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A comprehensive update on successful clinical trials of curcumin

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Abstract: Curcumin, an important constituent of turmeric used in the traditional medicinal system has suffered considerable controversy. Classification as pan-assay interference compounds and invalid metabolic panaceas contributed toward its inability as a lead compound. The conclusions were drawn on the basis of various clinical trials that failed to prove the medicinal effect of curcumin. The inclusion of high throughput screening studies also contributed to this entitlement. Still, researchers didn't put an end to explore on curcumin probably due to the traditionally accepted role of turmeric in medicines. Extensive investigation on curcumin multiplied enormously and more than 27,000 documents results in Scopus with one click on curcumin. It being a pharmacologically significant molecule or "Much Ado about Nothing" will always be debatable. In the present review, we have compiled successful clinical trials with curcumin in several diseased conditions including the results of such clinical trials where the prescribed medicine failed to respond.

Key-words: Curcumin, pharmacological effects, clinical trials, solid gold, curecumin, golden milk.

1. Background

To fight against COVID-19, the prescription of golden milk by the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Sidha, and Homeopathy) as an immunity booster motivated us to explore the active ingredient of turmeric i.e. curcumin. Turmeric has been in NEWS in the last decade of the 20th century due to its patent controversy where the Council of Scientific and Industrial Research (CSIR), INDIA revoked the US patent 540154. During our research we came across different statuses attributed to this molecule and found that the molecule enjoys the status of being a panacea [1-2], solid gold [3], curecumin [2], however, its dark side [4] is also reported. The basis of our study was the miniperspective by Nelson et. al. [5] where the authors in a phase-wise manner described the curcumin as a "failed missile", and pan-assay interference compounds (PAINS), invalid metabolic panaceas (IMPS), and poor lead compound; and curcumin related research as "hyperbolic black hole of natural product". Moreover, the authors opined that the analogs of curcumin are based on a weak foundation. In the review, the question

was raised about being it is a "solid gold" or "curecumin". The conclusions of curcumin research as 'Much Ado about Nothing' were drawn based on various unsuccessful clinical trials [5]. However, the authors did not exclude the possibility that "an extract of crude turmeric might have beneficial effects on human health". In this review, we have to present various successful clinical investigations where curcumin has been found effective individually or in combination with other drugs.

2. Occurrence and Historical background

Curcumin is a yellowish-orange compound also called diferulolylmethane with IUPAC name 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxy phenyl)-(1E,6E). It is a polyphenolic compound extracted from the rhizomes of Curcuma longa, an herb that belongs to the ginger family, Zingiberaceae, it is native to tropical South Asia. The medicinal use of turmeric was reported in Sushruta Samhita, one of the elementary books of the traditional Indian medicinal system; Ayurveda first [6-7]. In ancient times, Chinese, Egypt, and Arabians have also used turmeric to cure colds, parasitic diseases, leprosy, skin disease, inflammatory conditions including arthritis, bronchitis, inflammation of the bladder, urinary tract infections liver, and kidney, and diarrhea [1, 8-10].

India has gained recognition as a global leader in the production, exportation, and consumption of turmeric. 80% out of the total production of turmeric comes from India and the rest of it, from South Asian countries like China, Egypt, Sri Lanka, and other tropical countries [2]. The excellent quality and high content of its bioactive compound curcumin make Indian turmeric preeminent on the international platform. Erode; a city of Tamil Nadu; also known as "Turmeric City" or "Yellow City" is the world's largest producer of it. More than 200 well-known compounds are present in turmeric; of which terpenoids, alkaloids, sterols, volatile oil, α-linolenic acid, ω-3 fatty acid, and other phenolic compounds are the prominent ones. Curcuminoids are the diarylheptanoids, the major biologically active constituents of turmeric including curcumin that constitutes only 3-5% of turmeric has been found responsible for biological activity. Commercial curcumin contains three components: curcumin (71.5%), demethoxycurcumin (19.4%) and bis-demethoxycurcumin (9.1%) show in fig.1 [7, 11-12].

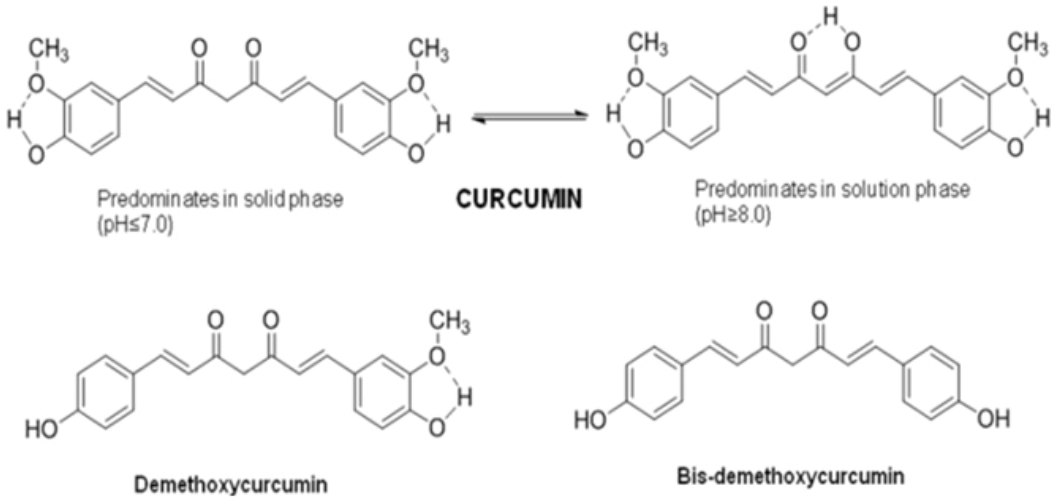

Figure1. Structures of curcuminoids

In 1818 for the first time, curcumin was isolated by Vogel and Pelletier, The crystalline form was reported by Daube in 1870 [13]. The structural skeleton as feruloylmethane was confirmed by Lampe in 1910 and the chemical structure was confirmed in 1973 [14].

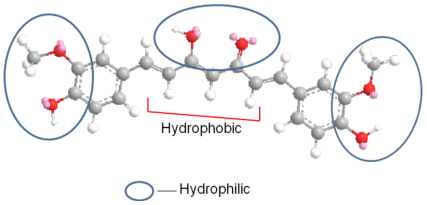

Figure2: Feasible centers of curcumin to interact with biomolecules

3. General Structural Information

The molecular formula of curcumin is $C_{21}H_{20}O_6$ and its molecular weight is 368.37a.m.u. It has poor aqueous solubility but is easily soluble in acetone, methanol, dimethylsulfoxide, dichloromethane, ethanol, ethyl acetate, and chloroform. Spectrophotometrically, the maximum absorption of curcumin (^max) is around 420 nm. Curcumin has more probability to interact with biomolecules due to its interesting structure. The diverse pharmacological activities of curcumin have been attributed to its structural diversity. The molecule has electron-rich moieties as well as electron-deficient centers, depicted in fig. 2. The symmetrical geometry of curcumin offers a conjugated system that can easy to access biomolecules in any direction without any steric restriction and may be one of the reasons for its interaction with different molecular targets.

It exhibits keto-enol tautomerism, keto geometry in acidic and neutral medium, and stable enolic geometry in alkaline medium. The simultaneous presence of the active methylene group in the keto-form renders the attack of the base resulting in numerous other possibilities of its interaction with various molecular targets. The fact that curcumin in solution exists in its enolic form is mainly responsible for the radical-scavenging potency of curcumin [11, 15]. It exhibits diverse pharmacological activities like antioxidant, antiviral, antifungal, anti-Alzheimer, anti-inflammatory, immunomodulatory, anti-tumor, anti-diabetic, and anti-rheumatic activities [16-19]. Curcumin is proved to be a hepato-, cardio-, and neuroprotective molecule. It is also reported as a thrombosis suppressing and myocardial Infarction protective molecule [20-25].

Figure 3: Titles acquired by Curcumin with time

Before going to the actual section concerning clinical trials of curcumin, we were curious to know about the existing reputation of curcumin in the scientific fraternity. To achieve our goals we conducted a survey on Scopus about the number of reports on curcumin. Since 2015, where Nelson et al reported around 15,000 references, the list grew to more than 27,000. Table 1 comprises a compilation of different studies carried out with curcumin. It can be observed that curcumin has received a significant amount of coverage and discussion. Most of it is related to its contribution is toward pharmacological effect.

It can be observed from this study that searches related to curcumin as PAINS, IMP, false clinical test and false test are not more than ten studies. However, the reports on the pharmacological activities of curcumin are quite large. These studies indicate the significance of curcumin research. In the succeeding section, various successful clinical trials have been listed where curcumin has been found to produce a

Table 1: Results of Scopus search on curcumin

S.No.	TITLE –ABS-KEY	Document results
1.	Curcumin	27,317
2.	Curcumin, Metabolism	6881
3.	Curcumin, Antioxidant	6397
4.	Curcumin, Oxidative stress	3744
5.	Curcumin, Inflammation	3573
6.	Curcumin, Bioavailability	2917
7.	Curcumin, Nanoparticles	2796
8.	Curcumin, Alzheimer	1878
9.	Curcumin, Neuroprotective	1072
10.	Curcumin, Antimicrobial	886
11.	Curcumin, Micelles	834
12.	Curcumin, pains (inflammation)	670
13.	Curcumin, Wound-healing	642
14.	Curcumin, Emulsions	606
15.	Curcumin, Lipoproteins	512
16.	Curcumin, Antiviral	430
17.	Curcumin, Anti-bacterial	426
18.	Curcumin, Cancer, tumor, metastasis & invasion	363
19.	Curcumin, Cosmetics	173
20.	Curcumin, Solubilization	143
21.	Curcumin, Lipid-lowering	95
22.	Curcumin, Radioprotective	84
23.	Curcumin, Anti-HIV	73
24.	Curcumin, Arrhythmia	57
25.	Curcumin, Anthelmintic	51
26.	Curcumin, Antiobesity	39
27.	Curcumin, Muscular dystrophy	38
28.	Curcumin, Anti-fungal	29
29.	Curcumin, Anti-mutagenic	19
30.	Curcumin, Anti-parasitic	15
31.	Curcumin, false test	10
32.	Curcumin, nematocidal	07
33.	Curcumin, pan assay interference	07
34.	Curcumin, IMPS	05
35.	Curcumin, false clinical test	04

pharmacological effect.

4. Clinical studies of Curcumin

Over the last two decades, clinical trials to explore in-vitro and in-vivo chemopreventive and therapeutic potential have increased. These trials were concerned with various ailments including inflammatory, neurodegenerative, and other disorders; and addressed the pharmacokinetics behavior, safety, and tolerance by animals as well as humans. Various pharmacological activities related to curcumin are reviewed as under:

4.1 Anti-oxidant Effect:

The antioxidant activity of curcumin has been accredited to hydrogens of the central methylene groups and the phenolic groups. It is a potent scavenger of reactive oxygen species including -OH hydroxyl radicals, O^-_2 superoxide anion radicals, and $-NO_2$ nitrogen dioxide radicals; appraised for protection against oxidative damage of DNA and proteins related to multiple chronic diseases such as neurodegenerative, atherosclerosis, cancer, and aging [26]. Curcumin exhibits anti-oxidant potential comparable to Vitamin C and E [27-28]; which lowers oxidative stress in animals. Oxidative stress is the prime factor for leading the pathogenesis of different ailments including hemorrhage, hypoxia, neural cell injury, myocardial ischemia, cerebral ischemia-reperfusion injury, and cancer [29] and is also responsible for inhibiting the lipid peroxidation in different animal models [30-31]. The efficacy and potential beneficial effects of curcumin in anti-depression and other psychiatric disorders are studied by Yinfeng et al. and compiled the effective various mechanisms including the modulation of neurotransmitter levels including DA, NE, 5-HIAA, moderating hypothalamus-pituitary-adrenal (HPA) disturbances, inhibiting the expression of monoamine oxidase enzymes, enhancing neurogenesis and neuronal plasticity typically increased BDNF levels [32].

Egan et al. found that curcumin in the homozygous DeltaF508 cystic fibrosis transmembrane conductance regulator (CFTR) also inhibited the multiplication associated with cystic fibrosis. [33]. A small study on curcumin exhibited that daily administration of 500mg curcumin to humans for 7 days lead to a significant increase (29%) in HDL cholesterol, a 12% decrease in total body cholesterol, and a 33% decrease in lipid peroxides [34]. In another study, administration of 10mg curcumin twice daily lowered the serum LDL and increased HDL significantly [35]. Alwi et al, (2008) reported the effect of varying doses of curcumin 0.045-0.18g/day on 70 patients having acute coronary syndrome; resulting in lowering the serum LDL and total cholesterol, and increased HDL and triglyceride content in patients [36]. A study on 21 patients of β-Thalassemia/Hb with 0.5g/day of curcumin extract for 12 months oral administration improved the oxidative stress parameters significantly [37].

A recent study has assessed that lipidated curcumin in healthy middle-aged persons (40-60 years old) with low-dose 80mg/day and placebo for 4 weeks possessed health-promoting efficacy [38]. Curcumin produced a drop-off in salivary amylase and plasma level of triglycerides, alanine aminotransferase, and beta-amyloid also. Therefore, curcumin administration increased the salivary radical scavenging capacities, myeloperoxidase, and nitric oxide production, and plasma catalase activities.

4.2. Immunomodulatory Effect:

Zuccotti et al. [39] examined the immunological and clinical effects of oral supplementation of lactoferrin and curcumin (LC) in healthy children with recurrent respiratory tract infections.

It was observed that infections decreased in children receiving LC. On LC supplementation skewed the maturation of CD8+T cells that responsible for adapting immunity increased. Additionally, CD14+, toll-like receptor (TLR) 2-expressing cells were found to be improved whereas CD14+/TLR4+ were diminished; and production of IL10 by CD14+ cells was reduced in children receiving LC. The authors enlightened the immune modulation by giving LC supplementation and gave a proposal to use it for clinical benefit.

The regulatory immune effect of curcumin in hepatic cirrhosis caused by carbon tetrachloride (CCl_4) injections in the rat model has recently been evaluated by Abo-Zaid et al [40]. The frequent injections of CCl_4 in experimental animals for 6 weeks induced chronic liver fibrosis. They have been subdivided into five groups: 1st group was injected with normal saline, 2nd group with CCl_4, 3rd, 4th, and 5th groups were injected with 3 ml/kg CCl_4 (i.p.), and 250, 200, and 150 mg/kg supplemented with curcumin twice weekly for 6 weeks respectively. The results showed that the estimated concentrations of IL-10 were significantly higher in the group which received curcumin compared to the CCl_4 group, whereas the concentrations of TNF-α and TGF-1β were significantly lower than those of the CCl_4 group. Also, the groups treated with curcumin almost retained the normal structure of liver tissues. The authors concluded that curcumin inhibited hepatic fibrosis and liver fibrogenesis by controlling the function of the immune system without any side effects [40]. In another study, curcumin therapy enhanced the lymphocyte immune response by increasing IgG production when experiments were performed on rat splenic lymphocytes [41].

In the immunomodulation of normal cells and transformed T cells, curcumin plays a crucial role that adversely influences the cell proliferation of these cells by suppressing the expression of the IL-2 gene and inhibiting the activation of NF-κB [42]. These findings indicate curcumin's antiproliferative activity against T cells and may be significant to T-cell leukemia.

In a recent study by Pawar et al. 2021, the effect of the oral supplement of curcumin with piperine as adjuvant therapy for the treatment of COVID-19 has been evaluated. A double-blind, randomized, controlled trial at a 30-bed dedicated COVID health care center was examined by receiving the curcumin (525mg) with piperine (2.5mg) in tablet form twice a day to the patients. Patients with mild, moderate, and severe symptoms who received curcumin/piperine treatment showed early symptomatic recovery (fever, cough, sore throat, and breathlessness), less deterioration, fewer red flag signs, better ability to maintain oxygen saturation above 94% on room air, and better clinical outcomes compared to patients of the control group. The authors concluded that administration of oral curcumin with piperine as an adjuvant symptomatic therapy in COVID-19 treatment could substantially reduce morbidity and mortality, and ease the logistical and supply-related burdens on the healthcare system. Curcumin could be a safe and natural therapeutic option to prevent Post-Covid thromboembolic events [43].

Elyasi et al. has been also worked on the oral nano-curcumin formulation for the treatment of COVID-19. In a triple-blind randomized placebo-controlled clinical trial, 60 mild to moderate COVID-19 patients in the outpatient setting who fulfilled the inclusion criteria were randomly allocated to treatment (n = 30) group to receive oral nanocurcumin formulation (Sinacurcumin soft gel which contains 40 mg curcuminoids as nanomicelles), two soft gels twice a day after food for 2 weeks or placebo (n = 30) group. All symptoms except sore throat resolved faster in the treatment group and the difference was significant for chills, cough, and smell and taste disturbances. The CRP serum

level was lower in the treatment group at the end of two weeks and the lymphocyte count was significantly higher in the treatment group. No significant adverse reaction was reported in the treatment group [44].

4.3. Anti-inflammatory Effect:

Curcumin is an interesting bioactive molecule efficient in interacting with numerous molecular targets related to inflammation. α, β-unsaturation present in curcumin structure plays an important role as an anti-inflammatory moiety. It decreases the inflammation associated with experimental colitis and down-regulates the elevation of Myeloperoxidase activity.

It is an established marker for inflammatory cells. It is also capable to suppress lipoxygenase, tumor necrosis factor-alpha (TNF-α), inhibiting the production of cytokines, and migration inhibitory proteins [45-47]. It also inhibits cellular proliferation, transformation, and tumorigenesis because inflammation is a critical component of tumor progression [48]. The inhibitory effect of curcumin on cyclooxygenase (COX), a key enzyme responsible for the conversion of arachidonic acid to prostaglandin, is also known to suppress prostaglandin synthesis [49]. Curcumin is found to inhibit cathepsins, lysosomal cysteine proteases as well [50].

Curcumin's anti-inflammatory activity was found in similar steroidal and non-steroidal drugs. Literature reveals that non-steroidal anti-inflammatory drugs (NSAIDs) mitigate the risk of Alzheimer's. Simultaneously long-term use of NSAIDs would toxicate the renal function, liver, and gastrointestinal areas. Curcumin provides a better substitute to NSAIDs due to its better anti-oxidant effect of scavenging free radicals without toxicating the organs [51].

4.3.1. Alzheimer Disease

Alzheimer's disease (AD): results of chronic inflammation due to activation of macrophages and increase the amount of cell signaling proteins that lead to cell damage and death. AD is a chronic neurodegenerative disease that is associated with plaques and neurofibrillary tangles in the brain. One study by Jiang et al. (2007), reported a significantly reduced infarct volume, the water content of the brain, and mortality, and improved neurological deficit when administered a single injection of curcumin (1 and 2 mg/Kg, i.v.) 30 min after focal cerebral ischemia/reperfusion in rats [52]. In another study, Rathore et al. (2007) [53] reported that Curcuma oil (500mg/Kg) was given by i.p. administration 15min before, 2 hr middle cerebral artery occlusion, followed by 24 hr reflow in rats. The resultant significantly reduced oxidative stress, infarct volume, and improved neurological deficit. Therefore, the authors concluded that curcuma oil would be a promising agent for the treatment of cerebral stroke and other oxidative stress-related conditions.

4.3.2. Arthritis

Arthritis, chronic inflammation in joints usually produces pain and may lead to crippling. It exhibits more than 100 different forms including rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and related autoimmune diseases. For the treatment of arthritis, the generally used therapeutics are analgesics, steroids, and NSAIDs, which can reduce the symptoms of severe pain and inflammation. However, owing to insufficient pain relief, immune disruptions, and other adverse side effects, these medications cannot be used for extended use. Curcumin is a potential alternative medicine for Arthritis due to lesser side effects, safety, and non-toxicity [54-55].

4.3.3. Uveitis

The major cause of visual impairment is Uveitis, an inflammation of the eye. In some cases, that is accounted for total blindness. Corticosteroids are commonly used to treat uveitis, but their use is limited due to adverse side effects. In one study, curcumin (375 mg) was administered orally to 53 patients three times a day for 12 weeks [56]. Its efficacy against recurrent anterior uveitis was improved only after 2 weeks of treatment. This research showed that curcumin might be the therapeutic agent for chronic anterior uveitis.

4.3.4. Peptic ulcer

A peptic ulcer is the most common ulcer that develops on the inner lining of the esophagus, stomach, and small intestine. The treatment line is to kill H. pylori, by using antibiotics, proton pump inhibitors, and histamine receptor blockers. A study on 60 patients was conducted for 6 to 12 weeks, where 30 patients have given turmeric 250mg four times per day, whereas 30 mL antacid four times per day was given to other 30 patients. Both exhibited significant improvement in gastric ulcer patients [57].

In another study, 25 patients with H. pylori infection were treated with curcumin (25mg), bovine lactoferrin (100mg), N-acetylcysteine (600mg), and pantoprazole (20mg) twice a day for 1-week. After the treatment course, 3 out of 25 patients were cured and significantly decreased in the overall severity of symptoms and serum pepsinogens (sPGI and sPGII) levels. The researchers concluded that the experiment was not productive for the H. pylori eradication but a significant decrease in serologic signs of gastric inflammation and improvement in dyspeptic symptoms were shown after 2 months [58].

4.3.5. Inflammatory Bowel Disease

The chronic inflammation of the digestive tract causes Inflammatory Bowel Disease (IBD). The major types of IBD are ulcerative colitis and Crohn's disease. Ulcerative colitis is long-lasting inflammation in the innermost lining of the intestine especially the colon and rectum and Crohn's disease may involve any part of the digestive tract. For the treatment of IBD, anti-inflammatory drugs, immune system suppressors, TNF blockers, and antibiotics are generally used [59]. In one study, curcumin was administered to 5 patients with ulcerative proctitis and 5 patients with Crohn's disease. The patients with ulcerative proctitis were received 550mg of curcumin twice daily for 1st month and thrice daily for the 2nd month. Whereas patients with Crohn's disease were given 360mg of curcumin three times daily for 1 month and four times daily for the second month. A significant decrease was observed in both the cases in symptoms and inflammatory indices CRP [60].

In a systematic review relating to IBD, Coelho et al. summarized the different studies and revealed that curcumin was well tolerated and was not associated with any major side effects. The studies have shown that curcumin when provided with standard therapies, can be a safe, efficient, and complementary therapy to maintain remission in the UC [61]. In another recent study, 500 mg/day of curcumin, along with prednisone associated with clinical and endoscopic remission, was administered orally to a 60-year-old woman who had been suffering for 17 years. For the treatment, multiple mesalamine preparations, sulfasalazine, and steroid enemas were used but were not found effective. 40mg of prednisone with 500mg/day of curcumin was given to the patient for 1 year. The colonoscopy displayed no ulceration and biopsies were reliable with chronic inactive ulcerative colitis. These studies represent a relevant and alternative treatment in the management of chronic ulcerative colitis using curcumin [62].

Fallahi et al. (2021) recently reported a study with IBD patients; oral administration of curcumin dosage was given i.e. 550 mg thrice daily for one month, and 1 g twice daily for six months. The results of the study concluded that curcumin would be utilized as a therapeutic agent for the treatment of IBDs [63].

4.4. Anti-Cancer Effect:

Cancer is a multi-stage process that has a variety of events and resulting from the multi-stage dysregulation of more than 500 genes in cell signaling pathways. Around 18,06,590 individuals are expected to diagnose various cancer forms in the U.S., according to the American Cancer Society, and around 6,06,520 are predicted to die in 2020 [64]. Cancer therapy describes the treatment of cancer with surgery, chemotherapy, radiotherapy, and monotargeted therapies. Currently, available targeted cancers therapeutic have adverse side effects and are expensive too. Therefore, there is a need to design drugs that can modulate multiple targets and is cost-effective. Curcumin has provided hope of being a unique therapeutic molecule and exhibited pharmacological activities against various cancer types in human clinical trials.

The anti-carcinogenic effect of curcumin on the molecular basis is ascribed to its effect on numerous targets including growth regulators, transcription factors, apoptosis, angiogenesis regulators, adhesion molecules, and cellular signaling pathways. It suppresses the activation of nuclear factor-kB (NF-kB) and inhibits the production of cytokines, protein kinase, and TNF [50, 67]. Curcumin acts as Michael acceptors due to the presence of two α,β-unsaturated moieties i.e. bis-conjugated enone structure, which may be responsible for its anti-cancer activities; and makes it readily available for various nucleophilic groups of enzymes and causes enzyme inhibition. Owing to its inhibitory effect against human malignancies, this molecule becomes attractive for cancer researchers [11, 66].

Curcumin radically acts at different phases of cancer; it blocks the transformation of cancer cells that are responsible for tumor promotion, angiogenesis, and invasion. The anti-cancer activity of curcumin shows its ability to suppress the activity of many common in-vitro and in-vivo mutagens and carcinogens in different types of cells. Curcumin inhibits different types of proliferating cells including ovarian, breast, prostate, skin, gastric, duodenal, colon, T- and B cell lymphomas, and oral epithelial carcinoma cells [67-68].

In a vibrant biological context, the effect of curcumin in evaluating in-vitro and in-vivo studies of specific cancer cell lines is emphasized by the different variables to assume the precise findings. Their emergence was led via interaction with the microenvironment of the tumor and pervaded in the tumor cell tissue of origin which is powered by oncogenotype [69].

Curcumin was shown to down-regulate the production of pro-inflammatory cytokines TNF- α, inhibited the activation of NF-kB and activator protein-1 (AP-1), which regulate the genes for pro-inflammatory mediators and protect antioxidant genes [70-71].

Curcumin is also a potent therapeutic agent useful against pathogenic processes initiated by H. pylori infection owing to inhibit the activation of NF-kB [72]. The comprehensive findings of several clinical trials and their studies have provided a strong base for the study in clinical oncology based on the implementation of curcumin [73]. Various molecular targets of curcumin are compiled in fig.4.

4.4.1. Colorectal Cancer

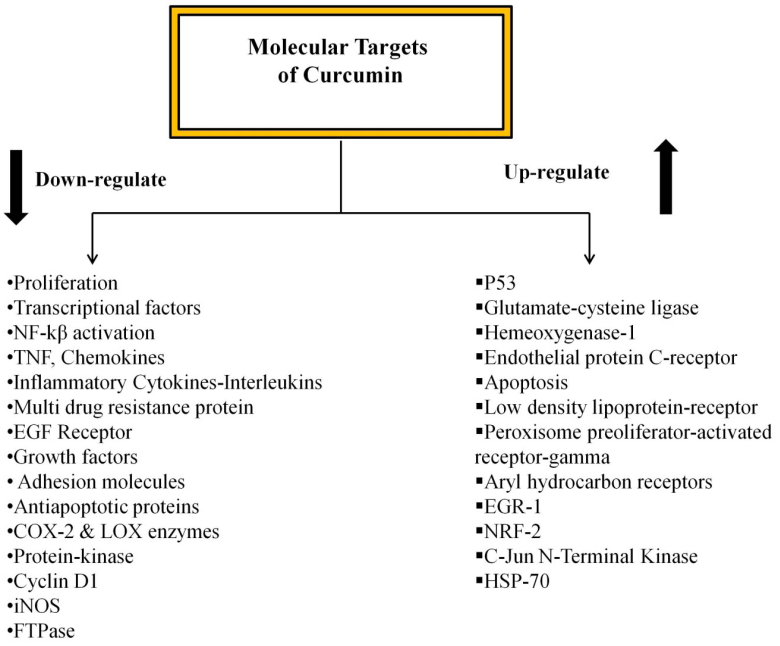

Figure4. Various molecular targets of curcumin in biological activities [2, 74]

The 2nd leading cause of cancer deaths in women and the 3rd in men is Colorectal Cancer (CRC). Nearly 1, 04,610 new cases of colon cancer are expected in the U.S., according to an estimation, and about 53,200 are likely to die of this disease in 2020 [64]. Curcumin can be one of the new strategies needed to improve the current status of CRC in patients as the potential of curcumin for CRC in several clinical trials has been demonstrated. In one such study, a 440 to 2200 mg daily dose of Curcuma extract (containing 36-180 mg of curcumin) was given to 15 patients for 4 months. Glutathione S-transferase activity and M1G levels have been assessed in the blood cells of patients. Given Curcuma extract dose was found well-tolerated while dose-limiting morbidness was not observed. A 59 percent decrease in the activity of lymphocytic glutathione S-transferase was observed when 440 mg of curcuma extract containing 36 mg of curcumin was delivered for 29 days [60]. In another report, 15 patients with advanced refractory CRC were given a dose of curcumin ranging from 0.45 to 3.6g/day for up to 4 months. A 62% and 57% decrease in the production of inducible prostaglandin E2 in blood samples when 3.6g daily dose of curcumin was given on days 1 and 29, respectively [75]. Curcumin was administered 36mg orally thrice a day for 10-30 days in another recent report. This dose increased apoptotic cell count, body weight, decreased serum level of TNF-alpha, and improved tumor tissue expression of p53. The authors indicated that curcumin therapy, through the mechanism of increased p53 expression in tumor cells and tissues, can improve the ordinary fitness of CRC patients. However, to validate these arguments, further studies are required [76].

In short, the findings described in this section illustrate the safety and efficacy of curcumin in CRC patients. The full effectiveness of curcumin against CRC will be further confirmed in randomized and well-controlled clinical trials.

4.4.2. Pancreatic Cancer

The fourth most common cause of cancer deaths worldwide is pancreatic cancer; an

estimated 57,600 new cases of pancreatic cancer are predicted and about 47,050 died in 2020 due to this cancer. It starts in the tissues of the pancreas and mostly progresses and is diagnosed at an advanced stage without early symptoms. Diabetes is one sign of pancreatic cancer, especially when it happens in the upper abdomen with weight loss, jaundice, or pain. The effect of oral piperine curcumin supplementation on pain and oxidative stress-related markers in tropical pancreatitis patients was examined in a single-blind, randomized placebo-controlled study conducted in India [77]. Twenty patients with tropical pancreatitis received 500 mg of curcumin along with 5 mg of piperine for 6 weeks or a placebo. The effects of MDA and GSH levels on the pain pattern and red blood cell (RBC) levels were assessed. A significant increase in GSH levels and decrease in erythrocyte MDA relative to placebo was observed after curcumin therapy. However, treatment with curcumin did not relieve the tenderness. The researchers deduced that oral administration of curcumin-piperine combination would reverse lipid peroxidation in patients suffering from tropical pancreatitis.

In another research performed by Epelbaum et.al [78] in an open-label phase II study, evaluated the efficacy of curcumin with gemcitabine against advanced pancreatic cancer. The study revealed that when taken with gemcitabine, the optimal tolerated dosage of curcumin was 8g/day, and the efficacy of this combination appeared to be moderate. The findings were re-reported by Kanai et al. [79], who assessed the safety and feasibility of curcumin and gemcitabine combination in 21 pancreatic cancer resistance patients and observed a safe and well-tolerated 8g/day curcumin dose with gemcitabine.

4.4.3. Breast Cancer

The major cause of death from cancer in women is breast cancer, the most common invasive cancer. According to estimation, nearly 279,100 new cases of breast cancer are predicted in women, and about 47,050 women are likely to die of this disease by 2020. Docetaxel (Taxotere) is used in the treatment of a wide variety of cancers, including breast cancer [80]. The safety and effectiveness of the combination of docetaxel with curcumin have been tested in patients who suffer from advanced and metastatic breast cancer in an open-label phase I trial. Docetaxel 100mg/mL was administered to 14 patients as an hourly intravenous infusion every 3 weeks for six cycles on day 1. Also for 7 consecutive days per period, curcumin was administered orally from 0.5g/day and increased before dose-limiting toxicity occurred. The vascular endothelial growth factor and tumor markers were measured after giving the maximum bearable dose of the combination of curcumin and docetaxel, and the target of patient compliance and clinical response to combinatorial therapy was also assessed. An 8g/day curcumin dose was found to be the highest tolerable amount, while the prescribed dose was 6g/day in conjunction with the normal dose of docetaxel for 7 consecutive days every 3 weeks [81].

In another study, 24 Swiss Albino mice (20-25g bodyweight, 8 weeks aged) randomly assigned for evaluation were divided into four groups (six each) [82]. After the tumor was introduced with MCF-7 cell suspension, 40mg/kg of pure curcumin nanosuspension (NS) formulation was given daily to group A. Similarly, docetaxel nanosuspension (10 mg/kg) was administered every 4th day in group B and curcumin-docetaxel co-loaded NS (10 mg/kg) was given orally to group C for every 4th day. Group D was kept in check. This research demonstrated substantial tumor healing and a higher rate of tumor inhibition relative to pure suspensions in the NS of the medications. The findings for curcumin-docetaxel co-loaded NS were more profound. When curcumin was co-administered

as a potent anticancer agent and a p-gp inhibitor with docetaxel as PEGylated nanosuspensions [82], the anticancer activity has been further enhanced.

4.4.4. Prostate Cancer

The most common cancer in men, prostate cancer, is caused by an increased level of prostate-specific antigen (PSA). According to the American Cancer Society in 2020, around 1, 91,930 new diagnoses of prostate cancer are expected and around 33,300 patients are died because of this cancer [64]. To mitigate the PSA level may help to prevent this cancer. The effect of curcumin on this disease was evaluated along with the feasibility and tolerability. A double-blind, randomized, and controlled study examined the impact of a combination of soy isoflavones and curcumin on serum PSA levels in men who had only elevated PSA levels but were found to have a negative prostate cancer test [83]. 85 participants were randomly assigned to take a 6-month daily dose of curcumin and isoflavones or placebo. Furthermore, the participants were given an interrupt of their baseline PSA value at 10ng per mL, 43 subjects received a combination of 100mg of curcumin and 40mg of isoflavones daily; however, 42 subjects received a placebo daily for the same treatment duration. As a result, in the patient group with PSA values was greater than 10 ng per mL. PSA levels decreased for those who had a supplement containing curcumin and isoflavones. These findings showed that serum PSA levels could be modulated by this combination. The researchers of this report concluded that curcumin possibly suppresses the development of PSA along with isoflavones.

4.4.5. Lung Cancer

Lung cancer is the most common cause of death from cancer in both men and women worldwide. According to the 2020 forecast of the American Cancer Society, nearly 2,28,820 new cases of lung cancer are predicted in the U.S. and this disease has caused over 1,35,720 deaths. The risk of lung cancer is strongly correlated with cigarette smoking. They have five times more risk of lung cancer than a non-smoker. The risk of mutagenicity is increased by smoking, and dietary factors with turmeric can minimize the risk. In one study, 16 chronic smokers and 6 controlled non-smokers who were considered as control were evaluated for the anti-mutagenic effect of turmeric. Participants were administered for 30 days at 1.5g/day; turmeric significantly decreased mutagen urinary excretion in smokers. However, there has been no improvement in the urinary excretion of mutagens in the control sample. Researchers have shown that dietary turmeric can minimize the risk of lung cancer in smokers by serving as an effective anti-mutagen. [84].

4.4.6. Ovarian Cancer

Ovarian cancer is the world's fifth leading cause of cancer deaths in women and the tenth most common cancer in the United States by women. Around 21,750 women in the U.S. are predicted to be diagnosed with this cancer, according to an estimate, and around 13,940 are expected to die from this disease in 2020. The effect of daily intake of dietary curcumin on the development and progression of spontaneous ovarian cancer was examined in a galline (hen) model in a study. A significant dose-dependent decrease in the overall incidence of ovarian cancer was observed and the regular consumption of curcumin decreased the size of the ovarian tumor and the number of tumors. The authors of this study have been concluded that daily curcumin intake leads to a significant and dose-dependent reduction in the incidence and growth of spontaneous ovarian cancer, which indicates a tremendous role of curcumin as a chemoprevention strategy for ovarian cancer

[85].

4.4.7. Cancer Lesions

A lesion is any damage or abnormal change in the tissue of an organism. Lesion tumors may be benign or malignant. Estimation of American Cancer Society in 2020, around 53,260 new diagnoses and 10,750 deaths are expected of oral cavity and pharynx disorder. The most common pre-cancerous oral lesions such as oral leukoplakia, oral submucous fibrosis (OSMF), oral erythroplakia, and oral lichen planus are occur due to tobacco chewing [86].

A study performed by Hastak et al. on healthy participants and patients with submucous fibrosis, the effect of the combination of alcoholic extracts of turmeric oil and turmeric oleoresin on the number of micronuclei has been observed. In healthy subjects, none of the extracts had any effect on the lymphocyte amount of micronuclei. In another series of experiments, patients received an oral dose of turmeric and turmeric oil every day; turmeric oleoresin and turmeric; and only turmeric for 3 months. The findings showed that all three treatment protocols resulted in a decrease in the number of micronuclei in both the exfoliated and circulating lymphocytes of the oral mucosal cells. However, in decreasing the number of micronuclei in oral mucosal cells, turmeric oleoresin was more effective. In patients with oral precancerous lesions, the authors indicated the ability of turmeric extract against micronuclei formation [87].

In another study, 100 patients with oral lichen planus were treated with curcuminoids. A randomized, double-blind, placebo-controlled trial included two interim analyses, and patients were given 2g/day of curcumin as well as in placebo received for 7 weeks. Besides, all participants received 60mg/day of prednisone for the first week. The findings of the first preliminary study showed that no substantial difference between placebo and curcuminoid groups was observed in 33 participants. The rest of the curcuminoid group had considerably better outcomes than the placebo group. Unfortunately, the study ended before completion. The study concluded with the recommendation of a greater sample size, a higher dose, and longer curcuminoid duration without initial prednisone standardization [88].

4.5. Anti-microbial effect:

Curcumin appears to be a potent molecule that inhibits the growth of various microbes including viruses, bacteria, and pathogenic fungi [89]. It has been found to restrain the growth of various species such as E. coli, B. subtilis, H. pylori, Human Immunodeficiency Virus (HIV), Herpes simplex virus (HSV), Hepatitis viruses, and Influenza type a virus (IAV), etc [58].

The human immunodeficiency virus (HIV), which interferes with the body's ability to combat infections and weakens the immune system, is caused by acquired immunodeficiency syndrome (AIDS). The virus primarily infects essential human immune system components, such as CD4+ T cells, macrophages, neutrophils, and dendritic cells, and kills CD4+ T cells directly or indirectly. There is neither a cure nor an effective HIV vaccine at present. Treatment consists of Highly Active Antiretroviral Therapy (HAART) which slows down disease progression [90-91].

The pathogenic perspective of HIV-1 is due to its fast replication, broaden, and regulation of cellular pathways [96]. HIV-1 TAT is an unfolded protein that increases viral replication by associating with the TAR region of the viral long terminal repeat (LTR). Curcumin inhibits HIV-1 protease, integrase, and also inhibits the essential NF-kB pathway for the expression of the HIV-1 gene [93-94].

The antibacterial activity of curcumin has been examined in one clinical trial against 65 clinical isolates of H. pylori in vitro and during protection against H. pylori infection in vivo. The MIC of curcumin ranged from 5µg/mL to 50µg/mL, showing its efficacy by inhibiting H. pylori growth in vitro studies. Additionally, the oral administration of 25 mg/kg curcumin once daily for 7 days consecutively was given to a group of C57BL/6 mice, while untreated infected ones received sterile water. The results showed that the eradication of H. pylori from infected mice and restoration of H. pylori-induced gastric damage was obtained highly productive by using curcumin therapy. The authors reported that curcumin showed immense therapeutic potential against H. pylori infection and suggested its potential as an alternative therapy, however, considered necessary for further studies on the identification of novel antimicrobial targets of curcumin [95].

Lin et al. have been recently reported that the antiviral effects of curcumin with different mechanisms against Enterovirus 71(EV71) In-vitro and In-vivo could be improved by the carbon quantum dots of curcumin [100]. Loczechin et al. also reported this important fact that carbon quantum dots alone were effective against human coronavirus (HCoV) by inhibiting the entry receptor of HCoV-229E [101]. These findings showed the potency of curcumin therapy in its transformed form and also showed an optimistic impact on antiviral activity, especially on COVID-19. The evaluation by Babaei et al. also explained the potential of curcumin to be effective against COVID-19 infection [98].

Wound Healing is a normal biological process in the living organism that is achieved by four organized steps: Haemostasis, Inflammation, Proliferation, and Remodeling. The advancement between these steps depends on the maturation of mast cells, fibroblasts, ECM, keratinocytes, and macrophages which play a pivotal role in wound healing processes. Due to its hydrophobicity and extensive first-pass metabolism, topical administration of curcumin has been shown to have a greater impact on wound healing than oral administration [99-100].In addition to the above discussed successful clinical trials in mentioned diseases and various other biological activities reported in the literature are further presented in Table 2 along with the route of administration and their outcomes.

5. Futuristic approach:

During the present study we found that despite the entitlement of curcumin as a failed missile, PAINS, IMP, for explaining its dark side, several reports are available in the literature to support its pharmacological significance. The results show that the use of turmeric in traditional medicinal systems certainly provides a cure and can provide a suitable platform for considering the molecule as a panacea. This entitlement of curcumin is further supported by the fact that the ingredients used in traditional formulations of turmeric contribute towards its solubility that has been evaluated by our research group [116-117]. Raghav and Mor encapsulated 28 different formulations of curcumin with different permutations and combinations of four ingredients in alginate hydrogels. Milk, sugar, cow milk fat, and piperine used in home remedies were selected and found that these ingredients are responsible for the solubilization of curcumin. The results have been monitored using release rate kinetic studies, anti-oxidant behavior, anti-cathepsin activities, and serum protein protecting activities. Milk was the crucial ingredient for the solubilization of curcumin. Piperine also contributed a lot when used in conjugation with milk in extending the solubilization of curcumin. Activities enhanced at a particular concentration of fat when used in conjunction with milk. It was concluded

Table 2: Effect of curcumin doses on various diseases compiled with the route of administration and their outcomes

1. **Activity/ Disease**	2. **Route/Model used**	3. **Dosage**	4. **Outcome**	5. References
6. Antioxidant activity	oral/Sprague Dawley rats: 6 males and 7. 6 females	8. Curcuminoids 9. (150mg/kg)	Significant reduction in the number of urinary biomarkers of oxidative stress such as allantoin, m-tyrosine, 8-hydroxy-2'-deoxyguanosine, and 3-nitrotyrosine.	[101]
Oxidative stress	oral/Wistar male rats	CUR (300 mg/kg)	Dose-dependent anti-seizure effect. Significantly increased the latency to myoclonic jerks, clonic seizures, and generalized tonic-clonic seizures.	[102]
Neuroprotective activity	oral/Wistar male rats	CUR (25 and 50 mg/kg)	CUR treatments increased neuronal viability and attenuated the immunoreactivity for COX-2 and TNF-a in the hippocampus.	[103]
Neuroprotective activity	oral/Streptozotocin-induced Wistar male rats	CUR (60 mg/kg)	Supplementation of CUR to STZinduced diabetic rats has beneficial effects in reducing the alterations in glutamergic receptors, oxidative stress, and imbalanced glutamate metabolism	[104]
Premenstrual syndrome (PM)	oral/70 women with PM	CUR (100 mg/kg)	CUR reduced severity of PMS symptoms can be through increasing serum BDNF levels	[105]
Alzheimer's disease	oral/Amyloid-b-peptide-infused Sprague-Dawley male rats	Curcuminoids (3-10 mg/ kg)	Curcuminoids increased synaptophysin expression.	[106]
Oral Lichen Planus	31 patients with erosive or ulcerative OLP	Curcumin Gel (1%) thrice daily	The efficacy index was significantly higher in nanocurcumin group. Enhanced the level of improvement of lesions	[107
Anti-arthritic activity	oral/Female albino Wistar rats	CUR (30 mg/kg)	Reducing arthritis. Significantly alleviating hepatocellular injury caused by methogtrexate.	[108]
Hepatoprotective activity	oral/Adult Swiss albino mice	CUR (5 mM)	The release of lactate dehydrogenase was significantly reduced along with lipid peroxidation	[109]
Neurodegenerative	Male Sprague-Dawley rats with chronic constriction injury (CCI)	curcumin (100 mg/kg, peritoneal, 14 days)	Block the Immunohistochemical and protein expressions of NMDAR-NR1 in spinal cord	[110]
Anticancer activity	Oral/ N-methyl-N-nitrosourea (MNU) induced mammary tumors in female Sprague Dawley rats.	1% curcumin with a western diet (W+Cur)	Reduced the tumor growth in rats and showed better results with decreasing breast cancer metastasis	[111]

Antidiabetic activity	oral/ 100-T2D patients aged 18–65 years	CUR (500mg/day)	Significantly decrease the level of glucose, HbA1c, insulin, C-peptide, creatinine, and reduced Hepatic damage	[112]
Anti-inflammatory activity	oral/ 5 consecutive patients with ulcerative proctitis (3 men & 2women)	CUR(1.1 g/day)	Significant reduction in symptoms of ulcerative proctitis as well as inflammatory indices in patients.	[113]
Chronic arsenic exposure	oral/ nonsmoker males or females aged 25–55 years	Curcumin with piperine (20:1) at a dose of 2x 500 mg/day	Exhibited activities against As-induced genotoxicity	[114]
Radioprotective effect	oral/Female Sprague Dawley rats	CUR (50 mg/kg)	Less cell necrosis. Lycopene and CUR reduced the structural damage to the salivary glands.	[115]

that studies in the field of nutraceuticals or functional foods can reveal the scientific background of traditional medicinal systems and can be the basis for sufficient scientific proof for formulations used to cure human ailments since ages prior to the existence of the modern medicinal system. In addition to the studies to enhance the solubility of curcumin, another approach has been to develop sustained release drug delivery systems for curcumin [118-119].

The sustained release system can supply the required amount of curcumin for the desired pharmacological effects at the site of action.

6. Conclusion

This review provided a comprehensive account of curcumin-related searches with successful clinical trials that indicated the pharmacological significance of curcumin. The study suggests ample scope in an exploration of the pharmacological potential of curcumin even though it has been classified as PAINS, IMP, and poor lead compound. In the present review, we have presented its role as a successful pharmacological agent in several diseases. This small effort, adds to the significance of curcumin as a therapeutic agent.

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Conflict of Interest

The authors of this study declare no conflict of interest.

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