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Short Review

Review of Curcumin and Its Different Formulations: Pharmacokinetics, Pharmacodynamics and Pharmacokinetic-Pharmacodynamic Interactions

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Abstract

Curcumin, the yellow principle of the Indian Turmeric, 'Haldi' has recently attracted renewed interest in the field of experimental medicine with pleiotropic activity. This review has emphasized three pharmaceutical studies of interest: the pharmacokinetics, pharmacology, and pharmacodynamics of curcumin. In this review, we attempted to review the general pharmacokinetics profile, pharmacokinetic interactions, and pharmacokinetic-

pharmacodynamic interactions of curcumin and its formulations. Different species of turmeric in India, as well as their cultivars, different forms of curcumin, and harvesting methods have also been discussed. Furthermore, pharmacokinetic studies of the interaction of curcumin and its different formulations with efflux transporters such as P-glycoprotein, ABC-transporter protein, multidrug-resistant protein, and cytochrome p450 metabolism enzymes have been broadly explained following data from preclinical and clinical trials reported in the literature. A few interesting chemical interactions between curcumin and its metabolites with the receptor have also been described. The pharmacological activities of curcumin and its related formulations and products have been reviewed in a few targeted disease pathologies of national concern, such as cancer, gastroduodenal disorder, immunodeficiency, liver disease, ophthalmology, diabetes and osteoarthritis among other metabolic diseases, and microbial and viral infections. The pharmacodynamics of curcumin, especially regarding the potassium/calcium ion channel pathway, apoptosis, calcium signaling pathway, endoplasmic reticulum stress, and other intracellular signaling pathways, have been documented. Lastly, the use of curcumin as a cosmetic and the value chain analysis of turmeric products, as well as curcumin, have also been placed appropriately. A total of 174 publications were reviewed and, overall, this review tried to cover various important therapeutic aspects of curcumin, which can generate new research interest in general.

Keywords
Curcumin; pharmacology; pharmacokinetics; potassium channel; calcium signaling; chemistry; spice; modeling

1. Introduction

Spices are the essential components in the preparation of household and commercial food products. A combination of spices such as turmeric, ginger, cumin, cardamom, caraway, pepper, etc. enhances the flavor, fragrance, color as well palatability, and digestibility of foods [1]. Spices are derived from different parts of plants, such as rhizomes, bulbs, leaves, seeds, fruits, barks, flower buds, and stigmata. Among them, turmeric is an essential component used as a food supplement, preservative, and coloring agent [2]. It also possesses immense medicinal value with enormous therapeutic potential against pathogens [1, 3]. Curcumin is the active ingredient of the yellow pigment of the Indian Turmeric (Curcuma), of which around 117 species have been identified worldwide, and 40 species have been reported in India [4, 5].

Curcuma longa is a rhizomatous perennial herb (family Zingiberaceae) native to tropical South Asia. For optimum plant growth, temperatures between 20°C and 30°C, and a considerable amount of annual rainfall are needed. The height of the plants is around 1 meter, and the leaves are long and oblong. Rhizomes are the most important part of the plant and are harvested annually and reseeded the following season. Structurally, the rhizomes are tuberous with rough and segmented skin [3]. Various bioactive components, such as volatile oils (turmerone, unique aroma) and colorant curcuminoids are enriched in the root [1-5]. India is the largest producer, consumer, and exporter of turmeric (*Curcuma longa*), which has a wide variety of cultivars. Andhra Pradesh has the highest

turmeric production (5,404 kg/ha), followed by Tamil Nadu (5,300 kg/ha), Karnataka (4,250 kg/ha), Odisha (2,178 kg/ha), Kerala (2,135 kg/ha), West Bengal (1,504 kg/ha) and Maharastra (1,261 kg/ha) [4]. Approximately 120 cultivars of *Curcuma longa* are known to be cultivated in India based on their unique floral characteristics, aerial morphology, rhizome morphology, and chemical constituents (rhizome yield, essential oil, and curcumin content). Cultivars have the characteristics of identifying turmeric types with high yield potential, high curing percentage, and high curcumin content, these are abbreviated by local name and place of occurrence [4]. The most popular turmeric cultivars of turmeric are Kaziranga, Lakadong, palapally, wynad local, etc. The crop improvement program of turmeric has been successful through germplasm selection, clonal selection, mutant breeding, and seedlings selection. Various improved varieties have been reported, for example, Prabha, Suguna, Alleppy, Prathiba, and Sudarsana. Well-known forms of curcumin are Surama (6.1%), Rajendra Sonia (8.4%), Suguna (7.3%), Varna (7.87%), Kanthi (7.18%), Sobha (7.39%), and Sona (7.12%), others are CO-1, BSR-1, BSR-2, Krishna, Sugandham, Roma, Ranga, Rasmi, Megha turmeric, Pant peetabh, Suranjana, Suvarana, Sudarshana, IISR Prabha, IISR Pratibha, IISR Alleppy Supreme, and IISR Kedaram [5]. In the Indian Ayurvedic system, *Curcuma longa* is mixed with nine other excipients (sweet flag, Indian costus root, Indian long pepper, ginger, small fennels, Ajamoda, liquorice, halite, and clarified butter from cow's milk in a 1:1:1:1:1:1:1:1:6 mixture) to make a semisolid preparation, known as Kalyanavaleha, which is used for the treatment of hoarseness and speech impairment. The value-added products of turmeric are ar-turmerone, curcumin, dimethoxy curcumin, and bis-demethoxy curcumin [1]. This review focuses mainly on the pharmacokinetics, and pharmacodynamics, as well as an update on the pharmacological activity of the said medicinal agents.

2. Physical Property

Curcumin (diferuloylmethane) is a polyphenolic, hydrophobic compound (structural scaffold is diarylheptanoid; melting point: 170-175°C; molecular weight: 368.39; molecular formula: $C_{21}H_{20}O_6$; logP range: 2.56-3.29). Curcumin is easily soluble in dichloromethane, methanol, ethyl acetate and other solvents but insoluble in water. The component is stable in the pH range of 1-6, its color in the solution is mainly due to its protonated-neutral-deprotonated form (giving rise to a distinct red-yellow-red color). It exhibits excellent physicochemical properties, such as lipid membrane affinity and interactions with the protein hydrophobic domains and can cross the blood-brain barrier. Turmeric paper with alcoholic extract of turmeric is a qualitative analytical method for the detection of boric acid and borates, which turns orange-red in acidic solutions, and greenish-black in alkaline solutions and oxalic acid [1, 6]. Francese *et al.* have utilized curcumin as a versatile and multipurpose matrix for MALDI-mass spectroscopy imaging applications [7]. Curcumin can be extracted from the turmeric via various processes such as Soxhlet, ultrasonic, microwave, supercritical CO_2, enzyme-assisted extraction, high-efficiency column chromatographic techniques [8], and detected by HPLC-MS in clinical samples, etc [9].

3. Chemical Property

Curcumin pharmacophore exhibits some unique properties: Michael addition to the sulfhydryl group of the peptides; the formation of a variety of metal chelates with the charged species as well as bivalent metal species. The structure of the curcumin can be best described as two aryl vinyl

scaffolds with a keto (or enol) extension (depending on the pH) overlapping (with the aryl group outside the binding space) with each other via a methylene spacer, this structure is utilized as an effective electron donor and thus the pharmacophore also exhibits antioxidant activity. Curcumin is a typical Bronsted-Lowry acid and undergoes protonation and deprotonation based on pH changes. This process is accompanied by profound changes in light absorption in the visible region so ion alteration is best studied using visible spectroscopy. At pH > 7, curcumin is unstable because of the decreased stability of multiple hydroxyl anions. Furthermore, conjugate bonds are also broken by carbon-carbon bond fission. The major degradation products are ferulic acid and feruloyl methane, and extensive degradation further yields vanillin and acetone. Similar to polyphenols, curcumin also undergoes chemical changes (through substitution and condensation reactions) upon interaction with free radicals. Curcumin exhibits nucleophilic addition reaction through its conjugated π-electron systems and exhibits reversibility, which is a typical property of α, β-unsaturated ketone, or ester. As curcumin can chelates with metal, there is a risk of iron chelation and an anemia threat in some groups of its consumers [1, 2, 6, 8].

4. Indian Turmeric Cultivar – Overview of Cultivation and Processing

While conducting genetic environmental interaction with 11 turmeric cultivars for fresh yield (in 10 environments), curing percentage, curcumin, and dry yield (in five environments) throughout India (four places in North and South India, two places in North East India at about 43 to 843 meter above sea level), due to environmental variation, resulted in a large portion (70.8%) variation – for genotypes multiplied by environmental variation was 25% and 4.2% for cultivars only. Curcumin varied significantly due to cultivar (31.2%), curing (boiling and subsequent drying 17.7%), curcumin, and dry weight (15.7%). Under environmental interactions (10 environments), Rajendra Sonia produced a high yield. The yield of IISR Kedaram was found to be 105 g/plant in one place and 1040.00 g/plant in other places for Rajendra Sonia, with a wide range of yield variation. Curing is boiling the rhizomes in water for 1 h and sundried for 72 h, and making the relative humidity reach 10%, and the percent curing is calculated by the difference between fresh and dry weight. Among the cultivars Mega Turmeric, IISR Alleppy Supreme, IISR Kedaram, Roma, Rasmi, IISR Prathiba, Suranjana, BSR-2, Duggriala Red, Narendra turmeric 1, Rajendra Sonia were employed, IISR Kedaram showed the highest curing percentage in different environments, whereas Narendra turmeric 1 scored the lowest. Besides, the curing percentage was found to be highest in North India (23.12%) and lowest in South India (16.35%). Curcumin content also varied in different locations. Dry yield and stability are important factors in crop science and the desire for higher values for promising crops. While addressing fresh yield, among all the cultivars, Mega turmeric and BSR-2 appeared promising. Specifically, Mega turmeric has an above-average and fairly stable yield in various environments, whereas Rajendra Sonia, IISR Prathiba, Duggriala Red, and BSR-2 are highly sensitive to environmental changes. While assessing medicinal promise for all environments among all 11 genotypes, Mega Turmeric, IISR Prathiba, and IISR Kedaram appeared promising, based on both curcumin content and curing percentage. While assessing the curing percentage and curcumin content, IISR Kedaram and Rajendra Sonia showed stability for curcumin, and Narendra Turmeric 1 had with the curcumin percentage (but with many environmental fluctuations). IISR Prathiba and IISR Kedaram exhibited the best curing percentages in all environments. Therefore, the effect of

genotype, environment, and the agro-climatic conditions is very crucial to assess the medicinal properties of any natural product to ensure maximum delivery [10].

Another group investigated the curing percentage by changing the curing parameters of the IISR Prathiba variety by curing and treating with 25 kg of fresh rhizome per treatment. The methods used were cooking in boiling water (WC, for 40, 60, and 90 min), steam cooking (30, 45, and 60 min), dipping the rhizome in boiling water for 10 min, slicing the fresh rhizome (3 mm thick) and then sun drying at 37°C (between 9 AM to 3 PM). The cured turmeric was assessed for essential oils (by reflux distillation method) and oleoresin (by acetone extraction method). Starch and curcumin were extracted by refluxing in alcohol and estimated spectrophotometrically at 425 nm. It takes 9-24 days to completely dry from an initial moisture content of 373.71% to 10%. Steam boiling took 24-18-12 days depending on the respective treatment. For the dipping procedure, it took 13 days to reach a final moisture content of 10%. In the case of rhizomes boiled for 40 min, the active constituent curcumin (5.9%), for steam cooking curcumin (6%), for rhizome cured for 30 min, and for slicing curcumin (5.71%). Other constituents like essential oil (3.6%, 3.3%, and 3.07%), oleoresin (13.33%, 13.96%, and 12.76%), and starch (66.96%, 63.33%, and 69.53%), which provides a detailed figure on the curing percentage and curcumin yield [11]. Another study explored the effect of different drying methods on the retention of curcumin color and quality and found that unblanched sliced rhizomes dried under hot air had higher amounts of curcuminoid than rhizomes dried on a black surface. The oil obtained from the fresh leaves and rhizomes in India has many similarities to that of Nigerian oil (except for a few components such as myrcene and β-pinene). Long-storage rhizomes can be attacked by *Lasioderma serricorne* (cigarette beetle) and can be stored for a maximum of two years in an air-tight container [12].

5. Curcumin and *in Vitro* Permeability

An *in vitro* intestinal permeability study conducted by Berginc K *et al.* through Caco-2 cell monolayers as well as rat jejunum found that the basolateral permeability of curcumin is much higher than the absorptive side, an effect that may due to the specific inhibition of breast cancer resistant protein (BCRP) (as demonstrated by Fumitromorgin C). Furthermore, a higher rate of curcumin efflux was found with curcumin conjugates such as glucuronide or sulfates through multi-drug resistance-related proteins (MRP1 and MRP2), which collectively accounts for the low bioavailability of curcumin [13]. Another study has demonstrated the uptake of curcumin by intestinal epithelial cells. Curcumin has also been reported to bind to intracellular Vitamin D receptors in intestinal epithelial cells. It has also been hypothesized that vitamin D interacts with histone deacetylase, which in turn regulates epithelial barrier function, further indicating that curcumin regulates barrier function by enhancing vitamin D signaling [14, 15].

6. Curcumin: Biological Targets and Bioavailability

Curcumin has many pharmacological activities, such as antioxidant, anti-inflammatory, antibacterial, antiviral, antidiabetic, anticancer, and immunomodulatory activities, against neurological disorders as well as digestive disorders [1, 3, 8, 16-18]. Curcumin acts as an antioxidant by potentially scavenging various free radicals, such as reactive oxygen and nitrogen species, and inhibiting lipoxygenase/cyclooxygenase and xanthine dehydrogenase/oxidase, enzymes that are thought to generate reactive oxygen species. In addition, it can act directly by upregulating the

antioxidant defense enzymes, such as superoxide dismutase and glutathione peroxidase [19]. Despite possessing potential pharmacological activity, as well as safety at high doses (12 g/day), curcumin therapeutics still face low bioavailability, low serum levels, and limited tissue distribution [20]. In humans and rodents, the basic metabolic pathway occurs via conjugation (glucuronide and sulfates, orally) and reduction (tetrahydrocurcumin, hexahydrocurcumin, and octa-hydro curcumin, intraperitoneal or systemic administration). Conjugated products, especially glucuronide, lack all biological activity, while reduced curcumin retains the activity compared with free curcumin [21]. In phosphate buffer at pH 7.4 for 30 min, 90% of the curcumin is degraded into trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, ferulic aldehyde, ferulic acid, feruloyl methane, and vanillin. The unique pharmacophore and scaffold of curcumin are built upon a flexible backbone, hydrophobicity, and several available H-bond donors and acceptors. The unique intact structure and degradation products that bind equipotently inside the pharmacophore pocket impart enzyme inhibitory properties. Curcumin itself has been shown not to bind to the active pocket of xanthine oxide and therefore metabolites with parent curcumin structure also lack enzyme inhibitory activity owing to improper binding [19].

7. Pharmacokinetic Interaction

This section detailed some interesting facts about the absorption, distribution, metabolism, and excretion (ADME) profile of curcumin in an attempt to understand the pharmacokinetics of crude curcumin. Due to its hydrophobicity, curcumin can cross the cell membrane and bind to the fatty acyl chain of the membrane lipid through various non-covalent weak bonds, reducing its availability in plasma [22]. When curcumin was consumed regularly at a 10-12 g load, only a 50 ng/ml C_{max} (peak serum concentration) value was obtained. In contrast with the glucuronide and sulfate conjugates, the C_{max} value is between 1-2 µg/ml and the T_{max} (value of drug absorption rate = drug elimination rate) value is 4 h, indicating quite poor bioavailability. When curcumin was used chronically (three months with a load of 4-8 g), the C_{max} value of 0.65 µg/ml was obtained in sera, with no appreciable values detected in urine. This study was specifically conducted in high-risk patients, and it seems that oral dose induces poor prognosis [23]. In a clinical study, the effect of once-daily administration of curcumin for 14 days was studied using different metabolizing enzyme changes as determining parameters, namely Cytochrome P450 1A2 (CYP1A2), Cytochrome P450 Family 2 Subfamily A Member 6 (CYP2A6), N-acetyltransferase 2 (NAT2), and xanthine oxidase (XO). On day 15, changes in urinary caffeine metabolite ratios in volunteers, as well as those treated were probed. The results showed a 28.6% decrease in the activity of CYP1A2, whereas a 49% increase in the activity of CYP2A6 [24].

The bioavailability of curcumin, piperine, and capsaicin (which share structural homology) was studied by oral administration of the respective components. Capsaicin administered at 30 mg/kg dosage was detectable rapidly within 1 h (94% absorption), <1% was excreted in the urine, and was untraceable after 4 days. When piperine (an alkaloid obtained from black pepper) was administered at 170 mg/kg, 10% was distributed into the tissue after 6 h (96% absorption), and no trace was detected in urine. When curcumin was administered at a dose of 500 mg/kg, curcumin concentration peaked in the intestine within 1 h. Peak plasma concentration (83.8 µg/ml) was reached by 6 h and the drug level (52.6 µg/ml) persisted for about 24 h (0.173% urinary excretion). In the liver and kidney, the maximum concentration was achieved at 6 h, and the compound was

localized in the liver for four days. Curcumin combined with piperine exhibited higher intestinal absorption (78%). In the brain, curcumin also accumulated within 24 h and T_{max} at 48 h (5.87 µg compared to 1.16 µg in the kidney). When co-administered with piperine, the $t_{1/2}$ (half-life) of curcumin was increased from 12.8 h to 28.9 h. Intact excretion of curcumin in feces rules out the prediction that the compound is not metabolized by gut bacteria [25]. In another study, the efficacy of piperine was evaluated in terms of the bioavailability of curcumin in rats and healthy human volunteers. Piperine exhibits glucuronide inhibition potential in the intestine and liver. Co-administration of piperine (20 mg/kg) and curcumin (2 mg/kg) increased the plasma concentration of curcumin in a short time, i.e. within 1-2 h, peak time was increased, elimination half-life decreased, and clearance decreased. Piperine increased the bioavailability of curcumin by 154%. In humans, even with a 2 g load of curcumin, the serum level was undetectable. A higher extent of absorption and higher bioavailability of curcumin (2000%) was observed in humans using 20 mg piperine which also had high plasma concentrations [16, 20, 25, 26]. Co-administration of curcumin with either sodium methyl lauroyl taurate (LMT) or sodium methyl cocoyl taurate (CMT) enhanced the oral delivery of curcumin [27].

Several studies have demonstrated the potential effect of curcumin in heightening the pharmacological effect of known drugs, based on its general efficacy in downregulating different P-glycoproteins, ABC-transporter proteins, multidrug-resistant proteins, as well as metabolizing enzymes such as cytochrome p450 and other variants. In one study, New Zealand white rabbits, pre-treatment with curcumin (60 mg/kg, 3 days, p.o.) enhanced the effect of norfloxacin (100 mg/kg *p.o.*), as observed by the significant increase in plasma concentration-time curve, $t_{1/2}$ (elimination) as well and V_d (volume of distribution), and further treatment exhibited a reduction around 20% in loading and maintenance dose [28]. In the second study, it was shown that in curcumin-pretreated rats, the pharmacokinetics of docetaxel can be modulated: at 100 mg/kg alone, curcumin could not modulate the pharmacokinetics of docetaxel, but when docetaxel was administered p.o. 30 min in curcumin-pretreated rat for 4 consecutive days, C_{max}, *AUC* (area under the curve), and absolute bioavailability were increased by 4-10 times. Mechanistically, curcumin was believed to downregulate intestinal P-glycoprotein and CYP3A levels and can modify the substrate of these transporters, such as docetaxel, which is a substrate for ATP-binding cassette transporters such as p-glycoprotein [29]. In another study, curcumin at 50 mg/kg for 3 days was efficient in potentiating the activity of paclitaxel, when the drug was administered orally at a dose of 20 mg/kg dose in the form of a nanoemulsion to SKOV 3 tumor-bearing nude mice. The results showed a 4.1-fold increase in plasma $AUC_{0-\alpha}$ (a non-compartmental analysis in which AUC from 0 h to the last measurable concentration), a 5.2-fold increase in relative bioavailability, and a 3.2-fold increase in paclitaxel accumulation in tumor cells, suggesting that curcumin-paclitaxel may be an effective drug combination in the treatment of ovarian adenocarcinoma [30].

In addition, a study showed a significant effect of oral administration of curcumin in rats to increase the bioavailability of loratadine, as evidenced by a 30-60% increase in plasma concentration-time curve as well peak plasma concentration and 1.39 to 1.67 fold increase in the absolute bioavailability. As curcumin is a down-regulator of different efflux proteins, the increased bioavailability of loratadine in the intestine was mainly achieved by the reduction of the reverse diffusion of P-glycoprotein in the intestine, as well as by reducing the rapid metabolism via the CYP3A subfamily in the liver and small intestine [31]. In another study, in wild-type as well as ABCG2$^{-/-}$ mice, the C_{max} and relative bioavailability of sulfasalazine were increased with oral curcumin at a

nanomolar concentration by selectively inhibiting ABCG2 (ATP binding cassette subfamily G member 2 or breast cancer resistance protein, studied in mouse brain capillaries) function [32]. In addition, curcumin in a syrup solution at a dose of 2-7 ml/kg 1 h before rifampicin dosing significantly increased the volume of distribution (225.8%) and total clearance of rifampicin by 225.60% [33]. The study found that rats with 60 mg/kg curcumin concentration for 4 consecutive days (via intragastric gavage) could downregulate intestinal P-glycoprotein levels, and CYP3A levels, upregulate hepatic P-glycoprotein levels and induce CYP3A levels in the liver or kidney (with no effect on renal P-glycoprotein levels). Regular administration of curcumin (via downregulation intestinal P-glycoprotein activity) together with 30 mg/kg celiprolol (another P-glycoprotein substrate) increased C_{max} and $AUC_{0\text{-}8\ d}$. Besides, when rats were treated with curcumin (by way of downregulation of the CYP3A activity) for four consecutive days, oral administration of 20 mg/kg midazolam (a P-glycoprotein -independent CYP3A substrate), exhibited high $AUC_{0\text{-}4\ d}$ and total *AUC* and lower CL_{oral} [34]. Curcumin, a CYP3A4 inhibitor (IC50 2.7 μM), significantly increased the bioavailability of etoposide in rats (2 mg/kg) at doses of 2-8 mg/kg. In addition, curcumin inhibited the p-glycoprotein efflux pump in the small intestine and suppressed the isoforms of CYP enzymes. Therefore, it was inferred that the enhanced oral bioavailability of etoposide in the presence of curcumin might be mainly due to the inhibition of the P-glycoprotein efflux pump and CYP3A activity in the small intestine [35].

8. Pharmacokinetic and Pharmacodynamic Interaction

Curcumin has been shown to potentiate the effects of different drugs without influencing serum concentration. Reeta *et al.* showed that pre-treatment of curcumin 1 h before seizures in rats could augment the putative effect of valproate in PTZ-induced seizures. Studies by the same group have also shown that curcumin could augment the effects of phenytoin, phenobarbitone, and carbamazepine at sub-therapeutic doses in maximal-electroshock-induced seizure as a means of improving cognitive function. Therefore, curcumin appears to be a good adjuvant for epileptic diseases by preventing the impairment of learning and memory in epileptic seizures [36]. Another study reported the effect of chronic curcumin administration (21 days) on the deterioration of cognitive impairment and oxidative stress induced by phenobarbitone and carbamazepine in rats. The results showed a significant potential for curcumin to repair cognitive deterioration and oxidative damage in rats [37]. In addition, diarylidenylpiperidone (DAP) compound HO-3867, a synthetic derivative of curcumin with higher bioavailability, was studied in cancer cell lines. The analog has better efficacy in terms of uptake by cells within a short time (15 min), 100 times faster than the parent compound curcumin. In *in vivo* rat models, also by i. p. injection, high levels of HO-3867 transport were evident in the liver, kidney, stomach, and blood after 3 h [38].

In another study, curcumin was reported to improve behavior (climbing, swimming, and immobility) and degree of depression (inhibitory activity of brain mono amino oxidase MAO-A) after ng-level administration in a forced swimming test in mice. Single and repeated oral doses of the compound (three times per hour) at concentrations of 2.5, 5, and 10 mg Kg^{-1} could reach peak plasma concentration at 0.75 h (single) and 2.75-3 h (repeated) until detected at 6 h (single) and 14 h (repeated). Maximum MAO-A inhibitory activity in the frontal cortex and hippocampus as well as behavioral improvement was evident within 1-2 h (single) and 3-4 h (repeated), indicating the

indirect role of curcumin in the behavioral improvement and plasma concentration independent antidepressant activity [39].

In a clinical trial, the effect of curcumin administered orally at 8 g per day in gemcitabine-resistant patients with pancreatic cancer and concomitant gemcitabine-based chemotherapy was studied. Results showed that curcumin administration improved the median survival time at 161 days with a 19% 1-year survival rate, at a serum plasma concentration of 29-412 ng/ml [40]. The beneficial effects of curcumin capsule as a lipid-lowering and p-glycoprotein inhibitor were assessed in an open-level randomized controlled trial conducted over 11 days in eight patients with type 2 diabetes treated with glyburide. In this case, patients took curcumin for ten consecutive days. The results showed that glyburide concentration remained unchanged for the second hour, C_{max} remained unchanged, and glucose level was lowered. The area under the first movement curve also showed enhancement, indicating a potential role for curcumin in controlling the pharmacological function of glyburide [41]. Another combined pharmacokinetic study using turmeric extract and bevacizumab in colon cancer mice showed turmeric extract significantly enhanced the drug activity of bevacizumab, indicating that this combination would serve as an effective therapy in colorectal cancer treatment [42]. Besides, cisplatin curcumin combined nanoparticles also exhibited better potential in human hepatocellular carcinoma (HCC) HepG2 xenograft models and thus appeared to be promising against HCC [43]. The effects of resveratrol and curcumin on high-fat-induced inflammation were studied in a double-blind, crossover, randomized, placebo-controlled study with 11 men and 11 postmenopausal women. The dosage regimen was once after the consumption of a dietary supplement (200 mg resveratrol and 100 mg curcumin). Only a reduction in soluble vascular cell adhesion molecule-1 (sVCAM-1) postprandial response was observed compared to placebo, without any effect on the reduction of postprandial inflammation [44]. In another randomized, double-blind, placebo-controlled, prospective clinical study, 50 patients with knee arthritis received Theracurcumin which contained 180 mg of curcumin orally every day for 8 weeks. After 8 weeks, a significant reduction in knee pain VAS score, as well as a reduction in dependence on celecoxib was observed in patients treated with Theracurcumin compared to placebo [45].

9. Pharmacokinetics of Different Curcumin Dosage Preparations

In this section, we review a few cases of curcumin formulations, such as nanoparticles, liposomes, microparticles, nanocrystals, gelatin microspheres, and nanoemulsions, the synthesis of each formulation was accessed through the corresponding references [22, 23]. The rationale for incorporating curcumin in different formulations is its smooth intestinal permeability, inhibition of degradation in an acidic environment, enhancement of long retention in plasma, and heightening efficacy. Different formulations have been attempted by incorporating oil, reducing particle size, and adsorption or desorption onto matrices [46]. After intravenous administration of liposomal curcumin, polymeric nano curcumin (5 mg/kg), and polylactic glycolic acid copolymer (PLGA) curcumin (20 mg/kg) to rats, only 0.5% material localized in the brainstem, striatum, and hippocampus within 1 h, with varied accumulation and clearance rates [47]. In human erythroleukemic K562 cells, curcumin enhanced the action of the dual nanoparticle form of doxorubicin (which is sequestered into the cancer vesicle and drug resistance would occur) by inhibiting the expression of multidrug resistance gene and was reported to enhance cytotoxicity by promoting apoptosis at low doses, which is useful in intractable diseases like leukemia [48].

One study also investigated the penetrability of curcumin and its nano-formulation and showed that curcumin was detected throughout the liver, heart, spleen, lung, kidney, and brain, but for nanoparticles, the target organs were the spleen followed by the lungs. Curcumin and C-NPS (curcumin-loaded PLGA nanoparticles) readily crossed the blood-brain barrier and were localized in the cerebral cortex and hippocampus and curcumin concentration was enhanced from this formulation [49]. Moreover, curcumin-encapsulated PLGA nanoparticles (nano-CUR6) showed an improved anti-cancer potential in inhibiting cell proliferation and clone (2-fold and 6-fold, respectively) against cisplatin-resistant ovarian cancer cells (A2780CP) as well as metastatic breast cancer cells (MDA-MB-231), and enhanced tumor-specific targeting by attaching antibody conjugation to nanoparticles for further modifications [50]. Subcutaneous injection of single dose of injectable sustained-release curcumin microparticles in mice, induced sustained curcumin levels in the blood and other tissues for 1 month, and in the lung and brain (where breast cancer metastasis), the curcumin concentration exceeded 10-30 fold than the blood concentration. In addition, in nude mice bearing MDA-MB-231, curcumin exhibited a significant antiangiogenic effect [51]. In another study in patients with late-stage osteosarcoma, free curcumin levels after administration of a solid lipid curcumin particles (SLCP) (at a dose of 650 mg) formulation in 11 patients was compared with those in healthy volunteers taking unformulated curcumin: in healthy subjects, the mean peak curcumin concentration of the formulated product was 22.43 ng/ml, and the pharmacokinetics involving osteosarcoma patients showed a nonlinear and complex absorption kinetics pattern, with both groups of patients exhibiting good tolerability [52].

In vitro study with curcumin-loaded gelatine microspheres (for targeting the lung) showed that 50% of curcumin could be released from the gelatine microspheres within 22 h and 77% within 48 h [53]. The effect of the curcumin-dropping pill with polyethylene glycol 6000 was also interesting, with a relative bioavailability of 1046% of curcumin intact [54]. In another study, curcumin-entrapped nanoparticles exhibited 9-fold higher oral bioavailability than unformulated curcumin preparations with piperine enhancers [55]. When curcumin was administered at a dose of 4 g to 12 volunteers, the parent curcumin level was undetectable by HPLC-ITMS/MS/MS, but curcumin-O-glucuronide (COG) was detected at 30 min [56]. In another randomized, double-blind, cross-over human study in healthy volunteers, the bioavailability of a curcumin phytosome (CP) formulation, as well as the volatile oil of turmeric rhizome (CTR) was compared to that of a standardized curcumin mixture (CS). The CTR and CP formulations exhibited 1.3-fold and 7.9-fold higher concentrations of curcuminoid (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), than those of the standard mixture, respectively. Another curcumin formulation with a hydrophilic carrier, cellulosic derivative, and natural antioxidants (CHC) showed 49-fold higher absorption than CS and 5.8-fold higher absorption than CP and CTR [57]. Another study compared the bioavailability of colloidal nanoparticles of Theracurcumin to that of curcumin powder. After oral administration, the AUC appeared to be 40-fold higher in rats, whereas healthy human volunteers receiving 30 mg of Theracurcumin orally exhibited 27-fold higher blood concentration than normal curcumin powder [58]. In another study, curcumin diethyl disuccinate, a prodrug, did not exhibit any bioavailability advantage, but it showed a higher tissue-to-plasma ratio of curcumin and curcumin glucuronide in several organs 1-4 h after intravenous dosing. The excretion pathway of glucuronide is mainly via biliary and fecal routes and with an entry into enterohepatic circulation [59].

A study exploring the compartmental distribution, and targeted pharmacokinetics of liposomal curcumin (16 mg/kg) following intrapleural and intravenous administration in rats showed that total

curcumin content peaked at 1.5 h after intrapleural administration without erythrocyte abnormality. In contrast, erythrocyte abnormalities were observed 1.5 h after intravenous administration, demonstrating the potential of targeted curcumin formulation in the pleural cavity in pleural-based tumors [60]. Another study investigated the combination of curcumin and tetrahydrocurcumin in cancer patients given intravenous liposomal curcumin. Of the 44 comedication studies, three studies involving Lisinopril, Ramipril, and Valsartan, elevated plasma levels of both curcumin and tetrahydrocurcumin. In terms of both plasma concentration and elimination, intravenous infusion of liposomal curcumin was more effective in patients with cancer than in healthy volunteers [61]. When evaluating the pharmacokinetic study of oral nano-emulsion in rats, a 10-fold increase in *AUC* and more than a 40-fold increase in C_{max} was observed as compared with 1% suspension. The formulation also facilitated the pharmacokinetic study of demethoxycurcumin, bisdemethoxycurcumin, and three metabolites, tetrahydrocurcumin (THC), curcumin-O-glucuronide and curcumin-O-sulphate in plasma, thereby providing an opportunity for correlation studies with pharmacokinetic and pharmacodynamic (hypomethylation) *in vivo* [62].

A study investigated the pharmacokinetics of curcumin ethosomes in rats using compartmental and non-compartmental models. In the non-compartmental model, the total area under the blood concentration (AUC) was 1.6 times higher, peak concentration (C_{max}) was 1.5 fold higher, and relative bioavailability was 152.2% whereas in the compartmental model, $AUC_{0\text{-}72\ h}$ of curcumin ethosome was 1.4 times higher and relative bioavailability was 128.2% [63]. H10, a novel curcumin analog was identified as a potential 17β hydroxysteroid dehydrogenase type 3 (17β-HSD3, a key enzyme in testosterone biosynthesis) inhibitor. A study exploring its pharmacokinetic profile found the molecule to be safe at a dose of 100 mg/kg. Furthermore, the molecule was also studied in three different routes following intraperitoneal (*i.p.*), intravenous (*i.v.*), and oral (*p.o.*) administration. Single-dose pharmacokinetic studies were fitted to a linear dynamics model. H10 inhibited CYP3A4 by selectively targeting the testes. It accumulates in the spleen followed by the liver. In addition, H10 was found to have weaker inhibitory activity towards liver CYP3A4, even after long-term administration [64]. H10 was also reported to inhibit the Adione-stimulated growth of prostate cancer cell xenografts established in nude mice [65].

A study in healthy volunteers compared the pharmacokinetics of Curcugen (a novel dispersible 50% curcuminoid extract) with standard extract (i.e., 95% curcuminoids). Curcugen was 16.9-, 39-, 49.5-, 43.5-, 46.8-, and 52.5-fold higher than C-95 in terms of $AUC_{0\text{-}t}$, C_{max}, total curcumin, total DMC, total BDMC and total curcuminoids, respectively, as well as 31-fold higher relative bioavailability [66]. In another study comparing the pharmacokinetics of nano-curcumin with free curcumin (500 mg/kg dose) in rats, it was found that the concentration of free curcumin in the plasma, liver, kidney, and colon was higher than nano-curcumin. Furthermore, there was no statistically significant difference in blood concentration, but ovary-targeted nano-curcumin was 3.6-fold higher than free curcumin, which has therapeutic promise in ovarian cancer [67]. In addition, the effect of particle size of nanosuspensions on pharmacokinetics was also investigated. The results showed that the smaller particle size nanosuspensions (CUR-NS-70 nm) exerted equipotent activity against free curcumin, whereas the larger particle size nanosuspensions (CUR-NS-200 nm) exhibited augmented activity after intravenous administration. Both forms localize well to the lungs, liver, spleen, and brain [68]. Furthermore, it was observed that gut microbiota enhanced the bioavailability of curcumin by 5-fold, which was beneficial against HCC [69].

Curcumin was embedded in PLGA-TREN-gambogic acid (2 molecules), a double-headed nanosystem, and its pharmacokinetics were studied in rats. The results indicated a T_{max} of 30 min for PLGA-TGA2. The AUC in PLGA-TGA2 was also 1.5-fold higher and C_{max} was 7-fold higher than in the PLGA preparation, indicating that the double-headed nanosystem exhibited better active transport properties than the curcumin-containing PLGA monomer. Furthermore, the tissue concentration of curcumin and its PLGA-TGA2 glucuronide was 2-fold higher in plasma as well as in various other tissues such as the intestine, liver, kidney, brain, and eye [70]. Another pharmacokinetics study of curcumin hydroxypropyl-β-cyclodextrin phospholipid complex (50 mg/kg) in rats showed a 5.89-fold increase in bioavailability compared to free curcumin [71]. In addition, intravenous administration of curcumin solid lipid nanoparticles improved bioavailability, with the $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and $t_{½}$ appearing 1.50-fold, 1.63-fold, and 4.08-fold higher, respectively, compared to free curcumin [72]. In another study, curcumin was dispersed into LipiSperse, and its pharmacokinetics was studied in 18 healthy human volunteers. LipiSperse exhibited 2.5 times higher bioavailability than free curcumin in parallel and cross-over studies [73]. Moreover, curcumin nanoparticles embedded in chitosan hydrochloride (CHC)-hyaluronic acid (HA)-PEG (CUR-PNPs) exhibited higher bioavailability than free curcumin, which was also effective in brain cancer therapy [74]. PEGylated form of curcumin nanoemulsion exhibited 2-3 fold improved bioavailability and plasma residence time within 20 min after intravenous infusion compared with non-PEGylated nanoemulsion or free curcumin solutions [75].

Pulmonary pharmacokinetics of proliposomes have been reported to exhibit improved bioavailability in terms of the rate and extent of lung tissue absorption and mean residence time, thus highlighting novel therapeutics as alternatives to oral or parental drugs [76]. Another study evaluating the pharmacokinetic profile of curcumin phospholipid complex (CPC) with Soluplus (solidified CPC and complex, termed as CPS) and without Soluplus showed that the CPS form exhibited higher bioavailability. Namely, the $AUC_{0\text{-}\infty}$ with CPC appeared at 205.84 μg h/ml whereas augmented activity was observed with CPS at 330.47 μg h/ml [77]. Besides, the sophorolipid-coated curcumin exhibited 2.7-3.6 fold higher bioavailability than the free curcumin [78]. In patients with pancreatic or biliary tract cancer who failed standard therapy, daily oral treatment with Theracurcumin and gemcitabine-based chemotherapy showed enhanced bioavailability owing to repetitive systemic exposure to a high concentration of curcumin from Theracurcumin [79]. In another study, curcumin-loaded nanostructured lipid carriers (Cur-NLC) exhibited specific targeting to the lungs in rats. The bioavailability of Cur-NLCs was higher than that of free curcumin in terms of AUC, maximum plasma concentration, mean residence time, and total plasma clearance indicating its potential in the treatment of lung carcinoma [80].

Embedding curcumin in micro-emulsifying drug delivery systems (SMEDDS) using oleoresin from *Curcuma longa* and *Curcuma aromatica* as curcumin bio-enhancers increased the solubility of curcumin. A pharmacokinetic study in rats showed that the bioavailability of oleoresin from *C aromatica* as well as *C longa* was 26-29 and 22 times higher than that of the curcumin suspension, respectively [81]. An oral bioavailability study of the microparticles in rats showed that curcumin (40%) embedded in spray-dried ternary solid dispersion containing Gelucire 50/13 aerosol compared to unformulated curcumin, its blood concentration was increased 5.5-fold [82]. In a randomized, crossover, double-blind, comparator-controlled pharmacokinetic study with 12 healthy volunteers, a novel formulation of curcumin lipid droplet micromicellar (CLDM containing 64.6 mg curcumin) was compared to 95% curcumin in capsule form (containing 323 mg curcumin)

in a 400 mg dose. In terms of C_{max} (after 1 h), CLDM provided 20 ng/ml of curcumin sulfate and 300 ng/ml of curcumin glucuronide. The free curcumin level was 2 ng, compared to 95% curcumin (0.3 ng/ml). For CLDM, another secondary curcumin peak occurred at 12 h and a tertiary 1.5 ng/ml peak appeared after 24 h. The total absorbed curcumin was 522 times higher than that of the free form [83]. A study demonstrated the potential of nano-curcumin in mice required a 20-fold reduction in dose to achieve therapeutic concentration in the plasma and central nervous system as compared to unformulated curcumin [84]. Moreover, curcumin encapsulated in a supersaturated self-micro emulsifying drug delivery system exhibited a 53.14-fold increase in absorption compared with the free form [85].

In a double-blind cross-over study of 12 healthy volunteers, a new γ-cyclodextrin curcumin formulation (CW8) was evaluated and compared with standard unformulated curcumin extract (StdC), curcumin phytosome preparation (CSL) and a formulation of curcumin with essential oils of turmeric rhizome (CEO), with the latter two formulations reported to have increased bioavailability. The results showed that CW8 exhibited the highest plasma concentrations of curcumin, demethoxycurcumin, and total curcuminoids, whereas CSL exhibited the highest level of bisdemethoxycurcumin. In terms of $AUC_{0\text{-}12\ h}$, CW8 exhibited a 39-fold higher plasma curcumin concentration than unformulated curcumin StdC [86]. In another study, saponin-coated nanoparticles exhibited a 3.3-fold increase in bioaccessibility *in vitro* and an 8.9-fold increase in bioavailability in rats [87]. In another study comparing the bioavailability of polysaccharide-adsorbed nanoparticles with unadsorbed preparation, nanoparticles without adsorbed polysaccharides exhibited a C_{max} value of 61.3 ng/ml, with sustained plasma concentration up to 24 h and 117% absolute bioavailability, whereas galactose polysaccharides arabinogalactan and kappa-carrageenan adsorbed nanoparticles showed rapid absorption with C_{max} value of 109.5 ng/ml and 92.3 ng/ml respectively, but the elimination rate was faster and the absolute bioavailability was also greater than 25%. The lack of bioavailability of polysaccharide-coated nanoparticles may be due to the high metabolism of curcumin in the intestine due to faster gastric elimination and higher intestinal localization [88]. Moreover, an open-level, two-way crossover single oral dose (capsule), comparative pharmacokinetics were performed in 14 healthy volunteers using a natural water-dispersible turmeric extract containing 60% curcuminoids (WDTE60N, one capsule of 150 mg curcuminoid) and compared with standard 95% curcumin (three capsules of 500 mg curcuminoid each). The C_{max} of WDTE60N was 43.5 ng/ml compared to 21.3 ng/ml for STD95. WDTE60N had a higher level of $AUC_{0\text{-}t}$ for free curcumin, total curcumin, and total curcuminoids than STD95, and a 10-fold lower dose [89].

Curcumin-containing oil-in-water nanoemulsions were modified with phosphatidylcholine (NEPC) and high medium-chain fatty acids-rich phosphatidylcholine with glycerol as a cosurfactant (NEPCE) and their pharmacokinetic profiles were studied. The results confirmed that in terms of AUC and C_{max}, NEPCE showed higher bioavailability than NEPC and curcumin coarse suspension (CCS), with a higher localization level in the liver and lungs [90]. Another study reported enhanced bioavailability using curcumin chitosan microspheres containing ascorbic acid to design a colon-targeted system for curcumin delivery [91]. The amorphous solid dispersion of curcumin with disodium glycyrrhizin exhibited a 19-fold higher bioavailability in rats compared to free curcumin [92]. An amorphous solid dispersion of curcumin with hydroxypropyl methylcellulose, lecithin, and isomalt exhibited 13-fold higher activity than unformulated curcumin [93]. Evaluation of standard curcumin extracts and phosphatidylcholine curcumin extracts using randomized, cross-over studies

showed that phosphatidylcholine extract yields 20-30% plasma demethoxycurcumin and bisdemethoxycurcumin conjugated, tissue concentration was also improved by 5-fold [94]. Besides, the pharmacokinetics of drinkable Theracurcumin were assessed in 24 healthy volunteers and compared with three other beverages sold in Japan. The $AUC_{0\text{-}8\ h}$ was found to be 1.5-4.0 fold higher and the C_{max} value was 1.8-3.8 fold higher with Theracurcumin [95]. Another study investigated the effect of soybean Bowmann-Birk inhibitors (proteolytic enzymes in the gastrointestinal tract) containing curcumin nanoparticles and found improved bioavailability and clathrin-mediated endocytosis in rats [96]. A single oral dose of 500 mg of curcuminoids in native powder, micronized powder, or liquid micelles form was compared in a crossover study of 23 healthy human volunteers. The results demonstrated that micellar curcumin exhibited better bioavailability than micronized curcumin and more than 100 times higher than native curcumin [97]. Another study reported a phase I, single-center, open-label study in patients with metastatic tumors in which liposomal curcumin (lipocurc) was administered intravenously weekly for 8 weeks (dose regimen: 100 mg/m^2 over 8 h, and the dose increased to 300 mg/m^2 over 6 h.). Stable but rapidly decreasing curcumin concentration was found during infusion, and the result indicated that 300 mg/m^2 over 6 h is the maximum tolerated dose for use in anticancer trials [98]. Another study investigated the bioavailability of CurQfen (curcumagalactomannoside [CGM]), a food-grade formulation of natural curcumin with dietary fiber from fenugreek for stress relief. Sixty patients with occupational stress were randomized to CGM, standard curcumin, and placebo for 30 days (dose 500 mg twice daily). The results showed that CGM administration significantly improved life quality including anxiety, stress, and fatigue. In addition, CGM also exhibited enhanced absorption and improved pharmacokinetics [99].

10. Curcumin and Pharmacology

10.1 Gastroprotective Activity

Curcumin (500 mg) has been shown to be effective in treating Crohn's disease by attenuating the levels of inflammatory markers, such as erythrocyte sedimentation rate, and C-reactive protein. In addition, curcumin can also reduce irritable bowel syndrome, alleviate symptoms such as cramping, abdominal pain, bloating, flatulence, diarrhea, and constipation, increase bowel motility, and activate hydrogen-producing bacterial flora in the colon. In patients with peptic ulcers, 300 mg of turmeric given orally five times daily for 4 weeks could abolish ulcer formation. Curcumin 30 mg twice daily for 7 days could alleviate dyspeptic function and reduce serological signs of gastric inflammation. While a parallel comparison of omeprazole/amoxicillin/metronidazole (OAM) treatment and turmeric (40 mg curcumin, three times a day) were performed, OAM therapeutic levels were consistently higher, limiting the efficacy of curcumin against *Helicobacter pylori* therapy [100].

Seven predominant bacterial phyla were found in the gut: Bacteroidetes, Firmicutes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobiota, and Cyanobacteria, of which Bacteroidetes, and Firmicutes predominate. Species dominated by Firmicutes include Clostridium, Eubacterium, and Ruminococcin. Curcumin had a significant effect on the number of several bacterial families in the gut, including Prevotellaceae, Bacteroidaceae, and Rikenellaceae. Curcumin significantly increased the ratio of beneficial bacteria to pathogenic bacteria, and the load of Bifidobacteriaceae, Lactobacilli and Butyrate-producing bacteria was higher than that of

Coriobacteriaceae, Prevotellaceae, Enterococci and Enterobacteriaceae, which strengthened immune modulation in the colon [101].

Curcumin also plays a therapeutic role in resting intestinal barrier function by downregulating lipopolysaccharide-induced IL-1β secretion, preventing tight junction protein disruption, and decreasing p38 MAP kinase activation. Oral administration of curcumin (100 mg/kg) in mice was also found to restore intestinal alkaline phosphatase activity as well as the expression of tight-junction proteins ZO-1 and claudin-1. Additionally, curcumin also reduced nonalcoholic fatty liver disease (NAFLD) progression by downregulating oxidative stress and inflammation by changing the bacterial strain [18, 102].

But studies also show that curcumin is not recommended for people with liver disease, cirrhosis, gallstones, gallbladder, biliary obstruction, acute gall colic, obstructive jaundice, people taking a blood thinner, reserpine, and NSAIDs [102].

11. Cancer

Curcumin-loaded nano-pharmaceuticals have been found to be used in the treatment of cancer with the aim of inhibiting ATP-binding cassette (ABC) efflux transporter, restoring ROS production, DNA N-methyltransferase (DNMT) function, inducing apoptosis, inhibiting the cell cycle, downregulating apoptotic protein expression, as well as cell survival signaling pathways, EPR effect (enhanced permeability and retention effect) and modulating immune responses. Several forms have been reported, including microemulsions, metal-organic frameworks [103], Eudrajit RS 100 nanoparticles, dextran curcumin conjugate nanoparticles, and implantable drug delivery systems. Curcumin can also modulate transcription factor NF κB, JAK/STAT, and the TGF-β pathway and is an inhibitor of COX-2, eventually leading to a reduction in the synthesis of cytokines and pro-mitotic proteins. Other notable related pathways are Wnt/β-catenin, SP-1, induction of caspase, ER and mitochondrial stress induction, inhibition of growth factors EGFR, deactivation of PI3K/Akt/mTOR pathways, Warburg effect, dysregulation of HGF/mesenchymal-epithelial transition factor (MET), inhibition of the Hedgehog pathway, inhibition of the EGFR/MAPK pathway, and downregulation of the stem cell marker (CD44) [104, 105].

The role of curcumin in clinical studies of cervical precancer lesions, intestinal adenoma, prostate cancer, breast cancer, colorectal cancer, advanced cancer as well as non-small cell lung cancer, gastric cancer, and adenoma of the intestinal tract has been reported [16]. Mukherjee and Vishwanatha showed that curcumin-loaded PLGA nanospheres dispersed well in aqueous media and robust uptake was observed in prostate cancer cells (DU145, PC3, LNCaP cells) compared to free curcumin. The formulation produced lower IC_{50} values for cancer cells than for normal cells, indicating selective activity against cancer cells. PLGA nanospheres also exhibited a greater degree of NF-κB inhibition than free curcumin, as demonstrated by electrophoretic mobility shift assay [106]. Link *et al.* reported curcumin-induced epigenetic alteration of DNA methylation patterns in colorectal cancer cells as a novel therapeutics against colorectal cancer [107].

12. Immunomodulatory Activity

Curcumin has been found to ameliorate inflammation by inhibiting the activation of the TLR4/MYD88/NF κB signaling pathway. It also inhibited the nuclear translocation of NF-κB [101]. Curcumin could exhibit different effects by downregulation or upregulation of microRNAs such as

miR-21. miR-33b, miR-205-5P, etc., and stimulating tumor suppressor genes [108]. Curcumin combined with IFN-γ stabilized the cell index in impedance analysis, a slight decrease in the index for IFN-γ was observed, whereas the index for sole curcumin increased due to a change in cell morphology or adhesion. Curcumin also significantly reduced IL-17 secretion, therefore inducing a protective effect in intestinal epithelial cells (IL-17 is believed to play a crucial role in inducing bacteria-induced cytokine, and therefore contribute to secondary lymphoid structure). Inhibition of higher levels of IL-17 has also been beneficial in inflammatory bowel disease [109]. Curcumin has also been shown to inhibit the activation of dendritic cells by downregulating CD83, CD28, B7-DC, CD40 and TLR-2, to promote dendritic cells to balance Th1 and Th2 ratio and to act on JAK/STAT/SOS pathway [110]. Starch nanoparticles have also been shown to improve intestinal barrier function by downregulating the secretion of IL-1β, IL-8, and IL-6 as well as by increasing the production of anti-inflammatory cytokines IL-10 [15]. Curcumin also inhibited lipopolysaccharide-stimulated IgM secretions in purified splenic B cells [111].

13. Liver Disease

Curcumin has been shown to inhibit transaminase, alkaline phosphatase, plasma levels of γ-glutamyl transpeptidase, and thiobarbituric acid lipid peroxide levels, as well as increase plasma levels of glutathione, Vitamin C, Vitamin E to prevent carbon tetrachloride-induced nephrotoxicity in rats. Furthermore, curcumin could induce portal vessel thickening and deposition of fat droplets in the vessel wall, inhibit the activation of NF-κB, and induce antioxidant activity. Curcumin has also been shown to inhibit hepatic cancer by inhibiting tumor growth in an animal model [105, 112].

14. Ophthalmology

Dry eye induces alteration of tears at the ocular surface, and curcumin at a 5 mM dose has been found to prevent dry eye syndrome by inhibiting IL-1β production, p38 and NF κB activation, and JNK activation. Curcumin prevented secondary retinal detachment by inhibiting cell proliferation that induced caspase 3/7-dependent cell death and necrosis. Curcumin has been found to have a preventive effect on streptozocin-induced diabetic retinopathy by reducing VEGF expression or reducing glutathione, superoxide dismutase, catalase, TNF-α, and VEGF levels, and concurrently protecting cellular antioxidant activity or downregulating IL-1β, VEGF and NF-κB levels without influencing blood glucose levels. In cataracts, curcumin induced reduction in free radical levels in the lenses via Ca^{2+}-ATPase inactivation, altering the level of Ca^{2+} accumulation, as well as the activation of calpain-mediated proteolysis and lens clouding. It can also act through the inhibition of lipid peroxidation, advanced glycation end products, and protein aggregation. Curcumin, a PPARγ agonist, can be effective against age-related macular degeneration (AMD) and downregulate proinflammatory cytokines in microglia, such as MMP-9. Curcumin has also been shown to reduce optical nephritis by increasing PPARγ levels [113].

15. Curcumin and Metabolic Disorder

15.1 Diabetes

Dietary curcumin treatment (curcumin C3 complex, 95% standardized curcumin extract) has been shown to attenuate insulin resistance and hyperglycemia (characteristic of Type2 Diabetes

Mellitus) in genetically obese leptin-deficient mice fed a high-fat diet by downregulating adipose tissue and liver inflammation. Curcumin has also been shown to be a direct inhibitor of the proteolytic core of the mammalian chymotrypsin-like activity of the 20S proteasome (via the ubiquitin pathway), thereby enhancing pancreatic β-cell function. Curcumin treatment of leptin-deficient obese mice in Kalis (Ks) background blocked the development of hyperglycemia, elevated circulatory insulin levels, prevented the β-cells loss, and prolonged life span. This result parallels that of the proteasomal inhibitors epoxomicin and celastrol, which increase insulin sensitivity and production [114].

Several studies have reported the antidiabetic potential of curcumin in streptozocin-induced diabetic rat models, as well as in alloxan-induced models. Its effects are mainly mediated by reducing blood glucose and lipid levels, increasing insulin sensitivity, increasing muscle and fat glucose uptake, increasing mitochondrial biogenesis, anti-inflammatory activity, reducing oxidative stress, downregulating lipid peroxidation, improving liver and urinary function, and increasing pancreatic β-cell function. In diabetic nephropathy, curcumin improves kidney function [115].

Curcumin has also exhibited antidiabetic potential in several *in vitro* models of adipocytes, hepatocytes, and muscle cells. In human adipocytes, differentiation was increased (as evidenced by glycerol release from triglycerides), and peroxisome proliferator-activated receptor (PPAR) gamma ligand binding activity was increased. In other adipocytes, a downregulation of adipocyte differentiation and a decrease in macrophage infiltration was observed. It reduced adipogenic gene expression and improved mitochondrial biogenesis and membrane potential. In the hepatocyte model, curcumin resulted in reduced proliferation and decreased mRNA levels of α1 (I) collagen, alpha-smooth muscle actin (α-MSA), and fibronectin. It also downregulated cell cycle stimulating cyclins D1 and D2, enhanced inhibitory p21 and p27 levels, and induced apoptosis by increasing caspase 3 and reducing BCL-2 mRNA levels. It also increased PPAR-γ mRNA, NF κB, and PPAR-γ activity, thereby reducing transcriptional regulation. In muscle cells, curcumin augmented glucose uptake and GLUT4 translocation to the cell surface. Curcumin treatment of pancreatic cells *in vitro* resulted in increased insulin release, increased open channel probability of volume-regulated anion channels (chloride channels), irreversible augmentation of membrane conductance, and increased glucose-induced depolarization. In mouse pancreatic cells, curcumin reduced oxidative stress, increased Cu/Zn SOD levels, and reduced peroxynitrite, NO, and activated PARP levels, leading to more cytoprotection effects [116].

Curcumin has been shown to modulate glucose release by blocking the membrane translocation of GLUT2, interrupting the p38 MAPK signaling pathway, activating PPAR γ and reducing oxidative stress. Curcumin has also been shown to suppress the membrane translocation of GLUT4 by interrupting the insulin receptor substrate (IRS)/PI3K/AKT pathway. The effect of curcumin on GLUT4 was tissue-specific or signaling pathway dependent [117].

Curcumin also modulated lipid metabolism by downregulating the gene expression of transcription factors involved in hepatic lipogenesis, such as sterol regulatory element-binding protein 1C, which is mainly involved in cholesterol synthesis, as well as carbohydrate response element binding protein (ChREBP). Other lipids metabolizing enzymes, such as carnitine palmitoyltransferase 1 (CPT1) and acyl-CoA cholesterol acyltransferase (ACAT) were also found to be modulated by curcumin [118].

16. Osteoarthritis

Curcumin and bis-demethoxy curcumin were encapsulated in soybean phosphatidylcholines as liposomes, and the formulation could efficiently inhibit macrophage inflammation and osteoclast differentiation activity. Curcumin-loaded nanoparticles have also been shown to inhibit the expression of inflammatory markers in IL-1β-stimulated osteoblasts and maintain a high osteoprotegerin (OPG)/receptor activator of nuclear factor kappa B ligand (RANKL) ratio to prevent osteoclastogenesis. It has also been shown that curcumin-loaded liposomes can inhibit NO production in RAW264.7 macrophages and present osteoclast differentiation by downregulating the expression of cathepsin K and TRAP [119]. In another study, Meriva, a curcumin-phosphatidylcholine complex, decreased joint pain and improved joint function in 50 osteoarthritic patients [120]. Curcumin has also been shown to alleviate pain and discomfort in osteoarthritis, improve disease prognosis, reduced joint degradation, and enhanced chemoprotective activity. The intra-articular injection of curcumin precursors has been shown to reduce cartilage damage. Curcumin can reduce oxidative ER-stress-induced damage in THBP-stimulated chondrocyte cells [121]. In a study, ovariectomized obese rats were injected with monoiodoacetate in the knee joint to induce osteoarthritis, followed by feeding with curcumin and tetrahydrocurcumin to prevent postmenopausal and osteoarthritis syndrome, both forms decreased the expression of TNF-α, IL-1β, IL-6, MMP-3, and MMP-13. Tetrahydrocurcumin enhanced glucose tolerance while reducing advanced glycation end products in articular cartilage, which in turn slows down the pathological consequences of cartilage breakdown [122].

Curcumin has also been reported to prevent osteoporosis by inducing ER stress, resulting in the upregulation of osteogenic genes, such as BiP, SMILE, ATF6, and CREBH. Furthermore, it increased the expression of Runx2, OC mRNA, and ALP [123].

17. Pharmacodynamics of Curcumin

17.1 Curcumin and (Potassium/Calcium) Channel Activity

Various types of symporter and antiporter ion channels exist in biofilms along the apical side as well as the basolateral side. The facile transport of Na^+, K^+, Ca^{2+}, and Cl^- maintains cellular homeostasis, and alteration of any of these leads to disease pathology. Several studies have found that curcumin exhibits pharmacological effects on ion channels with IC_{50} ranging between 5-50 µM. In acute myeloid leukemia, curcumin can effectively block voltage-gated potassium channel Kv 11.1 activity expressed in THP-1 cells, which results in depolarization of the cell membrane potential and also inhibits cell proliferation [124]. Curcumin inhibited hERG K^+ currents in HEK293 cells *in vitro* by decreasing the repolarization current and interacting with pore-blocking sites [125].

Curcumin has also been shown to be a strong inhibitor of TREK-1, a two-pore domain potassium channel associated with major depression. Further, it increased the viability and proliferation of neuronal stem cells [126]. Curcumin in a calcium-free medium increased TRPA1 (a channel that is stimulated in presence of pollutant-inducing pain, and synaptic plasticity) currents in HEK293 cells expressing human TRPA1 (hTRPA1-HEK) and native mouse vagal neurons (along with marked tachyphylaxis at a higher dose) without affecting the function of recombinant TRPM8 and TRPV1 [127]. Curcumin effectively blocked the TNF-α/NF-κB signaling pathway, which was involved in inflammation, apoptosis, and neoplasia. The downstream pathway involves increased production

of prostaglandin E2 via cyclooxygenase-2 (COX-2) in myofibroblasts, which is Ca^{2+} dependent and an important component of gut signaling, as observed in CCD-18Co (human colonic myofibroblast cell line), where curcumin acts by decreasing store-dependent Ca^{2+} influx and increasing TRPC1 expression [128]. Curcumin has been shown to increase whole-cell and single-channel currents in G551D-CFTR (G551D mutation in the cystic fibrosis transmembrane conductance regulator, which results in extremely low open probability without affecting normal trafficking along the plasma membrane), and also exerts additive activity over genistein [129]. Curcumin has also been shown to induce cross-linking of Δ1198-CFTR and ΔF508-CFTR in airway epithelial cells (human airway epithelial cell line CFBE41o; mature and immature CFTR protein in the cell membrane as well as endoplasmic reticulum), stimulating macroscopic CFTR current [130] and PLGA-nanoparticle showed improved activity compared with the curcumin [131]. In bovine Adrenal Zona fasciculate cells, curcumin reversibly inhibited the Kv 1.4 K^+ current [132].

Curcumin has been shown to reverse the induction of aquaporin-4, which results in the development of cellular edema following head trauma, an effect mediated by the downregulation of IL-1β-induced aquaporin expression, with inhibition of the p50 and p65 subunits of NF-κB [133]. Curcumin has been shown to inhibit store-operated calcium entry (CRAC, an important signaling function in lymphocytes), and dose-dependent inhibition of ICRAC in Jurkat and HEK cells overexpressing Orai1 and STIM1. Curcumin has also exerted its ameliorating effect on voltage-gated K^+ channels (K_v) and intermediate-conductance Ca^{2+}-activated K^+ channels (IKCa1/SK4) to regulate the immune response and together contribute to the anti-inflammatory property of curcumin [134]. Curcumin binds to the Vitamin D receptor alternative pocket, and in VDR wild-type-transfected COS-1 cells and TM4 Sertoli cells, curcumin-triggered voltage-gated outward rectifying chloride channel (ORCC) currents can be blocked by the VDR antagonist 1β,25(OH)(2)-vitamin D(3) and a chloride channel antagonist (4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid) [135]. The vanilloid moiety of curcumin exhibited a dose-dependent reduction in capsaicin-induced current in both trigeminal ganglionic neurons and TRPV1-expressing HEK293 cells, alleviating TRPV1-mediated pain hypersensitivity [136]. Curcumin has been found to inhibit adrenocorticotropic hormone and angiotensin II-stimulated cortisol secretion, possibly by inhibiting the Cav3.2 current [137]. Curcumin also inhibited Ca^{2+}-dependent and independent CAMK II kinases, thereby providing a protective effect on brain functions such as learning and memory [138]. Besides, curcumin could induce an immunosuppressive effect by blocking T-cell-activation-induced Ca^{2+} mobilization, which in turn, prevents NFAT activation and NFAT-regulated cytokine expression [139]. Curcumin also potentiated DIDS-sensitive chloride channel (i.e., CIC-3) currents in the proliferation of breast cancer cell line Mcf-7 [140].

18. Apoptosis

Several studies have shown that curcumin (in the dose range of 20-70 μM) has the potential to act selectively on the mitochondrial membrane and subsequently induce apoptosis (via the production of ROS, intracellular calcium, reduction in membrane potential, overexpression of the apoptotic protein, and increased endoplasmic reticulum stress), some of which are presented in this section. Curcumin has been shown to independently prevent isoprenaline-induced increases in mitochondria permeability transition pore (mPTP) in isolated cardiomyocytes [141]. Curcumin induces apoptosis in fibroblasts in a caspase-independent manner. Subsequently, three signaling

events are upregulated, mitochondrial formation of ROS, VDAC, Bax, and possibly ceramides-mediated mitochondrial pore opening and nuclear translocation of apoptosis-inducing factor (AIF) [142]. In nasopharyngeal carcinoma cell line NPC-TWO 76, curcumin has also been shown to induce cell cycle arrest by inducing G2/M phase arrest and attenuating the expression of proteins such as cyclin A, Cyclin B, and cyclin-dependent kinase 1 (CDK 1). Curcumin-induced apoptosis triggers sequential events such as upregulation of Bax protein expression, downregulation of Bcl-2 protein level, subsequent mitochondria dysfunction, cytochrome C release, and sequential activation of caspase 3 and caspase 9 [143]. In hepatocellular carcinoma cell line (HepG2) [141], as well as in highly malignant metastatic rat mammary gland cell line ENU 1564, curcumin-induced apoptosis was shown to be caused by disruption of mitochondria membrane potential with the disturbances of intracellular free Ca^{2+} concentration, decreased expression of BCL-2 and procaspase-3 and increased production of reactive oxygen species [144, 145]. In mouse-rat hybrid retina ganglion cells (N18), curcumin induces apoptosis via the production of reactive oxygen species and Ca^{2+}, with a reduction in the mitochondrial membrane potential. Increased endoplasmic reticulum stress can also trigger curcumin-induced apoptosis via changes in GADD153 and GRP78 and cause Ca^{2+} release [146].

19. Endoplasmic Reticulum Stress

In the myogenic C2C12 cell line, brief exposure to low doses of curcumin (3 h, 5-10 μM) induces endoplasmic reticulum stress responses with an increase in the protein levels of the ER chaperone Grp 94, which in turn acts as a regulator of calcium homeostasis and protects against oxidative stress [147]. In the human airway epithelial cystic fibrosis cell line CF15, curcumin (an inhibitor of ER calcium pump) can maintain a threshold level of calcium correlated with the recovery of endogenous F508 del-CFTR transport activity (cAMP-dependent chloride transport) [148]. In Madin Darby Canine kidney cells, which express nine endoplasmic reticulum retained vasopressin type-2 receptor (V2R) mutants involved in nephrogenic diabetes insipidus, curcumin could specifically induce maturation of V2R-V206D and plasma membrane rescue, Calcium measurements showed that the rescue of V2R-V206D by curcumin was due to an increase in cytosolic calcium levels rather than decrease in endoplasmic reticulum calcium levels [149]. Curcumin has been shown to repress ER Stress-responsive gene transcription of LKB1/AMPK/SMILE/PGCα (liver kinase B1/adenosine monophosphate-activated kinase/small heterodimer partner-interacting leucine zipper protein gene expression/peroxisome proliferator-activated receptor α PGC-1 α) [150].

20. Curcumin as Anti-Infective Agent

20.1 Antimicrobial Activity

Curcumin is a potent broad-spectrum anti-infective agent. It is active against several microbes such as *Helicobacter pylori* (through inhibiting NF-KB) [17], protozoa malaria [151], *Leishmania* [152], (by reactive oxygen species formation and elevation of cytosolic calcium through the release of calcium ions from intracellular stores as well as by influx of extracellular calcium by initiating programmed cell death), *Shigella flexneri* (clinical isolates), *Listeria monocytogenes*, *Salmonella enterica serovar Typhimurium*, *Staphylococcus aureus*, *Yersinia enterocolitica* [153], and tuberculosis [154]. Curcumin can act by inhibiting bacterial virulence factors, adhesion to the host

cell, and biofilm formation through regulation of the quorum sensing regulatory system [155]. Curcumin derivatives also exhibited antifungal activities [156]. Silver nanoparticles of Curcuma longa tuber powder and extract immobilized on cotton cloth exhibited potent inhibitory activity against *Escherichia coli* [157].

21. Antiviral Activity

Curcumin has been found to be effective against several viruses, such as arbovirus, Zika Virus, hepatitis virus, respiratory influenza virus, herpes virus, papillomavirus, and HIV [158]. Additionally, aqueous turmeric root extracts, curcumin-containing nutritional supplement capsules, and pure curcumin all exhibit antiviral activity against SARS-CoV-2 [159]. Curcumin ameliorated severe pneumonia caused by *Influenza A* virus *in vitro* and *in vivo*, downregulating inflammatory cytokines and inhibiting NF-κB signaling in macrophages [160]. Curcumin interacts with and binds to the SARS-CoV-2 virus protein, which is capable of viral entry, replication, and infection. Curcumin is an inhibitor of SAR-CoV-2 3Clpro (chymotrypsin-like protease). Curcumin can bind to the spike protein of SARS-CoV-2 and the human ACE2 receptor and has also been found to be effective in dampening the COVID-19 cytokine storm, thereby preventing pulmonary fibrosis. Curcumin has also been found to bind to the main protease (MPro) with a docking score of -9.2. The main protease (MPro or 3ClPro) cleaved the 16 polypeptide components into 11 fragments. It exhibited the ability to form multiple hydrogen bonds, van der Waals interactions, as well as hydrophobic and pi-based interactions with key amino acids within the active site. The binding energy of curcumin and MPro complex (based on MD combined with MM-GBSA calculation) was -19.8 Kcal/mol (E_{ele}). E_{vwd} interaction was the dominant force for curcumin binding affinity with an average value of -47.5 Kcal/mol. Curcumin exhibited the following properties of drug-likeness: mLogP value (satisfactory permeability across cell membrane) 3.0, low molecular weight 370 (enhancing readiness for transfer, diffusion, and absorption) and topological polar surface area (116 ºA), indicating intermediate cell membrane permeability and oral bioavailability load [161]. Curcumin also showed the highest binding affinity to the viral RBD of the SARS-CoV-2 spike protein. This, in turn, inhibited viral attachment to the human angiotensin-converting enzyme 2 receptor and the cellular entry of the pseudotypes of SARS-CoV-2 virions. In addition, curcumin decreased the activity of transmembrane serine protease 2 to a greater extent. Curcumin treatment has been found to significantly reduce the SARS-CoV-2 RNA levels. Curcumin also showed the potential to bind to transmembrane serine protease 2 (TMPRSS2), which facilitated the binding and endosomal egress of SARS-CoV-2 and increased lysosomal pH [162].

22. Miscellaneous Activity

In a cell-based inflammation model, solid lipid curcumin nanoparticles exhibited downregulation of NO and PGE2 production, and further downregulated IL-6 expression through inhibition of NF-κB [163]. In another study, CNB-001 (a pyrazole derivative of curcumin) exerted efficacy in both *in vitro* and *in vivo* models and was essential for maintaining neuronal function by maintaining calcium-calmodulin-dependent kinase signaling pathways associated with neurotropic growth factors [164]. In addition, bisdemethoxycurcumin exerted anti-inflammatory activity in Ca^{2+}/calmodulin-CaMKII-ERK 1/2-NRF2 pathway, ultimately leading to heme oxygenase 1 (HO-1) expression in LPS-stimulated macrophages [165]. Curcumin has also been found to act on the mammalian target of rapamycin

raptor complex, by inhibiting the phosphorylation of P 70 S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E (eIF4E) binding protein 1, two downstream effector molecules of the mammalian target of rapamycin complex 1 (mTORC) in numerous cancer cell lines [166]. In the cardiac and skeletal sarcoplasmic reticulum (SR), curcumin (1-5 μM) reduced the concentration of phosphate or oxalate required to reduce slippage of the Ca^{2+} pump. Besides, curcumin improved Ca^{2+} transport and its slippage in cardiac and skeletal SR, raising the possibility of pharmacological interventions to correct defective Ca^{2+} homeostasis. Higher curcumin concentration (5-30 μM) inhibited the overall ATPase activity and Ca^{2+} transport [167]. In alveolar macrophages, curcumin inhibited an LPS-induced increase in the mRNA levels of interleukin (IL-1) beta. However, curcumin failed to inhibit the LPS-induced tumor necrosis factor-α (TNF-α) expression [168].

In another study performed on rat alveolar macrophages, curcumin strongly inhibited nitric oxide levels (which can aggravate endotoxin lethality) under low magnesium conditions [169]. Aromatic turmerone has been shown to inhibit α-alpha melanocyte stimulating hormone (α-MSH) and IBMX-induced melanin synthesis and tyrosinase activity, as well as downregulate the expression of tyrosinase, TRP-1, and TRP-2 in B16F1O melanoma cells [170]. Curcumin supplementation has also been shown to reduce diabetes-induced alterations in dopamine D1 and D2 receptors, transcription factors CREB, and phospholipase C, which in turn can regulate diabetes-induced malfunctions of dopaminergic signaling, CREB, and phospholipase C expression in the cerebral cortex and cerebellum, thereby improving the cognitive and emotional functions associated with these regions [171].

23. Curcumin and Cosmetics

In food products, turmeric has a shelf life of around 6 weeks. Black carrot leaf extract is commonly used as a dye and turmeric can be used for textile dyeing and as a mordant to intensify the color of black carrot [172]. Curcumin has the potential to enhance skin beauty when continuously used. It was also effective against acne vulgaris. Curcumin-based formulations can cross the hair follicles, making them active in inhibiting collagenase, elastase, and hyaluronidase. It thus has the potential for use in hair coloring, essential oils, and the perfume, cosmetic, and soap industries [173].

Furthermore, a value chain analysis of OTC turmeric products has also been performed by the researchers to obtain a broader pharmaco-economic usage [174]. Comparing the production, area, and export (quantity and value) of different spices, turmeric ranks second in production, fifth in area, and third in exports (quantity and value). Further, the ratio remained (in tones) 6,53,600:16,13,000: (35,556:121.7) during 1999-2000. The European Spice Association (ESA) has specified minimum quality standards for herbs and spices: for whole turmeric species, total ash (%), acid-insoluble ash max (%), moisture (%), and volatile oil (v/w) min to be 8:2:12:2.5, and the ratio for the ground turmeric has to be 9:10:10:1.5. There are many advanced products of turmeric, such as whole turmeric, ground turmeric, curcuminoids, dehydrated turmeric powder, oils, and oleoresin [1].

24. Conclusion

This review was conducted from a preliminary search of Sci-finder. In this review, the physical, chemical, and pharmacological spectrum of curcumin were presented. The highlighted issue with curcumin is its poor bioavailability, and its potentiating effect on the bioavailability of other drugs

specifically with drugs that downregulate p-glycoprotein, MDR gene, and ABC transporters, which has been explained everywhere in different ways. The entire review article presented the general situation of curcumin and its various pharmacokinetics experiments, its potential activity related to channels as well as intracellular signaling pathways, its different pharmaceutical formulations, metabolites, and its effect on cancer, and other diseases of concern. This article also focussed on its general antimicrobial activity. Attempts have been to extensively compile curcumin research conducted in the past years in hopes of generating new preclinical/clinical interests among a new generation of researchers.

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Author Contributions

SG designed and wrote the manuscript; DG helps in searching the literature; SB acts as advisor.

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Competing Interests

The authors have no conflicts of interest to declare.

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