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Current Curcumin Studies

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STORY AT-A-GLANCE -

- Curcumin, the major biologically active phenolic compound in turmeric, ranks in the top five out of 25 compounds for effectiveness in lowering severity of COVID-19
- The top drug, proxalutamide, is an androgen antagonist that limits the expression of transmembrane protein serine 2 (TMPRSS2), a receptor the virus uses to infect cells. One study found curcumin could also decrease expression up to 50%
- Curcumin has poor absorption and rapid metabolism and elimination.
- Evidence shows curcumin also reduces pain and inflammation in those with arthritis, may improve cognitive function, and could help reduce chronic inflammation associated with cardiovascular disease, obesity and insulin resistance

Curcumin is the major biologically active polyphenolic compound of turmeric and gives the spice its yellow color. Recent research shows the biological activity of curcumin reduces the severity of COVID-19. The results rank curcumin in the top five substances of 25 tested when used early to reduce illness and death from COVID.[1]

Turmeric is a perennial plant in the ginger family and found native to southern India and Indonesia.[2] Like ginger, it is the underground rhizome that is used in cooking and for medicinal purposes. Traditionally, it was used in Ayurvedic medicine and traditional Chinese medicine.[3]

The cosmetic and fabric industry has also found uses for turmeric, having been used to dye fabric for more than 2,000 years.[4] According to Linus Pauling Institute,[5] evidence continues to mount showing that curcumin can exert antioxidant, anticancer, anti-inflammatory and neuroprotective activities.

Clinical trials are underway to evaluate the safety and efficacy of the compound as an adjuvant or as a treatment for patients with several types of cancer, including pancreatic, lung, prostate and colorectal cancers. The variety of positive health benefits found with curcumin may be a result of its highly pleiotropic capability, or ability of interacting with a variety of molecular targets.[6]

In the current environment, researchers have been studying anti-inflammatory compounds in an effort to reduce the severity of COVID-19. After multiple studies, curcumin outranks zinc, quercetin, melatonin and remdesivir, which ranked 24 out of the 25 substances.[7]

Current Curcumin Studies

The ranking was based on several studies performed in 2020 and 2021. In one study,[8] researchers engaged 41 patients who met the inclusion criteria of mild to moderate COVID-19. There were 21 in the group who received nanocurcumin and 20 received a placebo.

The researchers monitored symptoms and laboratory data, finding that symptoms in the intervention group resolved significantly faster and patients' oxygen saturation was higher after just two days of treatment. It remained higher than the control group through 14 days. Researchers also found it noteworthy that none of the patients who received the nanocurcumin deteriorated during the 14-day follow-up period, but 40% of the control group did.

A second study[9] using nanocurcumin recruited 40 patients with COVID-19 to look at inflammatory cytokine expression. They were divided into 20 patients who received nanocurcumin and 20 who received a placebo. The researchers measured cytokine

secretion of interleukin-1 beta (IL-1B), IL-6, tumor necrosis factor-alpha and IL-18. They concluded that the data demonstrated nanocurcumin modulates:

> *"… the increased rate of inflammatory cytokines especially IL-1β and IL-6 mRNA expression and cytokine secretion in COVID-19 patients, which may cause an improvement in clinical manifestation and overall recovery."*

Another study published in Frontiers in Pharmacology[10] in early 2021 measured the differences in mortality between a control group and intervention group, each of which included 70 patients. The control and intervention groups received conventional COVID-19 treatment.

In addition, those in the intervention group received curcumin with piperine twice a day and those in the control group received probiotics twice a day. The researchers found patients who had mild, moderate and severe symptoms in the intervention group showed early symptomatic recovery and less deterioration.

Overall, they had better clinical outcomes and a lower death rate than the control group. Based on their results the researchers also concluded that curcumin may be a therapeutic option to prevent post COVID thromboembolic events.

Curcumin's Action Is Similar to Proxalutamide

The drug in the No. 1 position for early treatment of COVID-19 is proxalutamide. It is an androgen receptor antagonist that was in clinical trials for the treatment of prostate cancer and breast cancer.[11] At the start of the COVID-19 outbreak, the company found the drug could limit the expression of transmembrane protein serine 2 (TMPRSS2) and ACE-2 receptors, both which play a critical role in severity of COVID-19.

Ability of the virus to enter pneumocytes depends on TMPRSS2 that is expressed on the surface of human cells in much the same way as ACE-2.[12] Interestingly, TMPRSS2 is regulated by an androgen receptor, which means that the ability of the virus to infect the cells is directly dependent on androgenic status.

Past research indicated that men who had androgenetic alopecia hair loss had a greater risk of severe disease and men taking antiandrogenic drugs had a reduced risk of severe disease. This led to the hypothesis that proxalutamide would be beneficial, as it is an androgen receptor antagonist.

The hypothesis was supported in a study[13] that engaged 236 men and women with COVID-19. By Day 7, the virus was not detected using a PCR test with a cycle threshold of greater than 40 in 82% of the subjects taking proxalutamide. The average time it took patients to show clinical remission in the treatment group was 4.2 days versus 21.8 days in the placebo group.

In one study[14] evaluating the ability of three polyphenols to suppress SARS-CoV-2 viral penetration into human cells, researchers found that curcumin treatments decreased the TMPRSS2 activity by up to 50%. This is similar to the mechanism demonstrated by proxalutamide in the recent studies.

Curcumin Alone Has Poor Bioavailability

Turmeric and curcumin have been challenging to study since curcumin has a low bioavailability when taken orally, which researchers attribute to the body's limited ability to absorb the compound, as well as rapid metabolism and elimination.[15] However, researchers have found there are different compounds, that when taken with curcumin, can raise bioavailability and therefore enhance the multiple health benefits attributed to curcumin.

For example, piperine is an alkaloid found in black pepper, which is responsible for the distinct taste. On its own, it has several health benefits, including anti-inflammatory effects and insulin resistance properties.[16] When scientists combine it with curcumin it can raise the bioavailability of curcumin by up to 2,000%[17] by blocking the metabolic pathway,[18] thus increasing the amount available in the body.

One study published in the journal Medicine[19] in 2021 addressed the issues of bioavailability of curcumin as it relates to conflicting dosing strategies and the ability to compare research data. The writers described clinical trials in which purified curcumin

was given in relatively large doses, up to 12 grams per day, without achieving measurable plasma levels.[20]

In addition to combining curcumin with piperine to raise bioavailability, the writers acknowledge manipulating curcumin in other ways can also enhance bioavailability, such as reduced particle size, emulsions, essential oil complexes or the addition of whey protein or surfactants.

At the completion of one study, 17 healthy men between 18 years and 45 years participated in the double-blind, randomized crossover study.[23] People who were using any products or food with turmeric within the 14 days before the study started were excluded. The researchers used several serum measurements to determine bioavailability, including the bioactive metabolite, tetrahydrocurcumin.

They found individuals taking curcumin had 39 times higher the amount of free curcumin, 31 times higher the amount of tetrahydrocurcumin, 49.5 times the amount of total curcumin and 52.5 times the amount of total curcuminoids over the compared standard curcumin reference product.[24]

Curcumin May Reduce Pain in Those With Arthritis

A 2019 report from the Arthritis Foundation[25] found that there were 54.4 million people in the U.S. between 2013 and 2015 that had been diagnosed by their physician with arthritis. Conservatively, they estimate this number will increase 49% to 78.4 million people by 2040.

This represents 25.9% of all adults. Additionally, the number whose activities are limited due to their arthritis are estimated to jump from 43.5% of all people with the condition in 2015 to 52% by 2040. The condition is painful, and people often turn to anti-inflammatory and pain medications to relieve the discomfort.

The Arthritis Foundation[26] lists topical and oral nonsteroidal anti-inflammatory drugs, steroid, hyaluronic acid, platelet rich plasma and stem cell injections as a means of reducing pain and thus potentially improving activity levels.

However, many of these treatments come with a list of side effects and are not always well tolerated. Since the safety and nontoxicity of curcumin, even at high doses, has been documented in human trials[27] studies have evaluated whether the anti-inflammatory effects of curcumin could help those with osteoarthritis, which is the most common form of arthritis.[28]

One study[29] engaged 139 people with knee osteoarthritis for a randomized, open-label, active controlled clinical study to receive either curcumin or diclofenac twice daily for 28 days. Baseline measurements were taken before the interventions began and then again at Days 7, 14 and 28.

The main outcome measure was pain. Researchers also had secondary outcome measures that included anti-ulcer effect, anti-flatulent effect, altered weight and a global assessment of therapy. By Days 14 and 28, there was no statistically significant difference between those taking curcumin and those taking diclofenac in pain measurements.

Those taking curcumin had fewer episodes of flatulence and by Day 28, had a statistically significant weight loss and anti-ulcer effect. No patient using curcumin required an H2 blocker, while 28% of those using diclofenac needed an H2 blocker to reduce excess stomach acid. Researchers found that curcumin had a similar effect in reducing pain to diclofenac but was better tolerated and had fewer side effects.

Additional Health Benefits for Curcumin

Natural plants have been used for medicinal purposes throughout history, and turmeric is not an exception. There is evidence it was used in human health as far back as 4,000 years ago and modern medicine has seen over 3,000 papers published on it within the last 25 years.[30]

In addition to pain relief, curcumin has also demonstrated the ability to make significant changes in cognitive function and mood in older adults who took the supplement for at least four weeks.[31] Researchers found significant improvement in working memory,

general fatigue and state of calmness. Additionally, it significantly reduced total and LDL cholesterol.

A second study[32] performed at the University of California Los Angeles and published in the American Journal of Geriatric Psychiatry examined the effects of curcumin on individuals who had no history of dementia. The study's first author, Dr. Gary Small, said in a press release:[33]

> *"Exactly how curcumin exerts its effects is not certain, but it may be due to its ability to reduce brain inflammation, which has been linked to both Alzheimer's disease and major depression."*

The study followed 40 people between ages 50 and 90 who had mild memory complaints. Researchers found those who took the curcumin had significant improvements in memory and attention abilities, as well as mild improvement in mood and significantly fewer amyloid and tau signals in the amygdala and hypothalamus, areas of the brain that control some memory and emotional functions.[34]

One paper published in 2019[35] postulated that since chronic inflammation plays such a significant part in obesity, cardiovascular diseases and impaired glucose tolerance, increasing the bioavailability of curcumin may help modulate many of these lifestyle-related diseases.

A meta-analysis of three studies[36] that included 326 patients, also found that curcumin has a beneficial effect on irritable bowel syndrome symptoms, and another analysis showed curcumin a being effective and well-tolerated agent for the treatment of some skin diseases.[37]

Researchers continue to evaluate the effects curcumin has on many conditions driven by chronic inflammation, including rheumatoid arthritis, ulcerative colitis, cognitive decline, major depressive disorders and premenstrual syndrome.[38]

Although curcumin is generally recognized as safe (GRAS),[39] it has been found to increase the risk of bleeding in people taking medications that affect platelet aggregation, such as Lovenox, heparin or warfarin. People who are on chemotherapy

should consult with their physician before including curcumin as it has inhibited chemotherapy-induced apoptosis in the lab.[40]

Additionally, curcumin may interfere with the metabolism of some drugs used in the U.S. and piperine, sometimes included with curcumin to increase bioavailability, may also affect the elimination and bioavailability of certain drugs.