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Applications of Turmeric Starch and Curcumin

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Turmeric starch, Curcumin, Turmeric (Curcuma longa L.)

Abstract

In Asia and Central America, turmeric (*Curcuma longa L.*), sometimes known as "Indian saffron," is a perennial plant that belongs to the Zingiberaceae family. Due to the dried turmeric rhizomes' high concentration of minerals, proteins, carbs, and lipids, as well as the fact that it is available in a form that is simple to use and contains heat, light, and oxygen. Its excellent storage stability against environmental factors makes it more desirable, particularly in the context of the food business. In this study, based on the research on turmeric, curcumin, and its starch, the molecular mechanisms and pharmacological properties underlying its use in various diseases such as anti-inflammatory, anti-diabetic, antioxidant, anti-obesity, cardio-liver, anti-cancer, anti-arthritis. And its effects on metabolism. In addition to the lack of sufficient studies, it has been argued that its use in the food and pharmaceutical industry is promising when the results of the research are examined.

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1 INTRODUCTION

A prevalent dietary component in plants, starch makes up between 75 and 85 percent of the calories consumed worldwide [1]. The industrial usage of starches has been the subject of extensive investigation. The affordable and easily accessible nature of starch may contribute to its frequent overutilization [2]. The selection of starch for industrial applications is influenced by factors such as its physicochemical characteristics and availability, which are important considerations for optimizing its utilization in the production of various products. [3]. Compared to other natural polymers, starch can be obtained in a highly purified form using relatively straightforward techniques [4]. Despite the availability of various botanical sources of starch, maize remains the dominant source, contributing over 80% of the world's starch output [2]. However, research into alternative starch sources for industrial crop usage is becoming increasingly interesting given the economic impacts of maize consumption on food safety [2]. Curcuminoids, which are present in significant amounts in turmeric and turmeric starch, have been demonstrated to be harmless and well-tolerated at extremely high dosages. As a result, it is becoming increasingly important to increase the commercial utilization of starches like turmeric starch [5]. Varieties of medicinal turmeric are among the approximately 130 species that make up the Curcuma genus, which belongs to the Zingiberaceae family [6]. Even among turmeric types, there are differences in terms of pharmacological effect and bioactivity in terms of starches. For example, When *C. caesia* starch was obtained from turmeric rhizomes and *C. longa* starch was compared, it was stated in the study that *C. longa* starch had a higher total phenolic and curcumin content as well as a higher antioxidant capacity [6]. Curcuminoid pigments, a significant component of turmeric derived from its rhizomes, have been shown to offer a wide variety of positive pharmacological effects, including anticancer, anti-inflammatory, anti-diabetic, and anti-tumor properties [6, 7].

This review mentions the general structure of turmeric starch, its biological and medical properties, its effects on human health, its pharmacological effects, and future research and contributions, as shown in Figure 1.

2 STRUCTURE

Due to its simplicity of usage and cultivation, turmeric (*Curcuma Longa*), a member of the ginger family (Zingiberaceae), is commonly produced and consumed in nations with temperate climates including India, Iran, Malaysia, China, and Thailand. Starch is an important structural and nutritional component of many dietary items [8]. Figure 2 depicts the growth of turmeric, a tropical plant that may be found in both the tropics and subtropics. Although it may thrive in the dark, it can grow more lushly and yield healthier and more widespread rhizomes when exposed to light. The turmeric plant, also known as cylindrical turmeric, produces yellow and orange rhizomes [9, 10]. Figure 2 illustrates that turmeric starch has a light-yellow color, which sets it apart from turmeric powder, which typically has an orange hue. One of the most important components of fresh turmeric is turmeric starch, which is made from curcumin, fibers, and fresh turmeric oil after the undesirable components have been removed [11]. Curcumin is what gives turmeric starch its yellowish tinge. A well-known nutraceutical, curcumin(Figure 2) has well-known bioactivities including antioxidants [11]. Turmeric starch is regarded as a distinctive starch with considerable commercial potential since it may include residues of oleoresins and curcuminoids (yellow pigment) [12]. The physicochemical characteristics of turmeric starch were examined, and it was discovered to have a stable viscosity, a resistant gel, and to be easily digestible. The color removal process had an impact on the properties of turmeric starch, including changes in viscosity and swelling volume. This demonstrates the potential for turmeric starch to be prepared for use in cuisine [1].

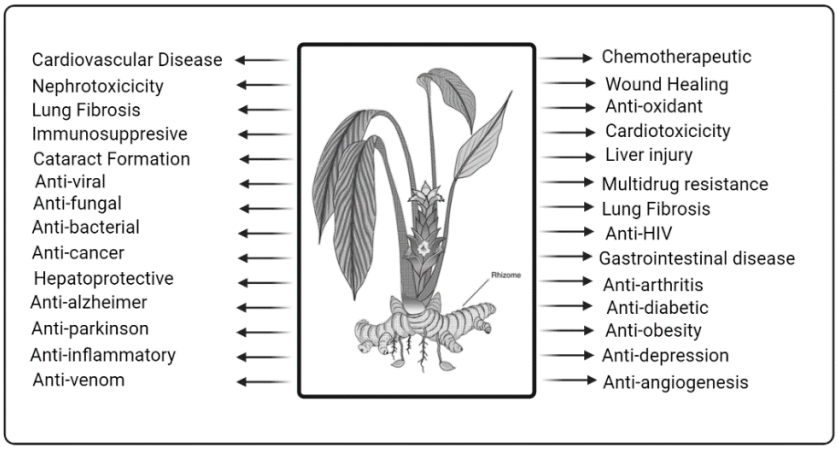

Figure 1. Therapeutic properties of turmeric and curcumin

Figure 2. Derivatives of curcumin and turmeric

2.1 Chemistry

Numerous healthy ingredients are included in turmeric starch. In terms of its overall composition, turmeric starch has 5.7 percent oleoresin, 2.5 to 6 percent curcumin, 3.5 percent essential oil, 6.3 percent essential oil, 5.1 percent mineral, 69.4 percent carbs, and 13.1 percent moisture. Along with its starch content, turmeric starch is a good source of vital nutrients, including vitamins E, C, and K, and minerals like potassium, calcium, copper, iron, magnesium, and zinc, as well as antioxidants, fiber, and niacin [7]. Through phytochemical investigation, turmeric has been found to contain a range of bioactive constituents, such as starch, protein, vitamins, essential oils, curcumin, and curcuminoids, which have distinct pharmacological effects [5]. The primary components of turmeric are "curcuminoids," which are a group of molecules with a similar structural makeup known as diarylheptanoids: (1E,6E)-1,7-biscurcumin (4-hydroxy-3-methoxyphenyl) crude extract 1, 60–70% Dethoxycurcumin and bis-demethoxycurcumin make up the remaining 20% and 10%, respectively, of the compound, which mostly consists of 6-heptadiene-3,5-dione [13]. When exposed to alkalis, curcuminoid (Figure 2) melts around 176–177°C and transforms into red-brown salts. Turmeric starch is soluble in methanol, ethanol, ketone, acetic acid, and chloroform, but exhibits low solubility in pure water, with a solubility of less than 0.6lg/mL [14]. Turmeric contains essential oils, curcumin, carbohydrates, proteins, and resins, which contribute to its pharmacological effects. Curcumin, which typically makes up 0.3% to 5.4% of raw turmeric, has been studied more extensively than other bioactive compounds in turmeric [15].

2.2 Biological and medical properties

While turmeric is used as a spice in the food industry, it is also used in traditional medicine due to its biological activities. Turmeric starch has many pharmacological activities such as anti-inflammatory, anti-coagulant, wound healing, anti-microbial, anti-ulcer, anti-diabetic, anti-fertility, and anti-oxidant[5]. Since *C. longa* rhizome starch is an attractive low-cost renewable bioplastic base material, the antioxidant, antibacterial and anticancer effects of phenolic compounds in *C. longa* rhizome starch cannot be ignored [7]. The anti-inflammatory benefits of turmeric are most likely attributable to a combination of all three factors. For the first of these, turmeric reduces the formation of inflammatory histamine. Turmeric boosts circulation, pushes toxins out of small joints where cellular wastes and inflammatory substances are usually held, and also increases and prolongs the function of cortisol, the body's natural anti-inflammatory adrenal hormone [15]. The digestive benefits of turmeric have also been proven by research. Turmeric is a cholagogue, meaning it increases the body's capacity to digest fats, improves digestion, and eliminates toxins from the liver by promoting bile production [15].

2.3 Formulation process

Starch is separated from conventional and unconventional sources and is often employed across a variety of fields. Starch may be produced via a variety of techniques. There have been global changes in the traditional ways that the researcher's region, climate, and nation produce starch [16]. When traditional and non-traditional foods are compared, there is a difference in the amount of starch in each. For instance, the starch ratio in legumes is between 25% and 50%, while in carbs, it is between 60 and 70%, and in turmeric starch, it is about between 75% and 80%

[1]. Approximately 40% (w/w) of the turmeric rhizomes and root tubers' weight is composed of starch that is recovered after removing the oil using supercritical fluid extraction (SFE) technology [1]. The technique introduced by Badenhuizen in 1964 is employed for the extraction of starch from turmeric [17]. When making turmeric starch, fresh turmeric is harvested when it is around ten months old, washed, and thoroughly dried [2]. The freshly harvested turmeric rhizomes are then meticulously peeled and cut into tiny pieces. In order to prevent oxidation, it is crucial to use a 1% sodium metabisulfite solution when preparing turmeric starch. Fresh turmeric slices are blended to create a slurry, which is then combined with the solution and filtered. The resulting material is then centrifuged, washed three times with distilled water, and suspended. The starch is purified by washing with methanol and dried in an oven at 50 °C to preserve it for future use. [17].

2.4 Sources and analogs of turmeric starch

Various effects of curcumin, one of the most important ingredients of turmeric starch, have been investigated for years. Curcumin has attracted attention because it is a natural and bioactive molecule and of its low toxicity even at high doses [18]. However, considering its pharmacological effects, it is a problem that curcumin, which gives good results, can be in drug ingredients due to its low bioavailability and low solubility. Its hydrophobic nature (poor absorption ability), rapid metabolism (short half-life), and low bioavailability by rapid liver excretion are the main causes of this problem [19]. Curcumin analogs can be divided into two as follows; synthetic analogs or derivatives and formulations [20]. Dethoxycurcumin, bisdemethoxycurcumin, cyclocurcumin, curcumin sulfate, hexahydrocurcumin, tetrahydrocurcumin, dihydrocurcumin, hexahydrocurcuminol, curcuminglucuronide can be given as examples of natural curcumin analogs. Synthetic analogs are diacetyl, diglycinoyl, diglycinoyl-di-piperoyl, dipiperoyl and dialanoyl derivatives, Pyrazole analogs, Hydrazinocurcumin, Mono-carbonyl analogs, 2,6-dibenzylidenecyclohexanone, 2,5-dibenzylidenecyclopentanone and 1,4-pentadiene-3-one substituents. Examples are asymmetric units such as curcumin analogs, an alkyl amide phenyl group, chloro-substituted benzamide, or heteroaromatic amide moieties[20]. These analogs also have advantages and disadvantages relative to each other, or inactive or inactive. Curcuminoids, one of the main components that give turmeric its unique yellow color, show different bioactivities in vivo and in vitro analyses[21]. For example, Bisdeme-thoxycurcumin is more active than curcumin against cytotoxicity in ovarian cancer cells. In contrast, curcumin is more active as an antioxidant and an oxidative DNA-clearing agent than bisdemethoxycurcumin [20]. Among the natural analogs found in turmeric, curcumin is the most basic, well-known, and one of the most abundant curcuminoids in turmeric, as well as others; Dethoxycurcumin is bisdeme-thoxycurcumin and cyclocurcumin (Figure 2) [20, 21]. Several curcumin analogs have been produced, which are beneficial in all three stages of carcinogenesis: initiation, progression, and promotion [22]. When looking at its morphological analogues, mango starch; Although the rhizome is not very similar in shape and size to ginger and turmeric starch, it still appears to be a mixture of both ginger and turmeric, falling somewhere between ginger starch and turmeric starch [23].

3 FUNCTIONS OF TURMERIC STARCH

Curcumin metabolism is crucial for its solid biological activity and positive effects [24]. Curcumin can suppress the carcinogenic activity of other carcinogens, including colon, stomach, liver, breast, and leukemia. Although curcumin is unstable in various settings and easily destroyed or converted to other forms, it has been shown to have therapeutic or preventive benefits against a wide variety of ailments [24]. For example, curcumin has anti-influenza virus action. It can reduce type A influenza virus (IAV) infection by significantly reducing viral HA activity by interfering with the receptor-binding domain of the viral hemagglutination (HA) protein [25]. Curcumin can induce apoptosis and prevent metastatic invasion by various molecular pathways in the treatment of prostate cancer, lower low-density lipoprotein cholesterol (LDL) and lipid peroxidation levels while raising high-density lipoprotein cholesterol (HDL) levels[14]. Curcumin has shown promise as a neuroprotective agent due to its antioxidant and anti-inflammatory properties and capacity to maintain chemical balance in the brain. According to some studies, pre-treatment curcumin can induce caspase activation, poly (ADP-ribose) polymerase (PARP) cleavage, DNA damage, and ROS accumulation. In addition, it reduces HO-induced neurotoxicity in PC12 cells by inhibiting the deregulation of MAPK and Akt pathways. These anti-inflammatory properties can be used to treat human neurodegenerative disorders [26]. Curcumin remains a promising natural element for creating relevant functional meals as potential options for preventing certain chronic diseases [24].

3.1 Mechanism of action

Curcumin, the central bioactive molecule found in the rhizome of *Curcuma longa L*., is a privileged structure due to its potential to affect many signaling pathways that play a role in disease development [20]. Looking at the action mechanisms of turmeric starch, the Inhibition of COX-2 inhibitors is observed with lipoxygenase inhibitor (Anti-inflammatory activity). It prevents the formation of reactive oxygen species (ROS) such as superoxide anion,

H_2O_2, and nitrate radicals (antioxidant activity). It prevents platelet aggregation caused by collagen and adrenaline (anti-coagulant activity). In shallow doses, it prevents the development of galactose-related cataracts (anti-diabetic activity) (Figure 4). It stops the growth of many bacteria, parasites, and harmful fungi (anti-microbial activity). An open phase II trial was conducted on 25 patients diagnosed with gastric ulcer endoscopically (anti-ulcer activity). It works by increasing the action of the nitric oxide synthase enzyme while increasing the beta-converting growth factor levels (Wound healing). It inhibits the 5α-reductase enzyme, which converts testosterone to 5α-dihydrotestosterone, thereby inhibiting hamster side organ growth (Anti-fertility) [5]. Curcumin binds with heavy metals such as cadmium and lead, reducing their toxicity. This feature explains the protective effect of curcumin on the brain. It has been discovered to have anti-inflammatory and antioxidant properties and antiviral and antibacterial potential. Curcumin is a pleiotropic chemical with multiple pathways in which it mediates chemotherapeutic and chemopreventive effects on cancer while remaining safe and causing few or no side effects [27]. Curcumin modulates a variety of molecular targets that contribute to its efficacy against various human malignancies [28]. The action mechanisms of curcumin are mentioned in Figure 3.

3.2 Pharmacokinetics and pharmacodynamics activity with mode of action

Turmeric has various components, including chemical compounds that are remarkably efficient for health. Curcumin, one of the curcuminoids found in turmeric, is the most biologically active turmeric component[29]. Although many pharmacokinetic characteristics need to be investigated, turmeric and its bioactive component, curcumin, have significant anti-disease benefits. Although it can dissolve well in polar solvents, its solubility in water is relatively low[30]. Pharmacologically, the absorption, distribution, metabolism, and excretion features of curcumin in the body indicate low bioavailability[31].In both human and animal models, several administration methods of turmeric and curcumin have been used, including oral, subcutaneous, intraperitoneal, intravenous, nasal, and application on the body surface[32]. Orally administered curcumin molecules have been demonstrated to be useful in various cancer types and minimize dermatitis severity in patients receiving radiation[33].

Several studies indicate that turmeric and its bioactive constituent curcumin absorption are rapid, and also they are rapidly metabolized in the body[31]. Yang et al. stated that the bioavailability of orally administered curcumin is just one percent[34]. A small amount of orally administered curcumin is absorbed in the intestine, while the majority is excreted in the feces[35]. Then, a small amount of curcumin absorbed is rapidly metabolized in the liver and plasma[36]. Several reports stated relatively low amounts of curcumin in serum after administration[19]. Various clinical trials tested curcumin levels in plasma and tissues with different administration routes and dosages (Table 1).

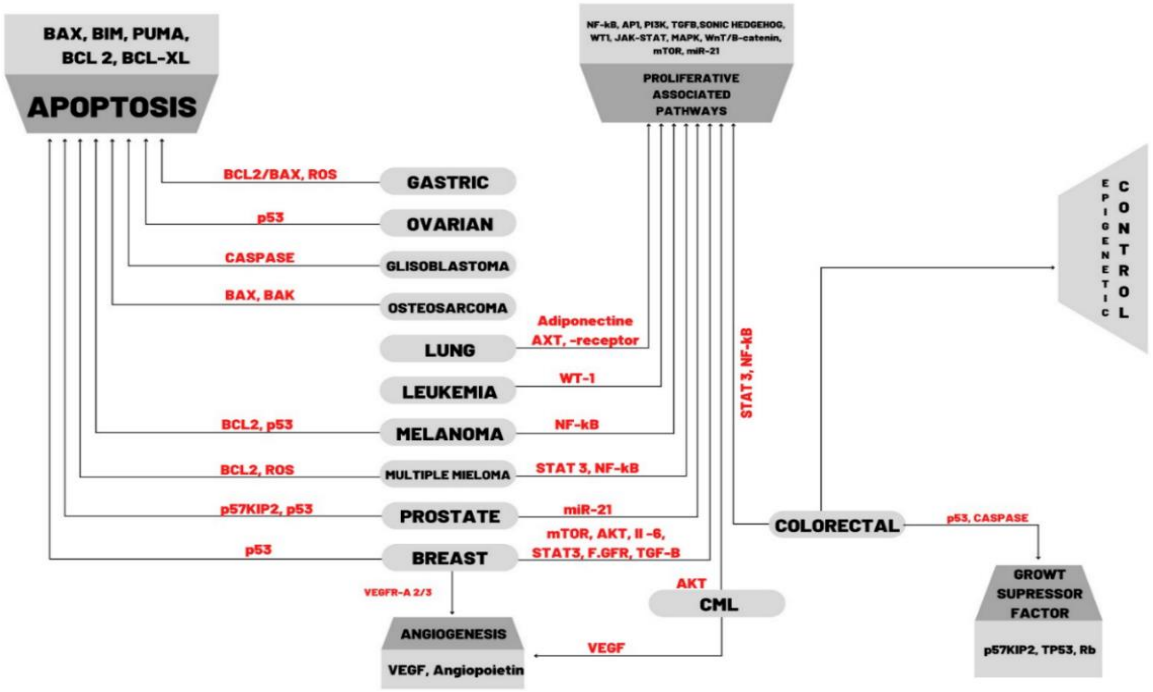

Figure 3. Curcumin's mechanisms of action

Table 1. Levels of curcumin from different experiments

Species	Administration Route	Dosages	Levels in Plasma/Tissue	Ref.
Human	Oral	2 g/kg	Serum 0.006±0.005 μg /mL	[37]
Human	Oral	4-8 g	Serum 0.4μM	[38]
Human	Oral	10 g	Serum 50 ng/m	[39]
Human	Oral	12 g	Serum 51 ng/mL	[39]
Human	Oral	3.6 g	Plasma 11.1±0.6 nmol/mL	[40]
Mice	Oral	100 mg/kg	Plasma 0.22 μg/mL	[41]
Mice	Intraperitoneal	100 mg/kg	Plasma 25 nmol/mL	[42]
Mice	Intraperitoneal	100 mg/kg	Liver 50-90 nmol/g	[42]
Rat	Intravenous	10 mg/kg	Plasma 0.36 μg/mL	[34]
Rat	Oral	1g/kg	Serum 0.5 μg/mL	[43]

3.2.1 Safety

Turmeric is a compound traditionally used as a spice and colorant in low doses for many years and is safe for human consumption[44].In addition, the safety of curcumin has been approved by the FDA and stated in many studies[45]. However, while using turmeric in high doses may affect the taste of food, studies have also found that it can cause problems such as diarrhea, headache, and nausea. In short-term studies in small groups, it has been reported that some subjects developed gastrointestinal problems, headaches, and rash[39, 46]. Many studies have studied the toxicity of the turmeric and bioactive compound curcumin with varying doses and durations of use in sick or healthy individuals[47]. While no toxicity and side effects were observed in the trials with healthy people[48, 49], conditions such as nausea and diarrhea have been reported in the use of curcumin in patients with metabolic syndrome[50] and diabetes[51], although toxicity has not been detected.

3.3 Bioavability and metabolism

Several articles indicate that the liver is the primary organ for the metabolism of curcumin[52].In the liver and plasma, two major metabolic pathways are involved in the metabolism of the curcumin molecule[35]. Phase 1 metabolism of curcumin is carried out by reducing enzymes in the liver and intestinal tract. As a result of the reduction reaction, four double bonds in the heptadiene-3,5-dione system are reduced by NADPH-dependent reductase[53]. Additionally, the reduction process of curcumin is followed by conjugation. Especially, orally administered curcumin goes into the conjugation process, which results in glucuronidation and sulfation[54] (Figure 4).

Curcumin has been classed as a class IV drug by the Biopharmaceutics Classification System due to its relatively low water solubility, low serum levels, and poor intestinal membrane permeability[55]. Due to its hydrophobicity and dependence on pH for the solubility properties, curcumin has an insoluble feature at neutral or acidic pH[39]. As stated in human trials and animal models, curcumin concentration in plasma is deficient, even at high doses administered orally[37, 56].

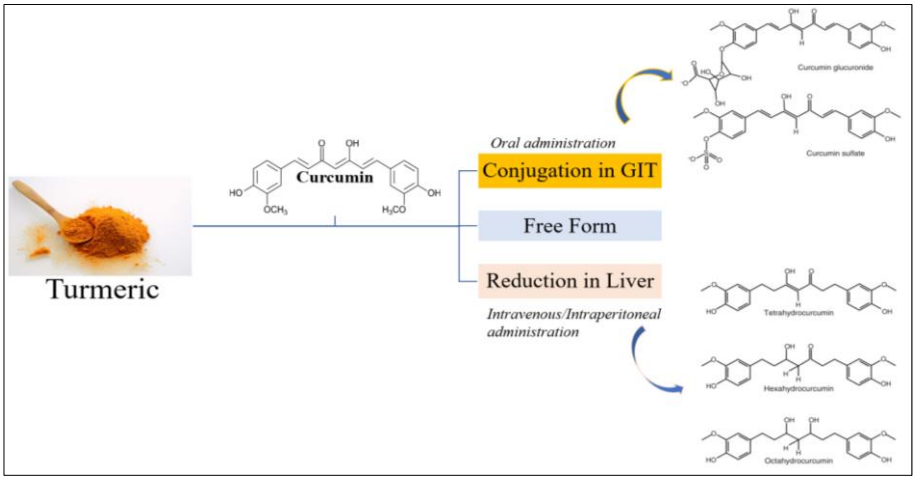

Figure 4. Metabolism of curcumin, the bioactive component of turmeric

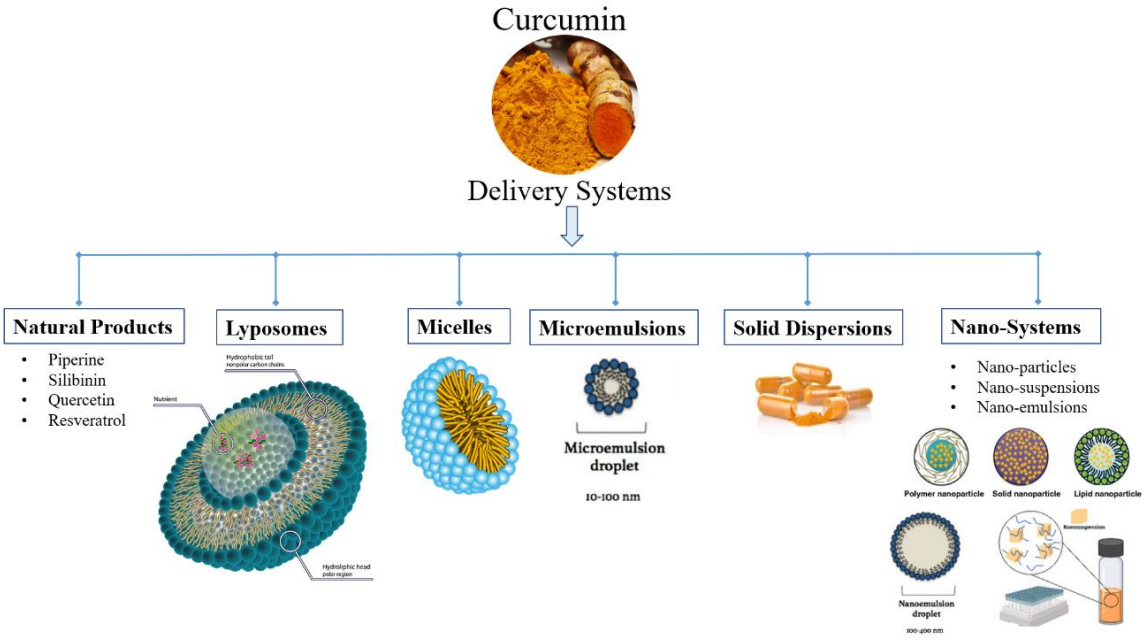

Figure 5. Developed delivery systems to increase the bioavailability of curcumin

Many formulations and techniques have been developed to increase the bioavailability of the bioactive curcumin molecule in turmeric extracts. One of the methods used for enhancing curcumin's bioavailability is using adjuvants. Piperin is the best effective adjuvant used to prevent the glucuronidation process of curcumin[57]. Thus, curcumin's bioavailability improves with increased absorption.

Liposomes are one of the drug delivery systems used to increase hydrophobic compounds' solubility. The combined use of substances such as chitosan and soybean lecithin in liposomes developed for the transport of curcumin has been reported as a method that further reduces hydrophobicity and increases the bioavailability of curcumin[58] (Figure 5). There are many techniques and substances for the preparation of liposomes. Feng et al. have reviewed the liposome preparation techniques for curcumin delivery and described the usage of curcumin liposomes in several cancer types[59]. Like liposomes, micelles are used to transport therapeutic compounds[60]. Micelles are typically formed by components that have hydrophilic heads and hydrophobic tails. Especially for transporting poorly aqueous soluble drugs, the usage of micelles is advantageous [61].

Another potential and successful delivery technique for enhancing the pharmacokinetic characteristics of orally taken curcumin, which has low water solubility, is using nanoparticles. Because nanoparticles expand the surface of pharmaceutical molecules for interaction with their solvent, they are employed to maximize chemical solubility[62]. Curcumin is usually carried by lipopolysaccharide nanoparticles, which have been confirmed to have a greater plasma concentration than the free form[63]. Furthermore, investigations revealed that oral administration of curcumin-loaded lipopolysaccharide nanoparticles might be delivered via the lymphatic system, a highly favorable delivery method to avoid liver metabolisms[63].

4 APPLICATION OF TURMERIC STARCH AND ROLE OF TURMERIC STARCH IN HEALTH

In recent years, with the awareness of the effects of nutrition in terms of health, the importance of proper nutrition can cure diseases and increase the quality of life has been better understood. In addition, the interest in more natural and organic new products has grown and has also been an incentive in the food industry. For this reason, nanotechnology has come to the fore in the food industry in recent years. In the production of products such as turmeric starch, nanotechnological developments provide significant benefits in terms of human health, safety, and duration of production in the diversity of products. Turmeric starch, frequently used as a spice in coloring, increasing the consistency and flavoring of foods, is used for antioxidant, pharmaceutical, and clinical purposes due to its biological activities with nanotechnology applications[14].

Turmeric starch is used to treat disorders such as cancer, depression, stress, skin problems, and several neurological diseases like Alzheimer's and dementia, in addition to being used as a spice.[64]. Curcumin, a yellow pigment found in the Indian spice turmeric (also known as curry powder), has been linked to anti-inflammatory properties,

tumorigenesis, diabetes, diseases of the cardiovascular, pulmonary, and neurological systems, as well as diseases of the skin and liver, bone and muscle loss, depression, chronic fatigue, and neuropathic pain [20].

4.1 Antioxidant

Curcumin, the main ingredient in turmeric, is as potent and an antioxidant as vitamins C, E, and Beta-Carotene, making it a popular choice among consumers for cancer prevention, liver protection, and anti-aging [15]. The antioxidant and antibacterial properties of turmeric are linked to the presence of phenolic derivatives known as curcuminoids, such as curcumin, dimethoxycurcumin, and bisdemethoxycurcumin as well as a bioactive peptide such as called turmerine[14]. Curcumin compounds such as demethoxycurcumin and bis-demethoxycurcumin have antioxidant properties. Due to this feature, curcumin has an antioxidant effect on normal cells. The second reaction is Michael addition, where curcumin serves as the Michael acceptor. Curcumin's efficacy as an anticarcinogenic drug is enhanced by this structural feature, which can be used to describe its biological chemistry in living cells [21]. Curcumin has been proven to reduce lipid peroxidation and scavenge free oxygen and peroxyl radicals [14]. The reported properties of curcumin, such as antioxidant activity, are related to the presence of diaryl moieties containing the phenolic OH group, which is essential for treating Alzheimer's disease [21]. Chronic diseases can be caused by an imbalance between free radicals and the body's immune system against oxidative stress. While overproduction of reactive oxygen species (ROS) can cause oxidative stress and damage important biomolecules, antioxidants such as antioxidant enzymes and antioxidant compounds can slow the progression of many chronic diseases by protecting the human body from free radicals and their effects [24]. The antioxidant activity of curcumin has been shown to contribute to its various therapeutic effects in both in vitro and in vivo studies. According to research on its chemical structure, Curcumin's electron-donating groups, especially the phenolic hydroxyl group, contribute significantly to its antioxidant effect[24]. The promise of turmeric in the food industry is also supported by studies showing that it can prevent lipid oxidation in various foods by acting as an antioxidant. Also, since it acts as an exogenous antioxidant, ingestion can help stabilize free radicals in the body [14].

4.2 Anti-inflammatory activity

Curcumin is an anti-inflammatory compound that affects inflammatory mediators like Interleukin types (IL-1,6,8,12), TNF, and NO by inhibiting their production [65]. Curcumin affects the body’s complex inflammation process by regulating or inhibiting inflammatory systems. The down-regulation of NF-kappaB can be done in two ways by curcumin: one directly regulation of NF-kappaB and the second: through regulation of peroxisome proliferator-activated receptor-gamma (PPAR-gamma)[66]. Besides, the curcumin molecule has a regulatory effect on the JAK/STAT signaling pathway[67]. Additionally, the NLRP3 receptor, a cytosolic multiprotein complex, is influential in forming inflammatory diseases. Curcumin can directly inhibit NLRP3 or regulation of the NF-kappaB pathway by activating NLRP3[68]. Curcumin enhances immunological homeostasis in inflammation by maintaining immune cell balance since T-helper 17 cells create pro-inflammatory mediators, and T-regulatory cells can suppress the inflammation response[69]. Furthermore, because oxidative stress is associated with inflammation, the effect of curcumin on oxidative stress should be mentioned. By influencing NADPH-oxidase and activating antioxidant enzymes, the curcumin molecule decreases ROS (reactive oxygen species), which directly leads to oxidative stress[70].

The effects of curcumin on inflammatory diseases have been shown in many clinical studies. Inflammatory bowel disease (IBD) is one of the diseases that the effect of curcumin has been studied. In IBD, which has become a global disease, destruction of the intestinal barrier is usually observed due to colon inflammation and excessive secretion of inflammatory mediators[71]. Many studies have shown that inhibition of T cell activation and proliferation by curcumin prevents the production of inflammatory mediators from T cells, thus reducing inflammatory responses[72, 73]. Like many other diseases, intense inflammatory cytokine release has been detected in COVID-19, which has become a pandemic today[74]. The fact that curcumin is a natural anti-inflammatory compound and can regulate the release of inflammatory cytokines and mRNA expression increases its availability as an adjuvant molecule that will reduce the disease severity in COVID-19 patients.

4.3 Anti-Diabetic

Diabetes mellitus (DM), a most common chronic metabolic disease seen in approximately 6% of the world's population, is among the most critical non-communicable diseases of a global health crisis [75-77]. Keeping blood sugar in the normal range and preventing complications due to long-term hyperglycemia are the main goals of DM treatment[78] (Figure 7). The current therapeutic approach to DM is to control blood sugar with the lifelong use of antidiabetic drugs. However, these oral antidiabetic drugs cause many unwanted side effects and drug

interactions and are expensive [79]. Therefore, it is necessary to find molecules with good therapeutic value and reduced side effects[78]. Turmeric, which is obtained from the root of the *Curcuma longa L*. plant, which is mentioned in the treatment of diabetes in Ayurvedic and Chinese medicine, has been the focus of attention for thousands of years [80]. Its rhizome is a highly effective phytochemical in sweetening, beauty, cosmetics, medicines, and coloring [81].

In recent studies, the antidiabetic effect of a biologically enhanced turmeric preparation with increased bioavailability has been demonstrated in animal models indirectly. In this animal study, the pancreatic toxin [82]Streptozotocin (STZ) was found to be a better substance for inducing diabetes than Alloxan, another pancreatic toxin that can be used to develop type 1 and type 2 diabetes in rodents models[83]. In one of the formulation studies, *C. longa* dried rhizome powder diluted in milk has antidiabetic, hypolipidemic, and hepatoprotective properties according to scientific and systemic studies, and it has been shown that it can be used as an effective and safe antidiabetic dietary supplement with great potential[84]. Curcuminoids have been shown to improve insulin resistance, decrease glucose and insulin levels, increase adiponectin secretion, and decrease leptin, resistin, interleukin IL-6, IL-1β, and TNF-α levels, which increase the risk of micro and macrovascular complications in patients with Type 2 Diabetes [85]. Patil et al. evaluated proteins from turmeric waste in terms of in vitro anti-diabetic activity and inhibition of α-amylase and α-glucosidase enzymes. With a different view, the effect of various process parameters affecting the three-phase partition (TPP) and UA-TPP was investigated and optimized to achieve maximum protein recovery from waste turmeric [86]. Thus, while developing a treatment method with a natural product, it has been shown that it costs less and protects the environment compared to modern and synthetic therapeutics.

4.4 Anti-Obesity

Clinical studies show that weight gain affects the deterioration of metabolic indicators such as lipid disorders, carbohydrate metabolism disorders, and increased blood pressure [87]. It is known that a low-calorie diet and high exercise are absolute requirements for the treatment of obesity. However, it is also known that diet is a risk factor for chronic obesity patients[88]. Therefore, there is a constant effort to discover natural compounds with minimal side effects for weight management [89].

According to recent studies, curcumin benefits obesity and diabetes[90]. In a sample study, dietary supplementation with curcumin up to 80 mg/kg body weight improved insulin sensitivity by reducing fasting plasma glucose in obese rats[91]. Many researchers have shown curcumin to inhibit adipogenesis by blocking the mitotic clonal expansion process, regulating adipocyte energy metabolism[92-94]. Also, the Wnt/β-catenin signaling pathway has been reported to participate in curcumin-mediated suppression of adipogenesis in 3T3-L1 cells [95, 96], although the mechanism is not yet fully understood. In a good look at investigating this mechanism, a polyphenol, EGCG (epigallocatechin gallate), was found to inhibit adipogenesis in an mRNA m6A-YTHDF2-dependent manner [97]. N6-methyladenosine (m6A) is eukaryotes' most abundant internal RNA modification[98]. It has been suggested that M6A may regulate adipogenesis by mediating mRNA splicing [99], mitotic clonal expansion [100], and JAK2-STAT3-C / EBPβ [101], and the autophagy pathway. [102]. Curcumin has been shown to alter m6A abundance in various mammalian tissues [103, 104]. This raises the question of whether curcumin's anti-obesity effect is also related to RNA methylation. A recent study reported that curcumin inhibited ALKBH5 expression, increased the m6A methylation of TRAF4, and increased the expression of TRAF4 proteins mediated by YTHDF1 to contribute to this literature. As TRAF4, acting as an E3 ligase of PPARy, caused the PPARy protein to become widespread, the PPARy protein decreased, and adipogenesis was further inhibited. This suggests that m6A is an entirely new way curcumin mediates its anti-obesity effect [105] (Figure 6).

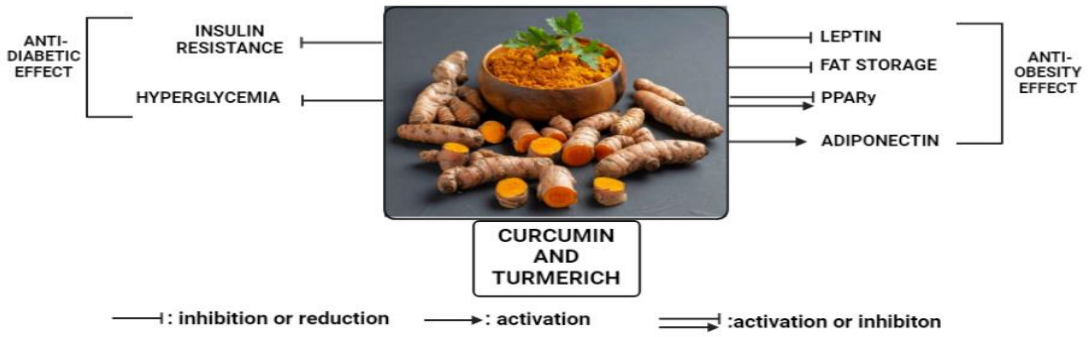

Figure 6. Anti-diabetic and anti-obesity effects of curcumin and turmeric

4.5 Cardio/Liver toxicity protection activity

Non-alcoholic fatty liver disease (NAFLD), caused by elevated liver transaminases, is a clinicopathological condition characterized by lipid accumulation in the liver [106-109]. A global health concern, NAFLD includes various disorders, from simple adiposity to nonalcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma [110, 111]. Fat accumulation in the liver, which is the cause of NAFLD, is also involved in the pathogenesis of other morbid diseases such as heart failure or DM[112, 113]. TNFα, adiponectin, and oxidative stress play a vital role in the progression of NAFLD[114, 115]. Oxidative stress also triggers the production of inflammatory cytokines, causing inflammation and a fibrogenic response[116, 117]. Existing strategies have been produced for treating NASH with the correction of risk factors such as obesity, diabetes mellitus and hyperlipidemia, and the concern of oxidative stress[117, 118]. *Curcuma Longa*, or its component, one of the hepatoprotective herbs to treat acute and chronic liver diseases, has been used not only as a dietary spice but also as a traditional medicine for centuries [118-122].

Randomized double-blind, placebo-controlled studies were conducted to determine whether daily consumption of turmeric (and its active phenolic compounds such as curcumin) supplementation could be effective in managing NAFLD and lowering the serum level of liver transaminases. Jarhahzade et al., according to the results of his study, it was observed that the turmeric group caused a significant decrease in liver enzymes [109]. In a study of curcumin to reduce iron-induced oxidative stress and iron toxicity in T51B cells without blocking iron uptake, it was reported to reduce cytotoxicity, block ROS formation, and abolish signaling to iron-induced cellular stress pathways [123]. Although there are ideas that curcumin has beneficial properties on iron toxicity, more in-depth investigations are needed in light of histopathological analyzes and the numerous and newly identified features of curcumin's mechanism of action (Table 2).

Curcumin is a natural compound easily obtained from turmeric and is widely used in middle eastern diets. Many studies have sought to uncover its role in the modulation of many biological mechanisms involved in liver injury. More in-depth studies are needed to reach a precise means of Curcumin, which affects different tools. While the results from studies have been encouraging, some critical issues must be overcome before curcumin can be used in clinical practice. The afore mentioned poor bioavailability of curcumin is a critical limiting factor influencing drug pharmacodynamics. Then, a new drug delivery system for curcumin should be considered when testing its clinical effects.

Table 2. Randomized clinical studies using curcumin to treat patients with various liver conditions

Number of patients	Patient Type	Criteria	Research Design	Results	Ref
48	Subjects ≥ 20 years of age with ALT between 40 and 200 UI/l	AST, ALT, GGT, lipid profile, total bilirubin	(Random) placebo-controlled	Significant reduction in ALT levels in the treatment group ($p = 0.02$).	[124]
102	NAFLD patients	Anthropometric measurements, lipid profile, glucose, insulin, glycated hemoglobin, uric acid levels	(Random) placebo-controlled	Decreased serum levels of total cholesterol ($p < 0.001$), low-density lipoprotein cholesterol ($p < 0.001$), triglycerides ($p < 0.001$), non-high-density lipoprotein cholesterol ($p < 0.001$) and uric acid ($p < 0.001$).	[125]
80	Patients with NAFLD evidence on ultrasonography	Anthropometric measures, lipid profile, liver fat content, and the severity of NAFLD glycated hemoglobin, fasting glucose levels, AST, ALT, and	(Random) placebo-controlled	Reduced severity of NAFLD (p 0.001). Body mass index ($p = 0.002$), total cholesterol (p 0.001), low-density lipoprotein cholesterol (p 0.001), triglycerides ($p = 0.001$), AST ($p = 0.002$), ALT (p 0.001), glucose ($p = 0.048$), and glycosylated hemoglobin (p 0.05) all showed decreases.	[126]

[i] AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT – γ-glutamyl transpeptidase, NAFLD – non-alcoholic fat liver disease, QD – quaque die (once a day), BID – bis in die (twice a day).

4.6 Anti-Cancer

Cancer formation is mainly associated with a disrupted cell cycle that includes processes between cell proliferation and cell death[127]. The common feature of all cancer types is the absence of an apoptotic signal that will lead to the death of the cell and the inability to control the proliferation of the cell[128]. Two main pathways regulate apoptotic signaling in the cell. One of the apoptotic pathways, the intrinsic pathway, involves inhibition of antiapoptotic proteins called Bcl-2 and Bcl-xL based on stimulation of the mitochondrial membrane. The extrinsic pathway, which is the second apoptotic pathway, includes the processes of increasing DRs (death receptors) in the cell, as well as triggering TNF (tumor necrosis factor)-related apoptosis[129, 130].

Moreover, a recently published study found that curcumin downregulates the pyruvate kinase M2 (PKM2), thereby reducing the cancer cell's glucose uptake and lactate production. Because the metabolism of cancer cells requires regulatory PMK2 activation, curcumin's inhibitory effect on PKM2 expression gives a promising way to prevent cancer cell proliferation[131].STAT3, one of the STAT family transcription factors, is involved in many critical processes for the cell cycle, such as cell progression, proliferation, and also cell migration and invasion, depending on STAT3 activation[132]. It has been found that curcumin inhibits STAT3 expression in many types of carcinoma and thus prevents tumor progression[133-135]. Both *in vitro* and *in vivo* studies have shown the curcumin molecules' preventing effect on several cancer types like prostate, brain, breast, collateral, and so on in terms of inhibiting critical pathways required for cancer cell progression and proliferation (Figure 7).

4.7 Anti-Arthritis

The excellent anti-inflammatory properties of curcumin also it has an effect on arthritis. One of the main types of arthritis, osteoarthritis (OS), is commonly an inflammation-related disease in individuals over 50. In particular, synovial fluid inflammation increases OS's pathogenicity [136]. The mRNA expression of major matrix-degrading enzymes such as MMP-1, MMP-1.3, disintegrin, metalloproteinase, and ADAMTS-5 can be inhibited by curcumin[137]. Since curcumin inhibits the manufacture of inflammatory mediators such as TNF, IL-17, and IL-1, as well as transforming growth factor-beta and cyclooxygenase-2 (COX-2), it lowers synovial inflammation[138].

Furthermore, curcumin's control of the NF-kappaB pathway reduces the generation of inflammatory cytokines while inhibiting the development of matrix-degrading enzymes[139]. Curcumin suppresses the regulation of some cytokines and can also regulate the release of cytokines such as IL-10 from macrophages[140]. Several clinical trials have shown curcumin anti-arthritis effects, especially in knee OS. One study used the turmeric extract treatment for the knee OS, and they found that the turmeric inhibits the production of inflammatory cytokines and improves the OS symptoms [141].

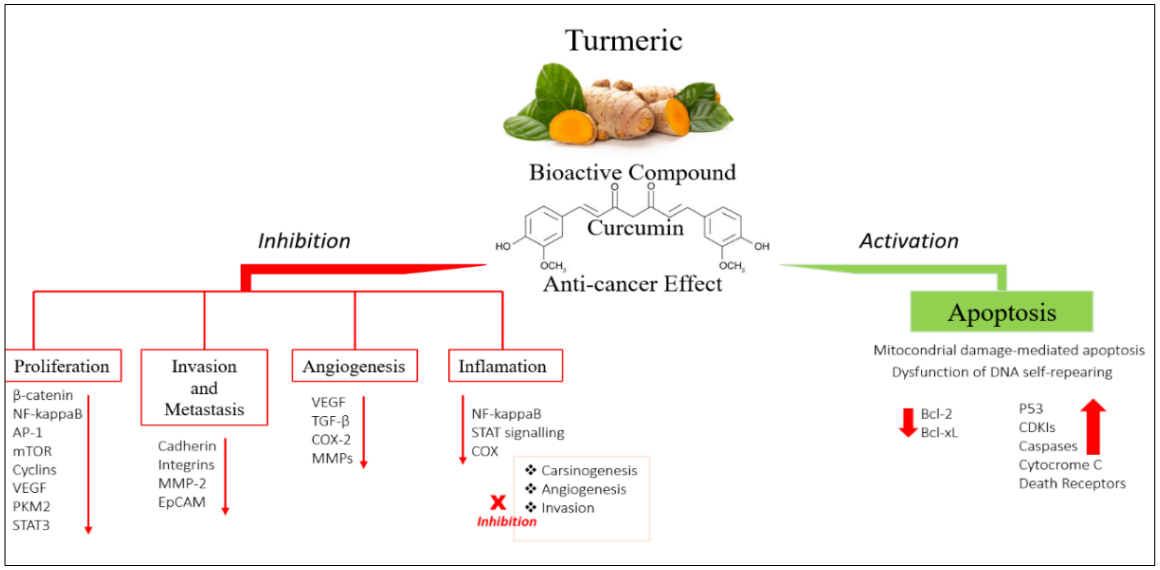

Figure 7. The processes that the curcumin molecule affects the life cycles of cancer cells

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4.8 Turmeric starch used in eye disease

High vascularization, prolonged exposure to light, and high mitochondria density cause the retina to be exposed to oxidative stress. This may lead to pathological processes such as cell apoptosis, angiogenesis, and inflammation ending in retinal pathologies. Curcumin, the most active ingredient of turmeric, is an excellent protective agent because it prevents the formation of reactive oxygen species (ROS). In addition to its anti-inflammatory and antitumor properties, Curcumin is a natural product that can be a treatment option for various retinal diseases due to its pleiotropic properties. The sensitive nature of the retina to oxidative stress is due to the environment of photoreceptors and RGCs, high oxygen, glucose oxidation, and polyunsaturated lipid fat (PUFA) content[142]. For retinal is chemia-reperfusion injury (RIRI) causing vision loss, Wang et al. discovered the protective effect of curcumin on retinal neurons and microvessels via inhibition of NFκB and STAT3 (signal transducer and activator of transcription) followed by overexpression of monocyte chemoattractant protein 1 (MCP-1) in Wistar rats and appeared to exert significant protective effects in a dose-dependent manner [143].

There are prominent suggested applications for treating and preventing retinal diseases using curcumin, but many different studies are still needed to understand its underlying mechanisms fully. The effect of curcumin should be evaluated in all aspects for non-unifactorial eye diseases. In addition, studies should be conducted considering the limitations of curcumin.

4.9 Wound healing activity

Skin is a protective barrier for the body. The healing of skin injury needs several complex processes, such as hemostasis, inflammation response, proliferation, and remodeling skin injury. In the natural process of wound healing, blood clot formation is formed for the matrix that will allow the migration of cells to the wound area[144]. Then, blood cells such as neutrophils and macrophages migrate onto the formed matrix. Meanwhile, the secreted inflammatory cytokines control fibroblast migration and proliferation, while phagocytes clear foreign particles on the wound surface. Re-epithelialization continues as a continuation of proliferation as new blood vessels form[145]. Finally, fibroblasts and collagen form a new extracellular matrix, and collagen remodeling and scar tissue formation in the injured area is observed as the final stage of wound healing (Figure 10)[144, 146].

Curcumin can be effective in each process of wound healing. Inflammation has a crucial role in wound healing. Since un-controlling acute inflammation can cause harmful tissue damage, the regulation of inflammatory response gives an advantage to the optimization of wound healing[53]. As explained in section 4.2, curcumin has excellent anti-inflammatory effects by inhibiting cytokines released from macrophages and inhibiting the activity of NF-kappaB, a transcription factor that regulates inflammatory genes. A study applied a curcumin-loaded bandage topically on the wound of rat models. They found that the expression of several kinases was down-regulated in the NF-kappaB pathway[147].

4.10 Neurological diseases

Accumulating protein aggregates, oxidative damage, neuroinflammation, mitochondrial dysfunction, and proteasomal inhibitions cause neurodegenerative diseases. Multiple paths must be targeted simultaneously to interfere with such a complex process [148-152]. Perennial dietary consumption of turmeric has shown neuroprotection in a mouse model of Parkinson's Disease (PD) [153]. At the same time, curcumin can reduce oxidative damage and amyloid pathology in a transgenic mouse model of AD [154]. Specifically, the positive effects of curcumin on neurodegenerative diseases have been demonstrated in many studies. Concerning amyotrophic lateral sclerosis (ALS), curcumin is also known to suppress protein aggregation that delays the progression of ALS in a mouse model [155]. In a study showing that curcumin regulates IL-12 production by inhibiting JAK-STAT signal activation and regulates T-cell responses to IL-12 by blocking IL-12 signaling, it has been suggested that it can be used in treating MS and other Th1cell-mediated inflammatory diseases. It has also been observed that high-dose curcumin can directly induce T cell apoptosis and inhibit T cell proliferation by blocking the IL-2 signaling pathway and high-affinity IL-2R and interfering with IL-2R signaling. This way, it reduces TNF-α/β, IL-1, IL-6, COX-2, and IL-8 through proinflammatory cytokines and can provide a therapeutic effect by reducing inflammatory conditions [156-158].

Although there are many different in vitro and in vivo studies on PD, the mechanism and results have not been fully elucidated. In addition, despite increasing research interest in the non-motor symptoms associated with PD, such as depression, olfactory deficiency, constipation, sleep, and behavioral disorders, the effects of curcumin on PD require further investigation. Taken together, however, curcumin has shown promising effects in treating PD and other neurological diseases.

4.11 Anti-Alzheimer activity

Alzheimer's Disease (AD), like other chronic diseases, occurs due to multiple factors, not a single cause. Pathological hallmarks in the AD brain include extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). Amyloid-β (Aβ) forms a cleavage of the amyloid precursor protein by β- and γ-secretases. This results in natural Aβ monomers that have survival effects on neurons and protect mature neurons against excitotoxic death [159]. There is no currently available treatment for AD, but the impact of this disease can be reduced by delaying its onset. In addition, an optimal diet, especially rich in phenolic compounds, may provide inhibitory effects on the development of AD[160]. Ng et al. (2006) reported that consuming an Asian-type diet rich in soy and turmeric (containing significant amounts of isoflavones and curcumin, respectively) and high levels of seaweed also reduced the incidence of AD. These diets are rich in fruits and vegetables, primary sources of dietary polyphenols, glucosinolates, and vitamins. Curcumin is a natural phenolic substance that benefits various chronic conditions such as obesity, diabetes, and depression [161-163]. More importantly, such chronic diseases may be risk factors for AD and are associated with the etiology or outcome of AD [164, 165]. Curcumin, the active component of turmeric, has been mentioned to induce inflammatory responses and has also been shown to increase Aβ flux, which leads to further brain damage and cognitive impairment [166]. This suggests that curcumin intake may prevent AD progression by reducing the risk of AD[167].

Moreover, in vivo studies using a rat model of AD demonstrated that curcumin exerts a significant reduction in glial fibrillary acidic protein expression and astrocyte activity, contributing to the rescue of behavioral defects caused by Aβ intracerebral injection[168]. These results imply that the potent anti-inflammatory properties of curcumin may be responsible for inhibiting glial cell activation and attenuating Aβ pathology in AD.

4.12 Depression and anxiety

As in many neurological diseases, several dysregulated biological pathways have been described in major depressive disorder (MDD), including disturbances in monoaminergic activity, immuno-inflammation, oxidative stress, hypothalamic-pituitary-adrenal (HPA) activity, and neuroprogression [169, 170]. Examining biomarkers is particularly important as there are identified differences in immuno-inflammation markers such as C-reactive protein (CRP), interleukin-6, and TNF-α between depressed and healthy populations [171]. With the support of many biomarkers, interest in curcumin in treating major depression has increased. Therefore, curcumin exhibits a wide range of properties that are relevant to the pathophysiology of depression. It has been shown to have antidepressant activity in various animal models and clinical trials. Indeed, a dozen randomized controlled clinical trials have been conducted [172], and all suggest that curcumin may be effective as a treatment (or adjunct therapy) of MDD through multiple mechanisms of action. Three human-based trials have been completed on people with major depressive disorder. In one study, the addition of curcumin to antidepressant therapy provided no additional antidepressant benefit [173], whereas, in another study, curcumin had similar antidepressant efficacy as fluoxetine [174]. However, in this latest study, participants had no placebo control or blinding from treatment conditions. A recent randomized, double-blind, placebo-controlled study reported the efficacy of curcumin in reducing depressive symptoms in people with major depression, particularly in a subset of participants with atypical depression [175].

Animal experiments have shown that curcumin can alter the concentrations and activity of many neurotransmitters. For example, acute administration of curcumin ameliorated depression-like behavior in mice through its stimulatory effect on the 5-HT1A receptor [176]. In ovariectomized mice, curcumin modulated depression-like behaviors and improved serotonin in various brain regions by upregulating tryptophan hydroxylase-2 and 5-HT1A/2A. The receptor down-regulates messenger RNA (mRNA) and monoamine oxidase A mRNA in the limbic system [177].

4.13 Anti-viral including COVID-19

Viruses cause many health problems, and their working process for the disease progression has been studied in various research. Among the several beneficial effects of bioactive curcumin also impacts viruses by inhibiting their viral entry process, replications, protein expressions, and viral attachment to the cells[178].In the 1990s, curcumin’s inhibition effect on viral proteases was studied on HIV[179]. Since then, the clinical benefit of curcumin has been tested on various RNA and DNA viruses. Curcumin treatment of vaginal epithelial cells has been demonstrated to restore the impaired regulation of tight junction proteins caused by inflammation and lower the degree of viral infection[180].In addition, several studies have found that curcumin can disrupt the action of viral proteins such as integrases and proteases, preventing HIV replication.

Curcumin's effect on HIV entrance into cells has also been studied using various curcumin administration techniques. In an investigation involving silver nanoparticles containing curcumin, it was discovered that delivering curcumin with nanoparticles inhibited viral transcription even more than curcumin alone[181]. Curcumin and its analogs have been shown in experiments to inactivate the Zika virus, another RNA virus, or inhibit the virus from binding to the cell[182]. Found that curcumin reduces the Zika virus attachment to the cell; however, the studies did not detect any lowering effect of curcumin on viral particles[183]. Furthermore, curcumin treatment has been tried against Influenza A virus (IAV) infection, and beneficial effects have been found. It is known that the NF-kappaB signal pathway is required during the replication of IAV. The ability of the curcumin molecule to inhibit the NF-kappaB pathway has been evaluated as an effect that reduces IAV replication[184].In animal models, it has been reported that orally administered curcumin reduces IAV replication and the usability of curcumin therapy against viral diseases. In addition to inhibiting IAV replication, curcumin is also a promising treatment for curing IAV-induced lung disorders due to inhibiting the NF-kappaB pathway[185, 186].

Additionally, it has been reported that curcumin can inhibit viral replication and attachment of the virus to the cell in many viruses such as EV71, HRSV, norovirus, and some DNA viruses like HSV-2. Recently, a highly detailed review was published about the curcumin effect on various viruses[178]. It should be stated that we are facing the SARS-COV-2 infection, which has become a pandemic since 2019. Many methods and substances that reduce the severity of the disease are being tried against the COVID-19 epidemic. It is thought that the curcumin molecule may be effective against the SARS-COV-2 virus. Various studies have been carried out on this subject. In addition, it is known that curcumin inhibits the replication of another coronavirus type, SARS-COV-1[187]. For this reason, various studies have been conducted considering that curcumin may also be effective on SAR-COV-2.In silico studies obtained promising results for the treatment against COVID-19 that the curcumin molecule can interact with the viral spike protein by six hydrogen bonds. Also, studies found that curcumin has an affinity to ACE2. Moreover, have been found that curcumin down-regulates the viral protease, which facilitates viral entry[188]. The viral protease Mpro is required mainly for the SARS-COV-2 replication.

4.14 Anti-bacterial, anti-allergy, anti-asthma, anti-fungal

In the literature, various studies revealed that curcumin has antibacterial and anti-fungal effects. The adverse effects of multiple diseases introduced by certain bacterial strains accelerate the discovery of compounds with antibacterial properties and studies on these compounds. Generally, curcumin molecules can affect the bacterial cell membrane, bacterial DNA replication, and bacterial gene expression[189]. Also, curcumin can change bacterial cell membrane permeability due to its amphipathic feature, making the bacterial membrane more permeable to antibiotic uptake[190]. Marathe et al. have worked with *Salmonella typhimurium*, which can cause gastroenteritis, and they focused on the curcumin effect on bacterial flagella. As a result, they found that curcumin can break flagellar filaments by attaching to the flagella, which makes flagella fragile[191]. Also, the other group worked again with *S.typhimurium* and found that curcumin can decrease the proliferation of bacteria by inhibiting ciprofloxacin action[191]. The effect of curcumin on *Escherichia coli* was also reported by Bellio et al., who found that the curcumin molecule disrupts the DNA repair mechanism (SOS) of *E.coli*[192].

The anti-allergic activity of curcumin is mainly associated with inhibiting the production of inflammatory cytokines, NO, and, most crucial, the inhibition of histamine molecules released from mast cells[193]. The mast cell inhibition effect of curcumin has been shown in animal models[194]. As stated in the paper of Suzuki et al., the hydroxy group of curcumin molecule structure is mainly associated with the anti-allergic activities of curcumin[193]. The metabolism of curcumin creates glycosides that are water-soluble bioactive molecules with anti-allergic effects. One of the studies found that the glycosides of curcumin have a suppressive impact on IgE antibody production. The same study also stated the inhibition activity of glycosides on mast cells for histamine release[195]. Another study used a rat model infected with fungal allergens. They obtained results that the rat model demonstrated increasing IgE after being infected with allergens. After that, they applied curcumin treatment and found significant suppression of the IgE response[196].

Asthma, a chronic inflammatory disease, is prevalent worldwide and causes wheezing, chest tightness, coughing, cellular inflammation, and many other health problems[197]. Inflammatory mediators involved in asthma are mostly inflammatory cytokines, histamine, NO, chemokines, some adhesion molecules, and kinases regulated by the NF-kappaB signaling pathway[198]. Since curcumin regulates the inflammatory response by controlling signal proteins and pathways such as protein kinase C, AP-1, and NF-kappaB signaling pathways, the researchers thought curcumin's anti-inflammatory effect could be beneficial for treating chronic asthma[199]. Furthermore, the studies concluded that the anti-inflammatory feature of curcumin improves lung function in asthma and can be used as an anti-asthmatic compound[200].

4.15 Anti-Venom

Poisoning by various cobra species causes very harmful effects that can result in death. Traditionally known plant-based medicines are used to prevent snake venoms' hazardous effects. Since anti-venom products are limited, expensive, and have strict storage conditions, traditional compounds are preferred rather than using anti-venom compounds[201]. The venom of *Naja naja* (Indian cobra) contains deadly toxins. The toxins of *Naja naja* cause respiratory paralysis by binding to acetylcholine and chance the chemical signal into an electrical signal[201]. Turmeric extract is traditionally used as an anti-venom to prevent Indian cobra toxins. It is known that the turmerin protein, which is a compound found in turmeric extract, can inhibit enzymatic activity and also has the ability to neutralize cytotoxicity and myotoxicity of the Indian cobra[202].In addition, studies concluded that turmeric could inhibit the proliferation of lymphocytes and prevent their natural killer cell activity[203].

4.16 Nanomedicine

Curcumin’s usage as a therapeutic agent against diseases has been tested in much research due to its numerous positive anti-disease effects, and the processes and cell signal pathways controlled by curcumin have been identified. However, as described in its pharmacokinetic properties, the bioavailability of the free curcumin molecule in the body is relatively limited. Curcumin is a hydrophobic compound; its solubility is low, metabolism rapid, and its fast removal from the body reduces its therapeutic efficiency to be taken from curcumin[204]. As shown in Figure 5, many delivery methods have been developed and used in various diseases to increase the bioavailability of curcumin and improve its pharmacokinetic properties. Nowadays, with the development of nanosystems, various nanotechnologies have been developed to increase the bioavailability of curcumin, such as nanoparticles,nano-emulsions,nano-suspensions, and nano-gels[205]. Many studies in the literature used nanotechnology methods developed in the delivery of curcumin and reported that the bioavailability of curcumin was increased. It is stated that the use of the nanoparticle form of the lipophilic curcumin molecule increases the solubility and intestinal absorption of curcumin compared to the use of the free form[206]. Curcumin can also be easily entrapped in nano-gel, a 3D hydrophilic polymer absorbing a large amount of fluid. The usage of curcumin-loaded nano-gels boosts curcumin’s release activity[207]. Also, Mangalathillam et al. found that curcumin-loaded nano-gels show toxic effects on melanoma cells, and their toxicity does not significantly affect normal cells[208].In another study with similar results, solid nanoparticles prepared with cholesterol with good competitiveness were used for curcumin transport, and it was found that curcumin release was increased in this way.

4.17 Encapsulation process in turmeric starch

Encapsulation processes of curcumin have been developed to increase the solubility, stability, and bioavailability of curcumin under physiological conditions [209]. Curcumin, folic acid-labeled amine starch/ZnO coated iron oxide nanoparticles[210], polyethylene glycol-poly lactic acid-co-glycolic acid) copolymer[211], disulfide-linked hydrophobic backbone of a PEGylated copolymer conjugated with superparamagnetic iron oxide nanoparticles [212], graphene oxides nanocomposites [213], curcumin-loaded graphene quantum dots [214], cyclodextrin-metal organic frameworks [215], poly(ε-caprolactone) (PEG-PCL) copolymer [216], PEG-β-cyclodextrin, curcumin solid Interactions with many nanoparticles such as lipid nanoparticles [217], cholesterol-conjugated poly(D,L-lactide)-based micelles[218]and curcumin-loaded embryonic stem cell exosomes [219], curcumin-docosahexaenoic acid-loaded carriers have been reported. In an LPS-induced rat model of anterior uveitis, administration of curcumin/calyx [4] arene reduced ocular inflammation and inflammatory proteins to a greater extent than free curcumin.

Biocompatibility was studied in rabbits with no adverse effects after topical use of the hydrogel [220]. Research to date has highlighted the advantages of curcumin nanoencapsulation over its bioaccessibility and pharmacological activities. However, the preparation of large-scale curcumin nanoemulsions from pilot scale to industrial use should receive increasing attention. Extensive work has been done to optimize and design effective nanoemulsion systems with improved physicochemical stability and bioaccessibility. The main factors affecting the stability and bioaccessibility of curcumin in nanoemulsion-based systems are the nature and concentration of the emulsifier, oil type and volume ratio, and emulsifier-curcumin interactions. The bioavailability of curcumin may increase with increasing total lipid content when the lipid phase is fully digested. Also, the emulsifier type affects curcumin bioaccessibility by changing the droplet surface area within the digestive tract or by changing the ability of digestive enzymes to bind to the emulsion droplet surface. However, emulsifier-curcumin interactions may reduce curcumin bioavailability. Indeed, nanoencapsulation techniques have been widely applied to enhance the functional properties of curcumin, including its antioxidant, anti-inflammation, and anti-cancer activities. Nanoformulations of curcumin will be helpful for different products in the near future.

5 CONCLUSION

In this review, we discussed the critical effects of Turmeric Starch and its most active component, curcumin, in the health field, such as anti-inflammatory, anti-diabetic, antioxidant, anti-obesity, cardio-liver, anti-cancer, anti-arthritis, and disease. We explained its effect on these mechanisms through molecular and metabolic pathways. The fact that turmeric and curcumin is a safe, natural products and their cost is lower than drugs may lead to the idea that curcumin can be used to treat and prevent diseases. According to studies and results, the health-promoting effects of curcumin are well known. Many in vitro, in vivo, and clinical research-based studies have revealed that turmeric and its components are effective modulators of the biological process. It is essential in the pathogenesis of various diseases by modulating multiple genes and enzymes. In order to get more exact and unambiguous findings, more extensive research based on animal models and clinical trials are required in addition to in vitro tests to enhance the effectiveness, safety, and mechanism of action of turmeric and curcumin. The therapeutic benefits of curcumin are considerably constrained by its low bioavailability when taken orally. Curcumin's structural equivalents can be paired with more extensive and tightly regulated clinical studies since they are more bioavailable and effective. Since it is poorly absorbed, rapidly eliminated, and metabolized, drug-food and drug-food interactions should be determined more robustly. Studies should continue to elucidate biological activities and formulate recommendations for their use. Based on the research results, it is possible to consume turmeric powder in line with the guidance of experts, as it prevents the formation and progression of various diseases and has positive effects on health.

Author Contributions

Kevser Kübra KIRBOĞA: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisiton
Burcu TEKİN: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisiton
Münevver DEMİR: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisiton

All authors read and approved the final manuscript.

Conflict of interest

No conflict of interest was declared by the authors.

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