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Review article

Curcumin: An age-old anti-inflammatory and anti-neoplastic agent

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ABSTRACT

Curcumin is a natural anti-inflammatory agent that has been used for treating medical conditions for many years. Several experimental and pharmacologic trials have demonstrated its efficacy in the role as an anti-inflammatory agent. Curcumin has been shown to be effective in treating chronic conditions like rheumatoid arthritis, inflammatory bowel disease, Alzheimer's and common malignancies like colon, stomach, lung, breast, and skin cancers. As treatments in medicine become more and more complex, the answer may be something simpler. This is a review article written with the objective to systematically analyze the wealth of information regarding the medical use of curcumin, the "curry spice", and to understand the existent gaps which have prevented its widespread application in the medical community.

1. Introduction

Natural plant products have been used as the foundation of several medical treatments in humans.[1] Although modern aspects of Western medicine have become the forefront of clinical practice today, natural plant products continue to be used as remedies in alternative medicine throughout the world. It is estimated that 80% of individuals in developing countries depend primarily on natural products to meet their healthcare needs.[1] Even in the United States it has been found that approximately one in three Americans uses natural medicinal products daily.[1] It has been estimated that of the 877 small-molecule drugs introduced worldwide between 1981 and 2002, approximately 61% can be traced back to their origins in natural products.[1] Natural products are not only effective, but are relatively non-toxic and have therapeutic doses well below their toxic levels.[1] Curcumin is one such molecule that has shown promise since time immemorial. Nonetheless, there exists a significant barrier towards the utilization of these natural plant products in modern healthcare due to stigmatization of these "natural" remedies. Although the mechanisms of natural plant products and other plant-based drugs may not be well understood, it is important to uncover their mechanisms of action and determining their effectiveness. This will lead to a much more widespread acceptance of these alternative forms of treatment and allow it to be used in mainstream medicine.

2. Methods

The purpose of this article is to comprehensively review the literature on curcumin and its application in the field of medicine. Literature search was performed using Pubmed, Medline and Google Scholar to search for articles published in English language. The following key words were used – "curcumin," "turmeric," "curry," "chemoprophylaxis," "cancer chemoprevention" and "anti-inflammatory." All the papers were reviewed by two authors. The objective of this review was to present the published data on Curcumin to date and explore the lacunae in our current understanding which has withheld the medical community from its clinical use.

3. Results

Curcumin is the principle component of turmeric, a curry spice used as an edible component through different parts of Asia, mainly for its flavor and color profile and less so for its medicinal properties. In Ayurvedic medicine, curcumin is used as treatment for a variety of health conditions, including respiratory illness, liver

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disorders, inflammatory disorders and diabetic wounds.[1] In ancient Hindu medicine, it was used topically to treat sprains and swelling. In traditional Chinese medicine, curcumin is mainly used in treatment for conditions associated with abdominal pain.[2] Current evidence suggests that curcumin is a highly pleiotropic molecule with numerous targets and mechanisms of action. It has properties that alter the activity of enzymes, growth factor receptors, cofactors, and other molecules. Curcumin has been confirmed by scientific research to be anticarcinogenic, antimicrobial, hepatoprotective, cardioprotective and thrombosuppresive.[1]

Curcumin is traditionally an Eastern spice, and is consumed in great quantities in certain regions. One epidemiologic survey found that turmeric consumption in Nepal was up to 1500 mg per person per day.[3] In India, the average intake of curcumin can be as high as 2000–2500 mg per day.[4] In the 13th century, Marco Polo introduced turmeric to Europe, and only in the recent decades has scientific attention been given to its medicinal properties in the Western world.[5]

Curcumin was first isolated in 1815 and formulated into its crystalline form in 1870, and ultimately identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylmethane.[6] The first article published regarding the use of curcumin in human disease was in 1937. This article found that healthy persons injected with an intravenous solution containing curcumin had rapid emptying of the gallbladder, which demonstrated that curcumin could treat subacute, recurrent, or chronic cholecystitis.[7]

Today the United States Food and Drug Administration has approved Curcumin as “Generally Recognized As Safe” (GRAS), showing that the experts have determined that curcumin as a food additive is safe and tolerable under its intended use, and does not need to be subjected to pre-market review and approval by the FDA. It can be found worldwide not just as a medical treatment in the form of capsules and tablets, but as a supplement in ointments, energy drinks, soaps, and cosmetics.[7]

Treatment of all types of human disease, whether it is chronic, acute, or malignant, has evolved over time. In particular many of the drugs that have been developed recently over the last decade act at very specific pathways, modulating one particular aspect of a disease process. However many diseases today do not operate in such a unilateral fashion. These new mono-targeted drugs may also be expensive and carry large side effect profiles, in addition to lacking efficacy as well. A paradigm shift towards therapies that target multiple signaling pathways rather than therapies that target only one specific pathway may be on the horizon, especially given that many human diseases encountered in medicine are systemic in nature.[7] With this understanding, Curcumin is unique for medical treatments in that it has multiple targets and mechanisms of action.

4. Mechanism of action

Curcumin is a highly pleiotropic molecule with numerous targets and mechanisms of action, including altering the activity of enzymes, growth factor receptors, cofactors, and other molecules. Curcumin acts to modulate several pathways as enlisted in Table 1.[7] The wide range of action of curcumin can be demonstrated by its activity in inhibiting lipoxygenase by binding lipoxygenase itself or binding to phosphatidylcholine micelles.[8] Curcumin also inhibits tumor invasion and angiogenesis by irreversibly binding CD13/aminopeptidase.[9] It has also shown both in-vitro and in-vivo to block aggregation and fibril formation by directly binding small β-amyloid species.[10]

Curcumin affects tumor growth by disrupting the activity of several enzymes that allow for growth and proliferation. Its anti-fibrotic effects in glomerular disease is suggested in its action of blocking fibrosis in anti-Thy1 glomerulonephritis through up-regulation of hemoxygenase-1 gene expression.[11] Hemoxygenase-1 gene expression can also be induced by curcumin through the generation of reactive oxygen species (ROS), p38 activation, and phosphatase inhibition.[12] Another pathway of tumor growth is the Ras pathway in which its proteins must be isoprenylated to be activated. The intermediate in the mevalonate pathway, farnesyl pyrophosphate, donates this isoprenyl group to activate Ras. Curcumin was shown in a study to strongly inhibit FPTase activity, thereby inhibiting the mevalonate pathway and blocking the transforming effects of Ras oncogenes expression.[2] Curcumin has also been shown to inhibit xanthine oxidase activity, an enzyme that generates ROS, in PMA-treated NIH3T3 cells to inhibit PMA-mediated tumor promotion.[13]

Table 1
Mechanism of action of curcumin.

Curcumin mechanism of action[2,6–20]
Anti-inflammatory
Down-regulates activity of COX-2, lipoxygenase and inducible iNOS enzymes
Inhibits production of TNF-alpha, IL-1, -2, -6, -8, and -12, MCP, migration inhibitory protein
Down-regulates mitogen-activated and Janus kinases
Anti-neoplastic via cell-cycle arrest
Inhibits expression of cyclin D1 and CDK4 via acetylation and upregulation of p53
ATP-competitive inhibitor by down-regulating mRNA & protein expression of cyclin D1
Induction of CDK inhibitors p16(/INK4a), p21(/WAF1/CIP1), and p27(/KIP1)
Inhibits cyclin E/cyclin D1 expression
Hyperphosphorylation of retinoblastoma (Rb) protein (CDK2 substrate)
Induction of apoptotic signals
Induced upregulation of Fas, FasL, and DR5 expression
Enhances cleavage of procaspases and poly(ADP-ribose) polymerase
Upregulates the expression of DR 4 and 5
Inhibits the TNF-α-induced production of IL-6/IL-8 in HaCaT cells
p38-dependent upregulation of FasL in Huh7 cells
Inhibits TNF-α-induced activation of NF-κB, including NF-κB-P65

Mutations in tyrosine kinases cause uncontrolled activations that result in malignant transformation, growth, and metastasis of human cancers.[14] For instance, the overexpression of epidermal growth factor receptor (EGFR) and HER2/neu in cells stimulates the proliferation of cancer cells.[14] Both of these pathways act via Tyrosine kinase activation. Curcumin's effect on the activity of multiple kinases furthers the suggestion of its role in cancer therapy. Research shows that curcumin inhibits EGFR kinase activity and EGFR-induced tyrosine phosphorylation of EGFR in A431 cells and degrades cells of Her2/neu protein in-vitro.[15] Curcumin has also demonstrated that it has the ability to induce apoptosis in acute T-cell leukemia through inhibition of the phosphatidylinositol-3 kinase/AKT pathway and has also shown to induce G2/M arrest and non-apoptotic autophagic cell death in malignant glioma cells by abrogating Akt and Erk signaling pathways.[16] Additionally Curcumin can inhibit many pathways that contribute to its anti-inflammatory and anti-carcinogenic effects, such as various MAPK pathways leading to activation of the p44/42 MAPK (aka ERK1/ERK2), JNK, or p38 MAPK pathway.[6,13]

Other mechanisms of cancer proliferation are involved in inhibition of apoptosis, cell invasion, and adhesion for metastasis. Curcumin affects these pathways by being a potent inhibitor of TNF-α induced expression of intracellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin in a study using human umbilical vein endothelial cells. In human prostate cancer, curcumin can activate p53 and simultaneously down-regulate MDM2 oncogene expression via the PI3K/mTOR/ETS2 pathway in human prostate cancer