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CURCUMA LONGA: SPICE OR MEDICATION?

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ABSTRACT

Curcuma longa (turmeric) is part of the family Zingiberaceae, grows naturally in the Indian subcontinent and tropical countries and it is very used in the Indian Ayurvedic medicine. The primary compounds of the rhizome of *C. longa* are curcuminoids named curcumin, bisdemethoxycurcumin, and demethoxycurcumin. Due to its anti-inflammatory effects, may be used in the treatment of many diseases. It can also exert effects as antioxidant, antimicrobial, antifungal, antiviral, antibacterial, and neuroprotective. Due to the numerous benefits of *C. longa,* the objective of this study was to survey the therapeutic effects of this plant on some diseases common in modern societies. This review was based on bibliographic studies of in vitro studies and animal and human models. We used databases such as Pub Med, Scielo, and LILACS. Several *in vitro, in vivo* and clinicaltrials, have shown that *Curcuma longa* has several pharmacological activities with mainly anti-inflammatory and neuroprotective effects. It may positively interfere in several locals of inflammation, reducing the production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-10, TNF-α, and C-reactive protein. It also inhibits the NFκB path way leading to suppression of inflammation. Therefore, it can be considered with high potential for drug development and treatment of several diseases once the allopathic medications are linked with high costs and many undesireble side effects. On the other hand, curcumin is cheap, and, due to its non-toxic properties, is not associated with side effects. For these reasons, it may become an alternative or an adjuvant in the therapeutic approach of inflammatory diseases.

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INTRODUCTION

Curcuma longa (saffron or turmeric) is part of the family Zingiberaceae, grows naturally in the Indian subcontinent and tropical countries, and it is very used in the Indian Ayurvedic medicine (more than 6,000 years) (Schaffer *et al.,* 2011; Jurenka, Julie, 2009).The name of the plant comes from the Arabic Za'faran, which means yellow, the color that dyes the robes of the Buddhist Monks and which, in Hinduism, is associated with fire, a divine element. Because of its golden color, marine scent, and slightly bitter taste, saffron is an extremely versatile spice and can be used in any culinary preparation. Its use in the preparation of numerous foods is overgrowing (Lacerda *et al.,* 2013). Turmeric is chemically diverse in its composition. The qualitative and quantitative compositions often alternate according to varieties, locations, sources and growing conditions. Up to now, about 235 compounds, mainly phenolic compounds and terpenoids, have been identified from this spice. The main compounds of the rhizome of *C. longa* are the curcuminoids named curcumin, bisdemethoxycurcumin, and demethoxycurcumin. The concentrations of these compound in the plant is respectively 77%, 17%, and 3%. The typical yellowish coloration mentioned above occurs due to the presence of curcumin (Maziero *et al.,* 2018; Cunha-Neto *et al.,* 2018; Chin *et al.,* 2016; Yadav *et al.,* 2013; Aggarwal *et al.,* 2009).Curcumin is a flavonoid and designated as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene- 3,5-dione (Hu *et al.,* 2015). Clinical trials show that this plant has a potential therapeutic role in numerous chronic diseases. It can exert antioxidant, antimicrobial, antifungal, antiviral, antibacterial, anti-inflammatory, neuroprotective, radio-protective, as well as degenerative diseases such as osteoarthritis, antidepressant,

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Alzheimer's disease, obesity and chemo-preventive. It also has activity against several types of cancers including aggressive and recurrent. Figure 1 shows some parts of the plant and the powder obtained from the rhizomes (He *et al.,* 2015; Mobasheri, 2012; Akuri *et al.,* 2017; Prasad, Tyagi, 2015; Wang *et al.,* 2017).

Figure1. Flower, rhizome, and powder of *Curcuma longa*

A limitation of using curcumin is its low bioavailability once it is poorly absorbed, quickly metabolized, and systemically expunged. For these reasons, it is necessary to find delivery alternatives in order to its use as a therapeutic agent (Anand *et al.,* 2007). Due to the numerous benefits of *C. longa,* the objective of this study was to survey the therapeutic effects of this plant on some diseases common in modern societies.

METHODS

This review was based on the literature survey of articles associating the effects of *Curcuma longa* in animal and human models and *in vitro* essays. The search was performed in databases such as Pub Med, Scielo, and LILACS.

DISCUSSION

Curcumin has been and is still used as a medicine by the Chinese and Indians for the treatment of various diseases. It is known that the oxidative stress and oxidative damage can lead to chronic inflammation, which in turn can mediate most known chronic diseases. Due to its chemical structure, curcumin can act as a natural neutralizer of free radicals. The antioxidant activity of curcumin is closely related to their phenolic compounds. As oxidative stress activates the inflammatory pathways that lead to the progression of chronic diseases, researchers suggest that chronic inflammation, oxidative stress, and most chronic diseases are closely linked, and the antioxidant properties of curcumin may play a role prevention and treatment of these diseases (Vecchi *et al.,* 2014; Gupta *et al.,* 2013). Figure 2 shows the diseases in which *Curcumalonga* may produce positive effects.

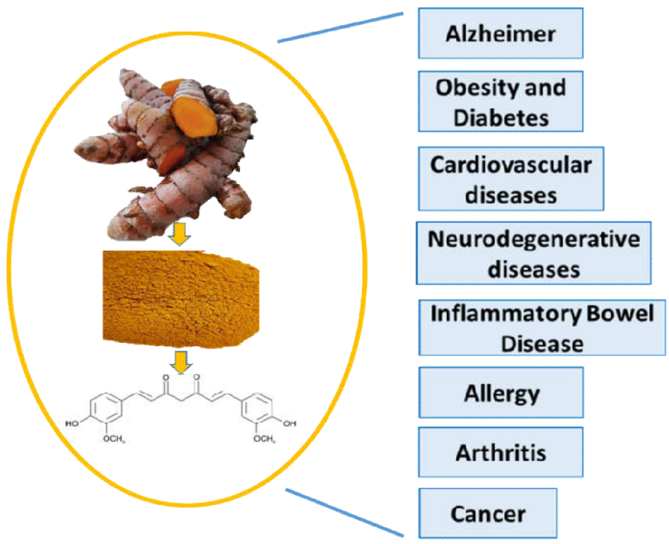

Figure 2. Diseases in which *Curcuma longa* (curcumin) may produce positive effects

Inflammation occurs in response to an adaptive physiological response led to deleterious circumstances that may include infection and injury of the tissues. On the other hand, inflammatory processes may be related to several physiological and pathological problems. It is linked to modifications in signaling pathways, resulting in augmented levels of inflammation markers, lipid peroxides, and free radicals. The inflammation may be characterized by two phases that include acute and chronic inflammation. The first one represents an initial phase of inflammation mediated by the activation of the immune system and persists for a short time and usually is beneficial for the host. The chronic inflammation persists for a longer time and is related to many chronic diseases such as diabetes, obesity, cardiovascular and neurodegenerative diseases, arthritis, pancreatitis, and cancer (Smith, Trinchieri, 2018; Sikora *et al.,* 2010; Schraufstatter *et al.,* 1988). Together with inflammation is the oxidative stress that is associated with the pathophysiology of several chronic inflammatory processes related to the increase of developing chronic diseases such as metabolic disorders, atherosclerosis, cancer, Alzheimer's disease, and many other disorders. These pathologies are generally represented by low grade inflammation promoted by the release of pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interferon- γ (IFN-γ), Interleukin-1 (IL-1), IL-6, IL-8, and up regulation of the Nuclear Factor kappa-B (NFκB) (Hill *et al.,* 2018; He *et al.,* 2015). The following items show the effects of *C. longa* on some diseases common in modern societies.

Osteoarthritis (OA): OA is a degenerative disease related to synovial inflammation and destruction of the extracellularmatrix leading to symptoms such as disability, pain, and morbidity. Curcumin has actions in several locals of inflammation, reducing the production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-10, TNF-α, and C-reactive protein (CRP). It also inhibits the Activator Protein 1 (AP-1) pathway and NFκB leading to suppression of inflammation (Akuri *et al.,* 2018). The results are the inhibition of pro-apoptotic genes expression in chondrocytes (caspase-3) and the production of inflammatory molecules. This process results in the down-regulation of cyclooxygenase-2, lipoxygenases, prostaglandin E2, and phospholipase A2 and reduces the degradation of collagen (Mollazadeh *et al.,* 2017; Jagetia, 2007; Fan *et al.,* 2018; Mobasheri *et al.,* 2012).

Allergy, Asthma, Bronchitis: Turmeric as an anti-allergic agent and acts with immune-regulatory effects through the maintenance of the balance between activation of T helper 1 (TH1) and TH2, necessary in the inflammatory responses. Therefore, the authors suggest that administration of saffron, including various components, is useful for improving allergic disorders such as food allergy, atopic dermatitis, and asthma (Shin *et al.,* 2015).

Psoriasis

There are strong indications that curcumin has the potential to suppress psoriasis by inhibiting the proliferation of keratinocytes. Studies have been conducted in patients with moderate to severe psoriasis and have shown that this compound, in addition to being well tolerated, it can lead to about 83% to 88% of improvement of the disease (Gupta *et al.,* 2012). Curcumin can alleviate inflammation of the skin by regulating the production of IFN-γ and TH1 (He *et al.,* 2015).

Inflammatory bowel diseases: Crohn's Disease (CD) and Ulcerative Colitis (UC) that are the primary forms of Inflammatory Bowel Diseases (IBD). These inflammatory conditions are increasing sharply in the last few decades and occur due to a reaction to a plethora of stimuli such as hyperactivity of the immune response, eating habits, and genetic factors. IBD leads to discomfort, pain, diarrhea, bleeding, increase of intestinal cancer and adecrease of quality of life (Hemperly, Vande-Casteele, 2018; Ilhara, Hirata, Koike, 2017). Curcumin may be used in patients with IBD due to its role as anti-inflammatory, antioxidant, and anticancer. It performs its effects once it is related to the down-regulation of inflammatory transcription factors, cytokines, protein kinases, and enzymes thatresult in inflammation. It may interfere with the release and action of TNF-α, IFN-γ (Interferon-γ), cyclooxygenase-1 (COX-1, COX-2), and NFκB. Once curcumin is useful in the regulation of inflammatory cytokines in inflammatory diseases, it could work as a new therapeutic agent for treating IBD patients (Shaffer *et al.,* 2015; Vecchi *et al.,* 2014; Gupta *et al.,* 2013).

Pancreatitis: Chronic pancreatitis (CP) is associated with progressive fibrosis, pain, and loss of endocrine functions, of which pain is the primary symptom. Curcumin has a pleiotropic effect capable of acting in numerous molecular targets in pancreatitis. Studies in induced pancreatitis mice revealed that curcumin reduced inflammation by dramatically decreasing activation of NF-kB and AP-1, as well as suppression of the induction of iNOS (inducible Oxide Nitric Synthase), TNF-α and IL-6. In a clinical study, curcumin was effective in treating patients with pancreatic cancer. Another pilot study was conducted to investigate the clinical efficacy of curcumin and showed that the oral administration was able to suppress lipid peroxidation in patients who had pancreatitis after lowering the levels of malondialdehyde (MDA) and glutathione (GSH) in cells red blood cells. For these reasons, some authors suggested that curcumin may be used as a treatment of pancreatitis (Anchi *et al.,* 2018; He *et al.,* 2015).

Obesity and diabetes: Inflammation is an essential component of obesity, which in turn, is associated with insulin resistance. Subclinical or chronic inflammation has been recognized as being involved in the development of obesity, type 2 diabetes, and atherosclerosis. Studies have shown that curcumin inhibits a number of signaling pathways and involved molecular targets, inflammation, and metabolic diseases related to these diseases (Shehzad *et al.,* 2011). Curcumin may directly produce effects in the white adipose tissue to profoundly reduce the chronic inflammation by inhibiting macrophage infiltration and activation of NF-κB induced by inflammatory agents. The Curcuminoidsdecrease the expression of pro-inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), TNFα, and plasminogen activator inhibitor type-1 (PAI-1). It also increases the expression of adiponectin, that may be considered the main anti-inflammatory molecule produced by adipocytes. Curcumin may also inhibit the adipocyte differentiation and produce antioxidant properties. For these reasons, it may reduce obesity and may avoid the occurrence of several diseases related to overweight and obesity (Bradford, 2013). Curcumin may act as an antidiabetic agent because of its anti-inflammatory and antioxidant potential that can affect enzymes and also increase the function of the islets of Langerhans and therefore can reduce the damage caused by oxidative stress (Karlowicz-Bodalska *et al.,* 2017). It decreases the levels of glucose in the blood, as well as the amounts of glycosylated hemoglobin due to the induction in the balance of the polyol pathway. Furthermore, it plays a beneficial role in the reduction of endothelial dysfunction and in down-regulating NFκB. It also acts against advanced glycation products and its complications that are the leading causes of damage caused by diabetes (Nabavi *et al.,* 2015; Rivera-Mancía *et al.,* 2015).

Cardiovascular diseases: As mentioned above, *C. longa* can positively influence the prevention and treatment of diabetes and obesity which are the main diseases related to the development of cardiovascular diseases. Also, studies have shown that this plant is protective against heart disease, through the attenuation of oxidative stress, apoptosis, and inflammation. Through these mechanisms, curcumin exerts protective effects against myocardial ischemia, diabetic cardiomyopathy, hypertrophic cardiomyopathy, arrhythmia and diseases related to doxorubicin cardiotoxicity. Notably, there are many questions about its therapeutic effects on the heart, including its low bioavailability and side effects, as well as endogenous or exogenous factors that influence the pharmacological effects (Jiang *et al.,* 2017).

Chronic renal disease: Chronic kidney disease is recognized to involve inflammation, oxidative stress, and apoptosis. Curcumin has been shown to act significantly on markedly reduced renal morphological injury and histopathological markers, inflammation, fibrosis, and apoptosis. In studies with rats, curcumin reduced hypertension, urinary albumin, inflammatory cytokines IL-1β, IL-6 and TNFα, and cystatin C. It restored plasma sclerostin and reduced oxidative stress. This work shows that curcumin significantly decreased most of the physiological, biochemical, histopathological and molecular aspects of adenine in rats and strengthening the antioxidant defense in the kidney (Ali *et al.,* 2017).

Neurodegenerative diseases: *In vitro* study confirmed that curcumin improves survival of cortical neurons submitted to oxygen and glucose deprivation. Also, the results also revealed that curcumin reduced the risk of infarction and inhibited the oxidative stress after cerebral injury after ischemia/reperfusion in rats Studies suggest that curcumin significantly modulates arsenic-induced cholinergic dysfunctions in the brain and has also demonstrated neuroprotective efficacy, as well as modulating levels of norepinephrine, dopamine, and serotonin (Rahmani**,** *et al.,* 2018; Costa *et al.,* 2018). It is considered safe, FDA-approved, and rapidly crosses the blood brain barrier after oral ingestion. On the other hand, it is not stable in plasma and suffers excessively glucuronidated in the intestines and by first pass metabolism, leading to low penetration into the brain. After oral ingestionit promotes effects such as antioxidant, anti-inflammatory, and can inhibit the amyloid aggregation. In animal models, it reduces plaque burden and improve cognitive function (Maiti *et al.,* 2014).

Cancer: Cancer is a disorder related to the increase in the cell proliferation rate, resulting from a disrupted cell cycle, genetic and epigenetic mutations. It has a robustantineoplastic role due to its anti-inflammatory, antioxidant, antiproliferative, and proapoptotic pathways. There are several molecular pathways promoted by this pleiotropic molecule that may include the nuclear factor-like 2 (Nrf2), NF-κB, p53 (p53 protein), the AMP-activated protein kinase/cyclooxygenase 2 (AMPK/COX-2) pathway, Wnt/b-catenin signaling pathway, the Janus kinase/signal transducers activators of transcription (JAK/STAT) signaling, the Notch-1 signaling pathway, the Akt pathway, and STAT3 signaling (Deguchi, 2015; Shehzad, Lee, 2013). The chemical structure of curcumin shows a low level of hydrogenation and a high level of methoxylation, which promotes an action to increase the scavenging of free radicals, helping in the reduction of the oxidative stress (Sandur *et al.,* 2007; Sugiyama *et al.,* 1996). Chemoprevention and treatment of various types of cancer with curcumin, and the impact of anti-inflammatory curcumin and its effects on human carcinogenesis still need to be more elucidated. However, animal research demonstrates inhibition at the three stages of carcinogenesis which are initiation, promotion, and progression (Jurenka, 2009). Authors postulate that curcumin is one of the most promising compounds that may target many types of cancers, such as the stomach, esophageal, colorectal, breast, and multiple myeloma. The effects of curcumin on the three first types of cancer cited are summarized below (Deguchi, 2015; Devassy, Nwachukwu, Jones, 2015).

Stomach cancer: Gastric cancer is a very common malignancies around the world. Studies suggest that curcumin exerts anti-tumor activity and effects on atypical gastric hyperplasia, reversing the metaplasia of atrophic gastritis, decreasing recurrence of atypical hyperplasia, and improving patients' quality of life. Researchers have indicated that curcumin can stimulate the immune system and improve apoptosis of cancer cells by inhibiting the proliferation of gastric carcinoma cells and causing tumor cell death. Furthermore, curcumin demonstrates its antitumor effect by interfering with various signaling pathways that result in abnormal cell proliferation (Wang, *et al.,* 2017).

Esophageal Cancer: Curcumin is considered a potential candidate for the treatment and prevention of esophageal cancer due to its inhibition of inflammatory markers. It modulates a variety of molecular targets and induces apoptosis-independent death by mechanisms such as autophagy in cancerous cells of the esophagus. In addition, curcumin inhibits NFκB and promotes apoptosis *in vivo*, suggesting its chemo-preventive use. Animal studies show that curcumin decreases the initiation and post-initiation stages of cancer and repressed the occurrence of esophageal carcinogenesis in 27 and 33% of cases (Vageli *et al.,* 2018).

Colorectal Cancer: Studies have shown that curcumin reduces the stability of colorectal cancer by suppressing its oncogenicity (Lee *et al.,* 2018). In preclinical studies, this component has been shown to decrease the incidence of this cancer (Sharma *et al.,* 2001) and promotes apoptosis in the small intestinal mucosa (Collett *et al.,* 2001; Moradi-Marjaneh *et al.,* 2018).

Conclusion

Several*in vitro, in vivo* and clinical trials have shown that *Curcuma longa* has several pharmacological activities with mainly anti-inflammatory and neuroprotective effects. Therefore, it can be considered with high potential for drug development and treatment of several diseases once the allopathic medications are linked with high costs and many undesireble side effects. On the other hand, curcumin is cheap, and, due to its non-toxic properties, is not associated with side effects. These aspects make *Curcumalonga*much more than a spice, it may play a roleasa therapeutic agent or an adjuvant in the therapeutic approach of many diseases.

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