Kuwait Pharmacy Bulletin
DRUG INFORMATION FOR THE HEALTH PROFESSIONAL
Vol 21 No 2 Summer 2017 ISSN 1028-0480

# Curcuminoids: chemistry and therapeutic uses

Curcuminoids are a group of chemically related compounds found in the turmeric plant that have attracted attention for their medicinal properties. *Curcuma longa* is the domestic species of turmeric and the wild type is called *C. aromatica*. These species belong to the ginger family Zingiberaceae. Turmeric, dry or fresh, is used as a culinary spice, preservative and household remedy. Curcuminoids, mainly curcumin, give turmeric the bright yellow-orange color. Therefore, it is sometimes called indian saffron, and is widely used as a food colourant and flavouring agent. It is a principal ingredient in curry powder and colourant in mustard. Turmeric is also used in cosmetic and skin products to give a natural golden glow. This review will describe the sources, chemistry and metabolism of curcuminoids, their biosynthesis, methods of chemical synthesis and isolation and their therapeutic usefulness.

## Introduction

The two main curcumin derivatives are demethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III). Cyclocurcumin (Curcumin IV) is a new addition to the curcuminoids family that was isolated in trace amounts from turmeric rhizomes [1]. Fig 1 shows the chemical structures of curcuminoids.

Over the past few years, there has been an increasing interest in turmeric due to its anti-carcinogenic, anti-diabetic, anti-oxidant, anti-inflammatory and anti-microbial activities. It has been used for wounds, as well as disorders of the skin, liver, joints, lung and GI tract. Furthermore, it has potential therapeutic and preventative effects in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.[2]

## Biosynthesis

Initial studies on the biosynthesis of curcuminoids using radioactive tracers suggested that they were derived from the phenylpropanoid pathway (Fig 1). Phenylalanine ammonia lyase (PAL) is the first enzyme in the biosynthesis sequence that is involved in amino acid metabolism and the transition point between primary and secondary metabolism. Two type III polyketide synthase (PKSs) enzymes were isolated from the herb *C. longa*, curcumin synthase (CURS) and diketide-CoA synthase (DCS) [3]. Diketide-CoA synthase (DCS) catalyzes the reaction of feruloyl-CoA with malonyl-CoA to form feruloyl-diketide-CoA.

Curcumin synthase has three isoforms (CURS1, 2, and 3), which are involved in the decarboxylative condensation reaction in the biosynthesis of curcuminoids. Each enzyme, (DCS) and (CURS1, 2 and 3), has preferred starter substrates to be converted to one of the curcuminoids. CURS convert feruloyldiketide-CoA esters into curcumin using feruloyl-CoA mainly as a starter substrate. These enzymes can also produce the asymmetric curcuminoid demethoxycurcumin from p-coumaroyldiketide - CoA and feruloyl-CoA. Other identified enzymes in the curcuminoid biosynthetic pathway include *p*-coumaroyl shikimate transferase (CST), *p*-coumaroyl quinate transferase (CQT), caffeic acid *O*-methyltransferase (COMT) and caffeoyl -CoA *O*- methyltransferase (CCOMT or CCoAOMT). Depending on the combination, different curcuminoids are produced, namely bisdemethoxycurcu-

## In this issue

min, demethoxycurcumin and curcumin. The hypothesis of caffeic acid as the precursor to curcuminoids was not proven to occur *in vivo* in *C. Longa* [4].

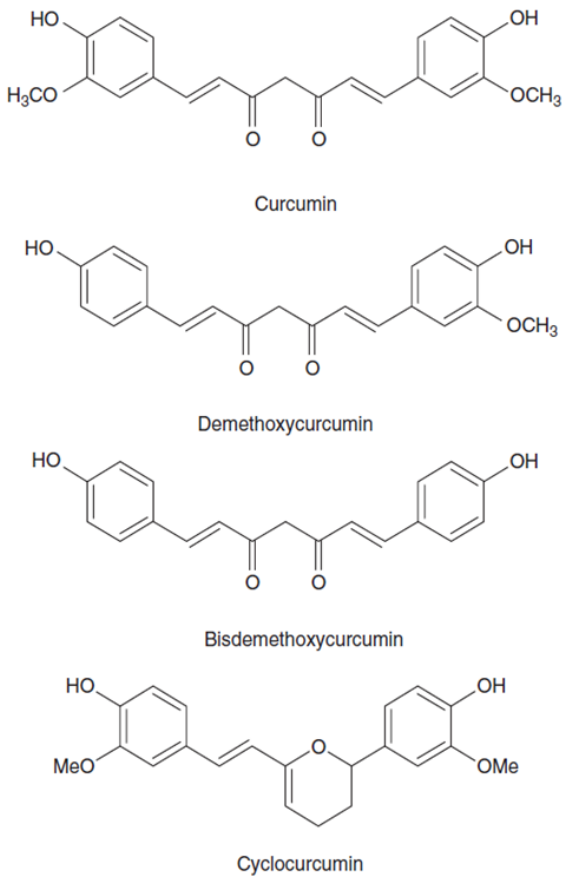



*Figure 1 Curcuminoids: chemical structure*

## Extraction and isolation

Curcuminoids can be extracted from dried and ground turmeric rhizomes by several methods. Soxhlet extraction is one of the most common that gives a high extraction yield. However, the extraction takes a long time at high temperature and utilizes large amounts of solvent and several extraction cycles to obtain the extracted product (turmeric oleoresin).

The most recently applied extraction methods include microwave-assisted, ultrasound-assisted, enzyme-assisted and supercritical carbon dioxide extraction. They were developed to overcome the limitation of the traditional methods and utilise more environment- friendly technologies [5].

Microwave-assisted extraction is a combination of the conventional solvent extraction and electromagnetic energy. This energy is converted to thermal energy that enhances the solvent extraction capability. Acetone is commonly used as the extracting solvent. This extraction has several advantages including shorter time due to fast heating, high extraction efficiency and low energy requirement.

Ultrasound-assisted extraction works by mechanical and thermal effects. These effects cause cell wall disruption (microcavities), particle size reduction and enhanced mass diffusion from the solid materials (curcumin from turmeric powder) to the solvent.

As for enzyme-assisted extraction, the pretreatment of turmeric with hydrolytic enzymes such as α-amylase and glucoamylase breaks down the plant cell structural integrity leading to significant increase in curcumin yields.

Supercritical carbon dioxide extraction is an option to extract curcumin with relatively low temperature and without the need for toxic and flammable solvents such as acetone and hexane. Carbon dioxide will act as solvent to extract curcumin at pressures between 25-30 MPa and a temperature of 318 K. When the applied high pressure is removed, $CO_2$ will evaporate without leaving a trace in the extracted product.[6]

A study comparing curcumin extraction yields using different methods showed that Soxhlet yield (6.9%) was considerably higher than microwave-assisted (3.72%), ultrasound-assisted (3.92%) and enzyme-assisted (4.1%) extractions [5].

In another study the highest yield (27%) was also obtained in the Soxhlet extraction using ethanol as a solvent, while the lowest yield was with a hydrodistillation process (2.1%) [7].

All these methods need optimization of extraction conditions including extraction time, temperature, solvent types, solid to solvent ratio and particle size to improve the yield and get better quality index of the extracted product.

Quantification and separation of curcuminoids is carried out by high-performance liquid chromatography (HPLC) and thin layer chromatography (TLC) analysis as well as column chromatography (CC) for large quantity separation using silica gel as stationary phase. The HPLC method is more sensitive and accurate than other methods and is done mostly using reverse phase C18 columns as stationary phase and different gradients of solvents containing acetonitrile/water or chloroform/methanol as the mobile phase. UV-Vis spectroscopic analysis is conducted after the extraction is completed. Absorption between 420-430 nm confirms the presence of curcuminoids.[6, 8]

## Chemical synthesis

Pure curcumin is rare and hard to isolate from turmeric. One method involves five step condensation

reactions between carbomethoxy feruloyl chloride (1) and ethyl acetoacetate (2), as shown in Fig 3. After condensation and subsequent ester hydrolysis and decarboxylation, the intermediate product (4) is again exposed to carbomethoxy feruloyl chloride (5) to give the diferuloyl compound (6). This compound undergoes de-acetylation and de-carboxymethylation to give curcumin (8) identical to the natural curcumin.

Knoevenagel condensation. Due to the shielding, the terminal methyl groups will undergo aldol condensation reaction instead of the methylene group. N-butyl amine or other primary and secondary amines are used as basic catalysts to remove a hydrogen atom from the alkyl groups of the diketone. Then, a nucleophilic attack with the substituted benzaldehyde takes place at both terminal methyl

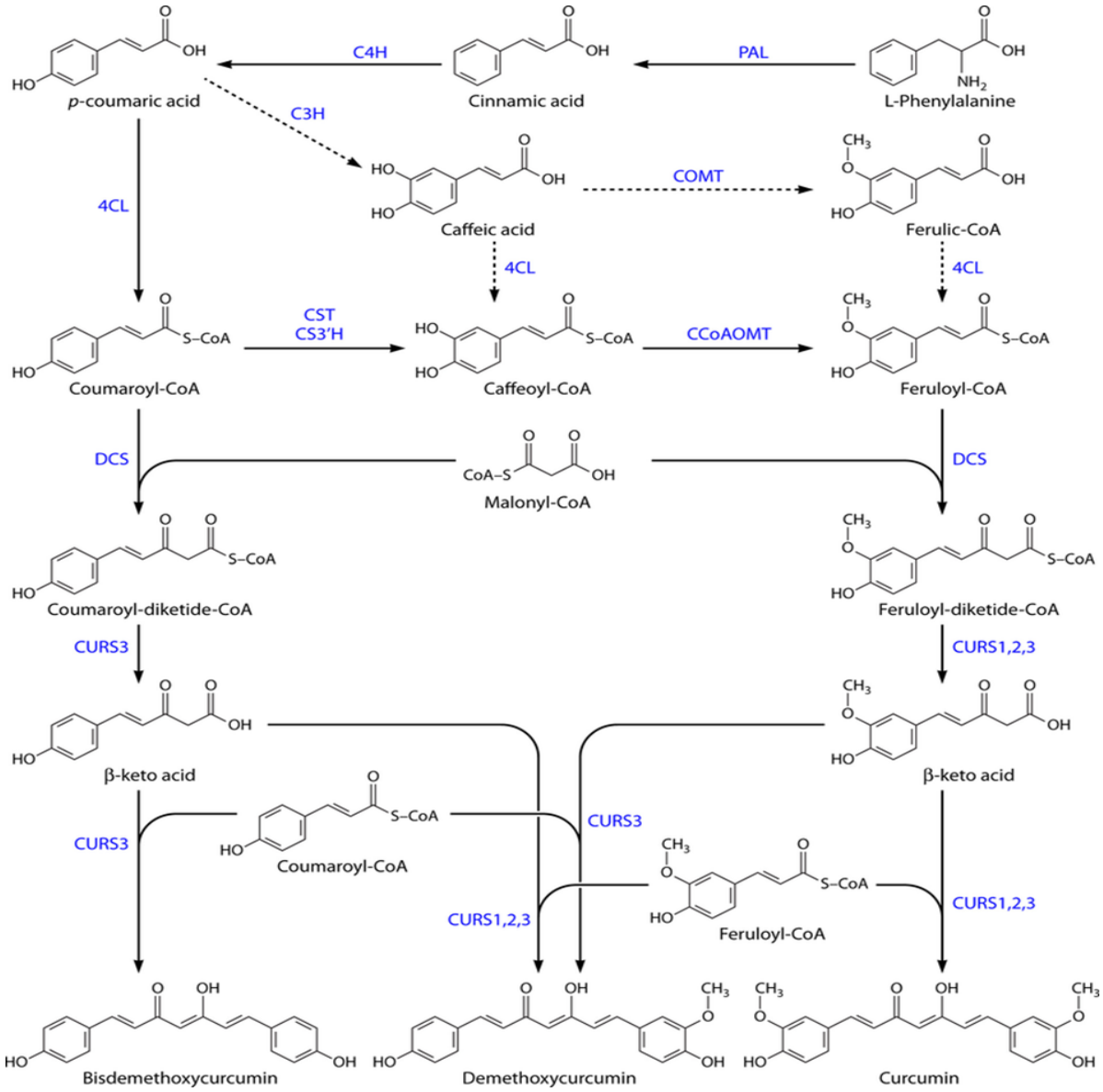



*Figure 2. Curcuminoid biosynthetic pathway in Curcuma longa* [6]

Another method of synthesizing curcumin is from acetylacetone (pentan-2,4-dione) and vanillin (4-hydroxy-3-methoxybenzaldehyde) in the presence of boron trioxide. Trialkyl borates and n-butylamine are added (Fig 4) to increase the yield of curcumin from 10 to 80%. Curcumin derivatives can be obtained using other substituted aromatic aldehydes other than vanillin. Initially, acetylacetone (9) is complexed with boron trioxide (10) to protect the methylene groups from undergoing

groups. Since this reaction is water-sensitive, trialkyl borates are used as scavengers to remove the water produced during the condensation reaction. The presence of water can reduce the production yields of curcumin by reacting with the diketone complex. The boron complex (11) dissociates in the final step by the addition of a hydrochloric acid solution (slightly acidic environment) into two equivalents of the corresponding curcuminoid (12). The reaction is performed in anhydrous condition using

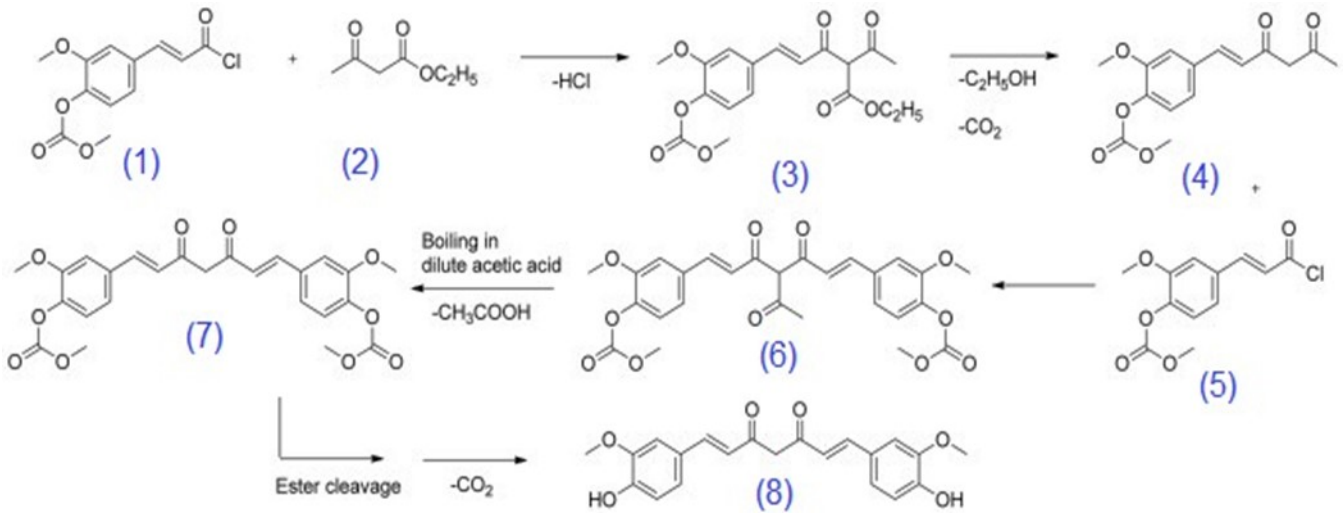



*Figure 3. Synthesis of curcumin according to Lampe [9]*

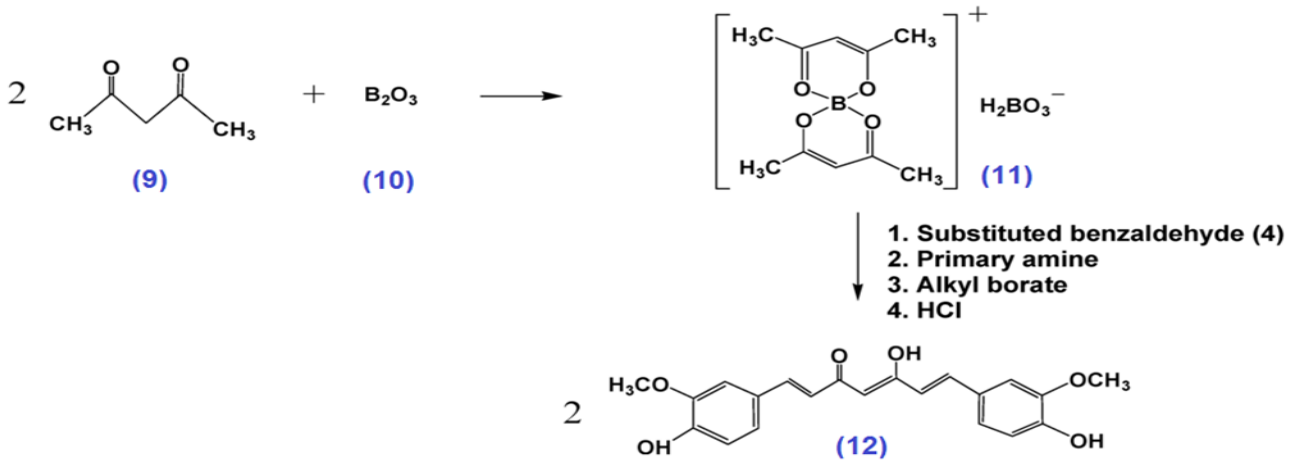



*Figure 4. Synthesis of curcuminoids according to Pabon*

polar aprotic solvent such as ethyl acetate to provide the proper solubility for reactants and intermediates. [9]

## Physicochemical properties

Curcumin ($C_{21}H_{20}O_6$) is a linear diarylheptanoid polyphenol that has a symmetric structure consisting of three chemical entities: two aromatic ring systems containing ortho-methoxy phenolic groups, connected by a seven carbon linker of an α,β-unsaturated β-diketone moiety [6].

Between the β-diketone group, intramolecular hydrogen atoms transfer leads to the existence of keto and enol tautomeric conformations in equilibrium. The equilibrium favors keto-enol form, which is stabilized by a hydrogen bond, over the diketo form, as shown in Fig 5. Besides keto-enol tautomers, curcuminoids also exist in several *cis* and *trans* geometrical isomers partly dependent upon temperature, pH, polarity of solvent and substitution on aromatic rings. This equilibrium has a crucial role in the physicochemical properties and antioxidant activities of curcumin.

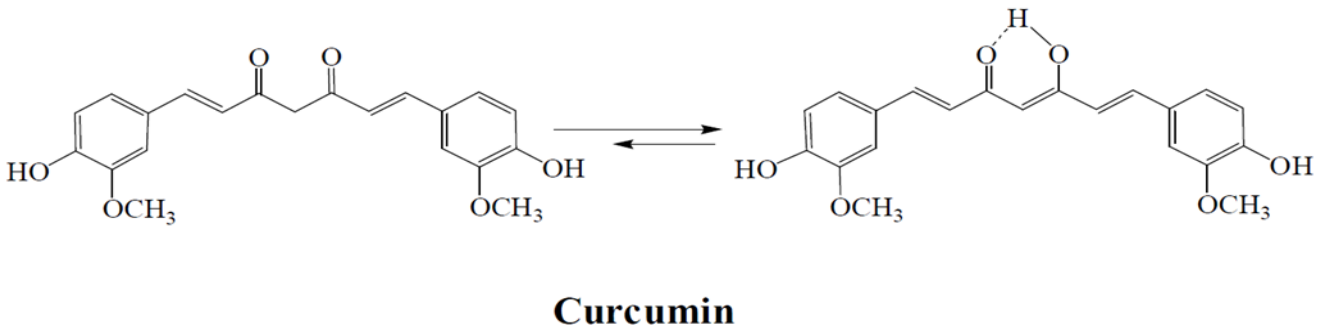



*Figure 5. Diketo and keto-enol form equilibrium*

In acidic and neutral conditions (i.e. pH 3–7), the diketo form becomes the major constituent and acts as a proton donor, whereas at alkaline condition (i.e. pH > 8) the keto-enol form predominates and serves as an electron donor.[10] In non-polar solvents, curcumin exists in the keto-enol form due to intramolecular hydrogen bond formation, while in polar solvents it exists in the diketo form. [9] Curcumin has three acidic protons: one enolic and two phenolic protons.

Curcumin is yellow-orange crystalline powder that has a pungent, bitter flavor. Its colour is due to the conjugated system and phenyl groups. Curcumin colour changes depending on the pH which makes it useful as an acid–base indicator. At pH<1, curcumin becomes protonated and displays a red color, while at acidic and neutral pH (pH 1–7) it is bright yellow and exists in the neutral state. At basic pH (pH>7), curcumin is deprotonated and again becomes red in color [9].

### *Solubility*

Curcumin and other curcuminoids are hydrophobic molecules[6] practically insoluble in water, neutral and medium acidic pH. On the other hand, they are readily soluble in polar organic solvents, such as ethanol, methanol, isopropanol, acetone, acetonitrile, chloroform and dimethylsulfoxide (DMSO) and sparingly soluble in hydrocarbon solvents including hexane, cyclohexane, tetrahydrofuran and dioxane.

### *Stability*

Curcumin is most stable in acidic pH (pH 1-6), becoming unstable and degrading rapidly in basic pH (pH>7) conditions. Curcumin degradation increases in the presence of light. Since the degradation occurs through the β-diketo moiety, the stability of curcumin can be enhanced by adding proteins, lipids, surfactants, cyclodextrins and starch to the solutions, including phospholipid liposomes or bovine serum albumin. The addition of antioxidants such as ascorbic acid, N-acetylcysteine or glutathione to culture media can also inhibit its degradation. These compounds can bind β-diketo moiety, thus it will not be available for hydrolytic degradation. [9]

## Metabolism

Curcumin is metabolised by phase I and II liver enzymes. In phase I metabolism, reduction of the double bonds in the heptadienedione system results in reduced dihydro-, tetrahydro-, hexahydro- and octahydrocurcumin derivatives, with tetrahydrocurcumin and hexahydrocurcumin being the major products. This mainly happens by the action of alcohol dehydrogenase and other hepatic reductases (using $NADP^+$ and NADPH). In phase II, curcumin and its reduced metabolites are conjugated to form glucuronides and sulfates at the phenolic positions. Other minor curcumin metabolites have been identified including dihydroferulic acid and ferulic acid. [9, 11]

Intestinal microorganisms have also been shown to metabolise curcumin. Curcumin metabolising microorganisms were isolated in samples of human faeces and the organism with the highest curcumin-converting activity is *E coli*. In this metabolic pathway, curcumin is converted by NADPH-dependent curcumin/dihydrocurcumin reductase" (CurA) [12] into the intermediate product, dihydrocurcumin, and then to the end product, tetrahydrocurcumin (Fig 6).

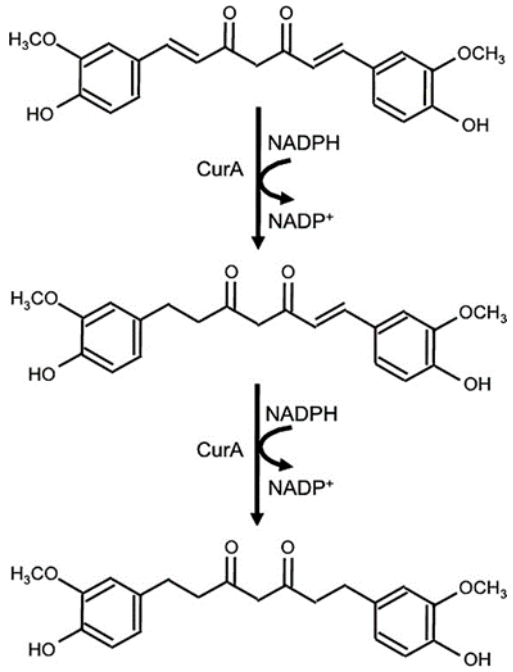



***Figure 6. Intestinal microorganisms' curcumin metabolic pathway [11]***

Curcumin has low systemic bioavailability due to low gastrointestinal absorption, rapid metabolism and systemic elimination. This poor bioavailability limits the therapeutic application of curcumin and has led to the use of parenteral administration and development of novel formulations that include nanoemulsions, liposomes and phospholipid complexes. Another option is to use adjuvants like piperine (a component of pepper), that can block the curcumin metabolic pathway; this inhibits hepatic and intestinal glucuronidation and therefore extends the half-life of curcumin. [13]

### *Chemical reactivity*

Curcumin interacts with other molecules to exert its biological activity. These include nucleophilic addition reactions, reactions with reactive oxygen species

(ROS) and curcumin-metal complexation.

Curcumin is a ROS scavenger. ROS include free radicals such as superoxide anion ($O_2^{\bullet-}$), hydroxyl ($OH^{\bullet}$) and nitric oxide ($NO^{\bullet}$) radicals as well as non-free radical species such as hydrogen peroxide ($H_2O_2$) and singlet oxygen ($^1O_2$) and nitrous acid ($HNO_2$). The *o*-methoxyphenyl group (mainly) and methylenic hydrogen are responsible for the anti-oxidant activity of curcuminoids. The phenoxyl radical can be regenerated back to curcumin by water soluble antioxidants like ascorbic acid. Curcumin is a more efficient antioxidant than its derivatives due to the presence of two *o*-methoxyphenyl groups. [14]

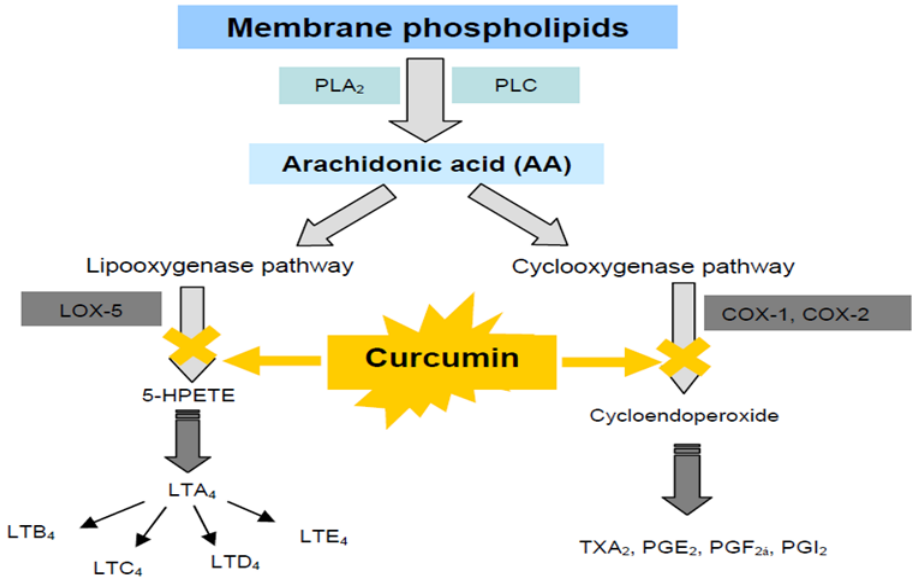
Curcumin is an excellent chelating agent which forms strong complexes with most metal ions and metal oxides through α,β-unsaturated and β-diketo moieties. Complexation with curcumin reduces the toxicity of heavy metals such as $Hg^{2+}$, $Cd^{2+}$ and $Pb^{2+}$, while some metal-curcumin complexes like $Cu^{2+}$, $Mn^{2+}$, act as antioxidants and superoxide dismutase enzyme mimics. $Zn^{2+}$-curcumin complexes showed anti-cancer, gastro-protective and anti-depressant effects in rat models [6]

## Therapeutic uses

Recently, many pre-clinical and clinical studies showed that curcuminoids interact with many cellular pathways, which results in anti-inflammatory and anti-oxidant therapeutic activities.

### *Anti-inflammatory activity*

Curcumin and its derivatives modulate the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) enzymes (Fig 7). Furthermore, they inhibit the production of pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), nuclear factor- κB (NF-κB), interleukins (IL-1, IL-2, IL-6, IL-8, IL-12), monocyte chemoattractant protein, and migration inhibitory protein. These activities are attributable to the hydroxyl and phenol groups in curcuminoid molecules, which inhibit prostaglandins, PG synthetase and leukotriene synthesis. Due to their anti-inflammatory activity, they are potential therapeutic agents in inflammatory bowel diseases pancreatitis ad arthritis, as well as certain types of cancer.[15, 16]




COX: Cyclooxygenase; HPETE: Hydroperoxyeicosatetraenoate; LOX: Lipooxygenase; LT: Leukotriene; PL: Phospholipase; PG: Prostaglandin; TX: thromboxane.

*Figure 7. Curcumin blocks arachidonic acid pathway [17]*

### *Anti-oxidant effect*

ROS are continuously produced during the mitochondrial electron transport of aerobic respiration or by oxidoreductase enzymes and metal-catalyzed oxidation. ROS play vital roles in energy production, immunity, intercellular signaling and synthesis of biologically important compounds. The imbalance between production and removal of ROS toward the pro-oxidative state is often referred to as "oxidative stress".

Prolonged and excessive exposure to ROS may lead to cell membrane damage by lipid peroxidation, which eventually results in cell death. Also, ROS interact with nucleic acids, lipids, proteins and carbohydrates leading to DNA damage and consequent-

ly genetic mutation.

It is documented that ROS are involved in aging and inflammation as well as various human diseases such as Alzheimer's, cancer, rheumatoid arthritis and atherosclerosis. Aerobic organisms have several defensive mechanisms to detoxify the body from ROS such as intracellular glutathione and superoxide dismutase (SOD) enzymes, as well as vitamin C (ascorbic acid) and E (α-tocopherol), which are present in food. Curcumin can protect cell membranes against lipid peroxidative damage by scavenging reactive free radicals.[18]

### *Anti-mutagenic and anti-cancer properties*

Curcumin can modulate intracellular signaling pathways on multiple targets that control tumor growth, angiogenesis, metastasis, inflammation, invasion and apoptosis. Animal studies and human clinical trials have found that curcumin has therapeutic and preventative potential for patients with colorectal, liver, pancreatic, lung, breast, uterine, ovarian, prostate, bladder, kidney, renal, brain, non-Hodgkin lymphoma and leukemia cancers.[19]

A randomized controlled trial concluded that curcuminoids use as adjuvant therapy suppressed systemic inflammation and improved quality of life in patients with solid tumors. The study detected lower level of systemic inflammatory mediators including interleukins 6 (IL-6), TNF-α, transforming growth factor-β (TGFβ), high-sensitivity C-reactive protein (hs-CRP), calcitonin gene-related peptide (CGRP), substance P and monocyte chemotactic protein-1 (MCP-1) in curcuminoid treated groups [20]. One study exploring the effect of pyrimidine-substituted curcumin analogues on colon cancer cells found that hydroxyl groups in curcumin and its analogues were critical in the suppression of epidermal growth factor receptor (EGFR) expression. This suppression led to anti-cellular proliferation, pro-apoptosis and cell cycle arrest.[21]

### *Anti-viral, anti-microbial and anti-parasitic activity*

Several studies have reported the broad-spectrum anti-microbial activity of curcumin against different bacteria, viruses, fungi and parasites. A study showed that curcumin has bacterial membrane damaging property against Gram-positive (*S aureus* and *E faecalis*) and Gram-negative (*E coli* and *P aeruginosa* [22]. Studies have further highlighted that curcumin possesses a synergistic anti-bacterial effect when combined with other antibiotics against resistant bacteria such as methicillin-resistant *S aureus* (MRSA) [23, 24]. Curcumin also has shown anti-viral activity against human immunodeficiency virus (HIV), herpes simplex virus (HSV), human papillomaviruses (HPV), Japanese encephalitis virus (JEV) and other viruses [25]. Cyclocurcumin (curcumin IV) was first isolated and found to have synergistic nematocidal activity when used with other curcuminoids [1].

### *Arthritis*

A systematic review and meta-analysis was performed to evaluate 8 randomized clinical trials (RCTs) that studied curcumin effect in alleviating joint arthritis. It concluded that 8–12 weeks of treatment with turmeric extracts (about 1000 mg/day of curcumin) could reduce arthritis symptoms as effectively as ibuprofen and diclofenac. [26]

### *Cardioprotective properties*

Curcumin use can improve overall pancreatic β-cells function and lower the number of pre-diabetic individuals who eventually develop T2DM [27]. Curcumin was also shown to reduce several complications associated with diabetes including neuropathy, nephropathy, vascular diseases and fatty liver [28]. Furthermore, curcumin lowers the atherogenic risks of diabetes by reducing insulin resistance. In addition, it improves relevant metabolic profiles in type 2 diabetic population by slightly lowering FPG, HbA1c, total cholesterol, triglyceride and LDL-C and slightly elevating HDL-C. High body weight, waist circumference and body mass index (BMI) are risk factors of cardiovascular disease (CVD) which can be lowered by curcumin use. [29, 30] C-reactive protein (CRP), which is an indicator of inflammation, has been identified as a strong predictor and independent risk factor of CVD and other inflammatory diseases in general. A meta-analysis concluded that curcuminoids supplementation may reduce circulating CRP levels.[31]

### *Gastrointestinal system*

Gastrointestinal ulcer probably results from the imbalance between the aggressive (acid, pepsin, bile and *H pylori*) and the defensive (gastric mucus, bicarbonate secretion, prostaglandin, nitric oxide and innate resistance of the mucosal cells) factors. Curcumin decreases the severity of gastric ulcers symptoms including dyspepsia, however it has limited anti-bactericidal effect on *H pylori*.[32] Studies showed that curcumin has the potential to induce and maintain clinical remission in patients with active mild-to-moderate ulcerative colitis when combined with mesalamine or sulfasalazine [33, 34].

### *Depression*

Several studies showed that curcumin ameliorates depression and anxiety symptoms. Moreover, its supplementation enhances the efficacy of anti-

depressant medications in major depression. This effect is proposed to be due to anti-inflammatory action of curcumin and the reduction of C-reactive protein (CRP), IL-6 and TNF-α levels. [35-37]

### *Skin*

Curcumin is effective against acne, dermatitis, scleroderma, psoriasis and melanoma. Radiation dermatitis is a common side effect in patients receiving radiotherapy for cancer. A study concluded that oral curcumin 6g daily during radiotherapy, reduces the severity of radiation dermatitis and moist desquamation, but not erythema in breast cancer patients [38]. A study on patients having mild-to-moderate plaque psoriasis treated with topical steroids concluded that oral curcumin is considered as safe and effective adjunctive treatment. The potential anti-psoriatic activities of curcumin are due to down-regulation of T cell-mediated inflammation, particularly IL-22 which induces keratinocytosis and hyperplasia [39].

## Safety and toxicity profile

Turmeric is generally recognized as safe (GRAS) by the US FDA, the Natural Health Products Directorate of Canada and the Joint Expert Committee of the Food and Agriculture Organization/World Health Organization (FAO/WHO). (FAO/WHO) stated that 0.1- 3 mg/kg-BW daily intake of curcuminoids as a food additive is acceptable.

Studies showed that high curcumin oral dosage up to 12 g/day is safe for humans, but it is too bulky to use. All the detected side effects were considered mild (grade 1), including nausea, vomiting, dyspepsia, diarrhea, distension, headaches, rashes and yellowish stools [17]. Ames test, which uses the bacterium *S typhimurium* to test the mutagenic potential of chemical compounds, found curcuminoids to be non-mutagenic. In the same study, they found that curcumin has a dose-dependent anti-mutagenic effect [40]. Based on published laboratory and animal studies, curcumin may interact with anti-diabetic medications causing side effects. [17] Recently, the US Department of Health and Human Services - recommended to use curcumin cautiously when combined with NSAIDs or anti-coagulant drugs (heparin, clopidogrel, aspirin), which may result in an increased risk of bleeding.

## Conclusion

Due to the increasing interest in natural products, curcuminoids have a promising future in the pharmaceutical industry as a preventative and /or therapeutic option in many diseases. However, most of the studies done so far have insufficient sample size and poor methodological quality to draw definitive conclusions. Therefore, more rigorous and larger studies are needed in humans to confirm their therapeutic efficacy since they are affordable and have excellent safety profile. Due to their poor bioavailability, several curcumin analogues and novel formulations have been synthesized through structural modification and by using adjunctive drug delivery systems in order to improve their bioavailability and biological activity. Completed and ongoing curcumin clinical studies can be found on the website of the US National Institute of Health (http://www.clinicaltrials.gov).

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# TEST YOUR KNOWLEDGE

Answers on back page

1) ***Which of the following is the first enzyme involved in the biosynthesis sequence of curcuminoids?***

A. Curcumin synthase
B. Diketide-CoA synthase
C. Phenylalanine ammonia lyase
D. Amylase

2) ***Which of the following is down-regulated by curcumin to produce anti-inflammatory activity?***

A. Protease
B. Lipase
C. Cyclooxygenase
D. Maltase

3) ***Which of the following microorganism in the human intestine has the highest curcumin-converting activity?***

A. Staphylococcus aureus
B. Escherichia coli
C. Enterococcus fecalis
D. Haemophilus influenzae

**Is there a problem?**
A 25 year old female patient was given the following prescription for her newly diagnosed urinary tract infection. Is there any major error with the prescription?

**CDX HOSPITAL**

Patient Name: Mrs. Haila Age: 25 years
Address: Street No.20

Rx
Cefuroxime 125mg tablet
Three times daily
Send one pack

Signature Date: 21/06/17
Dr. Ali

**Answer (Prescription Exercise)**
The frequency of cefuroxime for urinary tract infection is wrong. It should be twice daily.

*Source: British National Formulary*

# TOPICAL ISSUES AND CONTROVERSIES

## Predicting the efficacy of cancer immunotherapy: T-cell receptor repertoires

Cancer treatment has expanded in the last decade with more than 185 US FDA approved drugs in the market which include multiple therapies targeting the immune system. However, most cancers have developed ways to evade the immune system by suppressing or hiding from it. Recently, experts have begun to design ways to turn the immune system against cancer, known as cancer immunotherapy.

FDA approved cancer immunotherapies have included multiple immune checkpoint inhibitors. To prevent inappropriate destruction of the host, the human immune system is composed of multiple checks and balances called immune checkpoints. These checkpoints consist of pathways that, when triggered, will deactivate the attacking immune cell. Unfortunately, many cancers have developed mechanisms of manipulating this system. One method is through the upregulation of immune checkpoint molecules, such as programmed death 1 (PD-1) and its ligand (PDL1), which deactivate T cells, a main attacker of tumor cells. Checkpoint inhibitors that block the activation of these molecules, such as anti-PD-1 or PDL1 antibodies, have shown promise in the clinic, with multiple drugs already receiving FDA approval for treatment of melanoma and lung cancer. Unlike chemotherapy, which acts directly on the tumor, immunotherapy acts on the immune system, which then acts on the tumor. This takes time. And if the treatment is not effective, the administration of immunotherapy can result in wasted time, time during which a patient could have received another treatment. Thus, it would be advantageous if a predictive test, in par-

ticular, a speedy non-invasive one, could be used to predict immunotherapy efficacy early in treatment.

To that end, experts are working to develop such a test, based on patients' personal T-cell receptor repertoires (TCRRs). Every person has a unique TCRR, one that's constantly changing in response to immune stimuli. For example, if a person gets the flu vaccine, the T-cell receptors responsible for recognizing flu antigens will become activated and those T cells will expand. The person now has a new TCRR, which consists of more flu-recognizing T-cell receptors. This is called clonal expansion.

Researchers have recently begun exploring changes in clonal expansion in response to cancer immunotherapy, especially those related to immune checkpoint inhibitors. The prevailing thought is: if blocking immune checkpoints leads to changes in a person's immune system, T cells with unique receptors will be activated, resulting in increased clonal expansion.

In one study, investigators from the University of California, Los Angeles (UCLA), and their colleagues, tested the effect of an anti-PD-1 on TCRRs in melanoma patients. To assess TCRR, the researchers isolated tumor samples before and after treatment, and then sequenced the T-cell receptor gene. Because every T-cell receptor is made antigen-specific through genetic recombination, sequencing enabled the researchers to identify the unique clones and, therefore, each patient's TCRR. They discovered that patients with clonal expansion showed a much greater response to anti-PD-1 treatment.

Separately, the UCLA team showed that treatment with another checkpoint inhibitor- a monoclonal antibody against CTLA4 (anti-CTLA4)- resulted in an increase in clonal expansion in melanoma patients' peripheral blood mononuclear cells (PBMCs). PBMCs are isolated from blood, paving the way for non-invasive screens to analyze a patient's TCRR.

Together, these studies have demonstrated that assessing patients' TCRRs could eventually help researchers predict the efficacy of cancer immunotherapy treatments much earlier, allowing more effective use of these treatments in the fight against cancer.

**Reference**

*Opinion: Predicting the Efficacy of Cancer Immunotherapy. Jacob Richards. http://www.the-scientist.com/?articles.view/articleNo/42777/title/Opinion--Predicting-the-Efficacy-of-Cancer-Immunotherapy/*

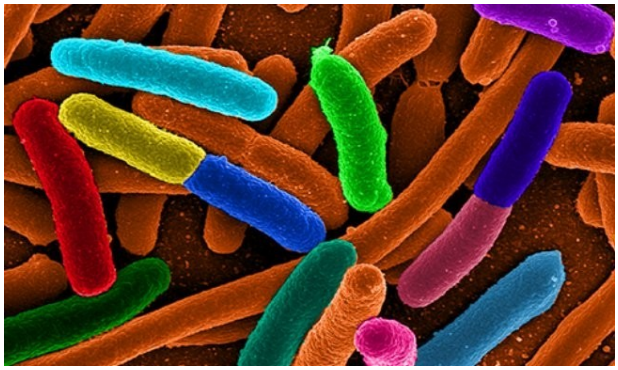
## Predicting anti-microbial resistance

Using computational algorithms and experimental evolution, researchers are predicting antimicrobial -resistance patterns to improve drug design. During microbial infections, the battle between a drug and a pathogen determines whether a patient will be cured. When extending the metaphor of drug resistance as an arms race between bacteria and antibiotics, the bacterial genome is the true battleground.

When faced with antibiotics, bacteria employ several evasive tactics. These include switching genetic sequences to mutate target sites on proteins and changing gene-expression patterns. Less drug-specific mechanisms, such as thickening cell walls or increasing the expression of efflux pumps (which can quickly clear drugs), are also common.

Using computational approaches and laboratory experiments, scientists are now trying to model such molecular defenses in an effort to eventually make drugs that are less likely to incite antibiotic resistance.

So far, most studies have relied on one of two approaches: experimental evolution, where bacteria are exposed to antimicrobials and their genomes tracked for signs of change, or in silico



approaches, where gene expression and protein-design algorithms are used to predict adaptive changes.

In a study published in January 2017, researchers tested whether the single nucleotide polymorphisms (SNPs) required for *S. aureus* to grow resistant to a specific folate metabolism inhibitor could be computationally predicted. Using a protein-design algorithm, the researchers predicted mutations in the bacterial dihydrofolate reductase (DHFR) enzyme that would confer resistance to this drug without hindering the enzyme's normal functions. In parallel, they conducted experiments to observe which mutations actually arose within bacterial genomes when *S. aureus* were experimentally exposed to the same inhibitor. When they compared the predicted

mutations with those discovered in the lab, two of the top four were identical. Their idea was to predict these mutations in silico ahead of time, before the inhibitors that are deployed are even used in resistance selection.

In the future, the researchers aim to prospectively apply this technique for rational drug design. According to one of the authors, one could run this algorithm for a new drug candidate and understand whether or not a particular mutation is likely to arise and can also create that mutation and test it.

Predicting drug resistance isn't just for microbes. Other researchers have applied predictive methods to understand the evolution of resistance in cancer cells and viral proteins like HIV-1 protease.

Although such studies can predict specific mutations that evolve in the active sites of target bacterial proteins, researchers concur that they are, at present, less effective at identifying non-specific changes that increase antimicrobial activities, such as tweaks to drug efflux pumps or thickening of bacterial cell walls.

To pinpoint these less-specific changes, researchers from RIKEN's Quantitative Biology Center in Japan recently combined laboratory experiments and algorithmic analysis to identify changes in *E. coli* gene expression in response to a range of antibiotics. The team selected laboratory bacterial strains that were resistant to multiple antibiotics and tested how these strains responded to drugs they had not previously encountered. Testing transcriptional and genomic responses, the researchers discovered a small subset of mutations and gene-expression changes that closely correlated with the evolution of resistance. The data hint that diverse molecular pathways might converge on common resistance mechanisms, such as ramping up the efflux pathways that bounce drugs out of cells.

Rather than relying on laboratory evolution, other studies have retrospectively analyzed how different genomic signatures might have contributed to drug resistance in clinical isolates. Mapping these changes can improve the predictive value of algorithms.

These data could help clinicians transition from giving patients a single antibiotic to prescribing tailored, multi-drug treatments early on. Quick genomic mapping of isolates from an infection could also improve diagnostic methods.

However, whether mutations predicted computationally can accurately foretell the changes that occur during a real-world infection requires further study. For example, the SNPs identified by algorithms may be more relevant to bloodstream-based infections than those arising from biofilms, or those involving multiple species of bacteria.

Nonetheless, compared to other diseases such as cancer, correlating mutations predicted *in vitro* to those that may occur *in vivo* is simpler in bacteria. The more we can predict it, the better we'll be in getting drugs that are less likely to face resistance.

***Source*:** *http://www.the-scientist.com//?articles.view/articleNo/42172/title/Anticipating-Resistance/*

## New insomnia drugs are coming on the market, but drug-free therapy remains the most durable treatment

There is clear evidence that insomnia is a significant health problem, a risk factor for depression, hypertension, and other medical conditions. In the early 1970s, a researcher in Stanford University remarked on the resemblance of a narcolepsy patient's symptoms to those of a recent canine patient he had read about, i.e. excessive daytime sleepiness, sudden switch from an awake state to rapid eye movement (REM) sleep, sleep paralysis, and muscle weakness called cataplexy.

More than a decade later he discovered an autosomal recessive mutation in the orexin receptor in the dogs' brains that was responsible for the disorder (*Cell, 98:365-76, 1999*). Although orexin receptor mutations have not been found in humans with narcolepsy, patients with the disorder do have reduced levels of orexin (also called hypocretin), a neuropeptide that regulates wakefulness (*The Lancet, 355:39-40, 2000*).


In 2014, the US FDA approved the first orexin receptor antagonist, Merck's suvorexant (Belsomra), and at least two more drugs of this class were in clinical trials. Previous sleep medications acted as sedatives, targeting GABA receptors to facilitate


brain inactivity. Suvorexant, on the other hand, decreases wakefulness by blocking the brain's orexin receptors. The orexin system is a super candidate as a target for insomnia treatment. There are lots of reasons to believe some people with insomnia are hyper-secretors of orexin, which is why they can't sleep. Toning down orexin was a brilliant idea.

## Treating insomnia

As many as 40 million people in the US experience some form of insomnia, making it the most common sleep disorder. Sufferers can have trouble falling asleep, staying asleep, or returning to sleep after waking in the middle of the night, and can experience persistent drowsiness, irritability, anxiety, and difficulty learning and remembering the next day. When chronic, insomnia can impede daily functions and increase the risk of cardiovascular disease.

Insomnia used to be divided into primary insomnia, which is not linked to any other medical condition, and secondary insomnia, trouble sleeping due to an underlying condition such as depression or chronic pain.


Researchers and doctors still distinguish between acute insomnia, short-term bouts of sleeplessness triggered by a stressful event such as an important exam or a job loss, and chronic insomnia, when someone does not sleep well at least three nights a week for three months. To treat acute insomnia, doctors often turn to drugs, such as zolpidem (Ambien).

For chronic insomnia, sleep experts recommend combining a drug with cognitive behavioral therapy for insomnia (CBT-I), which focuses on relaxation training, sleep hygiene (e.g., limiting caffeine before bed), stimulus control, cognitive therapy (changing beliefs and habits to promote sleep), and limiting the amount of time spent in bed not sleeping. Most physicians treating chronic insomnia aim to phase out the drug as the patient begins to have a more regular sleep pattern (*JAMA, 301:2005-15, 2009*) making the use of hypnotic drugs an adjunct therapy.

Patients treated with CBT-I took an average of 19 fewer minutes to fall asleep and slept for an extra 26 minutes (*Ann Intern Med, 163:191-204, 2015*). But CBT-I can be expensive and difficult to access, and can require as many as eight sessions with a certified physician. To broaden insomnia patients' access to CBT-I, researchers have created at least two commercial online programs backed by scientific evidence, SHUTi (Sleep Healthy Using the Internet), and Sleepio.

Still, the easiest form of insomnia treatment, at least in the short term, is a drug. Benzodiazepines were the first class of drugs used as sleeping pills. These agents, of which temazepam (Restoril) is now the most commonly prescribed for insomnia, bind to GABA receptors to enhance the sedative effects of the neurotransmitter. By the 1970s they had replaced the use of barbiturates, which also target the GABA system. Although effective at increasing total sleep time in some, benzos, also used to treat anxiety, panic disorder, and other psychiatric disorders, decrease the amount of time in those stages of sleep that are associated with cognitive restoration. The drugs can also be abused.

A newer class of GABA receptor agonists, the so-called Z-drugs, was approved for insomnia in the 1990s. These agents, including zolpidem, zaleplon, and eszopiclone, are chemically different from benzos: they tend to be more readily absorbed for faster sleep onset, and they have a shorter half-life that decreases next-day grogginess. But, while Z-drugs appear to improve sleep quantity without impairing sleep quality, they can also cause memory impairment, and some clinicians remain concerned about the drugs' safety profiles. (*BMJ Open, 2:e000850, 2012*). Like benzos, Z-drugs are effective for some insomniacs, but for others they decrease the amount of certain stages of sleep and can lead to lack of concentration. Other agents approved as sleep medications include melatonin receptor agonists, antihistamines, and antidepressants, but these have limited efficacy, according to most sleep experts.

### Re-inventing the sleeping pill

Suvorexant, approved by the FDA in August 2014, is a dual orexin receptor antagonist (DORA), meaning it binds to orexin receptors 1 and 2. While suvorexant can slightly increase the duration of REM sleep, the drug maintains the sequence and cycling of the REM/non-REM stages typical of normal sleep.

Initially, there were concerns that drug doses that dampened most orexin activity could lead to cataplexy or narcolepsy-like symptoms. But according to the company's clinical trial data, there were no signs of these side effects in the trial participants, though some did experience next-day sleepiness and a few rare cases of sleep paralysis not linked to narcolepsy. As a result, the FDA approved administration of the drug only at the two lowest (15 mg and 20 mg) of the four doses tested in the Phase 3 trials, and, subsequently, at two doses that are even lower (5 mg and 10 mg).

Johnson & Johnson company is teaming up with Massachusetts-based Minerva-Neurosciences to test JNJ-42847922, an orexin-2 single receptor antagonist (2-SORA). Also known as MIN-202, the drug is being evaluated for insomnia in a Phase 1 trial of patients who also have major depressive disorder as well as in a Phase 2 study of insomnia patients without comorbidities.

Whether it's better to target the two orexin receptors or just one remains to be determined. While DORAs typically result in faster REM sleep onset and slightly increase the total amount of REM sleep, rodent studies have shown that orexin receptor 2 mediates most of orexin's sleep effects. Targeting orexin receptor 1, for example, does not appear to improve animals' ability to fall asleep (*Neuron, 38:715-730, 2003; JPET, 330:142-151, 2009*). But 2-SORAs may not increase total REM sleep time to the same extent as suvorexant. There is a lot of debate right now on the potential risks and benefits of DORAs versus 2-SORAs.

### Re-thinking insomnia

Insomnia is complex and heterogeneous, and patients have different degrees of response to interventions. Even as more orexin-targeting sleep drugs make it to market, a fundamental challenge to treating insomnia remains: the risk of psychological addiction. Most clinicians prescribe insomnia pills to be used sparingly, only a few times per week. In a recent pilot study of 55 individuals, Perlis and his colleagues found that those who took a placebo on nights they would have skipped a dose maintained the effect of the sleeping drug and felt more rested (*Sleep Med, 16:1160-68, 2015*). On nights without a pill, those who followed the standard intermittent dosing slept more poorly and had next-day insomnia symptoms.

In conclusion, doctors who work with sleep-disorder patients still see medication as playing a supportive role to CBT. None of the available sleeping pills are curative, and therapy with hypnotics is considered a form of palliative care. Only CBT-I appears to confer durable results lasting months and years after treatment is discontinued.

*Source: http://www.the-scientist.com/?articles.view/articleNo/45356/title/Desperately-Seeking-Shut-Eye/*

## NEWS from the FDA


## Sweeping changes to opioid policies unveiled by FDA

In response to the ongoing opioid abuse epidemic, top officials at the US FDA announced plans to reassess the agency's approach to opioid medications.

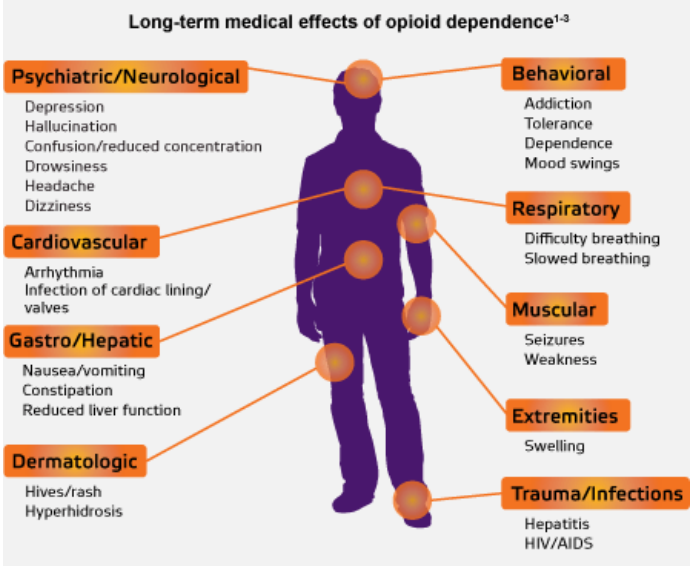
They are determined to help defeat this epidemic through a science-based and continuously evolving approach. The plan contains real measures the agency can take to make a difference in the lives of so many people who are struggling under the weight of this terrible crisis. The plan is further outlined in an article published online in the New England Journal of Medicine (*N Engl J Med 2016; 374:1480-1485*).


In the US, the annual number of deaths from opioid overdoses now exceeds the number of deaths

caused by motor vehicle accidents. Regardless of whether these issues are viewed from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable. As the public health agency responsible for over-sight of pharmaceutical safety and effectiveness, FDA recognizes that this crisis demands solutions, and urges all concerned to join FDA in this area. The multicomponent plan will focus on policies aimed at reversing the epidemic, while still providing pain patients access to effective medication. Specifically, the FDA plans to:

* Re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public-health effects;
* Convene expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties;
* Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved;
* Develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to those of the extended-release/long-acting (ER/LA) opioid analgesics labeling that is currently required;
* Update Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements;
* Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products;
* Improve access to naloxone and medication-assisted treatment options for patients with opioid-use disorders;
* Support better pain-management options, including alternative treatments.

The FDA says they will seek guidance from outside experts in the fields of pain management and drug abuse. The agency has already asked the National Academy of Medicine to assist in developing a framework for opioid review, approval, and monitoring that balances an individual's need for pain control with considerations of the broader public-health consequences of opioid misuse and abuse. They will convene independent advisory committees made up of physicians and other experts when considering approval of any new opioid drug that does not contain abuse-deterrent properties. The agency will also convene a meeting of its standing Pediatric Advisory Committee to provide advice on a framework for pediatric opioid labeling and use of opioid pain medications in children.




The FDA also plans to tighten requirements for drug companies to generate post market data on the long-term impact of using ER/LA opioids, an action, they say, that will generate the "most comprehensive data ever collected in the field of pain medicine and treatments for opioid use disorder. The data will further enhance understanding of the known serious risks of opioid misuse, abuse, overdose and death."

Drug overdose deaths, driven largely by overdose from prescription opioids and illicit drugs like heroin and illegally-made fentanyl, are now the leading cause of injury death in the US. The FDA is a vital component to combating this epidemic, and the innovation and modernization they have committed to undertaking is an important part of the overall efforts at HHS. The HHS had announced a major initiative to address the opioid abuse epidemic in the US. The initiative focuses on informing opioid prescribing practices, increasing the use of naloxone, and using medication-assisted treatment to move people out of opioid addiction. The FDA says it will provide updates on progress with the goal of sharing timely, transparent information on a regular basis.

*Source: http://www.medscape.com/viewarticle/858411*

# Novel FDA Drug Approvals for 2017

| Drug | Active agent | Date | Condition for approved use |
|---|---|---|---|
| Imfinzi | durvalumab | 5/1 | locally advanced or metastatic urothelial carcinoma |
| Trulance | plecanatide | 1/19 | Chronic Idiopathic Constipation (CIC) in adult patients. |
| Siliq | brodalumab | 2/15 | adults with moderate-to-severe plaque psoriasis |
| Xermelo | telotristat ethyl | 2/28 | carcinoid syndrome diarrhea |
| Austedo | deutetrabenazine | 4/3 | treatment of chorea associated with Huntington's disease |
| Kisqali | ribociclib | 3/13 | postmenopausal women with advanced breast cancer |
| Xadago | safinamide | 3/21 | Parkinson's disease |
| Symproic | naldemedine | 3/23 | treatment of opioid-induced constipation |
| Bavencio | avelumab | 3/23 | metastatic Merkel cell carcinoma |
| Zejula | niraparib | 3/27 | recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers |
| Ocrevus | ocrelizumab | 3/28 | relapsing and primary progressive forms of multiple sclerosis |
| Dupixent | dupilumab | 3/28 | moderate-to-severe eczema (atopic dermatitis) |
| Brineura | cerliponase alfa | 4/27 | a specific form of Batten disease |
| Tymlos | abaloparatide | 4/28 | osteoporosis in postmenopausal women at high risk of fracture or those who have failed other therapies |
| Rydapt | midostaurin | 4/28 | acute myeloid leukemia |
| Alunbrig | brigatinib | 4/28 | patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib |
| Radicava | edaravone | 5/5 | patients with amyotrophic lateral sclerosis (ALS) |
| Kevzara | sarilumab | 5/22 | adult rheumatoid arthritis |
| Parsabiv | etelcalcetide | 2/8 | secondary hyperparathyroidism in adult patients with chronic kidney disease undergoing dialysis |
| Emflaza | deflazacort | 2/9 | patients age 5 years and older with Duchenne muscular |

## STATE OF KUWAIT
## Pharmaceutical & Herbal Medicines Control and Registration Administration

### *New Pharmaceutical products approved from March to June 2017*

Amlophar Hard Gelatin Capsules; Amlodipine (as Besylate) – 5mg; Gulf Pharmaceutical Industries (JULPHAR)/UK

Dolo-Neurobion Forte; Cynacobalamin – 10mg, Diclofenac Sodium – 50mg, Thiamine Mononitrate – 50mg; Merck KGaA/Germany

Gaviscon Double Action (Mint) Chewable Tablets; Sodium Alginate – 250mg, Sodium bicarbonate – 106.5mg, Calcium carbonate – 187.5mg; Reckitt Benckiser Healthcare (UK) Limited/UK

Genvoya Film Coated Tablets; Elvitegravir – 150mg, Cobicistat – 150mg, Emtricitabine – 200mg, Tenofovir alafenamide (as fumarate) – 10mg; Gilead Sciences International Ltd/UK

Ibugesic Cold & Sinus Tablets; Ibuprofen – 200mg, Pseudoephedrine HCl – 30mg; Dar Al Dawa/Jordan

Imatinib Denk Film Coated Tablets; Imatinib (as Mesilate) – 100mg and 400mg; Denk Pharma Europe GmbH/Germany

Irovel Film Coated Tablets (150, 300mg); Irbesartan – 150, 300mg; Tabuk Pharma Manufacturing Co./ Saudi Arabia

Krolac Injection; Ketorolac Tromethamine – 30mg/ml; P.T. Novell Pharmaceutical Laboratories/ Indonesia

Krolos Film Coated Tablets; Rosuvastatin (as calcium) – 10, 20 40mg; Zentiva K.S./Czeck Republic

Lartruvo Solution for Intravenous Injection; Olaratumab (rDNA) – 500mg/50ml; Eli Lilly & Co./USA
Lataprost Eye Drops; Latanoprost – 0.05mg/ml (0.125mg/2.5ml); Riyadh Pharma/Saudi Arabia
Lynparza Hard Capsules 50mg; Olaparib – 50mg; Astra Zeneca/Sweden
Ninlaro Hard Capsules (2.3mg, 3mg and 4mg); Ixazomib (as citrate) – 2.3, 3, 4mg; Takeda Pharma/ Denmark
Nucala Powder for Solution for Injection 100mg; Mepolizumab – 100mg; Glaxo Smith Kline/ Ireland
Nurofen Coated Tablets; Ibuprofen – 200mg; Reckitt Benckiser Healthcare (UK) Ltd./UK
On.Setron-DenK Oro Dispersible Tablets (4, 8mg); Ondansetron – 4, 8mg; Denk Pharma GmbH & Co. KG/Germany
Optilone 0.1% Ophthalmic Suspension; Fluorometholone – 1mg; Jamjoom Pharma/Saudi Arabia
Otezla Film Coated Tablets 10mg + 20mg + 30mg; Apremilast; Celgene Europe Ltd/UK
Pandev Enteric Coated Tablets; Pantoprazole (as Pantoprazole sodium sequihydrate) – 40mg; Deva Holding S.A/Turkey
Privituss Oral Suspension 708mg/100ml; Levocloperastine fendizoate – 708mg (Equivalent to clospera-tine HCl 400mg); Aesculapius Farmaceutici s.r.l./Italy
Racser Cream; Lidocaine – 25mg, Prilocaine – 25mg; Zenta Healthcare Pvt. Ltd./India
Remifentanil Medis Powder for Solution for Injection/Infusion; Remifentanil (as hydrochloride) – 1mg and 5mg; Les Laboratoires Medis/Tunisia
Retacrit Solution for Injection; Epoetin Zeta (rDNA) Recombinant Human erythropoietin – 2000 IU; Hospira UK Limited/UK
Retacrit Solution for Injection; Terbinafine (as HCl) – 250mg Epoetin Zeta (rDNA) Recombinant Human erythropoietin – 4000 IU; Hospira UK Ltd/UK
Synagis Solution for Injection Vial 50; 100mg, Palvizumab – 50, 100mg; Abbvie Ltd/UK
Triumeq Film Coated Tablets; Dolutegravir (as sodium) – 50mg Abacavir (as sulfate) – 600mg Lamivudine – 300mg; Viiv Healthcare UK Ltd/UK
Urilax Film Coated Tablets (5mg, 10mg); Solifenacin Succinate – 5, 10mg; Tabuk Pharma Manufacturing Co./Saudi Arabia
Vidaza Powder for Suspension for Injection; Azacitidine – 100mg; Celgene Europe Ltd/UK
Volibris Tablets 5, 10mg; Ambrisentan – 5, 10mg; Glaxo Group Ltd/UK

## Answers to: Test your knowledge

**Correct answers:**
**1-A; 2-C; 3-B**

**The *Kuwait Pharmacy Bulletin*** (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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The *Bulletin* is printed by Kuwait University Press