

# Influence of Curcumin, Piperine and its Combinations on Health

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## ABSTRACT

Turmeric and piperine are the spices which have been identified and used in many medicines and culinary purpose since ages. Both these spices are largely used in many cuisines throughout the world. They contain large amount of polyphenol compounds. It has been noticed that medicinal plants are very high in demand in different conventional system of medicine because of their pharmacological effect and lower side effects in different biological systems. In this review article we are focusing on adjuvant which improves the bioavailability of curcumin in human body at the same time effect of this combination in different life-threatening disease. We have covered diseases like cancer, diabetes, neurodegenerative diseases, and arthritis, etc. There are many different components that can improve bioavailability of curcumin but piperine is the most popular and utmost component present in black pepper which increases the bioavailability of curcumin. It has been proven that bioavailability increase by 200%. Combining these types of active components provide multiple health benefits. The purpose of this review article is providing updated and recent advancements of pharmacognosy and pharmacological effect of curcumin and piperine.

**Keywords:** Curcumin; Piperine; Bioavailability; Pharmacological; Medicine; Alkaloids; Phenolic Components

## Introduction

Ayurveda holds promising treatment regimens for health medics, starting from simple gastric disorders to life-threatening ailments, and most of its hopes rely on herbs and plants. The prominence of medicinal plants and herbs is rich in phenolic components. The phenolic compounds include phenolic acids, flavonoids, alkaloids, tannins, stilbenes, curcuminoids, coumarins, lignans, quinones, etc. They are the active components imparting various effects such as antioxidant, anti-inflammatory, carcinogenic, and mutagenic Huang, et al. [1]. Phenolic compounds are not only secondary metabolites of plants bearing aromatic rings with at least one hydroxyl group. Till date, more than 8000 naturally occurring phenolic compounds have been investigated. They have been explored intensively due to remarkable cura-

tive actions against several health issues. Interestingly many of these herbal medicines include spices. Spices not only add delightful flavor to the food but also provide medicinal value, which acts both as preventive as well as therapeutic.

### Curcumin: Component

One of the active phenolic compounds is curcumin, a polyphenol present in turmeric. Turmeric is a vibrant yellow spice that holds importance in the culinary world and has been a part of folk medicine in India and China Fadus, et al. [2]. The use of curcumin is still being continued in India; it is given in the form of paste to treat burns, acne, skin diseases, and many more. On the other hand, powdered curcumin is given with milk to boost immunity, treat cough, digestive problems, acidity, and other related respiratory ailments Hatch-

er, et al. [3]. Curcumin is a symmetric molecule with the IUPAC name 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, also called as diferuloy methane, found in the rhizome of Curcuma species like Curcuma longa. Curcumin is structured with two aromatic rings, each containing o-methoxy phenolic groups. These two rings are connected by seven carbon linkers involving  $\alpha$ ,  $\beta$ -unsaturated  $\beta$ -diketone moiety. The diketo moiety further exhibits keto-enol tautomeric shifts. It assumes cis-enol configuration in crystalline state stabilized by resonance assisted hydrogen bonding, where the structure consists of three substituted planar groups interconnected through two double bonds. However, trans-isomer (two phenolic-methoxy groups on opposite sides of the curcumin backbone) is slightly more stabilized than cis-isomer in solution. Since curcumin is hydrophobic, it is almost insoluble in water and readily soluble in polar solvents including methanol, ethanol, DMSO, acetonitrile, chloroform, ethyl acetate, etc.

Moreover, in non-polar solvents, enol form is predominated over keto by about 5-8 kcal/mol. Although curcumin's medicinal properties have been known for thousands of years, its mechanism of action has been investigated recently. Pharmaceutical company Johnson & Johnson sells turmeric Band-Aids for the Indian market. Curcumin is also known to suppress initiation, progression, and metastasis of tumors by principally regulating transcription factors growth factors, inflammatory cytokines, protein kinases, several oncogenic molecules, inhibiting cell cycle progression at different phases, and inducing apoptosis Shanmugam, et al. [4].

### Piperine: Component

Another spice that holds importance is black pepper (*Piper nigrum*) and long pepper (*Piper longum*), which is used as a medicine, preservative, and perfume in many Asian countries. Ancient medicinal practices state many more benefits of black pepper. It was used to treat and reduce pain, chills, rheumatism, influenza, muscular ache, and fever. It used to be and is still an ingredient for tea. Black pepper was used to relieve migraine headaches and many respiratory ailments by this route. An active ingredient that imparts pungency to black pepper is an alkaloid named piperine. Its pharmacological activities include anti-inflammatory, anti-metastatic, anti-cancer, larvicidal, leishmanicidal, immunosuppressive, anti-mycobacterial, and antiparasitic Rather [5]. It is known to stimulate digestive enzymes of the pancreas and protect against oxidative damage, lowers lipid peroxidation, and mainly improves the bioavailability of many therapeutic drugs. Hans Christian was the first to isolate piperine in 1819 from the extract of pepper Gorgani, et al. [6]. It belongs to vinilloid family. Piperine is basically an amide alkaloid form plant of family Piperaceae family. It is slightly soluble in water and tasteless at the start but leaves a burning aftertaste. Chemically it's a trans-stereoisomer of 1-piperoyl piperidine and (E, E)-1-(5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl) piperidine Kumoro, et al. [7].

In spite of having great medicinal value, herbal medicine is not used routinely due to some limitations, including their absorption, bioavailability, lack of knowledge about their molecular targets, etc. Many of the known herbal medicines exhibit synergistic action, thereby enhancing the bioactivity and bioavailability of the herbs involved. This review sums up chemo preventive and therapeutic knowledge about curcumin and piperine and further attempts to enlighten the benefits of using curcumin and piperine together.

### Journey of Exotic Spices to Potent Drugs Effects Individually

Being considered a functional food, curcumin provides health benefits beyond their nutritive value and offers a potent part in drug development Moorthi [8]. Curcumin draws attention as it has shown promising outcomes for many health issues, right from simple wound healing to life-threatening diseases as big as cancer, epilepsy, Parkinson's disease. Curcumin is well known for its antioxidant potential, which makes it vital to fighting oxidative stress implicated in several pathological conditions. The antioxidant property of curcumin has been studied on hepatic encephalopathy Rosello [9], human monocytes, THP-1 (the human monocytic leukemia) cell line Rushworth, et al. [10], diabetes mellitus first phase cataractogenesis Manikandan, et al. [11], pancreatitis Durgaprasad, et al. [12], where curcumin becomes protective component against oxidative stress probably by increasing expression of natural antioxidant enzymes such as cyclooxygenase, lipoxygenase, catalase, superoxide dismutase, and glutathione peroxidase. In monocytes and THP-1 cell lines, curcumin acts by increasing the expression of heme oxygenase-1, NADPH quinone reductase-1, glutamyl cysteine ligase modulatory enzyme, and ferritin mRNA expression Rushworth, et al. [10]. Interestingly, curcumin induces  $\beta$ -oxidation of fatty acids, inhibiting its synthesis and lipid accumulation.

*In vivo* investigation on diabetic male Wistar rat model further enlightens anti-diabetic effects of curcumin by decreasing PDK4 expression and GS phosphorylation Na, et al. [13]. Increased expression of GLUT4 on the membrane with increasing glucose uptake in palmitate induced L6 myotubes was also observed. Clinical trial further suggests that daily supplementation of 1500mg curcumin for about ten weeks helps decrease fasting glucose level in type 2 diabetic patients Hodaie, et al. [14] with a fundamental mechanism involving peroxisome proliferator-activated receptor activity, an increase of glycolysis and liver gluconeogenesis, stimulation of pancreatic insulin secretion, increased glucose uptake by increased expression of GLUT4, GLUT3, and GLUT3. The development of cataracts is also somewhat related to the impairment in natural defense against oxidation. Curcumin appears to be a great preventive measure, but its low bioavailability and low water solubility make it the wrong candidate. However, curcumin derivatives salicylidene curcumin and benzalidene curcumin have anti-cataractogenic potential, reversing the antioxidant activity of

enzyme and calcium homeostasis to an average level in cultured selenite-induced cataract rat lenses Radha, et al. [15]. In neurodegenerative diseases Cole, et al. [16], curcumin acts by binding to and limiting the aggregation of  $\beta$ -sheet conformations of amyloid fibers. Yang, et al. [17] study suggest curcumin as a better inhibitor of  $\beta$ -sheet aggregation and oligomerization over drugs such as ibuprofen and naproxen in Alzheimer's disease.

Among the many novel activities, the anti-depressant activity of curcumin is well remarkable Bhutani, et al. [18]. Chronic unpredictable stress exhibits helpless behavior; increases corticosterone levels in blood serum, inhibits brain monoamine oxidase activity leading to depletion of monoamine level. Intraperitoneal dosing of 20-40mg/kg curcumin for 21 days reversed chronic unpredictable stress-induced depression like behavior in rat models. Also, at the pathological level, monoamine oxidase activity was inhibited, resulting in an increase in serotonin and dopamine levels Bhutani, et al. [18]. Curcumin and piperine are both known to work against hypertension. A study on experimental models induced for hypertension by L-NAME suggests the ability of both curcumin and piperine to prevent high blood pressure Hlavackova, et al. [19]. L-NAME causes a chronic increase in blood pressure in rats probably by inhibiting NO synthases and decreasing NO production Vrankova, et al. [20]. Nutrient bioavailability is one of the major concerns nowadays which is caused by either low intake of nutritious food or poor absorption of nutrients through the gut. A study suggests that simply oral administration of piperine may offer the solution at this level. It was shown that daily oral supplementation of 5mg piperine and 15mg beta-carotene for 14 days improves the level of beta carotene by 60% compared to its administration with placebo Badmaev, et al. [21].

Here piperine complements this benefit without affecting further beta-carotene metabolism to retinol, which predominantly occurs at the same site as piperine site of action, i.e., gastrointestinal epithelium. The anti-diarrhoeal activity of piperine has also been studied in mice models. Cathartics (castor oil, MgSO<sub>4</sub>, and arachidonic acid) induced diarrhea was found to be inhibited by oral administration of piperine, suggesting its inhibitory action on prostaglandins and cholecystokinins Bajad, et al. [22]. Piperine is known to be an anti-inflammatory, antinociceptive and antiarthritic agent. These effects of piperine were analyzed on rat models that induced acute paw pain and arthritis followed by oral administration of 20-100 mg/kg/day piperine for 8 days. It was found that piperine inhibited the expression of interleukin 6 (IL6) and matrix metalloproteinases 13 and reduced the production of prostaglandin E2 in a dose-dependent manner. Piperine reduced nociceptive and arthritic symptoms in about 8 days. It further reduced inflammation in the ankle joints, which was confirmed using histological staining. Among many metabolic activities, piperine's protective and antiulcer activity has been studied using a novel formulation named gastro retentive microspheres Bod-

dupalli, et al. [23]. These microspheres were found to prevent hepatotoxicity (indicated by cellular necrosis, fatty changes, ballooning, and broadened infiltration of kupffer cells) induced by paracetamol.

Furthermore, the anti-asthmatic effect of piperine has been explored by Kim SH [24] *in vivo*, where piperine was found to prevent the development of characteristics of asthma that included airway hyper responsiveness, airway, and airway eosinophilia, and lung inflammation in an ovalbumin-induced asthma model. Piperine also diminishes the level of oxidative damage, and its antioxidant activity has been studied on cadmium-induced oxidative stressed human peripheral blood lymphocytes Verma, et al. [25]. The effect of piperine on brain functioning is another advent of exploration in nutraceutical sciences. Piperine is known for its function on memory and behavior via monoamine neurotransmitters Joshi H [26]. Some articles concluded their finding revealed anti-depressant activity and cognitive enhancing effect of piperine at low doses on Wistar rats in about 4 weeks of treatment Wattanathorn, et al. [27]. Bipolar diseases, including Parkinson's disease and Alzheimer's disease that are routed from oxidative stress happened to arise byproducts of metabolism that can be taken care of by the antioxidant property of piperine. Piperine has been shown to reduce MTP-induced Parkinsonism and anti-apoptotic activity against MPTP-induced alteration in the ratio of Bcl2 and Bax in mice Yang, et al. [28]. Brazilian traditional medicinal practices also involve the use of curcuminoids. In an old study, curcumin was shown to abrogate hemorrhagic activity of Bothrops venom and lethal effects of Crotalus venom.

This explores another sight in anti-snake venom research Ferreira, et al. [29]. Curcumin and piperine face many challenges despite holding efficient therapeutic potential due to their structural chemistries. The high hydrophobicity of these molecules makes them suffer poor serum availability even after heavy oral dosing Cavaleri F [30]. Even after being a great candidate in folk and modern medical practices, curcumin and piperine still hold the non-appreciable place that stems from many physico-chemical limitations. Over the past decades, researchers have addressed numerous reasons that restrict the therapeutic utility of both curcumin and piperine. Poor serum level of curcumin was observed in rats upon oral administration of curcumin as heavy as 1g/kg Wahlstrom and Blennow [31]. However, highly absorptive curcumin capsules and drinks or beverages have been developed named Theracurcumin and are being sold in Japan Moriimoto, et al. [32].

### Combine Mechanism Action of Curcumin-Piperine

Limitations confronted by most of the chemotherapeutic drugs primarily devoted to their hydrophobic nature. A new approach called "combination therapy" has opened a new era of treatment that exploits the benefits of each drug involved and improves their reactivity many folds compared to when used alone. Recently formulation

of curcumin and piperine into emulsions was prepared to enhance their anti-cancer activity and bioavailability. The study presented that the so formed emulsions (7 $\mu$ M piperine and 25 $\mu$ M curcumin) additively contributed to the anti-cancer effect on human colon carcinoma (HCT116) cell *in vitro*. The anti-cancer effect was confirmed by morphological changes in HCT116 cells, cell cycle arrest at G2/M phase followed by apoptosis, and caspase 3 expression was also found to be elevated six-folds. Chemo preventive effects of the curcumin-piperine combination were studied on DMBA-induced buccal cancer (oral cancer) Manoharan, et al. [33]. The presence of a tumor in a tissue induced ROS production and may further cause lipid peroxidation. Tumor cells are identified to be resistant to lipid peroxidation due to increased proliferation as compared to normal tissues. Oral dosing of curcumin-piperine was found to restore lipid peroxidation and antioxidant levels in DMBA-painted animals.

### Curcumin-Piperine for Cancer Prevention

The probable mode of cancer in tissue stem cells is by dysregulating the normal pathway of self-renewal and progenitor cells by gaining the ability to self- renovate, which suggests that stem cells and progenitor cells are possible targets for transformation. An approach was put forth by the University of Michigan to use curcumin and piperine in combination to inhibit stem cell self-renewal and to reduce its multiplication using curcumin and piperine in varying ratios, Wnt signaling in MCF7 cells and breast stem cells self-renewal was demonstrated to inhibit. Further, these compounds did not show any adverse effect on differentiated cells, making this combination a potential cancer treatment module Kakarala, et al. [34].

### Curcumin-Piperine for Anti Diabetic Effect:

The postprandial peak in glucose level in type 2 diabetes is owed to the action of  $\alpha$ -glucosidase, a rate-limiting enzyme in the pathway that converts oligosaccharides and disaccharides to monosaccharides which are then absorbed by the gastro intestine. This condition can be overcome by using  $\alpha$ -glucosidase inhibitors, thus delaying glucose absorption. Curcumin happens to have a profound inhibitory effect on glucosidase Shrinivasan and Manjunatha [35], but its bioavailability issue upon oral intake limits its use. However, combination of curcumin with piperine and quercetin designated CPQ show increased anti-diabetic effect *in vitro* compared to curcumin alone Patel, et al. [36]. The cardioprotective role of curcumin is quite well-established; however, its combination with bio-enhancer piperine makes the formulation (50mg/kg curcumin and 20mg/kg piperine) novel, as it has been shown to increase its cardioprotective effect profoundly against cyclophosphamide induced cardiotoxicity Chakraborty, et al. [37].

### Curcumin-Piperine for Neuroprotective Effects

Neuroprotective and anti-apoptotic effects of curcumin have also been very well studied Thiagarajan [38]. However, it undergoes ex-

tensive reduction through alcohol dehydrogenase and conjugation in the liver and intestine Wahlstrom [31]. On the other hand, Piperine can be used in defense to protect curcumin from undergoing reduction. A study proved curcumin's enhanced neuroprotective, anti-apoptotic effect when given in combination with piperine to olfactory bulbectomized animals possibly by modulating oxidative-nitrosative stress Rinwa, et al. [39]. Among several neurodegenerative syndromes, peripheral neuropathy is widespread that affects sensory fibers manifesting paresthesias and pain. A formulation called "Lipicur" consisting of lipoic acid, curcuminphytosome, and piperine has been shown to relieve neuropathic pain by more than 66% in patients having lumbar sciatica (caused by chronic degenerative problems resultant in reduced quality of life) and carpal tunnel syndrome (involved median nerve that is compressed inside carpal tunnel between transverse ligament and carpal bones) Pierro [40].

### Curcumin-Piperine for Bone Health Improvements

Curcumin may also work in preventing bone disorders as its analogues have been found to stimulate osteoblastogenesis and inhibit osteoclastogenesis *in vitro* through Smad activation and NF- $\kappa$ B inhibition Yamaguchi, et al. [41]. This gives curcumin a new insight into the treatment of dental illnesses. Current antiresorptive agents are only partially effective, and many times they show side effects, which make it needful to look for new, effective, and biocompatible remedies. A study by Martins [42] explores the inhibitory activity of curcumin against receptor activator of nuclear factor kappa B ligand (RANKL)-induced osteoclast genesis of RAW 264.7 murine macrophage lineage and human osteogenic sarcoma cells (SAOS2) *in vitro* without causing any cytotoxic effect on periodontal ligament cells, when given along with piperine. This study suggests preventing and treating replacement resorption in replanted teeth after traumatic avulsion.

### Curcumin-Piperine Reduce Toxicity

Moreover, the curcumin-piperine combination has been shown to reduce allethrin-induced toxicity. Allethrin is a pyrethroid widely used for household pest control insecticide to which humans are exposed maximally since it is used as mosquito repellents. It is known to bring about hematological and biochemical alterations in mice. Administration of curcumin in combination with piperine was found to reverse the allethrin induced hematological and biochemical alteration significantly. It also protected the histological structure of the kidney, lungs, liver, brain, and heart Divakar, et al. [43]. The bioavailability enhancement role of piperine is well known, and many hypotheses are elaborating its mechanism have been proposed, although its precise mechanism is still obscure. It is hypothesized that piperine regulates the metabolic rate of curcumin. A simulation study reveals that piperine intercalates with curcumin forming a hydrogen bond complex. It was also shown that piperine competes for curcum-



in's intermolecular hydrogen bonding and its stacking propensities by hydrogen bonding with enolic protons of curcumin, facilitating metabolic transport of curcumin Patil, et al. [44].

## Conclusion

This review focuses on the combined effect of curcumin and piperine both as therapeutic as well as prophylactic drug. Curcumin possess many medicinal properties like antioxidant, anti-carcinogenic, anti-inflammatory, anti-angiogenic, antimicrobial, anti-parasitic and other activities. Despite having so many benefits, efficacy and safety, limited bioavailability of curcumin continues to be highlighted as a major concern since ages. However literature proves that to improve the bioavailability of curcumin, several studies have been conducted such as route and medium modulation of curcumin administration, blockage of metabolic pathways by concomitant administration with different agents, and chemical and structural modifications of curcumin. One of the suitable agents among all is Piperine which is considered as a potent bioenhancer. Combining these compounds help in improving the health benefits to the human race. However for proper understanding of the mechanism of its bio-absorption in the chemical level in our body urgent studies are required.

## Credit Authorship Contribution

- Srutee Rout: Writing – original draft, Visualization, Validation
- Sowmya R S: Review & editing
- Sugriv Shyamlal Gupta: Writing & editing.

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