Reconnoitering the Therapeutic Role of Curcumin in Disease Prevention and Treatment: Lessons Learnt and Future Directions

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Abstract: Turmeric is a plant with a very long history of medicinal use across different cultures. Curcumin is the active part of turmeric, which has exhibited various beneficial physiological and pharmacological effects. This review aims to critically appraise the corpus of literature associated with the above pharmacological properties of curcumin, with a specific focus on antioxidant, anti-inflammatory, anticancer and antimicrobial properties. We have also reviewed the different extraction strategies currently in practice, highlighting the strengths and drawbacks of each technique. Further, our review also summarizes the clinical trials that have been conducted with curcumin, which will allow the reader to get a quick insight into the disease/patient population of interest with the outcome that was investigated. Lastly, we have also highlighted the research areas that need to be further scrutinized to better grasp curcumin’s beneficial physiological and medicinal properties, which can then be translated to facilitate the design of better bioactive therapeutic leads.

Keywords: Curcuma longa; nutraceutical; curcumin; antiinflammation; antimicrobial; antioxidant; anticancer; antiviral; SARS-CoV-2; turmeric; functional food; clinical trial

1. Introduction

In recent times, there has been an increased impetus to reconnoitre the medicinal properties of food. Case in point, Rao et al., in a recent exploratory study, assessed the safety and prospective efficacy of Nigella sativa and fenugreek seed-supplemented chapattis (unleavened flatbread originating from the Indian subcontinent) in obese and type–2 diabetic subjects to demonstrate that the consumption of chapattis combined with N. sativa/fenugreek triggered a significant clinical improvement in obesity and diabetes. However, the other key highlight of this study was the long-term compliance of 100% [1]. Although the compliance regarding a clinical trial may vary from the compliance during the regular use of a food product in the community, the adherence to the dietary intervention in this study is a reason for optimism, whereby treatment for chronic diseases can be effectively delivered through food. Hence, this school of thought has coined the term “Functional Foods”.

The term “Functional foods (FFs)” was first created and defined in the 1980s by the Ministry of Health and Welfare of Japan when they established a regulatory system for foods that possess possible health benefits [2]. FFs were defined as foods that keep...
constructive effects on target functions in the physiological milieu of humans beyond nutritional effects, aiming for health promotion and wellbeing and/or the reduction of chronic diseases. With time, FFs have attained popularity, with a market value of USD 1.7 billion as of today. Further to the above, FFs have given way to the term “nutraceutical”.

The term “nutraceutical” was coined from “nutrition” and “pharmaceutical” in 1989 by the founder and chairman of the Foundation for Innovation in Medicine (FIM) situated in Cranford, NJ, Stephen DeFelice, MD [3]. According to DeFelice, a nutraceutical is “a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease” [3]. In other words, the term “nutraceutical” implies the pharmaceutical formulation of the bioactive compound, whose concentration often shifts from its natural concentration in food. No regulatory evaluations and no toxicological assessments are required. Therefore, one can say that when FF aids in the prevention and/or treatment of disease(s) and/or disorder(s) other than anaemia, it is called a nutraceutical [4]. However, an important point to remember is that the term nutraceutical, as commonly used in marketing, has no regulatory definition. Hence, broadly, nutraceuticals are foods or parts of food playing an important role in modifying and maintaining the customary physiological function that maintains healthy human beings. Case in point, allyl sulphur compounds in garlic, quercetin in berries, EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid) in fish oils, curcumin in turmeric, ginsenosides from ginseng roots and polyphenolic catechins in green tea are some of the nutraceuticals that have been studied extensively [6].

There is an increased interest in the niche of nutraceutical research because nutraceutical(s) are generally associated with lesser side effects. For example, oleocanthal (OC), present in significantly high concentrations in extra-virgin olive oil (EVOO), is a structural analogue of ibuprofen and, like ibuprofen, mediates anti-inflammatory properties by the inhibition of cyclooxygenase (COX) enzymes in the prostaglandin biosynthesis pathway [7,8]. Similarly, lycopene, which is a tetraterpene compound abundant in tomato and tomato-based products, is essentially recognized as a potent antioxidant and a non-pro-vitamin A carotenoid. Lycopene has been shown to ameliorate cancer insurgences, diabetes mellitus, cardiac complications, oxidative stress-mediated malfunctions, inflammatory events, skin and bone diseases and hepatic, neural and reproductive disorders [9]. Likewise, resveratol, which is an activator of SIRT1, one of the mammalian forms of the sirtuin family of proteins, mediates its beneficial effects on metabolism, stress resistance, cell survival, cellular senescence, inflammation–immune function, endothelial functions and circadian rhythms [10]. Curcumin isolated from the turmeric plant is one of those single molecules that have been appraised extensively in numerous in vitro and in vivo studies. However, few of the effects observed in such studies have been replicated efficiently in the numerous clinical trials that have been conducted with curcumin (see below for details). This raises the question, “Should we continue to explore the beneficial properties of curcumin, which some have christened as “The Golden Spice”?” Furthermore, “is there a definite mechanism by which curcumin mediates its effect?” In this review, we tackle these aspects of curcumin structure-function and address some of the surrounding controversies.

Turmeric is a plant has a very long history of medicinal use, especially in Indian culture, dating back nearly 4000 years. It is used as a culinary spice and has immense religious significance. In India, turmeric is colloquially referred to as “Haldi”, which, when literally translated, denotes the color yellow and is responsible for the precise yellow color of the traditional Indian curry. Over time, the use of turmeric also reached other parts of the globe. It possibly reached China by 700 AD, East Africa by 800 AD, West Africa by 1200 AD and Jamaica in the eighteenth century. In 1280, Marco Polo alluded to this spice, marvelling at a vegetable that displayed virtues like saffron. According to Sanskrit medical discourses and the alternative medicinal disciplines of the Ayurveda and Unani systems, turmeric has a long history of therapeutic use in South Asia. In fact, Susruta’s Ayurvedic Compendium, dating back to 250 BC, endorses the use of an ointment containing turmeric to relieve the effects of poisoned food. The medicinal property of turmeric is attributed to the bioactive
main natural polyphenol compound curcumin, (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane. Curcumin mediates a plethora of beneficial physiological effects. Due to its ability to interact with various molecular targets, curcumin is one of the most interesting pleiotropic nutraceuticals [11]. The antioxidant, anti-inflammatory, anticancer and antimicrobial properties of curcumin have been extensively researched and appraised in different in vitro and in vivo experimental models. Figure 1 gives an overview of the pharmacological activities of curcumin, which will be further discussed in detail in the manuscript.

Figure 1. A flow diagram summarizing the plausible mechanism of action of curcumin.

This review aims to critically appraise the corpus of literature associated with the above pharmacological properties of curcumin, with a specific focus (Figure 1) on identifying the gaps that need to be addressed to obtain a better insight into the molecular mechanism through which curcumin mediates these advantageous effects. Lastly, we have also highlighted the research areas that need to be further scrutinized to better grasp the beneficial physiological and medicinal properties of curcumin, which can then be translated to facilitate the design of better bioactive therapeutic leads.

1.1. Source of Curcumin

Curcumin is the principal curcuminoid of the turmeric plant Curcuma longa. Curcumin was discovered around two centuries ago when Vogel and Pelletier reported the isolation of “yellow colouring-matter” from the rhizomes of Curcuma longa (turmeric) and named it curcumin [12]. The turmeric plant, Curcuma longa, is a rhizomatous herbaceous perennial plant belonging to the ginger family Zingiberaceae, which is native to tropical South Asia (Figure 2a–c) [13]. As many as 133 species of Curcuma have been identified worldwide [14]. Turmeric is derived from the mature tuberous rhizome of C. longa. Once the rhizomes mature underground (beneath the foliage), they become yellowish-brown with a dull orange interior (Figure 2b) [15]. This yellowish color is because of the presence of curcuminoids, which are natural polyphenol compounds classified into three diarylheptanoids (diferulolymethane derivatives): curcumin (77%), demethoxycurcumin (17%), bisdemethoxycurcumin (3–6%) (Figure 2d-f) and other less abundant secondary metabolites.
1.2. Chemistry and Bioavailability of Curcumin

Curcumin has been identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylmethane (Figure 2d) [16]. It is an orange-yellow crystalline powder that is relatively insoluble in water (limiting its medicinal use in humans when taken orally or injected) and ether but soluble in acetone, ethanol and acetic acid dimethylsulfoxide [17]. It has a melting point of 183 °C, a molecular formula of C_{21}H_{20}O_{6} and a molecular weight of 368.37 g/mol [18]. Spectrophotometrically, the maximum absorption (λmax) of curcumin in methanol occurs at 430 nm, and, in acetone, it occurs at 415–420 nm [19]. The powder gives a brownish-red color with alkali and a light-yellow color with acids [20]. Curcumin exists in enolic and β-diketonic forms. The fact that curcumin in solutions exists primarily in its enolic form has been the key to the radical scavenging ability of curcumin [21]. It is stable in acidic pH, but in neutral and basic pH, it gets degraded to ferulic acid and feruloylmethane. Curcumin rapidly degrades when placed in a phosphate buffer solution at a pH of 7.2, whereas in ascorbic acid, N-acetylcysteine and glutathione, it does not degrade, which explains the oxidative mechanism of these anti-oxidative agents [22]. Curcumin is poorly absorbed in the gastrointestinal tract (one of the key hurdles to increasing the bioavailability of curcumin). Case in point, a poor absorption from the gut was observed in rats after the oral administration of curcumin at a dose of 1 g/kg bw, which led to 75% fecal excretion with traces in the urine, and the concentration of curcumin was below 5 ug/mL in the plasma [23,24]. The oral administration of radio-labelled curcumin at a 0.6 mg/kg dose in rats resulted in 89% excretion in feces and 6% excretion in the bile after 72 h. At the same dose, when administered peritoneally, 73% fecal excretion was observed, and 11% excretion was observed in the bile [25]. A slightly better absorption rate of 60% was seen upon 400 mg of curcumin being administered orally, and 40% faecal excretion was observed over a period of 5 days [26].

1.3. Extraction of Curcumin

Several extraction strategies have been availed for the isolation of curcumin. Conventional methods such as solvent extraction, Soxhlet extraction and hydro/steam distillation are time-consuming, are not eco-friendly and have low efficiencies. In this review, we have not touched upon these techniques. The readers are referred to the excellent review of Zhang et al. for details, if interested [27]. Novel extraction techniques (summarized in Table 1, with the associated advantages and drawbacks of these techniques) have been...
effectively strategized to maximize the extraction efficiency, decrease the use of toxic solvents and concomitantly be cost-effective.

### Table 1. Methods for curcumin extraction.

| Method Name                        | Yield                  | Advantage(s)                                                                 | Drawback(s)                                                                 | Reference |
|------------------------------------|------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------|
| Microwave-assisted extraction (MAE)| The yield obtained using MAE is 4.98%. The *Curcuma longa* plant was soaked in methanol and extracted using acetone via a dual heating mechanism under microwave energy. | Safe and cost-effective method. Retains the biological activity of the extracted compounds. | Time-consuming, as the vessel needs to be slowly cooled to avoid the loss of volatile components. Involves an initial high cost for setting up the equipment on a large scale. | [28]      |
| Enzyme-assisted extraction (EAE)   | The yield obtained using EAE is 5.73%. Turmeric was pretreated using alpha-amylase and amyloglucosidase enzymes. Extraction was performed using N,N- dipropyl ammonium N,N'-dipropylcarbamate. | Mild reaction conditions are cost-effective, eco-friendly and feasible. | Low purity of the final product. | [29]      |
| Supercritical fluid extraction (SFE)| The yield obtained using SFE is 4.3%. A two-step extraction was performed using SFE, followed by pressurized liquid extraction using ethanol as solvent. | Short extraction time and mild operating temperature. The manufacturing costs are lower than those of conventional methods. | High technical complexity, and many operational parameters need to be optimized before the initiation of the extraction process. | [30]      |
| Ultrasound-assisted extraction (UAE)| The yield obtained using UAE is 1.03%. Optimal conditions were a 60% amplitude and a 3/1 (s/s) pulsed interval. Ethanol was the extraction solvent. | Greater solvent penetration into the samples increases the contact surface area, which increases efficiency. | Ultrasound can lead to the degradation of the final purified product. | [31]      |
| Ionic liquid-based extraction (ILE) | The yield obtained using ILE is 6.18%. The ionic liquid used for extraction was an anionic [Omin][Br–] aqueous solution. | Eco-friendly and increases extraction efficiency. | High cost involved in the preparation and use. | [32]      |

### 2. Methods

Relevant publications were searched for in PubMed (https://pubmed.ncbi.nlm.nih.gov (accessed on 29 April 2022) and Google Scholar (https://scholar.google.com (accessed on 29 April 2022), using the various names of curcumin and its related functions such as antimicrobial, anti-inflammation, anti-fungal, antibacterial, rheumatoid arthritis, cancer, diabetes, inflammatory bowel disease and gut microbiota as keywords. The lead author (BMS) and the corresponding author (YB) finalized the keywords, which were vetted and agreed upon by all the authors. The search was conducted independently by two authors (BMS and MA). Overlaps were eliminated, and the final list of selected articles was agreed upon and vetted by all participating authors. The search was restricted to articles published only in English. The images are shown in Figure 2a The turmeric plant, (b) the turmeric rhizome with a yellow-orange interior, (c) the powdered form of turmeric and (d) the chemical structure of curcumin were adopted with minor modifications from the Wiki commons [33,34].
3. Anti-Inflammatory Properties of Curcumin

Inflammation is a response to tissue damage caused by oxidative stress, pathogens, chemicals or radiation and triggers repair. Chronic inflammation lasts from several months to years due to tissue invasion by inflammatory cytokines and growth factors. Curcumin shows an anti-inflammatory property by interacting with Toll-like receptors (TLRs), which play a key role in innate immunity [35]. Upon binding, it regulates the production of inflammatory mediators such as Mitogen-activated protein kinases (MAPK), Activator Protein 1 (AP-1) and Nuclear Factor Kappa-B (NF-κB) [36]. The Janus kinase/Signal transducer and activator of the transcription (JAK/STAT) signaling pathway has been one of the main targets to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases. Curcumin has also been proven to regulate JAK/STAT signaling. Another way to decrease inflammation is by regulating inflammatory mediators. Case in point, curcumin has decreased the level of mediators such as Interleukin-1 (IL-1), IL-17, IL-27, IL-6, IL-8, IL-1β [37], Tumor necrosis factor-α, Monocyte chemotactic protein-1 (MCP-1) and Inducible nitric oxide synthase (iNOS). Nuclear factor erythroid 2 p45-related factor (Nrf2) overactivation is seen in neoplasms [38] and has also been linked with insulin resistance in diabetes. Curcumin has suppressed proteins such as Keap1, which interacts with Nrf2, thereby regulating its overexpression. In Figure 3, we have summarized curcumin’s anti-inflammatory property via the inhibition of signalling pathways.

![Figure 3. Role of curcumin in the inflammatory signaling pathway.](image-url)

One of the most important complexes that participate in inflammation is the inflammasome. Among the various inflammasomes, the NOD-like receptor pyrin domain containing 3 (NLRP3) detects the products of damaged cells and triggers an immune response. It mainly involves two plausible mechanisms:

1. Inflammatory bacterial products such as lipopolysaccharide (LPS) activate the NF-κB pathway to activate NLRP3, leading to Pro-Interleukin-1β (pro-IL-1β) synthesis.
2. Stimuli such as nigericin, aluminium crystal and monosodium urate crystal lead to NLRP3 activation, subsequently leading to the activation of caspase-1 along with the promotion of proinflammatory cytokines such as IL-1B and IL-18 [39].

NK-κB plays a vital role in aggregating NLRP3 components to form an active NLRP3 inflammasome. Curcumin has been shown to suppress the activation of the NLRP3 inflammasome and IL-1B secretion by regulating the NK-κB pathway [40]. Additionally, curcumin also inhibits the NLRP3 inflammasome by preventing Ca^{2+} influx and attenuating K^+ efflux, thereby disrupting the formation of NLRP3 components [41]. Therefore, NLRP3 is one of the best targets by which curcumin can treat various inflammatory diseases. The key
inflammatory diseases for which the beneficial effects of curcumin have been extensively investigated/appraised are depicted below.

3.1. Rheumatoid Arthritis (RA)

RA is a chronic inflammatory disease affecting the joints and causing irreversible bone, synovium and cartilage degradation, reduced mobility and discomfort. Curcumin has been found to suppress pro-inflammatory pathways crucial in the development of RA. A study by Wang et al. and Murakami et al. demonstrated that curcumin increased macrophage apoptosis and decreased the level of IKKα, thereby reducing the expression of COX-2 and inhibiting the activation of NF-κB [42,43]. Curcumin has also been shown to inhibit lymphocyte proliferation and decrease IL-4 and IL-5 levels and the granulocyte-macrophage colony-stimulating factor in lymphocytes [44]. Moreover, curcumin augments the activity of anti-inflammatory IL-10, inhibits BAFF (B cell-activating factor) expression and suppresses STAT1 signaling [45]. An in vivo study with curcumin by da Silva et al. revealed decreased infiltration and neutrophil activation, which prevents the migration of neutrophils from the blood to inflamed joints, acting as a proapoptotic agent in RA treatment. Curcumin also increases the surface expression of the cluster of differentiation (CD) 16+ and CD 56dim in natural killer cells, proving its immunostimulatory activity [46]. Experiments conducted by Moon et al. [47] and Dai et al. [48] explained the anti-inflammatory property of curcumin in synovial fibroblasts, where it suppresses COX-2 (this blocks the synthesis of prostaglandin E2), reducing synovial cell hyperplasia via the Mtor pathway and downregulating various NK-κB complexes, IL-1β and TNF-α [47,49].

Chondrocyte apoptosis seen in RA has been responsible for joint cartilage damage. In a study, curcumin inhibited IL-1β-induced IKKα phosphorylation and the activation of caspase-3 and COX-2 in chondrocytes isolated from cartilage (this might support cartilage regeneration in RA) and suppressed apoptosis in these chondrocytes [50]. In in vivo RA models, curcumin has been shown to decrease IL-1β, IL-18RA, IL-6, IL-18, TNF-α, IFN-gam, MMP3 [51] and IL-17 [42]. Bone degradation in RA by osteoclasts has been investigated by Shang et al., employing peripheral blood mononuclear cells (PBMCs) obtained from patients with RA with different concentrations of curcumin (2.5–10 µM) for 48 h. The results from this study demonstrated that curcumin inhibited M-CSF and RANKL-stimulated osteoclast differentiation via the suppression of ERK1/2, p38 and JNK activation. Another study evaluated curcumin’s capacity for inhibiting human osteoclastogenesis. Curcumin concentrations in the range of 1–10 µM inhibited osteoclast differentiation and bone-resorption, indicating that curcumin could be a potential therapeutic leading to managing bone deterioration in RA. It has also been reported that curcumin supplementation (500 mg for 8 weeks) [52] or curcumin nanomicelle administration (40 mg, 3 times a day over a period of 12 weeks) in RA patients tend to decrease the tenderness and swelling of the joints [53].

3.2. Osteoarthritis (OA)

Osteoarthritis (OA) is one of the leading causes of morbidity and disability worldwide. The prevalence of OA is projected to increase in the future [54,55]. The disease’s exact pathophysiology is not yet completely understood. Nonetheless, biomechanical (wear and tear), inflammatory and metabolic factors have been implicated in inducing the sterile inflammation and catabolism of the cartilage of the joint [56–58]. To date, there is no effective treatment to prevent or halt the progression of the disease that has been discovered [59]. The available pharmacological interventions, including non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, target the symptomatic treatment of pain [60]. Nonetheless, the prolonged use of NSAIDs is associated with significant cardiovascular, renal and gastrointestinal adverse events [61–63]. Curcumin emerged as a safe alternative for pain symptom relief and has been studied in preclinical and clinical trials.

In several preclinical studies, curcumin has shown positive effects on the reduction of inflammatory and catabolic markers in OA rat models [64,65]. Yan et al. have examined the
effects of intra-articular curcumin injections in OA-induced rat knee models. Inflammatory markers in OA, including the Toll-like receptor (TLR)-4 and its downstream pathway including NF-κB, IL-1β and TNF-α, were reduced significantly [64]. Additionally, curcumin preserved cartilage thickness and reduced the number of apoptotic chondrocytes in microscopic studies [64]. Zhang et al. showed similar findings with an intraperitoneal injection of curcumin [66,67]. The oral curcumin effects on rat OA models showed similar findings of decreased serum levels of cyclooxygenase-2 (COX-2) and 5-lipoxygenase, which are responsible for pain and inflammation. Matrix metalloproteinase-3 (MMP-3) proteins, which are highly expressed in osteoarthritic tissues and are responsible for breaking down cartilage by degrading the extracellular matrix in osteoarthritic joints, were also reduced [68]. Additional in vitro studies revealed the decreased activation of proapoptotic protein caspase-1 and the decreased expression of MMP-3 and displayed a dose-dependent inverse relationship between curcumin and MMP-3 levels [65].

Reduced autophagy and increased apoptosis have been indicated in the pathophysiology of OA [69,70]. In vivo experiments revealed that curcumin admiration decreased caspase-3 and Bax/Bcl2 levels, reducing apoptosis, while autophagic activity was high through the increased expression levels of light chain-3 (LC-3) [66]. Additionally, in vitro, mechanistic studies revealed the inhibition of the AKT/mTOR pathway by curcumin, which resulted in reduced apoptosis and enhanced autophagy [66,71].

Clinical studies of oral curcumin showed promising results in alleviating OA symptoms [72]. Several studies have shown benefits on the pain and functional scores of OA after administering oral curcumin alone or as an adjunct [73-77]. Previous lab studies revealed the synergism of COX-2 inhibitors and curcumin by reducing the expression of the enzyme and reducing prostaglandin E2 levels, which has translated in clinical trials into reducing pain symptoms and improving functional outcomes [78,79]. Additionally, Shep et al. showed that patients using NSAIDs and curcumin reported reduced GI pain as compared to patients receiving NSAIDs alone [77]. Patients on curcumin were able to decrease their daily dosage of NSAIDs owing to the analgesic effect of curcumin. Kuptniratsaikul et al. compared ibuprofen against ibuprofen and showed similar outcomes on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [76]. An exploratory trial has shown decreased Coll2-1, a novel OA marker in patients’ serum, after administering curcumin [75]. A recent systematic review and metaanalysis by Paultre et al. concluded that heterogeneous curcumin is safe and beneficial in terms of the pain and function of patients with knee OA [72].

3.3. Cancer

Inflammation causes an increase in the production of pro-inflammatory molecules such as cytokines, reactive oxygen species (ROS), cyclooxygenase (COX)-2, transcription factors such as NF-κB, protein kinases B, activator protein 1(AP-1) and the signal transducer and activator of transcription 3(STAT3), leading to the initiation and development of cancer [80]. Curcumin shows a similar activity as that seen in RA, where it suppresses NF-κB activity by inhibiting IκB. It downregulates the expression of inflammatory genes such as TNF-α [81] and downregulates cyclin D1, Bcl-2, Bcl-xL, IL-6, COX-2 and MMP9 through NF-κB inhibition [82]. Curcumin has also been shown to downregulate AP-1 (known to be related to anti-apoptotic genes). In addition, Curcumin is directly or indirectly related to the regulation of STAT3 (a protein that promotes oncogenesis) by inhibiting IL-6 [83]. The anticancer effects of curcumin observed in different cancer models are summarized in Table 2.
Table 2. Activity of curcumin against cancer.

| Cancer Type   | Curcumin Conc. | Signaling Molecules Up/Downregulated | Overview                                                                                                                                                                                                 | Delivery Modes                                                                                                                                  | Ref.       |
|---------------|----------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Prostate cancer | 10–100 µM      | Downregulates NF-κB, AP-1, Cyclin D1, CXCL-1 and CXCL-2, Bcl-2, Bcl-xL and XIAP. | -Curcumin is a potent inhibitor of NF-κB in both ADPC and AIPC cells, thereby preventing cell proliferation and inducing apoptosis.  
-Curcumin restores the response of AIPC cells to anti-androgen treatment.  
-Prevents metastasis in AIPC cells. | Free curcumin or in combination with chemotherapeutic agents such as TRAIL.  
-Curcumin in poly(lactic-co-glycolic) acid.  
-Using the nanoparticle formulation of curcumin.  
-Curcumin-loaded liposomes. | [84–95] |
| Breast cancer  | 10–40 µM       | Downregulates Bcl-2, CXCL-1, CXCL-2, MMP-9, urokinase plasminogen activator, intercellular adhesion molecule 1 and chemokine receptor 4, PECAM-1, Cyclin D1 and p65. | -Curcumin can suppress ODC activity and inhibit cell proliferation.  
-Inhibits the MPA-induced secretion of pro-angiogenic factors such as VEGF. | -Hyaluronic acid-modified mesoporous silica nanoparticles.  
-Chitosan nanoparticles.  
-Zinc oxide nanoparticles.  
-In combination with niclosamide using PLGA nanoparticles.  
-PEGylated PLGA nanoparticles  
-Nanovesicles. | [21,96–107] |
| Colon cancer   | 10–50 µM       | Downregulates TNFα, JNK activation, miR-21 and COX-2. | -Curcumin inhibits the activation of the TLR4/MyD88/NF-κB signaling axis.  
-Reduces IκB kinase activity and inhibits the degradation of IκBα.  
-Inhibits the production of TNF-α, IL-6 and IL-12.  
-Inhibits Foxp3 expression and enhanced interferon-gamma secretion in regulatory T cells. | -Curcumin in silica nanoparticle.  
-Polymeric nanocarrier.  
-Curcumin-loaded thiolated chitosan nanoparticle.  
-Dendrosomal carrier.  
-Curcumin-loaded micelles.  
-Curcumin–PLGA nanoparticles. | [108–119] |
| Pancreatic     | 10–50 µM       | Downregulates EGFR, COX-2, NF-κB, AKT and Prostaglandin E2. | -Inhibited cell survival and enhanced apoptosis in pancreatic adenocarcinoma cell lines.  
-Suppressed tumor growth by inhibiting the NF-KB pathway.  
-Induced apoptosis via ATM/Chk1.  
-Anti-proliferative activity by suppressing Sp1 and disrupting NF-κB translocation to the nucleus. | -Curcumin analogues  
-PEGylated Curcumin, [Dlys6]-LHRH and its analog called L49H37.  
-CDF and PEGylated curcumin.  
-Liposomal Curcumin.  
-Curcumin analogues with the hydroxyl group.  
-Magnetic particles that were used to encapsulate curcumin.  
-Ester-mediated conjugations of curcumin to cholesterol-hyaluronic acid nanogel. | [120–131] |
Table 2. Cont.

| Cancer Type | Curcumin Conc. | Signaling Molecules Up/Downregulated | Overview | Delivery Modes | Ref. |
|-------------|----------------|------------------------------------|----------|----------------|------|
| Gastric     | 10–100 µM      | Downregulates the Akt pathway, BCL-2, COX-2 and cyclin D1. | -Induced apoptosis by activating caspase-3, PARP; reduction in Bcl-XL levels. -Curcumin also activates the Fas pathway by stimulating the activity of caspase-8. -Activated Bax protein expression and inhibited the Bcl-2 protein. -Suppressed the transition of the cancer cells from the G(1) to S phase. | -Cyclodextrin complexes with curcumin. -Nanoparticles such as polymer-encapsulated ZnO nanoparticles. -Microsponges using polymers such as ethyl cellulose and polyvinyl alcohol. -Curcumin-loaded nanoemulsion. -Cationic polysaccharides such as chitosan. | [132–142] |
| Lung        | 5–50 µM        | Downregulates the Akt pathway, BRCA pathway, Beta-catenin signaling and MMP-2 and upregulates caspase-3, Bax and p53. | Induces apoptotic cell death by activating caspase-7 and 3. -Enhances PARP cleavage and stimulates ER stress. -Enhances ROS production to cause apoptosis. -Increases the sensitivity of cancer cells to chemotherapy. -Induces DNA damage and prevents the migration of cancer cells. | -Lipid-based liposome. -Polymeric carrier and micelle. -Chitosan microsphere. -Polymeric and lipid nanoparticle. -Nanocrystal. | [143–154] |
| Oral        | 10–100 µM      | Prevents cell proliferation and promotes apoptosis. | -Curcumin reduces the migration and progression of TSCC cells, promotes apoptosis and inhibits tumorigenesis. - Suppresses the CAF (cancer-associated fibroblast)-mediated proliferation and tumorigenicity of Cal27 by inhibiting TSCC CAFs. | -Nanohybrid formulation. -Lozenges. -Silica nanoparticles. -Mucoadhesive nanogel system. | [155–160] |
| Skin        | 10–50 µM       | Shows effective anti-proliferative activity. | -Antiproliferative effect, as they effectively inhibit the clonogenic ability in melanoma cells. | -Cationic liposomes. -Ethosomal nanocarriers. | [161,162] |

3.4. Diabetes

Inflammation plays a pivotal role in diabetes. In fact, a review of the possible mechanisms that drive the metabolic pattern in Type 1 Diabetes and Type 2 Diabetes (T1D and T2D) and the involved inflammatory pathways indicates that the effective management of diabetes requires the modulation of the inflammatory pathways. In line with this, in this review, we will critically appraise the different cell and animal models that have been employed in investigating the anti-diabetic effects of curcumin, identifying the key results obtained in these studies. First, stress-causing factors such as obesity stimulate NK-κB activity and cause insulin resistance in adipose tissue, the liver and leukocytes. Second, curcumin supplementation has significantly reduced the NLRP3 inflammasome by inhibiting its activation, downregulating the NK-κB pathway and thereby reducing
the caspase-1 activation and IL-1B secretion. Another anti-inflammatory activity of curcumin is the inhibition of ER stress in adipocytes by preventing the phosphorylation of phospho-inositol-requiring kinase 1 (p-IRE1) and phospho-eukaryotic Initiation Factor 2 (p-eIF2) [163]. It also reduced the glycerol level and FFA released from adipose tissues [164]. The third mechanism is the inhibition of the pro-inflammatory NF-κB signaling pathway activation. Therefore, curcumin has shown beneficial anti-inflammatory effects by suppressing the expression of IL-6, TNFα, IL-1β [165] and MCP-1 from adipocytes [166] by inhibiting the recruitment of macrophages in adipose tissues and inhibiting NLRP3 inflammasome activity [40]. The effect of curcumin on diabetes has been summarized in Table 3.

In experimental models, chemicals such as streptozotocin (STZ) and alloxan have been used to induce diabetes. In mice, low doses of STZ (i.e., 40 mg/kg intraperitoneally injected for 5 consecutive days) have closely resembled human T1DM, with chronic pancreatic islet inflammation, insulitis and insulin deficiency. In rats, a single dose of STZ (i.e., 65 mg/kg) is required to generate T1DM, and high doses of STZ cause the toxin-induced necrosis of B cells, hypoglycemia and cell death. For T2DM, the exposure to a high-fat diet (60% fat by caloric content) followed by a moderate dose of STZ has resulted in hyperglycemia and insulin resistance [167]. None of the above models mimic human T1DM and T2DM. Therefore, the choice of model depends on the aim of the study. Challenges such as the regulation of STZ specificity and toxicity, the careful monitoring of diets and other factors and the ethics involved in the use of animal models should be kept in mind for the appropriate induction of diabetes using STZ [168].

Alloxan has been effectively administered at 170–200 mg/kg BW intraperitoneally to induce diabetes in animal models. However, alloxan-induced hyperglycemia is not sufficiently stable for the proper evaluation of antidiabetic compounds. It induces diabetes by a mechanism characterized by reactive oxygen species toxicity, ketosis and a high mortality rate. Instability, poor diabetogenicity, easy auto-reversal and the route and speed of administration are the factors to be considered to improve the use of alloxan as a diabetogenic drug [169].

Table 3. Summary of the anti-diabetic role of curcumin and the mechanism of action.

| Model | Conc. of Curcumin | Increase | Decrease | No. of Mice/Rats Used | Route of Administration | Reference |
|-------|-------------------|----------|----------|-----------------------|-------------------------|-----------|
| Albino Wistar rats with Streptozotocin-induced diabetes | 0.5% of diet; 8 weeks | ATPase activity, PUFA/SFA ratio | Phospholipid, triglyceride, kidney weight, renal lesion progression, renal damage, urine ALT and AST, kidney alkaline and acid phosphatase, glucose-6-phosphatase | 48 | Intraperitoneal | [170] |
| Albino Wistar rats with Streptozotocin-induced diabetes | 300 mg/kg b.w./day for 8 weeks | Creatinine, kidney SOD activity, kidney catalase activity | Glucose, total cholesterol, triglyceride, urea, body weight, kidney lipid peroxidation | 10 | Intraperitoneal | [171] |
| Wistar Rats with Streptozotocin-induced diabetes | 80 mg/kg b.w./day; 45 days | Insulin, SOD, catalase, GPx activity, glutathione-S-transferase | Glucose, lipid peroxidation, TBARS, H₂O₂ | 24 | Intraperitoneal | [172] |
Table 3. Cont.

| Model | Conc. of Curcumin | Increase | Decrease | No. of Mice/Rats Used | Route of Administration | Reference |
|-------|-------------------|----------|----------|-----------------------|-------------------------|-----------|
| Sprague-Dawley rats with Streptozotocin-induced diabetes | 15 and 30 mg/kg b.w./day; 2 weeks | Creatinine clearance, SOD activity, catalase activity | Glucose, creatinine, renal changes, oxidative stress, urine albumin, proteinuria, lipid peroxidation, MDA | N/A | Intraperitoneal | [173] |
| Wistar-NIN rats with Streptozotocin-induced diabetes | 0.01% curcumin; 8 weeks | SOD activity, pancreas catalase activity | Glucose, insulin, TBARS, pancreas SOD activity, glutathione-S-transferase activity | 32 | Intraperitoneal | [174] |
| Sprague-Dawley rats with Streptozotocin induced type 1 diabetes | 50 mg/kg b.w./day; 6 weeks | Albumin, acetyl-histone H3, phospho-histone H3 | Urea, creatinine, HSP-27 protein, p38 protein | 12 | Intraperitoneal | [175] |
| C57/BL6J mice with Streptozotocin-induced diabetes | 7.5 mg/kg b.w./day; 10 h prior to STZ | Insulin, glucose clearance, GLUT2 mRNA | Glucose, IL-16, TNF-α, pancreatic IL-6 | N/A | Intraperitoneal | [176] |
| Wistar rats with Streptozotocin-induced diabetes | 80 mg/kg b.w./day; 45 day | Insulin, SOD activity, CAT activity, GPx activity, glutathione activity | Kidney and liver: morphological changes, oxidative stress, TBARS, HP | 30 | Intraperitoneal | [177] |
| Swiss albino mice with Streptozotocin-induced diabetes | 10 mM; 10 µL/mouse i.p.; 28 days and 106 BMCs, a single injection | Insulin, islet regeneration, SOD activity, catalase activity, GPx activity | Glucose, MDA levels | 40 | Intraperitoneal | [178] |
| Wistar rats with alloxan-induced diabetes | 0.08 mg/kg b.w./day; 21 days | Hemoglobin, glutathione, GPx activity | Glucose, HbA1c, TBARS, SDH activity | 36 | Oral | [179] |
| Wistar rats with alloxan-induced diabetes | 0.1 mg/kg b.w.; 2 h | Glucose | N/A | Oral | [180] |

3.5. Kidney Diseases

Acute kidney disease (AKD) and chronic kidney disease (CKD) have led to several cases of mortality worldwide. An increase in inflammation and decreased antioxidant activity are mostly seen in kidney diseases and in hemodialysis patients. The supplementation of curcumin has shown favorable effects on renal diseases, mainly due to its anti-inflammatory and anti-oxidant properties. Curcumin has decreased renal damage and inflammation by reducing the expression of inflammatory cytokines such as IL-1β, IL-6, TNF-α, adiponectin (which is associated with arterial stiffness, leading to death) and cystatin in rats with adenine-induced CKD [181].
Nuclear factor-erythroid-2-related factor 2 (Nrf2) is a crucial transcription factor, and in the case of oxidative stress, Nrf2 translocates into the nucleus and induces the production of detoxifying enzymes. The upregulation of transcription factor Nrf2 was seen in the kidney upon the administration of curcumin; this upregulation led to an increase in glutathione reductase and thereby exhibited the antioxidant property by decreasing glutathione levels [182]. Diabetic nephropathy (DN) is the cause of end-stage renal failure, and inflammation plays an important part in the development and progression of DN. Curcumin prevents inflammation by renal macrophage infiltration and modulates transcription factors such as AP-1 and chemokines such as IL-1, IL-6. The oral supplementation of curcumin at 100 mg/kg/day for 8 weeks in STZ-induced diabetic rats prevented macrophage infiltration by inhibiting the activity of NF-κB, IκBα and regulated MCP-1 at the nuclear level, thereby preventing glomerular injury and damage [183]. Curcumin analogues in diabetic rats were administered at 5 mg/kg/day for 6 weeks, causing a similar reduction in kidney inflammation via the inhibition of the JNK pathway and diabetes-related histone acetylation [184]. Chemotherapeutic agents such as cisplatin cause acute kidney injury. Curcumin prevents the mitochondrial bioenergetics alterations and redox balance by preventing the increase in the mitochondrial fission protein and decreasing NAD± dependent deacetylase sirtuin-3 in acute kidney injuries [185]. Heavy metals cause nephrotoxicity due to ROS overproduction, decrease the endogenous antioxidant property and suppress the autophagy flux (leading to cell damage). Curcumin modulates autophagy via the modulation of Akt/mTOR and by increasing the adenosine monophosphate-activated protein kinase (AMPK) and extracellular signal-dependent kinase (ERK) pathways [186]. Curcumin administered orally in wistar rats at 400 mg/kg/day (with AKI via a dose of potassium dichromate) could preserve mitochondrial bioenergetics by increasing the expression of mitochondrial transcription factor A and bring peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) back to a normal level [186]. Therefore, curcumin can be potentially used to treat renal diseases.

3.6. Antioxidant

Oxidative stress results from an imbalance between oxidants and antioxidative measures. It is hypothesized that damage from reactive oxygen species (ROS) and reactive nitrogen species (RNS) results in many chronic diseases (atherosclerosis, Alzheimer’s disease, liver disease) and the senescence of cells [187–190]. Curcumin has potent antioxidant properties due the fact that it has multiple functional groups including the β-diketo group, carbon–carbon double bonds and phenyl rings containing varying amounts of hydroxyl and methoxy substituents. These properties allow curcumin to protect lipid membranes from peroxidation induced by oxidation agents [191]. In fact, one study has shown that curcumin was more effective as an antioxidant than α-tocopherol [192].

Curcumin has multiple pathways to act as a direct antioxidant. Firstly, curcumin acts as an ROS (specifically H₂O₂) scavenger, as shown in vitro by Ak et al. [193]. Secondly, curcumin, through its phenolic or central methylenic groups, is associated with its hydrogen donor capacity [194]. Whatever et al. proved that the enol form of curcumin is more stable than the diketo form and that the bond-dissociation energy (BDE) of the phenolic O:H bond is lower than the BDE of the central O:H bond. Therefore, the hydrogen ion abstraction takes place in the phenolic form [195,196]. Thirdly, curcumin degradation products (ferulic acid and vanillin) under basic pH can act as potent antioxidants [191,197]. Lastly, curcumin can chelate heavy metal ions such as ferrous ions through its functional carbonyl group [193].

Additionally, curcumin exhibits indirect effects that combat oxidative stress on the cells. High-dose curcumin administration in albino rats by Faten et al. has shown the increased activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase (GST) in different tissues [198]. Furthermore, curcumin increased the mRNA expression (by 2–12 times) and protein levels (by 2–6 times) of antioxidant enzymes including glutamyl-cysteine ligase, quinone oxidoreductase and heme
oxygenase 1 (OH-1) in human islet cells [199,200]. The expression of HO-1 was induced by curcumin through the activation of the Nrf2/antioxidant-responsive element (ARE) pathway in rat kidney epithelial cells [201]. Curcumin also increased the expression of the heat shock protein HSP70 [202]. Several studies have shown that curcumin inhibits phase 1 enzymes and activates phase 2 enzymes, leading to reduced toxic metabolites and increased antioxidants effects [203–206]. Curcumin acts indirectly to reduce oxidative stress through the inhibition of inflammatory pathways through the inhibition of NF-κB, which will be discussed later in the article.

Paradoxically, curcumin can selectively induce oxidative stress in cancer cells, leading to apoptosis and autophagy [207–209]. This was further proven when N-acetyl cysteine or glutathione was added and the curcumin effect was nulled [209,210]. The etiology of the paradoxical action of curcumin is unclear, but one study points to the significantly higher intake of curcumin in cancer cells [211]. Multiple studies are leveraging curcumin in the treatment of different types of cancers.

Among the various benefits of curcumin, the regulation of ER (Endoplasmic Reticulum) stress by using curcumin is an important strategy in treating several diseases such as cancer [212], diabetes [213], osteoporosis [214] and neurodegenerative diseases [215]. ER stress is caused due to the accumulation of unfolded or misfolded proteins, leading to a stress response called unfolded protein response (UPR). Curcumin can regulate ER stress by causing cell apoptosis or cell survival based on the type of cell being examined. In normal cells, curcumin scavenges ROS and decreases UPR, thereby suppressing ER stress and inhibiting apoptosis. In the case of inflammatory diseases, curcumin activates the MAPK pathway and increases the proteins involved in apoptosis such as transcription factor 6, the glucose-regulating protein and the C/EBP homologous protein CHOP. In diabetes, ER stress has been shown to trigger beta cells dysfunction or cell death [216]. Curcumin suppresses NF-κB activity and reduces caspase-12 and caspase-3 levels (usually increased due to ER stress) [217]. In murine myelomonocytic leukemia cells, curcumin induced apoptosis by the generation of ROS, the cytosolic release of Ca^{2+} and the inducing of DNA damage [218,219]. In human lung carcinoma A-549 cells, curcumin prevented cell proliferation by inducing G2/M-phase arrest and increased p53 and p21 levels, which are hallmarks of ER stress [220]. Curcumin caused apoptosis via the activation of CHOP in human leukemia HL-60 cells [221]. The exact cellular mechanism underlying the effect of ER stress on cell death or cell survival still needs more evidence due to its dualistic response.

3.7. Gut Microbiota

The exceptionally complicated and abundant microbial community inhabits the GI tract, with 100 trillion bacteria which are, remarkably, 10–100 times greater than the number of eukaryotic cells [222]. Furthermore, the gut environment differs markedly between different anatomical regions regarding physiology, substrate availability, digesta flow rates, host secretions, oxygen tension and pH [223,224]. Aside from the poor systemic bioavailability of curcumin, it is expected to be found at high concentrations in the gastrointestinal tract after oral administration. Thus, it is suspected that curcumin could exert direct regulative effects on the gut microbiota, which could explain the paradox between curcumin’s poor systemic bioavailability and its widely reported pharmacological effects (Table 4).
Table 4. Effect of curcumin on gut microbiota and its mechanism of action.

| Curcumin Doses                  | Effect on Gut Microbiota                          | Molecular Mechanisms                                                                 | Model                          | Ref.  |
|---------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------|-------|
| Curcumin at a low dose (1 g/day) | Curcumin shifted the structure of gut microbiota | Curcumin enervated the Western diet-induced development of atherosclerosis and type 2 diabetes mellitus | Sprague Dawley rats          | [225] |
| 100 mg/kg/day                   | Lowers the increasing abundance of the genera Anoerotruncus and Helicobacter in the gut microbiota | Decreases the estrogen level, resulting in an increase in body weight                 | Wistar rats                   | [226] |
| 100 mg/kg/day                   | Curcumin affected the presence of Prevotellaceae, Bacteroidaceae, and Rikenellaceae in gut microbiota | Curcumin possesses anticancer activity in vitro and in preclinical animal models via the activation of caspases 3, 8 and 9 in the colon cancer cell lines | Fecal sample                  | [227] |
| 8000 mg per day                 | Increase in Lactobacillus and decrease in Coriobacterales | Induction of apoptosis through the COX-2 and non-COX-2 pathways. It targets cancer stem cells (CSC) through direct or indirect influences on the CSC self-renewal pathways. | Colon cancer cell lines, SW480 and SW62 | [228] |
| 0.2% (w/w) nanoparticles of curcumin | Increase in butyrate-producing bacteria and the fecal butyrate level | Mucosal mRNA expression of inflammatory mediators and the activation of NF-κB in colonic epithelial cells were suppressed by curcumin nanoparticles | BALB/c mice                   | [229] |

3.8. Inflammatory Bowel Disease (IBD)

TNF blockers, immunosuppressants and anti-inflammatory medications are commonly used to treat IBD, but due to the insufficient results and high cost involved in the treatment, there has been a need for alternatives. Bioactives have antioxidant and anti-inflammatory activity that could be used to effectively treat or prevent IBD. The use of curcumin in preclinical studies has suggested that it can target various molecular and cellular pathways involved in IBD pathogenesis. Recent studies have shown that the various molecular signaling pathways that participate in IBD development are targeted by curcumin, including PPAR-gamma, P13K, TLR-4, Akt, mTOR, ERK5, AP1, TGF-β, PAK1, Wnt, β-catenin, Shh, Rac1, p38MAPK, EBPα, NLRP3 inflammasome, Nrf2, Notch-1, AMPK, STAT3, STAT5 and MyD-88 [230,231].

Autophagy suppression has been linked with an excessive inflammatory response in IBD. In this regard, curcumin has shown an autophagy-regulating property by reducing the expression of genes such as Beclin-1, autophagy-related gene 5 and LC3II. In addition, curcumin has shown anti-apoptotic activity by inhibiting apoptotic cell death, thereby preventing damage to the intestinal epithelial barrier [232]. Studies have shown that curcumin suppresses NF-κB in chondrocytes by reducing the expression of cyclooxygenase, prostaglandin E-2 and inflammatory cytokines [233]. Curcumin can also interact with transient potential vanilloid receptor 1 in inflamed tissues to prevent intestinal inflammation [234]. Curcumin analogues such as non-electrophilic curcumin are known to suppress colitis in mice by inhibiting pro-inflammatory signals. Numerous clinical studies have linked inflammatory diseases to NLRP3. We agree with Karthikeyan et al. (2018) that curcumin can be a potential NLRP3 inflammasome suppressant by in vivo studies, and this could be a promising treatment for IBD [235].

However, due to its iron reduction property, curcumin should be carefully used for treatment since poor iron absorption is already seen in IBD patients. Therefore, monitoring
the erythroid parameters is essential. Although curcumin alone or in combination with other drugs could be used for treatment by optimising the dosage, rigorous randomized controlled and long-term clinical trials should be conducted to establish the role of curcumin in the treatment of IBD.

4. Anti-Microbial

The antimicrobial activity of curcumin dates back to the old days when it was used as an insect repellent in the house [236]. Later, it was introduced as a potential suppressor of microbial activity in the cotton and wool industries [237]. Curcumin and other antimicrobial compounds have been key ingredients in ointments for skin protection and wound-dressing properties [238]. Several studies have reported the broad-spectrum antimicrobial activity for curcumin, including antibacterial, antiviral, antifungal and antimarial activities.

4.1. Antiviral

Antiviral drugs are in high demand due to increasing viral infections globally and the lack of preventive and therapeutic options [238]. The first known antiviral activity of curcumin dates back to the 1990s, with the discovery that curcumin inhibits HIV viral protease in vitro. Since then, several studies have been conducted to understand its mechanism of action on different types of viruses. Each stage of the viral replication cycle, such as attachment/penetration, genome replication, gene expression, assembly and release, has been an attractive target for the effective inhibitory activity of curcumin. During the attachment step, the uptake of viral particles by binding to the receptors on the host cell membrane surface and entry into the host cell takes place by receptor-mediated endocytosis [239]. As a result, Curcumin has shown effective activity:

1. Against the viral envelope proteins by (a) modulating the membrane lipid bilayer of the host [240], (b) inhibiting its entry by interacting with viral surface proteins and reducing viral particle production [241], (c) disrupting the integrity of the viral membranes [242].
2. By targeting replication in two ways: (a) targeting the viral replication machinery and (b) modulating cellular factors to interrupt the replication process [243,244].

4.1.1. Human Immunodeficiency Virus (HIV)

Curcumin has been shown to impact the HIV function at several stages of the virus lifecycle. Ferreira et al. conducted a study to understand the anti-inflammatory activity of curcumin in the female genital tract, which leads to the downregulation of tight junction (TJ) proteins, resulting in barrier loss and thereby allowing HIV-1 to traverse the genital epithelium and infect the host. The treatment of genital epithelial cells with 5 µM curcumin reduced the expression of virus replication marker p24 and protected the epithelial barrier by preventing TJ protein downregulation, thus reducing the HIV infection rate [245]. Curcumin can inhibit HIV replication by interacting with the viral integrase, protease and trans-activator of the transcription (Tat) protein. Docking studies have suggested that curcumin could bind effectively to the active site of HIV-1 protease [246]. Pretreatment with curcumin has inhibited the induction of proinflammatory cytokines such as IL-6, TNF and chemokines IL-8, IP-10, RANTES, eotaxin, MIP-1α (Macrophage Inflammatory Protein-1 Alpha) and MCP-1. In one study, curcumin degraded the Tat protein through a proteasomal pathway [247] and reduced its transactivation in HIV-1-infected cells. Even curcumin analogues, such as curcumin A (which lacks the β-diketone moiety of curcumin), have been tested against HIV-1 [248]. This study showed that curcumin A lowered late viral genome copy levels and could inhibit the early reverse transcription of the virus [248]. The therapeutic activity of curcumin is due to its ability to activate heme oxygenase-1, thereby inhibiting HIV-1 [249]. Curcumin-stabilized silver nanoparticles have shown promising activity by lowering HIV-LTR (Long Terminal Repeat) expression and lowering the expression of TNF-α, IL-6, IL-1β and NF-κB [250]. Collectively, these studies show curcumin’s potential against HIV-1.
4.1.2. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Wen et al. (2007) have shown that curcumin can inhibit SARS-CoV-1 replication in the cultures of Vero E6 cells (EC_{50} of > 10 \mu M) [251]. Docking studies have concluded that curcumin could bind to target receptors such as protease, spike glycoprotein-receptor binding domain and PD-ACE2 (Angiotension Converting Enzyme-2). The ability of curcumin to modulate a wide range of molecular targets that are responsible for the attachment and internalization of SARS-CoV-2 could be used to effectively manage the coronavirus infection. Furthermore, Curcumin could block the entry of viruses into the cell by altering surface protein structures in the virus. Adding to this, a molecular docking study indicated that curcumin could bind to ACE2 to inhibit COVID19 entry into the cell. Curcumin could also interact with the viral protease, such as the main protease, which could be a potential therapeutic target [252]. Due to growing evidence on the effect of curcumin on interferons in different viral diseases, curcumin could trigger innate immunity by stimulating the production of interferon-stimulating genes and cytokines, as seen in the study on a porcine epidemic diarrhea virus model. Curcumin has played an important role in reducing the expression of crucial chemokines and cytokines such as IFN-\(\gamma\), MCP-1, IL-6 and IL-10 in lung infection [253] and against the human RSV, preventing viral replication, which could be used to treat pulmonary inflammation due to COVID-19 infection. Reduction in the ACE2 expression could decrease the risk of renal damage. In this regard, curcumin could upregulate ACE2, leading to improved renal blood flow [254]. Curcumin can be used as an effective anti-fibrotic agent in kidneys [143]. To sum up, the antiviral and anti-inflammatory activity of curcumin can be helpful in both preventing and treating COVID-19. Further in vitro studies could help us better understand the mechanism of action, if any exists.

4.1.3. Influenza A Virus (IAV)

Curcumin has been shown to inhibit NF-\(\kappa\)B signaling, which is required for IAV replication. Curcumin or its analogues have been shown to inhibit IAV by preventing entry, inhibiting replication or preventing viral exit. A study by Dai et al. showed that curcumin interferes with early-stage virus gene expression and replication and inhibits several IAV-induced toll-like receptor signaling pathways including TLR2/4/7, MyD88, TRIF and TRAF6 [255,256]. Additionally, curcumin reduced IAV replication and lung injury in an in vivo animal model, which explains its role in combating infection and viral-induced disease [257]. Another study by Han et al. made a similar observation on mice infected with the IAV strain PR8 and fed 30 or 100 mg/kg of curcumin. Curcumin-treated mice had lower levels of MCP-1, IL-6 and TNF-\(\alpha\) in bronchoalveolar lavage fluid and lung tissues as compared to untreated mice [257]. Curcumin analogues such as monoacetylcurcumin have inhibited plaque formation (IC_{50}=0.2 \mu M). Although curcumin and MAC mildly reduce neuraminidase activity, they act via different mechanisms to inhibit IAV. The authors have suggested a combined use of the two for better activity [258]. A study by Lai et al. on MDCK cells treated with curcumin showed reduced mRNA levels of the IAV M gene in infected cells. Additionally, curcumin reduced lung pathology in in vivo treated mice [259].

4.1.4. Herpes Simplex Virus (HSV)

Curcumin inhibited plaque formation by 88% and blocked viral adsorption by 92% in HSV1- and HSV2-infected Vero cell lines at a concentration of 30 \mu M. Curcumin treatment at a 5 \mu M concentration in primary human GECs reduced HSV-2 replication 1000-fold compared to the control group, and 50 \mu M of curcumin showed 100% inhibition [245]. To enhance the bioavailability of curcumin, it was encapsulated by Poly-(Lactic-Co-Glycolic Acid) and delivered via an intravaginal route against HSV-2 infection in mice. The results showed that curcumin-PLGA had no effect on the mice’s survival following the low or lethal dose of HSV-2 [260].
4.1.5. Dengue Virus (DENV)

Curcumin reduced the plaque formation of all four strains (DENV-1–4) examined in LLC-MK2 cells, with limited toxicity (CC\textsubscript{50} of 59.42 \textmu M). Another study showed that curcumin inhibits DENV-2 by the indirect interaction with cellular systems rather than directly on viral function. A study by Balasubramanian et al. evaluated the anti-DENV (Dengue virus) properties of curcumin and other synthesized analogues. Curcumin and the analogues showed inhibitory activity on viral protease activity (IC\textsubscript{50} 36–66 \textmu M) [261]. The MOA of curcumin was through cellular lipid metabolism, as it downregulated acetyl-CoA carboxylase and fatty acid synthase and lowered the lipid droplet formation, which is usually seen in a DENV infection. Mainly, actin filament disorganization and defects in polymerization were seen after the curcumin treatment. Therefore, curcumin shows anti-DENV activity by actin filament organization, cell lipogenesis and viral enzymes [261,262].

4.1.6. Enterovirus 71 (EV71)

Huang et al. evaluated the activity of curcumin against EV71 in HT29 human intestinal epithelial cells. A 10 \textmu M concentration of curcumin reduced the protein expression during the early stage of infection and the genome replication of the virus and prevented EV-71-induced cell death. Usually, cells infected with EV71 show the phosphorylated residue Tyr311 of protein kinase C-delta [263], but it was reduced in curcumin-treated cells. Lin et al. evaluated curcumin-derived carbon quantum dot formulations (Cur-CQD) against EV71 [264]. This formulation increased the water solubility of curcumin due to a better antiviral activity. In addition, cur-CQD lowered the expression of viral proteins such as structural protein VP1 and non-structural proteins such as 3CD\textsuperscript{pro} and 3D\textsuperscript{pol} in a dose-dependent manner. The treatment also reduced the amount of viral mRNA and proteins that were detected in the brain and limb muscle tissue [252].

4.2. Antifungal Activity

Curcumin has the potential to be used as an antifungal against a wide range of fungi in in vitro and in vivo studies including cryptococcus, candida, trichophyton and Paracoccidioides [265,266]. With the emerging antifungal resistance, candida and other fungi species, there is a need for novel antifungal agents [267–269]. In addition, traditional anti-fungal medications such as azoles and polyenes possess serious side effects, most commonly resulting in kidney damage. On the other hand, curcumin has displayed minimal toxicity in a few reports, but no long-term trials have been conducted to assess its safety [270–272].

The exact mechanism of curcumin is unknown, but evidence by Sharma et al. showed that curcumin affects candida by increasing the production of reactive oxygen species (ROS) through altering membrane ATPase activity, interfering with ergosterol synthesis and inducing apoptosis as a result of reactive oxygen species accumulation [273–275]. This was proved further by including an antioxidant that attenuated curcumin’s effects on the fungus. The effect of curcumin on fungal cells also extends to the inactivation of specific genes that affect growth and drug metabolism. Curcumin targets global suppressor thymidine uptake 1 (TUP1) in candida, leading to its transcription and inhibiting hyphae development. Curcumin restored the sensitivity to fluconazole, which might be due to its effect on the active transporters (ABC and MDR) of the drug [273,276]. Curcumin has phytochemical properties when combined with photodynamic therapy and can be genotoxic to many fungi (candida, aspergillus and dermatophyte) since it can prevent the repair process of DNA damage [277–279].

A study by Martinez et al. measured the minimal inhibitory concentration (MIC) of Curcumin against 23 human pathogenic strains of fungi in vitro. Although Curcumin was more potent in many strains of Paracoccidioides brasiliensis than fluconazole, the strain MG05 growth was inhibited at an MIC of 0.5 mg/L of curcumin compared to 16 mg/L of fluconazole. Curcumin exhibits the potential to be administered through multiple routes, including intravenous, topical and oral routes depending on the offending agent site of
infection. One study isolated the samples of candida from HIV patients with oropharyngeal candidiasis and exposed them to curcumin, which inhibited 90% of the yeast [280]. A study conducted on a vulvovaginal yeast infection model in rats benefited from 1.0% curcumin local cream application [281].

Owning to the phytochemical properties of curcumin. Many studies have examined the effect of curcumin with light on candida biofilm growth and dermatophytes infection. For example, Brasch et al. found that curcumin plus visible light inhibited the growth of different dermatophytes [278]. In addition, an experiment conducted by Dovigo et al. showed that candida growth and biofilm formation were inactivated using curcumin with photodynamic therapy [277].

Curcumin possesses the potential to be used as a monotherapy or in combination with azoles or polyenes. Sharma et al. proved that, when used in combination with Amphotericin b, curcumin showed a synergistic effect and a reduced side effects profile [273]. This can be leveraged in the future to reduce the dosage and, in turn, the side effects of current anti-fungal medications.

4.3. Antibacterial

Several antibiotics are available against specific bacteria. However, due to the extensive use of drugs, it is challenging to eliminate pathogens from the human body due to developed resistance. So, it is important to naturally get rid of bacterial infections. Curcumin, a known spice, shows antibacterial activities against most gram-positive and gram-negative bacteria [282]. Curcumin is known to be a relatively unstable molecule, with a particle size of 500–800 nm, impairing cellular uptake and resulting in low bioavailability [283,284]. A study found that curcumin kills several pathogenic gram-positive bacteria such as *Staphylococcus aureus, Staphylococcus epidermidis* and *Enterococcus*, which are the main causative agent of skin diseases, pneumonia, meningitis and urinary tract infections in human beings [282]. In addition, curcumin suppresses the adherence of *Streptococcus mutans* to human tooth surfaces and the extracellular matrix protein [285]. Curcumin possesses a synergistic effect with important antibiotics such as cefixime, vancomycin and tetracycline against *Staphylococcus aureus (S. aureus)* [286–288]. However, very few studies have demonstrated the mechanism of the antibacterial activity of curcumin, which seems to differ depending on the strain being studied. For instance, studies have shown that the antibacterial activity of curcumin against *Bacillus subtilis* occurs through the inhibition of bacterial cell proliferation by blocking the assembly dynamics of FtsZ in the Z ring [289]. In the case of *Pseudomonas aeruginosa (P. aeruginosa)* infection, curcumin was shown to have anti-infective activity by affecting virulence, quorum sensing and biofilm initiation [236].

Moreover, these mechanisms have not been confirmed in the case of other bacterial genera and, hence, could not be generalized for all bacteria. Therefore, a detailed study on the antibacterial mechanism of curcumin, including a large number of bacteria from different genera, is required. Furthermore, due to the increase of resistance in Gram-positive and Gram-negative bacteria, there is an urgent need to identify and assess alternative antimicrobials, including those from plant materials with low human cytotoxicity. Curcumin I showed no toxic effect on human health, even when taken at doses as high as 8 g per day [290].

5. Clinical Trials with Curcumin

Numerous clinical trials have been conducted with curcumin, appraising its therapeutic and pharmacological benefits across different patient populations. A summary of the concluded trials is depicted in Table 5, which will allow the reader to get a quick insight into the disease/patient population of interest. In this study, we have only considered registered and completed trials in the Clinical Trials registry. Of all the clinical trials, trial number NCT00927485 has studied the role of curcumin on intestinal adenomas for a significant duration of over 5 years, whereas others have done so for only a limited period of time.
Therefore, the obtained results should be taken with a grain of salt. Case in point, in trial number NCT04012424, the trial was conducted for only a period of two days. This indicates that further trials extending over longer periods are required. Another shortcoming that is observed in most of the trials is the low number of participants. For example, in trial number NCT03568513, the effect of curcumin on IBS was only studied in 4 people out of the 50 that were expected to enroll.

Additionally, the trial has been conducted at a single center and does not provide enough information about the physiological and genetic makeup of the participants, which has been shown to affect the intestinal microbial milieu. Thus, the trial from this and similar trials require further investigation and validation. In addition to the above, most of the trials available in the database have not posted the obtained results; this makes it difficult to conclude if their primary outcome was achieved. The open-label study of the curcumin CS complex in schizophrenia (trial number NCT01875822) (Sl No.18) concluded in 2012; no results are available in the study page or in the literature. Although curcumin exhibits beneficial pharmacological effects in cell and animal models, the results are not very well replicated in human subjects. This has drawn considerable skepticism, and curcumin has been labelled as a pan-assay interference (PAINS) compound in the case of different screening tests such as fluorescence interference, the covalent labelling of proteins, redox reactivity, etc. It is to be noted that these tests are limited to in vitro studies; the real results obtained from human trials and case reports are more valid than any theoretical warning to prove its activity. Additionally, there has not been any experiment to prove that the biological activity of curcumin is due to its unique structure. A paper [291] suggested that curcumin is a “bimolecular sensitive fluorescent probe.” This does not necessarily have to be related to a fluorescence interfering property. We also know that any molecule with an ability to interact with various targets could bring numerous side effects. When it comes to several in vivo studies, curcumin proved to be safe even at a very high dose. A clinical trial in healthy volunteers consuming 500 to 12,000 mg of curcumin showed no toxicity, but a very low serum availability was detected in 2 of the 6 patients who received the highest dose (10,000 mg and 12,000 mg) [292]. This could possibly be due to the genetic modifiers of curcumin metabolism or even to the preparation method of commercially obtained curcumin. The activity of curcumin has also been related to its metabolites, which are more of an advantage, as this could possibly be used to treat diseases with multiple causes such as cancer and diabetes. A letter to the editor by Burgos-Moron et al. entitled “The dark side of curcumin” [293] suggests that the cytotoxicity of curcumin and its ability to intercalate into DNA have been nullified by an experiment conducted by Kurien et al., stating that the cytotoxicity was not due to curcumin but due to the solvent used for the dissolution of curcumin (i.e., ethanol) [294]. The best possible explanation for the ineffectiveness of curcumin in certain studies could be the very low bioavailability or moderate biological activity of curcumin. The non-replication of activity is related to curcumin’s low bioavailability due to the high hydrophobicity caused by the cyclic rings in its structure. Studies have shown that the combination with piperine enhances the serum concentration, the extent of absorption and the bioavailability of curcumin. However, few clinical trials have employed this strategy. In this regard, further investigation is required.
Table 5. Effect of curcumin on the completed clinical trials.

| Sl No. | Clinical Trial Identifier | Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|---------------------------|-------------|---------------------|--------------------|-------------------|-----------------|-------------------|-----------------|
| 1.     | NCT03085680               | Curcumin and Function in Older Adults | 21                  | Aged above 65 years with a CRP level greater than 1.0 mg/dL | 2020             | To examine the effects of dietary supplementation with curcumin on changes in physical function, walking speed (400 m walk test) and grip strength | 2                | 90 days          |
| 2.     | NCT03211104               | Comparison of Duration of Treatment Interruption with or without Curcumin During the Off Treatment Periods in Patients with Prostate Cancer Undergoing Intermittent Androgen Deprivation Therapy | 107                 | Patients with localized prostate cancer or metastatic prostate cancer at the time of diagnosis who received intermittent androgen deprivation therapy (IAD) | 2015             | To determine whether the period from the first interruption of the androgen deprivation therapy to the time when androgen deprivation therapy needs to be retreated differs between the curcumin group and placebo group | NA              | 180 days         |
| 3.     | NCT04012424               | The Effect of Premedication with Curcumin on Post-endodontic Pain | 44                  | Patients in the age range of 20–55 years with acute pulpitis | 2020             | Change in postoperative pain after a single endodontic visit | N/A             | 2 days           |
| 4.     | NCT04870060               | Ability of Curcumin to Decrease Cytokines Involved in Mucositis in the Autologous Transplant | 40                  | Patients aged 18 years and above with a creatinine clearance greater than 50 mL/min and a serum bilirubin level greater than 2 mg/dL | 2015             | To calculate TNFa, IL-1, IL-6, IL-8, IL-17, TGF-B, IFN-gamma and E2 levels | 2               | 28 days          |
| 5.     | NCT01543386               | Effects of Curcumin on Vascular Reactivity | 21                  | 50- to 70-year-old smokers | 2012             | Changes in brachial flow-mediated dilatation | 2               | 5 days           |
| 6.     | NCT03568513               | Effect of Curcumin on Gut Microbiota in IBS | 4                   | Patients aged 10 to 18 years with diarrhoea-predominant IBS | 2020             | Alterations in gut microbiota | N/A         | 56 days          |
| 7.     | NCT03864783               | The Effect of Curcumin on Liver Fat Content in Obese Subjects | 39                  | BMI and haemoglobin greater than 30.0 kg/m² and 7.5 mmol/L, respectively | 2020             | Curcumin’s effect on steatosis | N/A | 42 days          |
Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|--------------------------|-------------|---------------------|--------------------|-------------------|-----------------|-------------------|------------------|
| 8.     | NCT04044417              | Curcumin-Simvastatin-EDTA in the Treatment of Periodontitis | 30                  | Patients aged 25 to 50 years suffering from at least a single posterior 2–3 wall periodontal pocket of depth | 2018              | Reduction in probing depth | 4                | 180 days         |
| 9.     | NCT04032132              | Curcumin Paste as an Adjunctive Therapy in Periodontitis | 24                  | Patients aged 25 to 45 years with at least a single posterior 2–3 wall periodontal defect of pocket depth | 2018              | Evaluate the influence of curcumin paste on the clinical outcomes of the surgical treatment | 4                | 180 days         |
| 10.    | NCT03746158              | Interindividual Variation in Excretion of Curcumin | 8                   | 18–30-year-old healthy adults. | 2019              | Determine the concentration of curcumin and its metabolites in human fecal samples | N/A              | 28 days          |
| 11.    | NCT01179256              | Effect of Supplemental Oral Curcumin in Patients with Atopic Asthma | 16                  | Patients aged 18–60 years on low- or medium-dose inhaled corticosteroids | 2010              | Improvement in post-bronchodilator FEV1 | N/A              | N/A              |
| 12.    | NCT01246973              | Oral Curcumin for Radiation Dermatitis in Breast Cancer Patients | 686                 | Females aged 21–120 years | 2015              | To measure the Mean Radiation Dermatitis Severity Score | 2                | 42 days          |
| 13.    | NCT04119752              | Effect of Curcumin on Microvascular Response and Tissue Oxygenation in Older People | 28                  | Aged 60–85 years with two or more risk factors for cardiovascular disease | 2020              | Changes in microvascular reactivity and tissue oxygen saturation. | N/A              | 120 min          |
| 14.    | NCT02255370              | Curcumin Associated with Thiopurin in the Prevention of Post-op Recurrence in Crohn Disease (POPCUR) | 61                  | Patients aged 18 years and older with Crohn’s disease | 2018              | Rutgeerts endoscopic score | 3                | 180 days         |
| 15.    | NCT02298985              | Curcumin Addition to Antipsychotic Treatment in Chronic Schizophrenia Patients | 38                  | Patients aged 18–60 years with schizophrenia and a SANS greater than 30 points | 2017              | Positive and Negative Symptoms Scale (PANSS) | 4                | 180 days         |
## Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Trial Title                                                                 | No. of Participants | Inclusion Criteria                                                                 | Year of Completion | Primary Outcome                                                                 | Clinical Trial No. | Follow-Up Period |
|--------|---------------------------|------------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------|--------------------|------------------|
| 16.    | NCT01383161               | 18-Month Study of Memory Effects of Curcumin                                 | 46                  | Aged 50–90 years with a modified Ischemic score of less than 4                      | 2017               | Change from the baseline to 18 months on the Brief Visual Memory Test-Revised    | 2                  | 540 days         |
| 17.    | NCT01333917               | Curcumin Biomarkers                                                         | 40                  | Healthy volunteers aged 40–80 years                                                 | 2013               | To understand the changes in gene expression, the ribonucleic acid (RNA) level and apoptosis | 1                  | 30 days          |
| 18.    | NCT01875822               | Open-label Study of Curcumin C-3 Complex in Schizophrenia                    | 17                  | Patients aged 18–65 years with DSMIV schizophrenia and a SANS greater than 30      | 2012               | To understand the change from the baseline negative symptoms: alogia, anhedonia, social withdrawal and lack of motivation | 2                  | 112 days         |
| 19.    | NCT02978339               | A Study Evaluating the Safety and Efficacy of Curcumin in Patients with Primary Sclerosing Cholangitis (PSC) | 15                  | Diagnosed with primary sclerosing cholangitis with alkaline phosphatase >1.5×       | 2019               | Change in Serum Alkaline Phosphatase (SAP)                                      | 2                  | 84 days          |
| 20.    | NCT04208334               | The Effect of Curcumin for Treatment of Cancer Anorexia-Cachexia Syndrome in Patients with Stage III-IV of Head and Neck Cancer (CurChexia) | 20                  | Patients with stage 3–4 head and neck cancer                                        | 2021               | To measure muscle mass                                                          | 2                  | 60 days          |
| 21.    | NCT01925287               | Oral Bioavailability of Curcumin from Micronized Powder and Liquid Micelles in Healthy Young Women and Men | 23                  | Healthy volunteers with a normal range blood chemistry value                        | 2013               | To determine total curcumin, demethoxycurcumin and bisdemethoxycurcumin after deconjugation with beta-glucuronidase | 1                  | 24 h             |
| 22.    | NCT02104752               | Curcumin as a Novel Treatment to Improve Cognitive Dysfunction in Schizophrenia | 39                  | Volunteers diagnosed with DSM-5 schizophrenia with a corrected vision of at least 20/30 | 2017               | Measurement and treatment research to improve cognition in schizophrenia        | 1                  | 56 days          |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|--------------------------|----------------------|--------------------|-------------------|-------------------|----------------|------------------|------------------|
| 23.    | NCT02369549              | Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease | 518                | Patients with an eGFR between 15 and 60 mL/min/1.73 m² with a minimum of 300 mg of protein in urine or with a albumin/creatinine ratio of at least 300 mg | 2020             | Change in albuminuria and the Estimated Glomerular Filtration Rate (eGFR) | 3                | 180 days         |
| 24.    | NCT02439385              | Avastin/FOLFIRI in Combination with Curcumin in Colorectal Cancer Patients with Unresectable Metastasis | 50                | Colon or rectal cancer patients aged above 19 years with an ASA score of less than 3 | 2019             | To evaluate progression-free survival in colorectal cancer patients | 2                | 730 days         |
| 25.    | NCT02474953              | A Study to Compare the Pharmacokinetic Profile of a Proprietary Curcumin Formulation to a Comparator Curcumin Product (15PCHB) | 12                | Volunteers aged 18–45 years with a BMI that is 18–29.9 kg/m² (±1 kg/m²) | 2015             | To measure the maximum concentration of curcumin and time until the max concentration of curcumin | 1                | 48 h             |
| 26.    | NCT04421716              | Testing the Bioavailability of Phytonutrients, Curcumin and Ursolic Acid | 18                | Men aged 18 years or older | 2021             | To evaluate the number, frequency, duration and relation of toxicity events to CURC and UA, the peak serum concentration, the half-life and the time taken to reach the maximum concentration | 1                | 14 days          |
| 27.    | NCT04258501              | Exploratory Study of Efficacy on Selected Natural Extracts Reducing Post Prandial Blood Glucose Response | 72                | 20–50-year-old healthy individuals with a normal BMI | 2012             | Change in post-prandial blood glucose | NA              | 2 h              |
| 28.    | NCT01035580              | Trial on Safety and Pharmacokinetics of Intravaginal Curcumin | 13                | Volunteers aged 18–45 years currently using a birth control method | 2012             | To reach the maximum selected dose or maximum tolerated dose of intravaginal curcumin without a dose-limiting toxicity | 1                | 14 days          |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|-------|--------------------------|----------------------|---------------------|--------------------|-------------------|----------------|-------------------|-----------------|
| 29.   | NCT01403545              | Evaluation of Liposomal Curcumin in Healthy Volunteers | 50                  | Volunteers in the age group of 18–45 years with a BMI between 18–27 kg/m² | 2012             | Safety and tolerability of increasing doses of intravenous liposomal curcumin | 1                | 7 days           |
| 30.   | NCT01225094              | Curcumin to Prevent Complications After Elective Abdominal Aortic Aneurysm (AAA) Repair | 606                 | Volunteers aged 18 years or above who have undergone the repair of AAA | 2016             | To measure urine IL-18, NT-ProBNP, hsCRP and serum creatinine | 2                | N/A             |
| 31.   | NCT01160302              | Curcumin Biomarker Trial in Head and Neck Cancer | 33                  | Volunteers aged between 18–90 years willing to undergo tumor biopsies | 2016             | Change in tissue biomarkers and pharmacokinetics of microgranular curcumin | 1                | 28 days          |
| 32.   | NCT01917890              | Radiosensitizing and Radioprotective Effects of Curcumin in Prostate Cancer | 40                  | Aged between 50–80 years with relapsed or treated basal skin cancer and no severe hypertension | 2013             | Biochemical or clinical progression-free survival | N/A              | 365 days         |
| 33.   | NCT00895167              | The Effects of Oral Curcumin on Heme Oxygenase-1 (HO-1) in Healthy Male Subjects (CUMAHS) | 12                  | Aged between 18–45 years with a BMI between 18 and 28 kg/m² | 2009             | The maximal HO-1 mRNA expression and HO-1 protein level in PBMCs | 1                | 48 h            |
| 34.   | NCT03542240              | Effects of Curcumin Supplementation on Gut Barrier Function in Patients with Metabolic Syndrome | 15                  | Waist Circumference— Female: ≥88 cm, Male: ≥102 cm B. Blood Pressure: ≥130/85 mm/Hg. Impaired fasting glucose or HbA1c. | 2020             | Change in intestinal permeability and intestinal barrier function | N/A              | 365 days         |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|-------|--------------------------|----------------------|---------------------|-------------------|-------------------|-----------------|-------------------|------------------|
| 35.   | NCT00927485              | Use of Curcumin for Treatment of Intestinal Adenomas in Familial Adenomatous Polyposis (FAP) | 44 | 21–85 years with FAP (with an intact colon or who have had surgery) | 2016 | To determine the number of polyps and the size of polyps | 5 years |
| 36.   | NCT01042938              | Curcumin for the Prevention of Radiation-induced Dermatitis in Breast Cancer Patients | 35 | Females aged 21 years or above with a diagnosis of non-inflammatory breast adenocarcinoma | 2011 | Severity of dermatitis in the radiation treatment site in breast cancer patients | 2 49 days |
| 37.   | NCT01490996              | Combining Curcumin with FOLFOX Chemotherapy in Patients with Inoperable Colorectal Cancer (CUFOX) | 41 | 18 years or above, diagnosed with metastatic colorectal cancer and with an ECOG status of 0 or 1 | 2017 | Completion of dose escalation over two cycles of therapy | 2 365 days |
| 38.   | NCT01975363              | Pilot Study of Curcumin for Women with Obesity and High Risk for Breast Cancer | 29 | Females with an increased risk of breast cancer and a BMI between 25–40 | 2016 | Determine the adherence, tolerability and safety of two doses of nanoemulsion curcumin | N/A 90 days |
| 39.   | NCT01859858              | Effect of Curcumin on Dose Limiting Toxicity and Pharmacokinetics of Irinotecan in Patients with Solid Tumors | 23 | Aged above 19 years with adequate bone marrow, renal and hepatic function and an ECOG status of 0 or 1 | 2016 | Maximum tolerated dose, pharmacokinetics of irinotecan and SN-38 | 1 28 days |
| 40.   | NCT04103788              | Evaluation of Increased Absorption of a Curcumin Emulsion (CurQ+) in Healthy Volunteers | 10 | Aged between 21 and 75 years | 2018 | Comparative effect of differing serum sample preparation methodologies on curcumin absorption levels | N/A 6 h |
| 41.   | NCT01925547              | Micellar Curcumin and Metabolic Syndrome Biomarkers | 42 | Total cholesterol > 5.2 mmol/L, LDL cholesterol > 3.4 mmol/L, Triglyceride > 2.26 mmol/L, CRP > 2 mg/L | 2014 | To measure the serum CRP level | 2 42 days |
| Sl No. | Clinical Trial Identifier | Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome Clinical Trial No. | Follow-Up Period |
|-------|--------------------------|-------------|---------------------|--------------------|-------------------|-----------------------------------|-----------------|
| 42.   | NCT01330810              | Curcumin Pharmacokinetics | 12                  | Aged between 16 and 65 years with a BMI in the range of 18–30 kg/m² | 2012              | To measure the AUC, Cₘₐₓ, Tₘₐₓ, Ke, T₁/₂, Vₚ and bioequivalence of tissue curcumin concentration | 1 48 h          |
| 43.   | NCT02908152              | Curcumin Supplement in Nonalcoholic Fatty Liver Patients | 50                  | Patients diagnosed with type 2 diabetes with a CAP score greater than 263 | 2017              | To measure hepatic steatosis | 2 72 days |
| 44.   | NCT01201694              | Phase I Study of Surface-Controlled Water Soluble Curcumin (THERACURMIN CR-011L) | 28                  | Patients aged 13 or older with an ECOG status of 3 or better and normal organ and marrow function | 2014              | To measure the Maximum Tolerated Dose (MTD) of surface-controlled water-dispersible curcumin | 1 28 days |
| 45.   | NCT04028739              | Theracurmin vs. Curcumin Bioavailability Study | 24                  | Healthy adults aged 19–60 years with a BMI of 18–30 kg/m² | 2019              | To compare the bioavailability of curcumin in healthy adults | NA 12 h |
| 46.   | NCT03795792              | Oral Curcumin Administration to Remit Metabolic Syndrome | 105                 | Men and women aged 20–55 years old with metabolic syndrome according to the ATP III criteria | 2019              | Remission of metabolic syndrome (≤2 components according to the ATP III criteria) | NA 3 months |
| 47.   | NCT00528151              | A Randomized, Double-blind, Placebo-controlled Trial of Curcumin in Leber’s Hereditary Optic Neuropathy (LHON) | 70                  | Aged 8 years or older with Leber’s hereditary optic neuropathy | 2007              | Visual outcome | 3 1 year |
| 48.   | NCT00889161              | Curcumin in Pediatric Inflammatory Bowel Disease | 11                  | 8–18-year-old patients with IBD who have been on IBD medication for 3 months | 2010              | To determine the tolerability of curcumin in pediatric patients with inflammatory bowel disease | 1 9 weeks |
| 49.   | NCT01514266              | Effect of Curcumin on Lung Inflammation | 57                  | ≥45-year-old patients with COPD and a stable clinical course | 2010              | Change in sputum dysplasia | NA 3 months |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|--------------------------|----------------------|---------------------|--------------------|-------------------|-----------------|-------------------|------------------|
| 50     | NCT00779493              | Curcumin (Turmeric) in the Treatment of Irritable Bowel Syndrome: A Randomized-Controlled Trial (CuTIBS) | 17                  | ≥18-year-old patients who conform to the Rome III criteria | 2009              | The primary outcome will be defined as at least a 50% reduction in the irritable bowel severity score (IBSS) | 4                 | 6 months         |
| 51     | NCT0329781               | Modulation of Endotoxaemia Via Curcumin Intake in Healthy Overweight Adults (ENDOCUR) | 16                  | 18–45-year-old healthy individuals with a BMI ≥ 25 kg/m² | 2018              | Level of endotoxin in plasma | NA               | 21 days          |
| 52     | NCT0094445               | Trial of Curcumin in Advanced Pancreatic Cancer | 50                  | ≥45-year-old patients with unresectable adenocarcinoma of the pancreas | 2014              | 6-month participant survival | 2                 | 6 months         |
| 53     | NCT01750359              | Efficacy and Safety Curcumin in Depression | 40                  | 20–60-year-old patients with a major depressive disorder | 2011              | Change in Hamilton Depression Rating Scale and Montgomery–Asberg Depression Rating Scale | 4                 | 6 weeks          |
| 54     | NCT00181662              | Pharmacokinetics of Curcumin in Healthy Volunteers | 6                   | ≥45-year-old healthy female individuals | 2007              | Curcumin pharmacology | NA               | NA               |
| 55     | NCT03598205              | Curcumin and Intravitreal Dexamethasone in Diabetic Macular Edema (DIABEC) | 72                  | 18–90-year-old patients with significant diabetic macular edema and a central retinal thickness of >300 microns | 2019              | Mean difference in central retinal thickness from baseline to 6 months | NA               | 6 months         |
| 56     | NCT00641147              | Curcumin in Treating Patients with Familial Adenomatous Polyposis | 44                  | 18–85-year-old patients with familial adenomatous polyposis | 2016              | The average number of polyps in the placebo arm at the end of the study is compared to the average in the curcumin arm | 2                 | 12 months        |
| 57     | NCT04385979              | Curcumin and Nanocurcumin in Oral Aphthous Ulcer | 48                  | Patients with minor and recurrent aphthous ulcers with ≥48 h | 2020              | Wound size and pain score | NA               | 1 week           |
Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Trial Title                                                                 | No. of Participants | Inclusion Criteria                                                                                       | Year of Completion | Primary Outcome                                                                 | Clinical Trial No. | Follow-Up Period |
|--------|---------------------------|------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------|-------------------|------------------|
| 58     | NCT01320436               | Curcumin + aminosalicyclic Acid (5ASA) Versus 5ASA Alone in the Treatment of Mild to Moderate Ulcerative Colitis | 50                 | 18–70-year-old patients with confirmed diagnosis of ulcerative colitis on a stable dose of ulcerative colitis medication | 2014               | The percentage of patients who achieve clinical remission compared between the two study arms | 3                 | 4 weeks          |
| 59     | NCT03072992               | “Curcumin” in Combination with Chemotherapy in Advanced Breast Cancer        | 150                | 18–75-year-old female patients diagnosed with breast carcinoma and adequate organ function            | 2019               | Objective response rate, assessed with the Modified Response Evaluation Criteria in Solid Tumours (RECIST) | 2                 | 24 weeks         |
| 60     | NCT00113841               | Curcumin (Diferuloylmethane Derivative) With or Without Bioperine in Patients with Multiple Myeloma | 42                 | Patients with multiple myeloma and adequate organ function                                            | 2009               | Percent change of NF-kB protein expression in peripheral blood mononuclear cells | NA                | 4 weeks          |
| 61     | NCT01909037               | Exploratory non comparative Study to Evaluate the Efficacy of Highly Bioavailable Curcumin (Flexofytol) in Patients with Knee Osteoarthritis | 22                 | 45–80-year-old patients with osteoarthritis and a symptomatic knee for more than 6 months who can avoid using analgesics during the study | 2012               | Change in the serum levels of biomarkers of cartilage metabolism and inflammation | 1                 | 84 days          |
| 62     | NCT00365209               | Phase II A Trial of Curcumin Among Patients with Prevalent Subclinical Neoplastic Lesions (Aberrant Crypt Foci) | 44                 | ≥40-year-old patients with a 3 pack-year smoking history                                               | 2011               | Change in prostaglandin E2 (PGE2) values found in rectal aberrant crypt foci (ACF) tissue | 2                 | 30 days          |
| 63     | NCT02494141               | Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults With ADPKD | 68                 | 6–25-year-old patients with an ADPKD diagnosis and normal renal function                                | 2021               | Change in brachial artery flow-mediated dilation (FMD-BA) and aortic pulse-wave velocity (aPWV) | 4                 | 12 months        |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Follow-Up Period |
|--------|--------------------------|----------------------|---------------------|-------------------|-------------------|----------------|-----------------|
| 64     | NCT04378972              | Anti-inflammatory Effect of Curcumin, Homotaurine, Vitamin D3 on Human Vitreous in Patients with Diabetic Retinopathy | 25                  | ≥18-year-old patients with diabetic retinopathy requiring vitrectomy | 2019              | Analyze human vitreous samples' pro-inflammatory cytokines | NA 7 days |
| 65     | NCT04972045              | Bioavailability of Curcumin Capsules in Healthy Adult Subjects | 12                  | 18–55-year-old healthy subjects with a BMI of 18–28 kg/m² | 2021              | Measure Peak Plasma Concentration, area under the curve, Tmax and bioavailability | 1 3 days |
| 66     | NCT01489592              | Effect of Curcumin on Iron Metabolism in Healthy Volunteer (CURHEP) | 18                  | 18–35-year-old healthy adults with a BMI of 18–25 and no HFE mutation | 2012              | Maximal variation of the serum hepcidin level after the oral administration of curcumin | 2 48 h |
| 67     | NCT01964846              | Effect of Antioxidant Intake on Cardiovascular Risk | 22                  | 45–70-year-old healthy patients with a stable weight | 2015              | Change in the blood levels of anti- and pro-inflammatory markers | NA 2 weeks |
| 68     | NCT02100423              | Curcumin and Cholecalciferol in Treating Patients with Previously Untreated Stage 0-II Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma | 35                  | ≥18-year-old patients with a CLL or SLL diagnosis and adequate organ function | 2018              | Overall response rate (biologic response rate + complete response [CR] + partial response [PR]) based on NCI-WG (for CLL) and the Cheson criteria (for SLL) | 2 2 years |
| 69     | NCT03530436              | Comparison of Curcumin Bioavailability | 12                  | 18–35-year-old healthy individuals | 2018              | Pharmacokinetics of curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) at different time frames | NA 24 h |
| 70     | NCT02529982              | Curcumin Supplementation and Patients with Type 2 Diabetes | 44                  | 44-65-year-old patients with type 2 Diabetes Mellitus with a BMI of 18.5-30 kg/m² | 2016              | Fasting blood sugar, insulin, HbA1c, homeostatic model assessment of insulin resistance and change in pancreatic B-cell function | NA 10 weeks |
| 71     | NCT03066791              | Turmeric and Curcumin on Sebum Production | 30                  | 18–50-year-old healthy individuals | 2017              | Sebum production | NA 8 weeks |
| Sl No. | Clinical Trial Identifier | Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|--------------------------|-------------|---------------------|-------------------|-------------------|-----------------|-------------------|-----------------|
| 72     | NCT01514370             | Dietary Supplement of Curcumin in Subjects with Active Relapsing Multiple Sclerosis Treated With Subcutaneous Interferon Beta 1a (CONTAIN) | 80                  | 18–60-year-old patients with multiple sclerosis under the treatment of IFN beta-1a for 6–12 months | 2016             | Number of subjects with active (new or enlarging) T2 lesions, as assessed by magnetic resonance imaging (MRI) at Month 12 | 2                | 24 months       |
| 73     | NCT00475683             | Curcumin for Prevention of Oral Mucositis in Children Chemotherapy | 8                   | 5–30-year-old patients diagnosed with cancer who received doxorubicin containing chemotherapy | 2010             | Measured change of an objective measurement of oral mucositis | 3                | 6 weeks         |
| 74     | NCT00164749             | A Pilot Study of Curcumin and Ginkgo for Treating Alzheimer’s Disease | 36                  | ≥50-year-old patients of Chinese ethnicity with a progressive decline in memory ≥6 months | 2006             | Measured change in the isoprostane level in plasma and the A-beta level in serum | 2                | 6 months        |
| 75     | NCT02152475             | Photodynamic Therapy (PDT) for Oral Disinfection | 30                  | 20–35-year-old healthy adults who do not perform any oral hygiene | 2013             | Microbiological analysis by the total number of colony-forming units | 1                | 2 h             |
| 76     | NCT01831193             | Effect of Oral Supplementation with Curcumin (Turmeric) in Patients with Proteinuric Chronic Kidney Disease | 120                 | 18–70-year-old patients diagnosed with proteinuric chronic kidney disease taking ARB or ACEi | 2014             | Change in proteinuria | 3                | 8 weeks         |
| 77     | NCT02556632             | Prophylactic Topical Agents in Reducing Radiation-Induced Dermatitis in Patients with Non-inflammatory Breast Cancer (Curcumin-II) | 191                 | ≥21-year-old patients diagnosed with non-inflammatory breast cancer or carcinoma in situ who are undergoing radiation therapy | 2016             | Measured mean Radiation Dermatitis Severity (RDS) score, incidence of moist sesquamation and change in the severity of skin reactions using RDS | 2                | 1 week post-radiation chemotherapy |
| 78     | NCT04465851             | Effect of Ferrous iROn and cUrcumin sTatus on Inflammatory and Neurotrophic markErS (Fe-ROUTINE) | 155                 | 18–40-year-old healthy individuals | 2020             | To assess the influence of curcumin administration on ferrous iron supplementation-associated inflammation | NA               | 42 days         |
Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|--------------------------|----------------------|---------------------|--------------------|-------------------|------------------|--------------------|------------------|
| 79     | NCT00192842              | Gemcitabine With Curcumin for Pancreatic Cancer | 17                  | ≥18-year-old patients suffering from advanced or metastatic pancreatic adenocarcinoma with no prior therapy | 2010              | time to tumor progression | 2 NA              |                  |
| 80     | NCT00099710              | Curcumin in Patients with Mild to Moderate Alzheimer’s Disease | 33                  | ≥50-year-olds with a diagnosis of Alzheimer’s disease | 2007              | Measured safety and tolerability of curcumin | 2 12 months        |                  |
| 81     | NCT01712542              | Curcumin Bioavailability in Glioblastoma Patients | 15                  | ≥18-year-old patients with glioblastoma | 2013              | Measured concentration of curcumin in glioblastoma | NA At time of tumor resection |                  |
| 82     | NCT01022632              | Effect of Curcumin as Nutraceutical in Patients of Depression | 60                  | 18–65-year-old patients with a diagnosis of depression | 2010              | Measured response and mean change in the Hamilton Depression Rating Scale (HAM-D17) | NA 6 weeks         |                  |
| 83     | NCT03144882              | Evaluation of Curcumin’s Effect on Inflammation in Hemodialysis Patients | 71                  | ≥18-year-old clinically stable patients receiving hemodialysis | 2017              | Measured mean Interleukin-6 levels | NA 1 year          |                  |
| 84     | NCT03141918              | Effect of Supplementation of Bioactive Compounds on the Energy Metabolism of People Living With HIV/AIDS | 20                  | 18–70-year-old patients with HIV receiving antiretroviral therapy ≥6 months | 2017              | Measuring the oxidation of energetic substrates; evaluation at rest | NA 10 days         |                  |
| 85     | NCT01740323              | Phase II Study of Curcumin vs. Placebo for Chemotherapy-Treated Breast Cancer Patients Undergoing Radiotherapy | 30                  | ≥18-year-old female patients undergoing breast radiotherapy | 2018              | Measured change in NF-κB DNA binding, Plasma TNF-alpha, sTNFR2, IL-1ra, IL-6 and CRP | 2 6 weeks after the completion of radiotherapy |                  |
| 86     | NCT04107987              | Berberine, Curcumin, Inositol, Banaba and Chromium Picolinate in Patients with Fasting Dysglycemia | 148                 | 18–75-year-old patients with impaired fasting glucose who are not on treatment | 2019              | Measured progression of dysglycemia | 3 3 months         |                  |
| 87     | NCT00027495              | Curcumin for the Prevention of Colon Cancer | NA                  | ≥18-year-old healthy individuals | 2007              | To determine the pharmacokinetics and measure the Maximum Tolerated Dose (MTD) | 1 72 h             |                  |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome Clinical Trial No. | Clinical Trial Follow-Up Period |
|--------|---------------------------|-----------------------|---------------------|-------------------|-------------------|------------------------------------|----------------------------------|
| 88     | NCT04723849               | Efficacy Evaluation of a Mixed Compound of Antioxidants in Terms of Endothelium Damage/Function in Pediatric Subjects with Obesity. (OBELIX) | 48                  | 6–17-year-old patients with a BMI > 95% for their age based on the CDC standard | 2020 | To test the effects of a mixed compound including curcumin on endothelium in a cohort of pediatric subjects with obesity | NA | 6 months |
| 89     | NCT00768118               | A Nutritional Supplement Capsule Containing Curcumin, Green Tea Extract, Polygonum Cuspidatum Extract, and Soybean Extract in Healthy Participants | 11                  | ≥18-year-old healthy individuals | 2008 | Measure the magnitude of change in the blood lymphocyte NF-kB level | NA | 15 days |
| 90     | NCT02017353               | Effect of Curcumin Addition to Standard Treatment on Tumour-induced Inflammation in Endometrial Carcinoma | 7                   | ≥18-year-old female patients with endometrial carcinoma and no life-threatening metastases | 2016 | Measured change in the inflammatory markers in peripheral blood from the baseline | 2 | 21 days |
| 91     | NCT00792818               | The Efficacy and Safety of Curcuma Domestica Extracts and Ibuprofen in Knee Osteoarthritis | 367                 | 50–75-year-old patients diagnosed with primary osteoarthritis | 2012 | Measured change in mean Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain subscale | 3 | 12 months |
| 92     | NCT03290417               | Correlative Analysis of the Genomics of Vitamin D and Omega-3 Fatty Acid Intake in Prostate Cancer | 37                  | Patients diagnosed with prostate cancer who are on active surveillance | 2019 | Measured gene expression of very low and low-risk prostate cancer patients on active surveillance | NA | 12 months |
| 93     | NCT00525421               | A Clinical Study of Curcuminoids in the Treatment of Oral Lichen Planus | 20                  | ≥21-year-old patients diagnosed with lichen planus | 2009 | Measured percent change from the baseline to two weeks in the symptoms and signs of oral lichen planus | 2 | 2 weeks |
| 94     | NCT02337192               | Antimicrobial Photodynamic Therapy Applied in Orthodontic Patients. | 24                  | 18–50-year-old healthy individuals with fixed orthodontic treatment | 2014 | Microbiological analysis by the total number of colony-forming units (CFU) | 1 | 1 h |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|-------|---------------------------|----------------------|--------------------|-------------------|------------------|----------------|-------------------|------------------|
| 95    | NCT01288859               | Physiological Effects of New Polyphenol-enriched Foods in Humans | 10                 | 18–45-year-old healthy individuals | 2011             | Measured serum polyphenol concentrations, urinary excretion of total polyphenols and the number of total fecal polyphenols | NA               | 24 h             |
| 96    | NCT01029327               | Effects of Curcumin on Postprandial Blood Glucose, and Insulin in Healthy Subjects | 15                 | ≥18-year-old healthy individuals | 2009             | To study the effect of curcumin on the postprandial blood glucose and plasma concentrations of insulin | NA               | NA               |
| 97    | NCT02815475               | Turmeric Anti-Inflammatory and Cell-Damage Trial (TACT) | 90                 | 18–80-year-old healthy individuals | 2016             | Measured change from baseline DNA methylation analyses and baseline oxidative stress determination | NA               | 6 weeks          |
| 98    | NCT03769857               | NEM® + BIOCURC® Versus Placebo in Exercise-induced Joint Pain, Stiffness, & Cartilage Turnover in Healthy Men & Women | 84                 | 40–75-year-old healthy adults with no diagnosis of joint arthritis | 2019             | Measured exercise-induced cartilage turnover | NA               | 2 weeks          |
| 99    | NCT03621865               | A Comparative Pharmacokinetic Study to Evaluate the Ability of a New Formulation to Enhance Curcuminoids Bioavailability (TURBIO) | 30                 | 18–45-year-old healthy individuals with a normal BMI and a stable weight | 2018             | Measured dose-normalized AUC of total curcuminoids plasmatic concentration | NA               | 24 h             |
| 100   | NCT03289832               | Effect of Orally Delivered Phytochemicals on Aging and Inflammation in the Skin | 25                 | 18–70-year-old healthy individuals willing to avoid sun exposure and follow a diet | 2019             | Measured change in erythema 1, 2 and 3 Days after UV exposure | NA               | 10 days          |
| 101   | NCT03140657               | The Effects of Nanocurcumin on Treg Cells and Th17 Cells Responses in Ankylosing Spondylitis Patients | 24                 | 23–46-year-old patients with a diagnosis of ankylosing spondylitis | 2018             | Assessments of ankylosing spondylitis signs and symptoms (BASDI) | 2                | 4 months         |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|---|---|---|---|---|---|---|---|---|
| 102 | NCT03192059 | Study of Pembrolizumab, Radiation and Immune Modulatory Cocktail in Cervical/Uterine Cancer (PRIMMO) | 43 | ≥18-year-old female patients with endometrial, cervical or uterine malignancy refractory to treatment | 2021 | Measured efficacy (objective response rate) at week 26 according to the immune-related response criteria (irRC) | 2 | 156 weeks |
| 103 | NCT03330787 | Cosmetic Effects of Topical Acetyl Zingerone | 31 | 30–60-year-old healthy individuals | 2018 | Measured change in wrinkle appearance and skin pigmentation | NA | 8 weeks |
| 104 | NCT03493997 | Multicentre International Study for the Prevention with Ialuril® of Radio-induced Cystitis (MISTIC) | 100 | ≥18-year-old male patients who planned to receive primary therapy for prostate cancer | 2018 | Measured rate of patients who stopped treatment with intravesical or oral Ialuril due to intolerance or adverse events | 2 | 12 months |
| 105 | NCT04849182 | Vertistop® D and Vertistop® L in Preventing Recurrence of High-recurrence BPPV | 128 | 18–85-year-old patients with benign paroxysmal positional vertigo (BPPV) | 2020 | Measured number of BPPV recurrences in patients supplemented with Vertistop D | NA | 6 months |
| 106 | NCT02099890 | The Effect of Diet on Chronic Inflammation and Related Disorders Following Spinal Cord Injury | 20 | ≥18-year-old patients with a spinal cord injury | 2015 | Measured change from the baseline in the nerve conduction velocity of somatic nerves at 3 and 6 months | 3 | 6 months |
| 107 | NCT03483376 | aPDT for the Remediation of Dental Black Stain | 30 | ≥12-year-old patients with a dental black stain in at least two teeth | 2020 | Area and depth of color of the black stain | NA | 6 months |
| 108 | NCT00235625 | Curcuminoids for the Treatment of Chronic Psoriasis Vulgaris | 12 | 18–75-year-old patients with chronic plaque-type psoriasis | 2007 | Physicians Global Assessment (PGA) of change | 2 | 16 weeks |
| 109 | NCT04382040 | A Phase II, Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC in Patients Diagnosed With COVID-19 | 50 | ≥18-year-old patients with a diagnosis of SARS-CoV-2 infection who are hospitalized and are in stable condition | 2020 | Time to clinical improvement, defined as a national Early Warning Score 2 (NEWS2) of ≤ 2, maintained for 24 h, and measurement of adverse events | 2 | 2 weeks |
Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Trial Title                                                                 | No. of Participants | Inclusion Criteria                                                                 | Year of Completion | Primary Outcome                                                                                   | Clinical Trial No. | Follow-Up Period |
|--------|---------------------------|------------------------------------------------------------------------------|---------------------|------------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------------------------|-------------------|-----------------|
| 110    | NCT03150966               | The Immunomodulatory Effects of Oral Nanocurcumin in Multiple Sclerosis Patients | 41                  | 18–65-year-old patients who are diagnosed with multiple sclerosis                   | 2017               | Measurement of the Expanded Disability Status Scale (EDSS)                                      | 2                 | 6 months        |
| 111    | NCT02442453               | Effect of Scaling and Root Planing Along with Topical Application of Commercially Available Curcuma Longa Gel on Superoxide Dismutase and Malondialdehyde Levels in Saliva of Chronic Periodontitis Patients | 100                 | 30–55-year-old healthy individuals with chronic generalized periodontitis          | 2014               | Measurement of the superoxide dismutase antioxidant enzyme levels in the saliva of chronic periodontitis subjects | 4                 | 1 month         |
| 112    | NCT02909621               | Evaluation of FLEXOFYTOL® Versus PLACEBO (COPRA)                             | 150                 | 45–80-year-old patients with knee osteoarthritis                                   | 2017               | Measuring the variation in the serum levels of the sColl2-1 biomarker between T0 and T3 by specific immunoassays and the variation in the global assessment of disease activity by the patient using a visual analogue scale (VAS) | NA                | 6 months        |
| 113    | NCT04439981               | Curcuma Extract Beneficial for Muscle Damage                                 | 20                  | 14–18-year-old healthy male individuals                                           | 2019               | Change in lactic acid, Hb, IL-6 and creatinine kinase                                           | NA                | 21 days         |
| 114    | NCT02251678               | Evaluate the Effect of Elimune Capsules                                      | 21                  | ≥18-year-old patients with plaque psoriasis with or without arthritis             | 2015               | Individual subject serum levels of biomarkers (CRP, TNFa, IL-6, IL-12)                          | 1                 | 28 days         |
| 115    | NCT04633551               | Vascular Inflammation and Anti-inflammatory Supplements After Adverse Pregnancy Outcomes (VIA) | 8                   | 18–45-year-old female patients who had a singleton pregnancy of < 3 years complicated by an adverse pregnancy outcome (APO) | 2021               | Measurement of blood pressure, arterial stiffness, augmentation index and endothelial function | NA                | 1 month         |
| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|---------------------------|----------------------|---------------------|-------------------|-------------------|-----------------|------------------|------------------|
| 116    | NCT02834078               | Effect of BGG on Glucose Metabolism and Other Markers of Metabolic Syndrome (Glucogold) | 126                | 20–60-year-old patients with a BMI ≥ 25 suffering from pre-diabetes or early diagnosed diabetes | 2016             | Measured change in the oral disposition index and HbA1c | NA               | 84 days          |
| 117    | NCT04149639               | A Study Investigating the Effectiveness of a LifeSeasons NeuroQ Supplement with Lifestyle Changes to Improve Cognitive Function in Healthy Adults Who Have One or More Risk Factors for Cognitive Decline | 40                 | ≥45-year-old patients with risk factors for cognitive decline | 2020             | Measured change in cognition as assessed by the change in the Neurocognitive Index (NCI) score from the CNS-Vital Signs (CNS-VS) panel | NA               | 135 days         |
| 118    | NCT01716637               | Short Term Efficacy and Safety of Perispinal Administration of Etanercept in Mild to Moderate Alzheimer’s Disease | 12                 | 60–85-year-old patients with a diagnosis of Alzheimer’s disease | 2016             | Difference in the effects of the treatment for 6 weeks with etanercept + nutritional supplements versus nutritional supplements alone on the Mini-Mental Status Examination (MMSE) score | 1                | 16 weeks         |
| 119    | NCT01752868               | Can Fish Oil and Phytochemical Supplements Mimic Anti-Aging Effects of Calorie Restriction? | 56                 | 40–60-year-old patients with a BMI of 21–30 kg/m² who are sedentary to moderately active | 2012             | Carotid-femoral pulse wave velocity | NA               | 6 months         |
| 120    | NCT00799630               | Effects of Nutraperf Consumption in Runners | 14                 | 18–46-year-old healthy male distance runners | 2008             | Measurement of different metabolic parameters (heart rate, oxygen consumption, respiratory quotient, ventilation, glycemia, lactatemia) on central and peripheral fatigue and on cognitive parameters | NA               | NA               |
Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|---------------------------|-------------|---------------------|--------------------|-------------------|-----------------|-------------------|-----------------|
| 121    | NCT04765527               | Turmeric and Exercise-Induced Muscle Damage and Oxinflammation | 53                  | 18–50-year-old healthy individuals who are willing to exercise | 2021              | Measuring a change in the serum concentration of creatine kinase | NA               | 4 days          |
| 122    | NCT02413099               | The Efficacy and Safety of New Herbal Formula (KBMSI-2) in the Treatment of Erectile Dysfunction | 44                  | 18–40-year-old male patients with a history of erectile dysfunction | 2013              | Measuring a change in the EF domain scores of the IIEF questionnaire from the baseline | 4               | 8 weeks         |
| 123    | NCT01906840               | Role of Turmeric on Oxidative Modulation in ESRD Patients | 48                  | ≥18-year-old patients who undergo regular dialysis | 2012              | Measuring the effects of turmerics on oxidative stress markers | 2               | 8 weeks         |
| 124    | NCT01646047               | Diabetes Visual Function Supplement Study (DIVFaSS) | 70                  | ≥18-year-old patients with a ≥5-year history of diabetes mellitus | 2014              | Measuring changes in visual function | NA              | 6 months        |
| 125    | NCT02369536               | Efficacy of a Natural Components Mixture in the Treatment of non-Alcoholic Fatty Liver Disease (NAFLD) (NUTRAFAST) | 126                | 18–80-year-old patients with non-alcoholic fatty liver disease (NAFLD) | 2016              | Hematocrit levels of hepatic enzymes AST, ALT and GGT | NA              | 3 months        |
| 126    | NCT02088307               | Study of the Cardiovascular Vitamin, CardioLife | 21                  | 18–90-year-old patients with cardiovascular disease | 2016              | Change in blood pressure | NA              | 6 months        |
| 127    | NCT05089318               | Evaluation of Flexofytol® PLUS in Hand Osteoarthritis. | 239                | ≥45-year-old patients with hand arthritis and a regular use of analgesia | 2021              | Pain using a Visual Analog Scale (VAS) | NA              | 84 days         |
| 128    | NCT03482401               | Disposition of Dietary Polyphenols and Methylxanthises in Mammary Tissues from Breast Cancer Patients (POLYSEN) | 40                  | ≥18-year-old patients diagnosed with breast cancer | 2019              | Quantification of dietary polyphenols and methylxanthises in breast tissues | NA              | 24 months       |
### Table 5. Cont.

| Sl No. | Clinical Trial Identifier | Clinical Trial Title | No. of Participants | Inclusion Criteria | Year of Completion | Primary Outcome | Clinical Trial No. | Follow-Up Period |
|--------|--------------------------|----------------------|---------------------|--------------------|-------------------|-----------------|-------------------|------------------|
| 129    | NCT04890704              | Curcuminoids and Contrast-induced Acute Kidney Injury | 96                  | 18–80-year-old patients undergoing elective CAG with a stable eGFR of 15–60 mL/min/1.72 m² | 2019              | The incidence of CI-AKI development between the addition of curcuminoids to the standard protocol and the standard protocol alone in patients who underwent CAG | 1 | 48 h |
| 130    | NCT00219882              | Safety Study of Orally Administered Curcuminoids in Adult Subjects with Cystic Fibrosis (SEER) | 11                  | 18–40-year-old patients who suffer from cystic fibrosis (homozygous for the ΔF508 CFTR genotype) | 2006              | Safety and tolerability of 14 days of treatment with orally administered curcuminoids, as assessed by adverse events, laboratory parameters and spirometry | 1 | 14 days |
| 131    | NCT04844658              | COVID-19, Hospitalized, Patients, Nasafytol | 51                  | ≥18-year-old patients with a recent hospitalization due to SARS-CoV-2 | 2021              | Improvement of the patient’s clinical condition based on the WHO ordinal outcomes score, the duration of hospitalization, mortality, fever, oxygen therapy, adverse events and several blood parameters | NA | 14 days |
| 132    | NCT03065504              | Turmeric and Turmeric-containing Tablets and Sebum Production | 30                  | 18–50-year-old healthy individuals | 2017              | Change in facial sebum production | NA | 4 weeks |
| 133    | NCT04281758              | Comparison of Plasma Caffeine Concentration After Oral Consumption of Caffeinated Beverages with Varied Bioactive Compounds in Healthy Volunteers | 16                  | 18–55-year-old healthy individuals willing to avoid caffeine and alcohol for a period of time | 2020              | Incremental area-under-the-concentration-curve (iAUC) | 1 | 210 min |
| 134    | NCT04258501              | Exploratory Study of Efficacy on Selected Natural Extracts Reducing Post Prandial Blood Glucose Response | 72                  | 20–50-year-old healthy individuals with a normal BMI | 2012              | Change in post-prandial blood glucose | NA | 2 h |

### 6. Limitations

In this paper, we have only focused on the key therapeutic activity of curcumin. Additionally, our focus has been on those activities of curcumin that are well characterized.
Other aspects of curcumin activity, such as those associated with beneficial effects in neurological disorders, were not reviewed in this study. This alludes to the fact that such results have not been investigated in detail or explicated in the clinical trials. For example, for the phase 2 trial—curcumin in patients with mild to moderate Alzheimer’s disease—no results are posted in the trial database. This aspect may be attributed to the fact that the trial did not exhibit any beneficial outcome, more so because the delivery of curcumin across the blood-brain barrier has always been challenging. On the same note, we have not touched upon the aspect of curcumin delivery, as this is not only outside the scope of the review but also requires a detailed discussion which will make the present manuscript inadvertently lengthy. Readers are directed to some excellent reviews published in recent times for further details, if interested [295–298].

7. Conclusions and Future Directions

Curcumin is a pleiotropic molecule with a flexible structure with diverse biological functions. It is a potent proteasome inhibitor that increases the p53 level and induces apoptosis by mitochondrial caspase activation. Curcumin also disrupts 26S proteasome activity by inhibiting DYRK2 in different cancerous cells, resulting in the inhibition of cell proliferation [299]. However, further research is required to establish curcumin’s precise epigenetic regulatory effect for preventing and curing lethal diseases such as cancers. Curcumin may also act as an epigenetic regulator in neurological disorders, inflammation and diabetes. It can be effectively used as a histones modifier (acetylation/deacetylation), which is among the most important epigenetic changes responsible for gene expression alterations, leading to the modulation of the risks of rheumatoid arthritis and cancer.

Curcumin has shown therapeutic potential against several human diseases. The underlying mechanism for curcumin’s clinical efficacy seems to be the modulation of numerous signaling molecules. However, because of the complex nature of some diseases, the underlying mechanism in many cases remains unclear. Pharmacokinetic data indicate an almost 40-fold increase in blood levels in cases where curcumin was administered via formulation compared to pure form [300]. The poor bioavailability and limited adverse effects reported by some investigators are a major limitation to the therapeutic utility of curcumin. Nanocurcumin has shown a higher solubility and bioavailability in comparison to curcumin in recent studies [301]. Curcumin linked to phosphatidylcholine (which forms the fytosome–curcumin complex) has shown better bioavailability upon oral administration in rats [302]. We hope that the results from ongoing clinical trials will provide a deeper understanding of curcumin’s therapeutic potential and help to place this interesting molecule at the forefront of novel therapeutics.

The use of nanotechnology and a targeted drug delivery system has been shown to improve the cellular uptake, tissue specificity and effectiveness of curcumin. Although several nanosystems have been explored for the delivery of curcumin, due to its ability to inhibit the ABC efflux transporter [303], the combination nanoparticles of curcumin must be tested in cancerous cells once the proper dosage is determined. Most of the experiments using curcumin formulations have only been tested in pre-clinical models. The issue of cellular toxicity needs to be addressed by studying its activity in humans. Cost-effective techniques for curcumin nanoencapsulation are an emerging industrial requirement. The clinical trials to date have been conducted on a limited group of patients. Moreover, the tissue specificity of nanoparticles needs to be evaluated.

The combination of curcumin with other therapeutic reagents can further be explored. Case in point, a recent study showed that fecal microbial transplantation (FMT) leads to favorable outcomes in metabolic syndrome [304]. It would be interesting to appraise what happens in a group where a combined approach of FMT, fiber supplementation and curcumin is employed. For example, Liraglutide is used in the treatment of obesity because it induces weight loss; curcumin can be supplemented in a combined formulation with liraglutide to add to its benefits [305].
Currently, in our group, we are assessing the therapeutic potential of curcumin in combination with vitamin D and lipids of minor physiological abundance in attenuating inflammation in chondrocytes treated with LPS. The rationale behind using such a combination is that lipids [198] of minor physiological abundance, such as lysosulfatide (which is present in HDL particles) and vitamin D (which has a steroid nucleus), will augment the solubility and thus the bioavailability of curcumin [199].

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**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| ACE          | Acetyl coenzyme |
| ADPC         | Androgen-dependant prostate cancer |
| AIPC         | Androgen-independent prostate cancer |
| AKT          | Protein kinase B (also called PKB) |
| ALT          | Alanine transaminase |
| AMPK         | AMP-activated protein kinase |
| AP           | Activator protein |
| AST          | Aspartate aminotransferase |
| BAFF         | B cell activating factor |
| BCL          | B cell lymphocyte |
| Bcl          | B cell lymphoma |
| Bcl-xL       | B cell lymphoma-extra large |
| CD           | Cluster differentiation |
| CHOP         | Cytoxan hydroxydaunorubicin oncovin prednisone |
| Coll2        | Collagen |
| COX          | Cyclooxygenase |
| Cur-CQD      | Curcumin carbon quantum dots |
| CXCL         | Chemokine (C-X-C motif) ligand |
| DHA          | Docosahexaenoic acid |
| DYRK         | Dual specificity tyrosine phosphorylation-regulated kinase |
| EAE          | Enzyme-assisted extraction |
| EBP          | Enhancer binding protein |
| EPA          | Eicosapentaenoic acid |
| ERK          | Extracellular-regulated kinase |
| ERK          | Extracellular-regulated kinase |
| FFA          | Free fatty acid |
| FOX          | Forkhead box protein |
| FtsZ         | Filamenting temperature sensitive mutant Z |
| GST          | Glutathione S-transferase |
| Hp           | Haptoglobin |
| HSP          | Heat shock protein |
| IFN          | Interferon |
| IKBα         | Inhibitor of kappa light chain gene enhancer in B cells |
| IL           | Interlekin |
| ILE          | Ionic liquid-based extraction |
| IL           | Interleukin |
| iNOS         | Inducible nitric oxide syntase |
| JAK/STAT     | Janus kinase/signal transducers and activators of transcription |
| JNK          | Jun N-terminal kinase |
| LPS          | Lipopolysaccharides |
| Acronym | Description                                |
|---------|--------------------------------------------|
| MAE     | Microwave-assisted extraction              |
| MAPK    | Mitogen-activated protein kinase            |
| MCP     | Methyl-accepting chemotaxis protein        |
| M-CSF   | Macrophage colony stimulating factor       |
| MDA     | Malondialdehyde                            |
| MIC     | Minimum inhibitory concentration           |
| MIP     | Macrophage inflammatory protein            |
| MMP     | Matrix metalloproteinase                    |
| MPA     | Medroxyprogesterone acetate                |
| MTOR    | Mammalian target of rapamycin              |
| MyD     | Myeloid differentiation                     |
| NF-kkB  | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NLRP    | Nod-like receptor protein                   |
| NOD     | Nucleotide oligomerization domain           |
| Nrf     | Nuclear respiratory factor                 |
| NSAID   | Non-steroidal anti-inflammatory drugs      |
| OC      | Oleocanthal                                 |
| ODC     | Ornithine decarboxylase                     |
| PECAM   | Platelet endothelial cell adhesion molecule|
| PLGA    | Poly(D,L-Lactic-co-glycolic acid)          |
| PPAR    | Peroxisome proliferator-activated receptors|
| Rac 1   | Rass-related C3 botulinum toxin substrate 1 |
| RANKL   | Receptor activator of nuclear factor kappa B ligand |
| RANTES  | Regulated on activation, normal T cell expressed and secreted |
| RNS     | Reactive nitrogen species                  |
| ROS     | Reactive oxygen species                    |
| SDH     | Succinate dehydrogenase                    |
| SFE     | Supercritical fluid extraction             |
| Shh     | Sonic hedgehog protein                     |
| SOD     | Superoxide dismutase                       |
| STZ     | Streptozotocin                              |
| TBARs   | Thiobarbituric acid reactive substances    |
| TLR     | Toll-like receptor                          |
| TLR     | Toll-like Receptor                         |
| TNF     | Tumor Necrosis Factor                      |
| TRAIL   | Tumor necrosis factor (TNF)-related apoptosis-inducing ligand |
| TRAIL   | Tumor necrosis factor-related apoptosis-inducing ligand |
| UAE     | Ultrasound-assisted extraction             |
| UPR     | Unfolded protein response                  |
| VEGF    | Vascular endothelial growth factor         |
| Wnt     | Wingless related integration site          |
| XIAP    | X-chromosome-linked inhibitor of apoptosis protein |
| ADPC    | Androgen-dependant prostate cancer         |
| AIPC    | Androgen-independent prostate cancer       |
| AP      | Activator protein                           |
| Bcl     | B cell lymphoma                             |
| Bcl-xL  | B cell lymphoma-extra large                |
| COX     | Cyclooxygenase                              |
| CXCL    | Chemokine (C-X-C motif) ligand             |
| FOX     | Forkhead box protein                       |
| IL      | Interleukin                                 |
| JNK     | Jun N-terminal kinase                       |
| MMP     | Matrix metalloproteinase                    |
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