an antidepressant. *TheScientificWorldJOURNAL*. 2009;9:1233-41.
14. Rush AJ, Trivedi MH, Wisniewski SR, et al. STAR*D Study Team.Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006 Mar 23;354(12):1231-42
15. Yu ZF, Kong LD, Chen Y. Antidepressant activity of aqueous extracts of Curcuma longa in mice. *J Ethnopharmacol*. 2002;83:161-5.
16. Xu Y, Ku BS, Yao HY, et al. The effects of curcumin on depressive-like behaviors in mice. *Eur J Pharmacol*. 2005;518:40-6.

17. Xia X, Cheng G, Pan Y, Xia ZH, Kong LD. Behavioral, neurochemical and neuroendocrine effects of the ethanolic extract from Curcuma longa L. in the mouse forced swimming test. *J Ethnopharmacol*. 2007;110:356-63.

18. Xu Y, Ku B, Cui L, et al. Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res*. 2007;1162:9-18.

19. Wang R, Xu Y, Wu HL, et al. The antidepressant effects of curcumin in the forced swimming test involve 5-HT1 and 5-HT2 receptors. *Eur J Pharmacol*. 2008;578:43-50.

20. Bagby RM, Ryder AG, Schuller DR, Marshall MB. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *Am J Psychiatry*. 2004 Dec;161(12):2163-77.

21. Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. A pilot cross-over study to evaluate human oral bioavailability of BCM-95CG (Biocurcumax), a novel bioenhanced preparation of curcumin. *Indian J Pharm Sci.* 2008 Jul-Aug;70(4):445-9.

22. 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 Jan;14(1):120-5.

23. 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 Jul;7(7):1894-900.

24. Lao CD, Ruffin MTt, Normolle D, et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med.* 2006;6:10.

25. Epelbaum R, Schaffer M, Vizel B, Badmaev V, Bar-Sela G. Curcumin and gemcitabine in patients with advanced pancreatic cancer. *Nutr Cancer.* 2010;62(8):1137-41.

26. Benny M, Antony B. Bioavailability of Biocurcumax (BCM-095). *Spice India.* 2006;September:11-15.

27. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res.* 2012 Nov;26(11):1719-25.

28. Hurley LL, Tizabi Y. Neuroinflammation, neurodegeneration, and depression. *Neurotox Res*. 2013 Feb;23(2):131-44.

29. Xi G, Zhang X, Zhang L, Sui Y, et al. Fluoxetine attenuates the inhibitory effect of glucocorticoid hormones on neurogenesis in vitro via a two-pore domain potassium channel, TREK-1. *Psychopharmacology (Berl).* 2011 Apr;214(3):747-59.

30. Kim SJ 1, Son TG, Park HR, et al. Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *J Biol Chem. 2008 May 23;283(21):14497-505.*

31. Kulkarni SK, Dhir A. An overview of curcumin in neurological disorders. *Indian J Pharm Sci*. 2010 Mar-Apr;72(2):149-54.

32. Nowakowska E, Chodera A. Inhibitory monoamine oxidases of the new generation. *Pol. Merkur. Lekarski* (in Polish). July 1997;3(13):1-4.

33. Available at: http://www.mayoclinic.com/health/ssris/MH00066. Accessed March 19, 2014.

34. Miller AH , Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry. 2009 May 1;65(9):732-41.*

35. *Pandey A, Gupta RK, Srivastava R. Curcumin—the yellow magic. Asian J Appl Sciences* . 2011;4(4):343-54.

36. Sofroniew MV , Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol. 2010 Jan;119(1):7-35.*

37. *Csaki C, Mobasheri A, Shakibaei M. Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1beta-induced NF-kappaB-mediated inflammation and apoptosis. Arthritis Res Ther.* 2009;11(6):R165.

38. Shakibaei M, Schulze-Tanzil G, John T, Mobasheri A. Curcumin protects human chondrocytes from IL-l1beta-induced inhibition of collagen type II and beta1-integrin expression and activation of caspase-3: an immunomorphological study. *Ann Anat.* 2005 Nov;187(5-6):487-97.

39. Lev-Ari S, Strier L, Kazanov D, et al. Curcumin synergistically potentiates the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis synovial adherent cells. *Rheumatology (Oxford).* 2006 Feb;45(2):171-7.

40. Shakibaei M, John T, Schulze-Tanzil G, Lehmann I, Mobasheri A. Suppression of NF-kappaB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. *Biochem Pharmacol.* 2007 May 1;73(9):1434-45.

41. Mathy-Hartert M, Jacquemond-Collet I, Priem F, Sanchez C, Lambert C, Henrotin Y. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. *Inflamm Res.* 2009 Dec;58(12):899-908.

42. Belcaro G, Cesarone MR, Dugall M, et al. Efficacy and safety of Meriva(R), a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Altern Med Rev.* 2010 Dec;15(4):337-44.

43. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860-7.

44. Banerjee M, Singh P, Panda D. Curcumin suppresses the dynamic instability of microtubules, activates the mitotic checkpoint and induces apoptosis in MCF-7 cells. *FEBS J*. 2010 Aug;277(16):3437-48.

45. Bayet-Robert M, Kwiatkowski F, Leheurteur M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol Ther*. 2010 Jan;9(1):8-14.

46. Liang YJ, Hao Q, Wu YZ, Wang QL, Wang JD, Hu YL. Aromatase inhibitor letrozole in synergy with curcumin in the inhibition of xenografted endometrial carcinoma growth. *Int J Gynecol Cancer*. 2009 Oct;19(7):1248-52.

47. Madden K, Flowers L, Salani R, et al. Proteomics-based approach to elucidate the mechanism of antitumor effect of curcumin in cervical cancer. *Prostaglandins Leukot Essent Fatty Acids*. 2009 Jan;80(1):9-18.

48. Prusty BK, Das BC. Constitutive activation of transcription factor AP-1 in cervical cancer and suppression of human papillomavirus (HPV) transcription and AP-1 activity in HeLa cells by curcumin. *Int J Cancer*. 2005 Mar 1;113(6):951-60.

49. Teiten MH, Gaascht F, Eifes S, Dicato M, Diederich M. Chemopreventive potential of curcumin in prostate cancer. *Genes Nutr*. 2010 Mar;5(1):61-74.

50. Piantino CB, Salvadori FA, Ayres PP, et al. An evaluation of the anti-neoplastic activity of curcumin in prostate cancer cell lines. *Int Braz J Urol*. 2009 May-Jun;35(3):354-60; discussion 61.

51. Khan N, Adhami VM, Mukhtar H. Apoptosis by dietary agents for prevention and treatment of prostate cancer. *Endocr Relat Cancer*. 2010 Mar;17(1):R39-52.

52. Thangapazham RL, Shaheduzzaman S, Kim KH, et al. Androgen responsive and refractory prostate cancer cells exhibit distinct curcumin regulated transcriptome. *Cancer Biol Ther*. 2008 Sep;7(9):1427-35.

53. Tsui KH, Feng TH, Lin CM, Chang PL, Juang HH. Curcumin blocks the activation of androgen and interlukin-6 on prostate-specific antigen expression in human prostatic carcinoma cells. *J Androl*. 2008 Nov-Dec;29(6):661-8.

54. Shi Q, Shih CC, Lee KH. Novel anti-prostate cancer curcumin analogues that enhance androgen receptor degradation activity. *Anticancer Agents Med Chem*. 2009 Oct;9(8):904-12.

55. Choi HY, Lim JE, Hong JH. Curcumin interrupts the interaction between the androgen receptor and Wnt/beta-catenin signaling pathway in LNCaP prostate cancer cells. *Prostate Cancer Prostatic Dis.* 2010 Dec;13(4):343-9.

56. Patel BB, Majumdar AP. Synergistic role of curcumin with current therapeutics in colorectal cancer: minireview. *Nutr Cancer*. 2009 Nov;61(6):842-6.

57. Yu Y, Kanwar SS, Patel BB, Nautiyal J, Sarkar FH, Majumdar AP. Elimination of colon cancer stem-like cells by the combination of curcumin and FOLFOX. *Transl Oncol*. 2009 Dec;2(4):321-8.

58. Patel BB, Gupta D, Elliott AA, Sengupta V, Yu Y, Majumdar AP. Curcumin targets FOLFOX-surviving colon cancer cells via inhibition of EGFRs and IGF-1R. *Anticancer Res*. 2010 Feb;30(2):319-25.

59. Milacic V, Banerjee S, Landis-Piwowar KR, Sarkar FH, Majumdar AP, Dou QP. Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo. *Cancer Res*. 2008 Sep 15;68(18):7283-92.

60. Watson JL, Hill R, Yaffe PB, et al. Curcumin causes superoxide anion production and p53-independent apoptosis in human colon cancer cells. *Cancer Lett*. 2010 Nov 1;297(1):1-8.

61. Han Y, Haraguchi T, Iwanaga S, et al. Consumption of some polyphenols reduces fecal deoxycholic acid and lithocholic acid, the secondary bile acids of risk factors of colon cancer. *J Agric Food Chem*. 2009 Sep 23;57(18):8587-90.

62. Wang BM, Zhai CY, Fang WL, Chen X, Jiang K, Wang YM. The inhibitory effect of curcumin on the proliferation of HT-29 colonic cancer cell induced by deoxycholic acid. *Zhonghua Nei Ke Za Zhi*. 2009 Sep;48(9):760-3.

63. Majumdar AP, Banerjee S, Nautiyal J, et al. Curcumin synergizes with resveratrol to inhibit colon cancer. *Nutr Cancer*. 2009;61(4):544-53.

64. Xu G, Ren G, Xu X, et al. Combination of curcumin and green tea catechins prevents dimethylhydrazine-induced colon carcinogenesis. *Food Chem Toxicol*. 2010 Jan;48(1):390-5.

65. Sandur SK, Deorukhkar A, Pandey MK, et al. Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NF-kappaB activity. *Int J Radiat Oncol Biol Phys*. 2009 Oct 1;75(2):534-42.

66. Bartik L, Whitfield GK, Kaczmarska M, et al. Curcumin: a novel nutritionally derived ligand of the vitamin D receptor with implications for colon cancer chemoprevention. *J Nutr Biochem*. 2010 Feb 11.

67. Koo JY, Kim HJ, Jung KO, Park KY. Curcumin inhibits the growth of AGS human gastric carcinoma cells in vitro and shows synergism with 5-fluorouracil . *J Med Food*. 2004 Summer;7(2):117-21.

68. Tang XQ, Bi H, Feng JQ, Cao JG. Effect of curcumin on multidrug resistance in resistant human gastric carcinoma cell line SGC7901/VCR. *Acta Pharmacol Sin*. 2005 Aug;26(8):1009-16.

69. Cai XZ, Wang J, Li XD, et al. Curcumin suppresses proliferation and invasion in human gastric cancer cells by downregulation of PAK1 activity and cyclin D1 expression. *Cancer Biol Ther*. 2009 Jul;8(14):1360-8.

70. De R, Kundu P, Swarnakar S, et al. Antimicrobial activity of curcumin against Helicobacter pylori isolates from India and during infections in mice. *Antimicrob Agents Chemother*. 2009 Apr;53(4):1592-7.

71. Uddin S, Khan AS, Al-Kuraya KS. Developing curcumin into a viable therapeutic for lymphoma. *Expert Opin Investig Drugs*. 2009 Jan;18(1):57-67.

72. Vyas HK, Pal R, Vishwakarma R, Lohiya NK, Talwar GP. Selective killing of leukemia and lymphoma cells ectopically expressing hCGbeta by a conjugate of curcumin with an antibody against hCGbeta subunit. *Oncology*. 2009;76(2):101-11.

73. Xiao H, Zhang KJ, Zuo XL. Reversal of multidrug resistance of the drug resistant human multiple myeloma cell line MOLP-2/R by curcumin and its relation with FA/BRCA pathway. *Zhonghua Xue Ye Xue Za Zhi*. 2009 Jan;30(1):33-7.

74. Purkayastha S, Berliner A, Fernando SS, et al. Curcumin blocks brain tumor formation. *Brain Res*. 2009 April 17;1266:130-8.

75. Zhang J, Du Y, Wu C, et al. Curcumin promotes apoptosis in human lung adenocarcinoma cells through miR-186* signaling pathway. *Oncol Rep*. 2010 Nov;24(5):1217-23.

76. Zhang J, Zhang T, Ti X, et al. Curcumin promotes apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells through an miRNA signaling pathway. *Biochem Biophys Res Commun*. 2010 Aug 13;399(1):1-6.

77. Chadalapaka G, Jutooru I, Chintharlapalli S, et al. Curcumin decreases specificity protein expression in bladder cancer cells. *Cancer Res*. 2008 Jul 1;68(13):5345-54.

78. Leite KR, Chade DC, Sanudo A, Sakiyama BY, Batocchio G, Srougi M. Effects of curcumin in an orthotopic murine bladder tumor model. *Int Braz J Urol*. 2009 Sep-Oct;35(5):599-606; discussion 06-7.

79. Chadalapaka G, Jutooru I, Burghardt R, Safe S. Drugs that target specificity proteins downregulate epidermal growth factor receptor in bladder cancer cells. *Mol Cancer Res*. 2010 May;8(5):739-50.

80. Tharakan ST, Inamoto T, Sung B, Aggarwal BB, Kamat AM. Curcumin potentiates the antitumor effects of gemcitabine in an orthotopic model of human bladder cancer through suppression of proliferative and angiogenic biomarkers. *Biochem Pharmacol*. 2010 Jan 15;79(2):218-28.

81. Lin YC, Chen HW, Kuo YC, Chang YF, Lee YJ, Hwang JJ. Therapeutic efficacy evaluation of curcumin on human oral squamous cell carcinoma xenograft using multimodalities of molecular imaging. *Am J Chin Med*. 2010;38(2):343-58.

82. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. *J Oral S*ci. 2010;52(2):251-6.

83. Shin HK, Kim J, Lee EJ, Kim SH. Inhibitory effect of curcumin on motility of human oral squamous carcinoma YD-10B cells via suppression of ERK and NF-kappaB activations. *Phytother Res*. 2010 Apr;24(4):577-82.

84. Wong TS, Chan WS, Li CH, et al. Curcumin alters the migratory phenotype of nasopharyngeal carcinoma cells through up-regulation of E-cadherin. *Anticancer Res*. 2010 Jul;30(7):2851-6.

85. Available at: http://www.cancer.gov/cancertopics/types/throat. Accessed March 19, 2014.

86. Glienke W, Maute L, Wicht J, Bergmann L. Curcumin inhibits constitutive STAT3 phosphorylation in human pancreatic cancer cell lines and downregulation of survivin/BIRC5 gene expression. *Cancer Invest*. 2010 Feb;28(2):166-71.

87. Jutooru I, Chadalapaka G, Lei P, Safe S. Inhibition of NFkappaB and pancreatic cancer cell and tumor growth by curcumin is dependent on specificity protein down-regulation. *J Biol Chem*. 2010 Aug 13;285(33):25332-44.

88. Kanai M, Yoshimura K, Asada M, et al. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. *Cancer Chemother Pharmacol*. 2011 Jul;68(1):157-64.

89. Lin L, Hutzen B, Zuo M, et al. Novel STAT3 phosphorylation inhibitors exhibit potent growth-suppressive activity in pancreatic and breast cancer cells. *Cancer Res*. 2010 Mar 15;70(6):2445-54.

90. Ramachandran C, Resek AP, Escal on E, Aviram A, Melnick SJ. Potentiation of gemcitabine by Turmeric Force in pancreatic cancer cell lines. *Oncol Rep*. 2010 Jun;23(6):1529-35.

91. Wahlgren T, Brandberg Y, Häggarth L, Hellström M, Nilsson S. Health-related quality of life in men after treatment of localized prostate cancer with external beam radiotherapy combined with (192)ir brachytherapy: a prospective study of 93 cases using the EORTC questionnaires QLQ-C30 and QLQ-PR25. *Int J Radiat Oncol Biol Phys*. 2004 Sep 1;60(1):51-9.

92. Michaelson MD, Cotter SE, Gargollo PC, et al. Management of complications of prostate cancer treatment. *CA Cancer J Clin*. 2008;58:196-213.

93. Akpolat M, Kanter M, Uzal MC. Protective effects of curcumin against gamma radiation-induced ileal mucosal damage. *Arch Toxicol*. 2009;83:609-17.

94. Aravindan N, Madhusoodhanan R, Ahmad S, Johnson D, Herman T. Curcumin inhibits NFkappaB mediated radioprotection and modulate apoptosis related genes in human neuroblastoma cells. *Cancer Biol Ther*. 2008;7:569-76.

95. Khafif A, Hurst R, Kyker K, et al. Curcumin: a new radiosensitizer of squamous cell carcinoma cells. *Otolaryngol Head Neck Surg*. 2005;132:317-21.

96. Hejazi J, Rastmanesh R, Taleban F-A, Molana S-H, Ehtejab G. A pilot clinical trial of radioprotective effects of curcumin supplementation in patients with prostate cancer. *J Cancer Sci Ther*. 2013;5-10.

97. Ryan JL, Heckler CE, Ling M, et al. Curcumin for radiation dermatitis: A randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res*. 2013;180:34-43.

98. Available at : http//www.fdable.com/basic_query/aers/ 08ced09907b9a949e92270776a382535. Accessed March 21, 2014.

99. Steingart A, Cotterchio M, Kreiger N, Sloan M.Antidepressant medication use and breast cancer risk: a case-control study. *Int J Epidemiol.* 2003 Dec;32(6):961-6.

100. Einarson A, Choi J, Einarson TR, Koren G. Adverse effects of antidepressant use in pregnancy: an evaluation of fetal growth and preterm birth. *Depress Anxiety*. 2010;27(1):35-8.

101. Kolli V, Ramaswamy S.Improvement of antidepressant-induced sweating with as-required benztropine. *Innov Clin Neurosci*. 2013 Nov;10(11-12):10-1.

102. Kurdyak PA, Manno M, Gomes T, Mamdani MM, Juurlink DN. Antidepressants, metoprolol and the risk of bradycardia. *Ther Adv Psychopharmacol*. 2012 Apr;2(2):43-9.