Turmeric, a Long-Standing Dietary Component with an Unprecedented Range of Benefits

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Turmeric *(Curcuma longa)*, a member of the ginger *(Zingiberaceae)* family, is used as a primary food staple in many countries. However, in addition to its use as a food staple, it also has a very long history of medicinal use, dating back nearly 4000 years.[1] The numerous compounds that comprise turmeric are used for their therapeutic properties predominantly in tropical and subtropical regions of the world, including India, Southeast Asia and Indonesia. In terms of its pharmacological activity, this activity has been attributed mainly to its curcuminoids. These primarily consist of curcumin, along with two closely related compounds, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC). Although curcumin is thought to be the most bioactive compound found in turmeric, turmeric contains and/or delivers more than 200 additional compounds of nutritional interest. These additional compounds include additional curcuminoids, sterols, and fatty acids. Turmeric is also considered to be a participant in a multitude of molecular targets, likely as a consequence of its many compounds.

Curcuminoids are classified as phenolic compounds, and are commonly used in food as a spice, pigment, or additive, but as stated above, they also have an extensive range of therapeutic benefits as well. Curcumin, derived from the rhizomes of turmeric, is both its principal bioactive ingredient and its chief curcuminoid. Both preclinical cell culture studies and animal studies have documented the wide-ranging biological activity of the curcuminoids, including curcumin. Among these actions evidence points to their function as an antioxidant, as well as to numerous other actions, including their benefit as a "neuroprotective, antitumor, anti-inflammatory, anti-acidogenic, and radioprotective"[2] agent. Besides these actions, numerous clinical trials have proposed that curcuminoids have valuable activity in numerous chronic diseases. Thus, not surprisingly, turmeric's range of proposed "pharmacological activities" is extensive, and includes antioxidant,[3] anti-protozoal,[4] anti-microbial,[5] anti-inflammatory,[6] anti-proliferative,[7] anti-angiogenic,[8] anti-tumor, and anti-aging.[9,10] Some of the known chief actions of curcumin are indicated in Table 1.

Curcumin has broad range of biological functions; however, it is particularly recognized for its antioxidant and anti-inflammatory actions. Numerous studies, including human *in-vitro* and animal *in-vivo* studies, have reported on the antioxidant effects of turmeric compounds, including its ability to effectively scavenge reactive oxygen and reactive nitrogen species, and to inhibit the activation and release of NFκB, resulting in the downregulation of the release of proinflammatory cytokines and chemokines.[11] *In-vitro* research has also demonstrated the prevention of oxidative damage to DNA.[12] Because of this action, it has been suggested that curcumin may also be beneficial as a preventive and supportive agent for cardiovascular ailments, particularly those associated with oxidative stress.[13] Additionally, its use has been correlated to the protection of endothelial cells against oxidative stress, and the deterrence of cardiovascular diseases associated with oxidative stress.[14] Other research suggests turmeric compounds other than curcumin contribute to its antioxidant activity.[15,16]

In-vitro results suggest that curcumin most likely inhibits cell proliferation, cell mediated cytotoxicity, and cytokine production by inhibiting NF-κB target genes involved in induction of these immune responses.[17] This study and others have concluded that curcumin has antioxidant activity and inhibits inflammatory mediators, including NF-κB, cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). Collectively, turmeric and its curcuminoid constituents have been found to inhibit lipoxygenase and cyclooxygenase *in-vitro*.[18]

Although Curcumin is the most important active polyphenolic ingredient responsible for the biological activity of turmeric,[19] as noted previously, other compounds in turmeric have been demonstrated to manifest these activities uniquely, additively, or synergistically with curcumin. If fact, it has been documented that tumeric possesses over 100 compounds which possess medicinal properties. A selection of these compounds and their actions are indicated in Table 2.

Curcumin is also recognized for its benefits in osteoporosis, as its use is predicted to be advantageous for bone remodeling, specifically affecting the "differentiation, activity and lifespan of osteoblasts and osteoclasts."[20] Glucocorticoid (GC) therapy (dexamethasone), often used in the treatment of osteoporosis, is a recognized inducer of elevated urinary calcium (hypercalciuria). Additionally, GC therapy is recognized as an inducer of the "inhibition of bone formation."[21] This form of inhibition includes "the suppression of osteoblast differentiation, maturation and activity, and the reduction of lifespan of osteoblast",[22] both viewed as an "important source for osteopenia or osteoporosis."[21,22,23] In an investigation of experimentally induced osteoporosis in mice undergoing dexamethasone (DXM) therapy, the benefits of curcumin on "bone microarchitecture of the proximal tibia" was confirmed. It was established that curcumin therapy "reversed DXM-induced bone resorption, including an increase in serum OCN" (osteocalcin), along with a decrease in bone resorption markers.[21] Besides these studies, additional studies have also correlated the use of curcumin with positive benefits on bone health.[24,25] In a separate study it was concluded that therapy with curcumin, "induces osteoblast apoptosis at the doses of 12.5–25 mM", however results in necrosis at higher doses (doses greater than 50 mM).[26]

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Surprisingly, studies have indicated that turmeric oil, present in turmeric, can enhance the bioavailability of curcumin. Indeed, curcumin-free turmeric (CFT) components have been demonstrated to possess numerous biological activities. Thus, supplementation with a complete turmeric compound, and not necessarily curcumin singly may be most advantageous.

In patients with chronic heart failure, gut permeability along with an "altered gut mucosa" is a commonly observed pattern.[27] In animals with the same pattern, it was determined that supplementation with oral curcumin can "improve intestinal barrier function" and "prevent the development of metabolic diseases." Additionally, orally administered curcumin was demonstrated to decrease diseases associated with a Western-type diet (WD), including the "development of type 2 diabetes and atherosclerosis."[28] Its action was noted to be by modulating the function of both the intestinal epithelial cells (IECs) and the intestinal barrier, and this was observed as its "major site of action".[28] As part of this action in reducing intestinal barrier dysfunction, its use was also associated with the modulation of chronic inflammatory diseases.[29]

Under ordinary circumstances, the absorption of orally ingested curcuminoid extracts is poor. However, recently companies have worked diligently to develop methods to enhance its bioavailability, and have had success. Some suppliers offering products containing 95% curcuminoids have significantly increased the bioavailability of the curcuminoid content. Unfortunately, many use surfactants or "Tweens" including polyethylene glycol, polysorbates, or other ionic detergents as forms of nanotechnology to enhance the absorption of curcuminoids. Recent research demonstrates that the use of these compounds may result in "leaky gut" and altered gut microbiota (dysbiosis), leading to a systemic inflammatory state. Studies suggest that those with a compromised intestinal tract (ulcerative colitis) have an increased risk of colon cancer.[30] This population is particularly sensitive to the use of surfactant agents such as Tween (polysorbate-80 and carboxymethylcellulose). Polysorbate surfactants are detergent-like molecules incorporated into many processed foods for the purpose of improving texture and stability. For this population, the use of some of these frequently used ingredients have been correlated with the induction of low-grade inflammation and promotion of colon carcinogenesis.[31] It has been well documented that these ingredients resulted in the promotion of microbiota encroachment, and increased levels of proinflammatory flagellin and lipopolysaccharide (LPS), leading to a change in microbiota composition and intestinal inflammation.[31,32]

Fortunately, another turmeric compound enhances bioavailability by 5-6X over the others via a specialized technology resulting in a dual phase emulsion, thus concentrating turmeric's many nutrients without the use of nanotechnology (Tweens, detergents). This new enhanced bioavailable form of turmeric offers a truly transformational product, as it supplies a nutrient dense turmeric complex, delivering 50% total curcuminoid conten, plus turmeric's numerous other naturally occurring comounds, including phenolic compounds, sesquiterpenes, sterols, fatty acids, and more. Consequently, this new enhanced bioavailable form of turmeric provides an unprecedented range of beneficial turmeric root nutrients.

The major site of action of curcumin has been postulated to likely be the intestinal epithelial cells (IECs) and the intestinal barrier. Recent studies have indicated that curcumin has the ability to modulate the function of the intestinal cells, and to reduce intestinal barrier dysfunction. Because of this action it has been proposed that, "because curcumin plays a key role in the inhibition of both the activation of NF-κB pro-inflammatory cytokines, and the IL-6/STAT3 signaling pathway, it could be proposed as a novel therapeutic agent in several inflammatory diseases", such as IBD.[33]

Table 1: Chief Actions of Curcumin

	Action
1.	Acts as an effective scavenger of reactive oxygen and nitrogen species
2.	Acts as an inhibitor to the activation and release of Nuclear Factor-Kappa B (NFκB)
3.	Acts as an activator of the nuclear response factor type 2 (Nrf2)
4.	Acts as an inhibitor of the enzyme Xanthine Oxidase (XO)
5.	Strong anti-oxidative and anti-inflammatory activities when used as a remedy for the prevention and treatment of chronic disease

Table 2: Tumeric Components and their medicinal importance

Curcumin	Anti-HIV, Anti-EBV, Antiadenoma – carcinogenic, Antiaflatoxin, Antiatherosclerotic, Antiaggregant, Antiangiogenic, Antiarachidonate, Antiviral, Antioxidant, Anticancer, Antiedemic, Anti-ischemic, Apoptotic, Antiinflammatory, Antileukemic, Antileukotrene, Antilymphomic, Antimelanomic, Antimetastatic, Antimutagenic, Antinitrososaminic, Antitumour agent, Antiperoxidant, Antiprostaglandin, Antisarcomic, Metal chelator, Antithromboxane, Cox-2inhibitor, Fibrinolytic, Hepatoprotective, Immunostimulant, Ornithine decarboxylase inhibitor, Protease inhibitor, Protein kinase inhibitor.
Bis-desmethoxycurcumin:	Antiangiogenic, Antiiflammatory, Cytotoxic, Anticancer
Desmethoxy Curcumin	Antiangiogenic, Antiinflammatory, Anticancer
Tetrahydro Curcumin	Antioxidant, Antiinflammatory
Alpha Curcumene	Antitumour, Antiinflammatory
Ar-turmerone	Anti-inflammatory, Antitumour, Cox-2 inhibitor, Choleretic, Hepatotonic
Curcumol	Anticancer, Antitumour (cervix), Anti-sarcomic
Curdione	Anti-leukopenic, Antisarcomic, Antitumour, Anti X-radiation
DehydroCurdione	Analgesic, Antiarthritic, Antiedemic, Antiinflammatory, Antioxidant, Antipyretic, Calcium channel blocker
Zingiberene	Antirhinoviral, Antiulcer, Carminative

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Table 3: Primary Molecular Targets/Main Therapeutic Activities Regulated by Curcumin:

Primary Molecular Targets of Curcumin:

Transcription Factors

NFκB
AP-1
β-Cat
PPaγ

Growth Factors (or receptors)

TGF-β 1
VEGF
PDGF
EGF/EGFR

Cytokines

IL-2, IL-2
IL-6, IL-8
IL-12, IL-18
TNF-α

Main Therapeutic Activities:

Anti-inflammatory
Antioxidant
Antiumoral

Regulation of these molecular targets contributes to its therapeutical interest in regards to the three main therapeutical activities noted above.

Ref: Bonekey Rep. 2016; 5:793. Published online 2016 Mar 2. doi. 10.1038/bonekey.2016.20

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