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CURCUMIN: AN AGE-OLD MEDICINAL BLESSING IN ERA OF 20TH CENTURY

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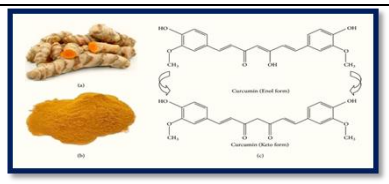
ABSTRACT
This review emphasizes on therapeutics and medicinal properties of curcumin. Turmeric is a spice which is commonly used by everyone in day to day life for different purpose. From ancient times, as prescribed by Ayurveda. Curcumin has been used to treat various disease conditions. In recent centuries curcumin has been used as active drug constituents as anticancer, anti-arthritic, antioxidant, antibacterial, anti-inflammatory, anti-amyloid and antiviral, anti-anxiety. Extensive research over the past half century has shown that curcumin (diferuloyl methane), a component of a golden spice turmeric (*Curcuma longa*), can modulate multiple cell signalling pathways. Extensive clinical trials over the past quarter century have addressed the pharmacokinetics, safety, and efficacy of this nutraceutical against numerous diseases in humans. The purpose of this review is to provide a brief overview of therapeutics and medicinal importance of curcumin in era of 20th century.

KEYWORDS: Curcumin, Therapeutics, Disease conditions, Drug.

INTRODUCTION
Curcumin is an interesting molecule which is constituent of the yellow pigments isolated from species Curcuma Longa belonging to ginger family (Zingiberaceae) Curcumin (1,7-bis(4-hydroxy 3-methoxy phenyl)-1,6-heptadiene-3,5-dione) is a natural polyphenol from the powdered rhizome of the medicinal plant Curcuma longa (also known as turmeric). It is an amphipathic molecule with polar-central and flanking regions that are separated by a lipophilic methine segment. Curcumin contains seven chemical functional groups. Among others, curcumin contains phenolic groups and thus can act as a reducing antioxidant and directly scavenge oxygen-centred reactive intermediates. Curcumin also displays oxidant activity partly due to its Michael acceptor functionalities. The unique chemical attributes of curcumin (e.g., log P ensuring curcumin's accessibility to its molecular targets, the capacity to undergo H-bonding and hydrophobic interactions, and activity as a Michael acceptor) are responsible for curcumin's pleiotropic biological activity.[3]

Drug Profile of Curcumin
Table No. I: Drug profile of drug Curcumin.

Molecular Formula	$C_{21}H_{20}O_6$
Synonyms	Curcumin Diferuloylmethane Natural yellow 3 Turmeric yellow
Molecular Weight	368.4 g/mol
Structure &Appearance	

DISCUSSION
Cancer
Cancer is one of the primary causes of death in industrialized countries. However, the growth of drug-resistant cancers necessitates the search for innovative and more effectivedrugs. It is worth noting that cancer cells are characterized by deregulated signalling pathways involving proliferation, apoptosis, and angiogenesis.[4] Curcumin, present in the Indian spice

"haldi" is one such agent that is currently under clinical investigation for cancer chemoprevention. Several studies of cancer prevention at different stages have shown the multi-targeted anticancer and chemopreventive effects of curcumin and have suggested it as a very favourable agent for chemoprevention. In a colorectal cancer trial, curcumin was shown to modulate biomarkers such as GST activity, deoxyguanosine adduct M(1)G, and PGE2. A decrease in lymphocytic GST activity of 59% resulted after administration of 440 Curcuma extract. The levels of M(1) decreased from 4.8 ± 2.9 adducts per 107 nucleotides to 2.0 ± 1.8 adducts per 107 nucleotides after curcumin administration. Oral administration of 3.6 g curcumin significantly ($P < 0.05$) decreased inducible PEG2 production in blood 1 hour after curcumin administration as compared with the predosing level. This result may also be very beneficial for colorectal malignancy because any possible toxicity outside of the area of interest can be minimized.[5]

Cardiovascular Disease

The global rise in obesity is associated with an increase in morbidity and mortality owing to cardiovascular disease (CVD), which remains the primary cause of death. Obesity accelerates both CVD-related morbidity and mortality in partthrough impaired metabolism, which results in alterations to bloodbiomarkers of glucose and cholesterol homeostasis, modifications in adipokine balance of adiponectin and leptin, elevated homocysteine and increased oxidative stress. Obesity is associated with elevated homocysteine levels when compared with normal weight counterparts. Curcumin reduces homocysteine concentrations by 3.6 mg/mL, or a 29.5% decrease, in obese men. Elevated homocysteine is associated with increased morbidity and mortality independent of traditional risk factors for CVD. Notably, adding homocysteine to the risk profile has been shown to improve risk predictions by 12.9% and 18.3% in the Multi-Ethnic Study of Atherosclerosis (MESA) and National Health and Nutrition Examination Survey (NHANES) cohorts, respectively. Thus, the reduction of homocysteine concentrations with curcumin supplementation has important clinical implications for lowering obesity-related CVD risk. Although the enhanced curcumin formulation lowered homocysteine in this cohort of obese men, the mechanisms by which this occurred are less clear. Increased plasma homocysteine is a result of complex metabolic processes, which are associated with lower amounts of betaine. As such, betaine supplementation reduces homocysteine concentrations in patients with CVD.[6] The anti-thrombotic, anti-proliferative, and anti-inflammatory effects of curcumin, together with the effect of curcumin in decreasing serum cholesterol levels, may protect against the pathological changes that occur with atherosclerosis. The p300-HAT inhibitory effects of curcumin have been demonstrated to ameliorate the development of cardiac hypertrophy and heart failure in animal models.

Oral Lichens Planus

Oral lichen planus (OLP) is a relatively common immunological mucocutaneous disease that causes pain and poor quality of life. Curcumin has been reported to be a safe and effective treatment for OLP.[8] Oral lichen planus (OLP) is characterized by hyperkeratosis and inflammation, and can involve the buccal mucosa and the gums. In two studies, capsules of Curcumin C3 Complex® were studied as a possible treatment for OLP. In the first study, 100 subjects were enrolled to assess if 2000 mg/day of curcumin improved the clinical severity of OLP. There was no significant difference between the treatment and placebo groups, and the study was ended early. In a similar trial in 2012, 10 men and 23 women with OLP were given 6000 mg/day of curcumin and statistically significant improvement was found at this higher do. The severity of OLP was lower in the curcuminoid group versus placebo, and no signs of toxicity were found.[9]

Uveitis

Uveitis is an inflammation of the uvea, the middle layer of the eye. Uveitis is a major cause of visual impairment and has been estimated to account for 10% to 15% of all cases of total blindness.[10] Curcumin has multiple modes of action. It weakly inhibits prostaglandin synthesis, it has a strong stabilizing effect on the lysosomal membrane, it has an inhibitory action on leukotrienes and thromboxane B4 without affecting prostacyclin synthesis. Moreover, curcumin has been reported to sensitize the tissues to endogenous corticoids and to increase adrenal steroidogenesis. It also has strong antioxidant and free radical scavenging properties. It has also been shown to inhibit neutrophil response and to induce nitric oxide synthetase in activated macrophages. Curcumin has been shown to increase IgG levels in rats following its oral administration with diet for 5 weeks. Its protective effect in rat against cyclophosphamide-induced lung toxicity is also documented. Curcumin is known to possess antifibrinolytic activity. The beneficial effect of curcumin could be due to one or more of the above properties. The antifibrinolytic activity may be responsible for breaking the anterior and the posterior synechiae. The main advantage of curcumin was that it acted like a corticosteroid but without any side effects of its own. Corticosteroids have been the main stay of the treatment of CAU so far. In fact, no patient reported any side effect of this drug. In addition, recurrences were almost equal in PPD reactors and non-reactors. Furthermore, HLA positivity did not appear to alter the course of CAU in this study. In view of the similar clinical results with curcumin and the standard corticosteroid therapy but without any side effects with the test drug, a larger double blind clinical trial in cases of chronic anterior uveitis is warranted to rule out any element of bias.[11]

Psoriasis

Psoriasis is a chronic, inflammatory, cell mediated disease, which involves the skin, and sometimes joints,

bones, tendons, ligaments, nails, and mucosal membranes. Although it may represent with different clinical variants, the most commonly described is the "vulgaris" one, which is characterized by erythematous round or oval lesions, covered by white-silvery scales.[12] The efficacy of the study drug was low with an intention-to-treat response rate of 16.7% (95% CI: 2%, 48%) and did not justify continuation of the study based on our a priori termination rules. However, those who did respond achieved excellent responses of 83% and 88% improvement in PASI scores at week 12. The CI for the 16.7% response rate is wide as a result of the small sample size and, therefore, we cannot exclude the possibility that the response observed is caused by a placebo effect or the natural history of skin disease in these participants rather than efficacy of the drug itself. In vitro curcumin has been shown to block pathways necessary to develop psoriasis, oral curcumin was well tolerated by patients with psoriasis.[13]

Acute Coronary Syndrome

The involvement of anti-inflammatory effects of curcumin in prevention of acute coronary syndromes (ACS) (i.e. unstable angina and myocardial infarction). ACS is the leading cause of death in both developed and developing countries. Coronary events often result from thrombi that form because of physical disruption of the atherosclerotic plaque. However, despite lipid lowing therapy with statins, significant numbers of cardiovascular events continue to occur indicating the need for additional agents for atherosclerosis management. curcumin therapy can stabilize vulnerable 'rupture-prone' plaques by normalizing plaque properties. Thus, co-administration of curcumin along with other present options may prove to be a useful and potent natural plaque stabilizing approach in the prevention of ACS. The inhibitory effects of curcumin on diverse range of inflammatory markers which have an established role in plaque destabilization and occurrence of ACS, the use of curcumin as a new intervention for second prevention of future cardiovascular events. Despite aggressive thrombolytic, anticoagulant, and antiplatelet therapy, patients with ACS still have a 12% to 16% incidence of major cardiac events at 4 to 6 months after hospital discharge.Therefore curcumin can be useful for prevention of those cardiac events. Furthermore administration of low-dose curcumin decreased total cholesterol level and LDL cholesterol level in ACS patients.[14]

Renal Conditions

Diabetic nephropathy (DN) is one of the main causes of end stage renal disease. DN is characterized by the presence of hyperfiltration, glomerular hypertrophy, tubular albuminuria, mesangial matrix expansion, and increased expression of extra cellular matrix proteins. Curcumin treatment attenuates proteinuria and improves creatinine clearance after 3 weeks of streptozotocin injection. Curcumin derivatives have also been proved to be effective in ameliorating diabetic nephropathy. Curcumin prevented interstitial, glomerular, tubular epithelial and endothelial cellular injuries by decreasing of iNOS and p65 (the active subunit of NF-κB) expression and serum nitric oxide levels. Curcumin is able to prevent mitochondrial dysfunction associated to renal injury. Curcumin is able to prevent lipid peroxidation and the decrease in the following mitochondrial determinations: oxygen consumption, activity of complexes I, II, II-III and V, activity of aconitase and antioxidant enzymes, GSH content, membrane potential, calcium retention and ATP content. Curcumin has been shown also to be able to reduce inflammatory process by reducing the inflammatory transcription factors such as NF- κB and TNF-α.[15]

Lupus Nephritis

Lupus nephritis an autoimmune disease characterized by polyclonal B-cell hyperactivity and defective T-cell function, which is responsive to immunosuppressive and steroids therapy, but often pursues a relapsing and, in a minority, a refractory course.[16] It is well known that when B cells come into contact with T helper 1 cells, they secrete IgG2a and IgG3, but that upon interaction with T helper 2 cells, they produce IgG1 isotypes. The present findings demonstrated that NZB/W mice treated with curcumin showed decreased levels of IgG1 and IgG2a. The production of IgG3 was slightly down-regulated. These results indicate that curcumin exerts immunosuppressive effects on both T helper 1 and T helper 2 immune responses and suggest that CD4+CD25+ Treg cells could be involved in this suppressive effect of curcumin. Indeed, the present study demonstrated that NZB/W mice treated with curcumin have up-regulated Foxp3 expression, which is a transcription factor specifically expressed in CD4+CD25+ Treg cells that programme its development and function.[17]

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is an exceedingly common and debilitating gastrointestinal condition, characterized by chronic abdominal pain and a change in the frequency or form of stool.Curcumin beneficial effects in IBS are likely related to its unique combination of anti-oxidant and anti-inflammatory activities. Curcumin has been shown to attenuate circulating interleukin-6 (IL-6) levels and regulate key mediators of cellular inflammation, including 5-lipoxygenase (5-LOX), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Current studies on patients with IBS have highlighted a pro-inflammatory phenotype in these patients, with higher circulating IL-6 levels, immune activation and chronic, low-grade, subclinical mucosal inflammation. Curcumin also has demonstrated mucosal protective effects in rat models of colitisand reported efficacy, even in patients with inflammatory bowel disease. Curcumin administration increased serotonin (5-HT), brain-derived neurotrophic factor (BDNF) and phosphorylation of cAMP response

element-binding protein (pCREB) expression in the hippocampus and colon.[18]

Diabetes mellitus

Diabetes mellitus (DM) is characterized by chronic hyperglycemia and its developed diabetic complications, in particular, macroangiopathy and microangiopathy. These pathophysiological complications are often responsible for a decreased quality of life in diabetic patients. The 4.45-fold increase in superoxide production in diabetic vasculature could be attenuated by daily oral curcumin supplementation. However, there was no difference between the low and high doses of curcumin in terms of reducing superoxide production at the diabetic vascular wall. Both doses of curcumin examined in this study were able to decrease superoxide production by almost two-fold. Curcumin has been reported as a potent scavenger of a variety of ROS[25], exhibiting anti-inflammatory activity as well as antioxidant properties.[17,26-29] The phenolic (OH) structure of curcumin was believed to be essential for curcumin's anti-oxidant activity.[19]

Crohn's Diseases

Crohn's Disease (CD) and Ulcerative Colitis (UC) result from an overreaction of the bowel to multifactorial stimuli leading to discomfort, pain, and it is associated with high morbidity and lethality. Crohn's Disease (DC) and Ulcerative Colitis (UC) are Inflammatory Bowel Diseases (IBD) and are characterized by chronic and destructive inflammatory process of the gastrointestinal tract. Curcuma longa may bring unique benefits in the inflammatory processes and oxidative stress. Turmeric compounds may reduce oxidative stress, neutrophil influx, and ROS-related cellular damage, and inhibits migration of neutrophils and iNOS in the intestine and liver of animals with colitis reducing oxidative damage in the intestine in 12 IBD patients. It may also improve micro and macroscopically lesions, a decrease of myeloperoxidase and malonaldehyde, prevent the apoptosis of intestinal cells and also induce the restoration of the immune reaction of mitogen-activated protein kinase (MAPK). For these reasoncurcumin decreases injury to the colon and is still associated with inflammatory reactions, lipid peroxidation, apoptosis, and further modulates p38 and JNK-MAPK.[20]

Vitiligo

Vitiligo is a depigmenting disorder characterized by the development of white patches with a varying distribution in the body. The appearance of skin lesions is due to the loss of functional melanocytes from the epidermis. Curcumin treatment protects cells from mitochondrial damage and apoptosis by: (i) inhibiting caspase and Smac/DIABLO activation, inhibiting p38 phosphorylation and increasing ERK activity, (ii) restoring mitochondrial permeability and mitochondrial membrane potential, and (iii) inhibiting NF-kB activation. Considering the consequences of aberrant NF-kB and MAPK signalling in keratinocytes from perilesional vitiligo skin, a major goal of our work is to develop specific inhibitors of these pathways. Curcumin may therefore represent a valid approach to limit keratinocyte damage in perilesional vitiligo skin and could be used as a therapeutical tool to protect against vitiligo progression.[21]

Arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that primarily affects various body joints and causes progressive destruction of articular structures, particularly, the cartilage and bone.[22] the mechanism by which curcumin elicits its effects, it does appear to be beneficial to several aspects of OA, as suggested by a recent systematic review and meta-analysis that concluded: This systematic review and meta-analysis provided scientific evidence that 8–12 weeks of standardized turmeric extracts (typically 1000 mg/day of curcumin) treatment can reduce arthritis symptoms (mainly pain and inflammation-related symptoms) and result in similar improvements in the symptoms as ibuprofen and diclofenac sodium. Therefore, turmeric extracts and curcumin can be recommended for alleviating the symptoms of arthritis, especially osteoarthritis.[23]

CONCLUSION

Curcumin is a great blessing as miraculous drug in 20th century as this drug is well known to human being from many centuries and now in this 20th century it really helpful to treat chronic disease conditions and so that Curcumin has received world wide attention for its multifunctional effect on health. Now a day's recent advance regarding Curcumin formulations may become great boon against all chronic disease conditions. In this review we have highlighted different diseases which can be cure by miraculous drug Curcumin.

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