A comprehensive review on physicochemical, pharmacological and analytical profile of curcumin

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ABSTRACT

In the rhizomes of curcuma longa (family zinziberaceae), curcumin is present as a pigment, due to which it has importance in spices, cosmetics and drugs. It shows a variety of biological and physiological activities, like anti-tumour, anti-inflammatory, antiviral, anti-oxidant, anti-HIV etc. It has low toxicity at higher doses and is well tolerated by the human body. In spite of the proven research that supports the medicinal benefits of curcumin, its medicinal uses are countered by its low aqueous solubility and potential to get degraded in the GIT, which ultimately contributes towards its poor bioavailability. The present review summarizes the uses and applications of curcumin in drugs and cosmetics, briefly describing its status in folk medicines. It also mentions the methods of its analysis in drugs and cosmetics formulations and foodstuffs. The use of turmeric in ayurvedic medicines is described with their recipe and references. From the ancient times, turmeric is being used in various cosmetic preparations. In Indian rituals, turmeric is an essential component. In this review, various uses of the turmeric in cosmetics is also summarised with references. In this review, the drawbacks of curcumin are also mentioned. As we know that turmeric is an ancient herb and have very beneficial properties beside this, it has some drawbacks, some negative properties etc. In the present review, we have discussed about various pharmacological, pharmacokinetic and medicinal properties of the curcumin and all this is summarized with the help of text, tables and figures. Various historical researches about curcumin are mentioned, including information about the discovery.

INTRODUCTION

Curcumin is one of the active constituents present in the turmeric. It is obtained as a yellow pigment from the rhizomes of the plant Curcuma longa (family Zinziberaceae) and imparts a yellow colour to turmeric. It was used as traditional Indian medicine and as a spice since ancient times. As a spice, it provides characteristic colour and flavour to the food. (Prasad et al., 2014) Curcumin is a lipophilic molecule, which can easily permeate through the gastro-intestinal membrane. It has been used for the treatment of various disease such as rheumatoid disease, atherosclerosis, infec-
tious disease, digestive disorders, wound healing etc., in China, India, and Iraq. It shows a variety of biological and physiological activities, like anti-tumour, anti-inflammatory, antiviral, anti-oxidant, anti-HIV etc. It has low toxicity at higher doses and is well tolerated by the human body. (Cui et al., 2009) In spite of the proven research that supports the medicinal benefits of curcumin, its medicinal uses are countered by its low aqueous solubility and potential to get degraded in the GIT, which ultimately contributes towards its poor bioavailability. Research also proves that curcumin is not completely absorbed through GIT, and 75% is excreted unabsorbed. The limiting factors of curcumin are, low bioavailability, less absorption rapid degradation in GIT, and rapid renal clearance {Cl (L/kg/min) 0.85 ± 0.24 oral route, 0.83 ± 0.19 i.v route}. For improving its bioavailability, various type of pharmaceutical approaches have been opted so far, such as liposome, nano-formulation, curcumin phospholipids complexes, structure analogues of curcumin etc. (Ravichandran, 2013). Table 1 succinctly describes various landmarks in the journey of research pertaining to the exploitation of curcumin in medicines. In spite of this, there is huge data available regarding its ongoing research in various spheres. (U.S. Patent No. 6,521,271)

Physiochemical properties

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is yellow-orange in colour and is also known as diferuloylmethane. Its molecular weight is 368.385 g/mol and its molecular formula is C_{21}H_{20}O_6. Chemically the molecule comprises of a seven-carbon atom chain attached to two aromatic rings. It is a heptanoid compound with its two alkyl groups substituted with phenolic and methoxy groups at the ortho position. Curcumin is practically insoluble in water and ether and very soluble in ethanol (10mg/mL), DMSO (74mg/mL), chloroform, acetone, DMF, and it is also soluble in 0.1 M NaOH to 3 mg/mL. (Fugita et al., 2012). Figure 1 shows the structure of curcumin. (Budhwar et al., 2018)

Curcumin has three acidic constant values due to the OH groups, which are phenolics and some of the enolic OH groups. The acidic constant having pKa< 8.5 is most acidic due to enolic proton, and the other two due to the phenolic protons are having pKa values 9.88 and 10.51 10.77 D was the ground state dipole moment of curcumin and hydrobicity parameter log (P) value in the range of 2.6 to 3.6 as obtained by the computed data. The data obtained indicates that the molecule would have very low aqueous solubility, which is predicted to be approximately 3 to 6 g/ml. The data also reveals that the predicted solubility of curcumin molecule in non-aqueous solvents would be more. Table 2 succinctly summarises some of the Physico-chemical properties of curcumin.

Stability

The two main factors which affect the stability of curcumin are neutral-basic pH conditions and visible light. The degradation of curcumin is further explained as follows-

Photostability

It is a yellow colour pigment which gets faded when exposed to sunlight with time. Its photodegradation follows the first-order kinetics. Its stability in visible light is also affected by the solvent system. It is more stable in methanol than chloroform, ethyl acetate, and acetonitrile. When exposed to visible light (450-750 nm), it gets degraded into ferulic aldehyde, ferulic acid, vanillin and vanillic acid. The mechanism behind the degradation of curcumin is the production of photo-induced reactive oxygen species (ROS). These ROS is either produced by type I (electron transfer to molecular O2) or by type II (energy transfer to molecular oxygen) photochemical reaction. Although these ROS formed are limited but sufficient enough to degrade the unmodified Curcumin. (Heger et al., 2014)

2. Effect of pH

The chemical stability of curcumin is more in acidic conditions with the increase in the pH, its stability starts decreasing, and it starts degrading at pH ≥7.4. Wang et al. reported that at neutral basic pH conditions (about ≥ 7.4), 90% of it degrades in various products. It gets degraded into Trans-6-(4′-hydroxy-Y-methoxyphenyl)-2,4-dioxo-5-hexenal as major and vanillin, ferulic acid and feruloyl methane as minor products. (Wang et al., 1997). Y. Nimiya et al. shows poor stability of curcumin in aqueous buffer at neutral basic physiological pH. Approximately 80-90% of curcumin degrades in approximately 12 min of incubation time, and rest degrades slowly. It degrades by two mechanisms alkaline hydrolysis and ROS formation. (Nimiya et al., 2016). Figure 3 shows the degradation products of curcumin at neutral basic pH.

Studies have shown that the degradation products formed have similar activities like curcumin against some disease like Alzheimer’s disease, cancer and in inhibition of some of the enzymes. So, there are chances that these products contribute to the pharmacological action of Curcumin. (Shen and Ji, 2012)

Pharmacological characteristics

The pharmacology of curcumin can be summarised as,
Table 1: Landmark research about Curcumin

| Years | Discoverer                  | Discovery                                                                                     |
|-------|-----------------------------|----------------------------------------------------------------------------------------------|
| 1815  | Vogel and Pelletier.        | Curcumin was first isolated in impure form.                                                   |
| 1842  | Vogel Jr.                   | Isolation of curcumin in pure form.                                                           |
| 1910  | Lampe et al.                | Structural characterisation of curcumin.                                                      |
| 1913  | Lampe et al.                | Curcumin was synthesised chemically.                                                           |
| 1937  | Albert O.                   | Curcumin use in biliary diseases was observed                                                  |
| 1949  | Schraufstatter and colleagues | The activity of curcumin as an anti-bacterial agent was observed.                             |
| 1953  | Srinivasan et al.           | By chromatography, separation and quantification of curcumin constituent.                    |
| 1971  | Patil & Srinivasan          | The first time hypocholesteromic effect of curcumin was observed.                             |
| 1972  | Srinivasan M                | Curcumin ability to lower the blood sugar level was reported.                                 |
| 1973  | Srimal and Dhawan           | Curcumin had identified as a non-steroidal anti-inflammatory agent.                          |
| 1976  | Sharma o.p.                 | Curcumin was identified as an antioxidant agent.                                               |
| 1980  | Kuttan et al.,              | The anti-cancer activity of curcumin was shown in both in vitro and in vivo models.           |
| 1995  | Singh & Aggarwal            | Observed that curcumin suppresses the pro-inflammatory transcription factor nuclear factor (NF-κB) and shows anti-inflammatory activity. |

Table 2: Physico-chemical property of Curcumin

| Molecular formula | Physico-Chemical Property of Curcumin |
|-------------------|---------------------------------------|
| C21H20O6          |                                       |
| Molar mass        | 368.365 g/mol                         |
| Appearance        | Orange-yellow needles                 |
| Melting point     | 183°C                                 |
| Solubility in water | 3.12 mg/L at 25°C                 |
| Acidity(pKa)      | 1st 8.54, 2nd 9.30 and 3rd 10.69      |

Figure 1: Structure of Curcumin
Figure 2: Shows the photo degradation products of Curcumin

Figure 3: Shows the degradation products of Curcumin at neutral basic pH
Pharmacokinetics

More than 30 years of research on curcumin's pharmacology have shown that it has poor bioavailability due to its poor absorption and rapid metabolism. The proven facts and ongoing research on the molecule about its clinical importance has persuaded the researchers to work to overcome these limitations by making changes in its formulations. Presently curcumin is either considered in the category of food supplements or ayurvedic drug in most of countries. The detailed description of its pharmacology is explained as under:

Absorption

Various studies on curcumin show that its serum concentration after a single oral dose is very low. First time in 1978, Wahlstrom and Blennow observed the absorption, excretion, and distribution in Spraguedawley rats. They observed that on oral administration of curcumin in a dose of 1g/kg to rats negligible amount of curcumin is found in their blood plasma. In 1980, (Ravindranath and Chandrasekhara, 1980) observed that when 400 mg of curcumin is given to rats orally, it is not present in heart blood. However, a small quantity (less than 5mg/ml) is available in portal blood from 15 min to 24 hours. (Ravindranath and Chandrasekhara, 1980). In one study with titanium-labelled curcumin, it could be easily observed when given in the range of 10 to 400 mg of curcumin per animal. Curcumin, when given orally at a dose of 2g/kg to rats, its serum concentration was observed from 0.23 mg/ml up to 1.35 mg/ml, whereas a negligible amount of curcumin is found in humans. Pan et al. examined the pharmacokinetics of curcumin when given orally and intraperitoneally in mice. 1g/kg of curcumin was administered to mice groups. When given orally plasma level of 0.13 mg/ml, 0.22mg/ml and below the detection limit was found after 15 min, 1 h and 6 h respectively. However, in intraperitoneal administration, plasma curcumin level reached up to 2.25 mg/ml, and it started falling off within 1 h. (Anand et al., 2007).

In a human clinical trial, 3.6 g of curcumin was given orally, and the plasma concentration of curcumin reached upto 11.1 nmol/L within an hour. Yang et al. examined the absorption of curcumin by administering it to rats by oral and intravenous routes. By i.v. route 10 mg/kg curcumin was admin-
registered to rats, and the serum curcumin level was found to be 0.36. By oral route its 50-fold more curcumin was administered, but a serum curcumin level of 0.06 was found. The study once again proved the poor absorption profile of this molecule through the gastro-intestinal route. These studies show the effect of route of administration on serum level of curcumin and that the serum level of curcumin in humans and rats are not completely similar. (Anand et al., 2007) Curcumin is sparingly soluble in an aqueous environment like that of the human gastrointestinal tract. Low water solubility and poor gastro-intestinal absorption are thus two main issues attributing towards the poor bioavailability of curcumin.

**Distribution**

Curcumin being a lipophilic molecule, is distributed in adipose tissue which volume of distribution is 1421.6 L. In a study on mice, an intravenous injection of 20mg/kg curcumin is given, and its tissue distribution was examined. In tested tissues, the curcumin was equally distributed in the liver, kidney and brain with the same tissue exposure. In the liver, kidney and brain, $AUC^{0-\infty}$ of curcumin was almost similar. The $t_{1/2}$ of curcumin in the liver and kidney were approximately similar and 2-fold greater than that in the brain. In this study, two metabolites of curcumin, i.e. tetrahydro curcumin (THC) and dihydro curcumin (DHC) were observed, in which THC plasma exposure was higher than DHC, which shows that it was the main metabolite of curcumin. The metabolites of curcumin was present in the brain, and DHC & THC was present in the kidney and liver, respectively. Ravindernath et al. orally administered 400 mg of curcumin to rats and observed that in the liver and kidney of rats, only a negligible amount of drug was found. In the stomach and small intestine, 90% and 1% of it was present at 30 min and 24h, respectively. (Ravindranath and Chandrasekhar, 1980) After oral administration, it has negligible bioavailability of less than 1%. Studies have shown that curcumin has no adverse effect on reproductive performance tested on Wistar rats in a dose of 847.4 mg/kg body weight, and it is safe.
Metabolism and Excretion

Rapid degradation and metabolism of curcumin in GIT is one of the limiting factors of its low plasma concentration. Auto oxidation and pH-dependent liability cause non-enzymatic degradation of curcumin. By the action of β-glucuronidase and sulfatase enzyme, curcumin converts into water-soluble metabolites. In vitro studies done with rat hepatocytes and liver, microsomes have shown 90% of curcumin metabolism by these two mechanisms in 30 minutes. Curcumin has a phenolic group which is susceptible to conjugation with glucuronide and sulfate groups. On human metabolism, monoglucuronides, monosulfates, and sulfate-glucuronides are produced. Curcumin metabolism in human produces curcuminmonoglucuronide, curcuminmonosulfate and curcumin sulfate-glucuronide. The α, β-unsaturated ketones are prone to both conjunction and reduction. The reduction of curcumin breaks its conjugated system, which leads to decolourization, producing a colourless compound, i.e. dihydro curcumin, tetra-hydro curcumin and hexa-hydro curcumin. These reduced compounds are further susceptible to a conjunction. In the liver, alcohol dehydrogenase and glutathione S-transferase reduces the curcumin into these metabolites. Figure 4 shows curcumin transformation pathways and major conjugates/metabolites. In the intestine, NADPH-dependent reduction microbial metabolism of curcumin occurs.

On oral administration of curcumin, most of it, which is unabsorbed, is excreted through faeces, and intestine absorbed curcumin is either metabolised in liver and plasma or excreted via urine. (Liu et al., 2016), Figure 2 shows the schematic degradation of curcumin in the human body.

Bioavailability

Besides various benefits of curcumin like low aqueous solubility, its use as modern medicine is restricted due to many reasons that ultimately result into poor bioavailability. There are various mecha-
nisms which contribute to the low bioavailability of curcumin. Some of them are discussed below (Liu et al., 2016)

**Bioaccessibility**

For the nutraceuticals, curcumin in particular, there is a need of bioaccessibility for in epithelium of GIT before its transportation into the systemic circulation. For this process, it is important that curcumin should be soluble in gastrointestinal fluid. However, curcumin being a hydrophobic compound, shows poor aqueous solubility, which leads to poor bioaccessibility and hence poor absorptivity. (Vareed et al., 2008)

**Instability**

As discussed earlier, it is notified that it shows rapid degradation in an aqueous solution in a manner which is pH-dependent. The half-life of curcumin is 100-200 min at pH 3-6.5, but when the pH raises to 7.2-8.0, it dramatically reduces to 1-9 min. (Nimiya et al., 2016) When chemical degradation of curcumin takes place, there is a formation of a series of compounds, including alkaline hydrolysis products such as ferulic acid, vanillin, ferulaldehyde etc. (Gordon et al., 2015). When these compounds were compared with parent curcumin, they showed less biological activity than curcumin.

**Absorption**

For the low bioavailability of curcumin, poor absorption in GIT is responsible, which is supported by the excretion of most of it through faeces. (Sanidad et al., 2019) This might be due to its poor aqueous solubility as a rate-limiting step (Prasad et al., 2014) or due to its poor absorption through the GIT. (Nimiya et al., 2016) It is also shown in a study that curcumin is back-flushed to the lumen by the efflux system. (Ravindranath and Chandrasekhara, 1980) Inspite of these researches, curcumin is still referred to as a BCS class II drug which suggests that once dissolved in the GI tract, it can easily get absorbed through it.

**Tissue Distribution**

For the biological activity of curcumin, it is an important factor in how curcumin is distributed throughout the tissues of the body. (Ravindranath and Chandrasekhara, 1980) Adipose tissues act as a compartment where curcumin is distributed and deposited. Resultantly, its availability to the systemic circulation is often low and variable in human subjects.

**Metabolic transformation**

After oral administration of curcumin, there is a rapid metabolic reduction due to Phase 1 metabolism and conjugation, i.e. phase 2 metabolism in the tissue of GIT and liver, which leads to poor systemic bioavailability. The metabolism of curcumin could be done by NADPH-reductase, a series of reduction products are formed, i.e. dihydro curcumin, tetra hydro curcumin, hexa hydro curcumin, and octa hydro curcumin. In a study, Hassaninasab et al. suggested that E.coli, the gut bacteria shows catalysis in the reductive metabolism of curcumin with the help of bacterial enzymes Cur A (NADPH- dependent curcumin or dihydro curcumin reductase). When the curcumin is metabolised by Cur A, the result is the formation of dihydro curcumin and tetrahydrocurcumin, and no further reduction takes place. Conclusively CurA enzyme helps in reductive catalysis of the C=C bond, not the C=O bond. As curcumin consists of two phenolic groups, that’s why it is susceptible to metabolism by phase II detoxification enzymes, i.e. glucuronosyltransferase and sulfotransferase. This results into the formation of conjugates of glucuronide and sulphate. When these conjugates were compared with curcumin, these shows less activity. (Nimiya et al., 2016). It suggested that when phase II metabolism of curcumin takes place, its biological activity is reduced.

To exploit the benefits of curcumin, the researchers are now focussing on the improvement of bioavailability of the molecule by preparing various formulations like preparation of its micelles and microemulsion by Poul and Moulik, Jin et al., (Ma et al., 2018) liposomes by (Cui et al., 2009), emulsions and nanoemulsions by Pawar and Hassani-nasab, and solid lipid nanoparticles by Tamijidi et al. Although all these researchers claim to have better aqueous solubility and bioavailability of their formulations as compared to the traditional way of administering the drug no marketed formulation exists till date.

**Pharmacodynamics**

Curcumin helps in the ailment of various diseases, which is observed by various clinical and pre-clinical trials. Curcumin can interact with various molecular targets and signalling pathways which help in ailments of disease. Curcumin is effective against disease like cancer, auto immune disease, inflammation, neurological disease, cardiovascular disease, lung disease, liver disease, skin disease, obesity etc. The mechanism of action of curcumin for various diseases is as follows:

**Anti-inflammatory**

Inflammation is caused by enzymes, cytokines, and polypeptides hormones, i.e. COX-2, 5-lipoxygenase (LOX), TNF-a, IL-1, IL-6, IL-8, IL-17, IL-21 and Monocyte chemotactic protein-1 (MCP-1). Curcumin sup-
presses these causative factors. The major factors affecting is TNF-a and curcumin either suppress its gene expression or acts as its blocker. (Aggarwal et al., 2013) Due to its anti-inflammatory effect, curcumin is used in cardiovascular disease, skin diseases and wound healing.

**Obesity**

Curcumin acts by reducing the vascular endothelial g.f. Expression, peroxisome proliferation-activated receptor-g and (CAAT) and enhances binding protein-ad. When mice were fed with curcumin, the result showed a significant weight loss and increment in lean tissue mass in them. Transcriptional proteins are involved in adipogenesis which are inhibited by curcumin leading to reduction of adipose tissue in curcumin fed mice. Curcumin shows an effect on the metabolism of lipid and decrease the synthesis of triglycerides and shows an increment in the oxidation of fatty acids. It may also help in weight reduction by increasing the basal metabolic rate and release of some cytokines.

**Anti-Oxidant Effect**

In living cells, red-ox balance is maintained, which is disturbed by the newly formed reactive oxygen species (ROS) and nitrogen analogues. It neutralizes these ROS into secondary, less harmful free radicals. Curcumin is 10-times more effective than toco-pherol in neutralizing ROS.

**Diabetes**

Due to obesity, adipocytes & hepatocytes gets enlarged by the stress-activated pathway. These enlarged cells signal macrophages, NF-kb, p38, JNK to produce TNF and IL-6. These TNF and IL-6 impairs insulin signalling and caused the resistance of insulin. Curcumin, by inhibiting this stress-activated pathway, help in the cure of type-2 diabetes. (Maradana et al., 2013)

**Cancer**

Cancer is caused by changes in the different genetic pathways. By activating or inactivating these pathways, curcumin helps in the prevention of various types of cancer, as shown in Figure 5. (Rahmani et al., 2014)

**Toxicity**

Curcumin is GRAS listed. In a clinical trial on 25 subjects, curcumin is well tolerated to the dose extent of 8 gm/day in human subjects. The overdose may cause gastric irritation in human subjects. Evidences also show that curcumin administered in rats at high doses cause hepatotoxicity. However, humans have more tolerance for curcumin than other animals, probably due to the high metabolism rate of curcumin in humans. In a dose response study was done on seven subjects given 500-12000 mg of the daily dose, examined for 72 hours shows effects like headache, rash, and yellow stool. One more study, done on subjects for 1-4 months. A dose of 0.45 to 3.6 g/day of curcumin was administered to them. Side effects like nausea and diarrhoea and an increase in serum alkaline phosphatase and lactate dehydrogenase concentration was observed. (Hewlings and Kalman, 2017)

**Clinical Significance**

1. By curcumin’s multiple signalling pathways, it is effective against various types of cancers.
2. Curcumin is effective against irritable bowel syndrome as it helps in increasing the motility of the bowel, and it can stimulate the hydrogen-producing bacterial flora in the colon.
3. Curcumin has comparable activity to phenylbutazone for arthritis on the basis of stiffness in the morning, during walking, and swelling of joints.
4. Due to its anti-oxidant activity, curcumin is an effective medication in vitiligo.
5. In psoriasis, curcumin work by non-competitive inhibition of PhK.
6. Curcumin is also active against other diseases like diabetes, CVS disease, acquired immunodeficiency syndrome etc. Figure 6 showing the various clinical significance of curcumin.

**Curcumin in Ayurveda**

From ancient times turmeric has a significant place in ayurvedic medicines. Ayurveda’s whole rhizome of curcumin was used to cure kapha, pitta and Vata, which are the principal categories of Ayurveda. Although the benefits of turmeric was due to the principle, active constituent curcumin was known from 1937 when used in biliary disease observed by Albert Oppenheimer. (Oppenheimer 1937) In Ayurvedic pharmacopoeia, turmeric is officially included as Haridra after establishing its benefical effects in humans.

In India, turmeric is used in many ayurvedic formulations as a principal ingredient. Haridra Kanda is a formulation used in the treatment of worm’s infections or in allergies. Rajayadi Churnam is a formulation having turmeric as the main drug used for paediatric disease. Lakshadi Tailam is used for cold and any upper respiratory having turmeric in carrier oils. Jathyadi Tailam is
an oil-based formulation used for the treatment of chronic wounds. For the regulation of diabetes, Nisha Katakadi Kashyam is an extremely good formulation. Brahma rasayanam boosts memory and body immunity. Kalyanka Ghritam is an antidote to mental disorder and used as an anti-inflammatory agent. Punarnavamanduram acts against anaemia, and in bodily fever, Sudarshana Churnam is used. These are the formulation in which turmeric is used either singly or in combination with other drugs. As curcumin is a principal active compound in turmeric, we may replace turmeric with curcumin as in ancient times, there were no sources of curcumin extraction, and the whole turmeric was used.

**Curcumin in Cosmetics**

Traditionally in many cultures and tribes of India, turmeric has been used in the form of upants and lepas to enhance the beauty of human. In modern cosmetics, turmeric power is incorporated in many semi-solid creams for the same purpose. The cream base increases the residence time of turmeric on the skin and consequently enhances its beauty effect. (Budhwar et al., 2018; Kole et al., 2005) Turmeric extract is generally used in a concentration range of 5-8% in marketed formulations. (Pawar et al., 2014) Curcumin in a concentration range of 1mg/ml to 20mg/ml with glycolic acid helps in the treatment of scars, pigmentation and skin ageing problems. (U.S. Patent No. 6,521,271)

Due to its anti-oxidant property, it protects the lipids to get rancid in moisturiser. (Burgos-Morón et al., 2010) It helps in the reduction of inflammation in various skin disease, i.e. psoriasis, atopic dermatitis, contact dermatitis, acne, etc.

**Negative properties of Curcumin**

Curcumin is highly metabolized in intestinal space and the liver. So, its bioavailability is very low in the targeted site as compared with the high dose of administration. For example, in a pharmacokinetic study of curcumin preparation, 12 healthy volunteers were selected, to whom an oral dose of curcumin preparation, that is, 10-12g was administered, observed for 0.25-72 h and in HPLC time point assay, only 50ng ML⁻¹ drug was detected. The problem is a high amount of curcumin was not achieved and maintained in the targeted tissue. (Burgos-Morón et al., 2010). If we increase curcumin concentration in plasma by using any technique, we should take it into consideration that with its benefits, its toxic effects may precipitate with its high concentration in plasma. According to a study by Goodpasture and Arrighi in 1976, it was demonstrated that curcumin induced a dose and time-dependent chromosome aberration in various cell lines (mammalian). Such kind of behaviour was shown when the concentration was 10µg ML⁻¹. At the concentration of 2.5-5µg ML⁻¹ may initiate alteration pod DNA both in nuclear and mitochondrial genomes in cells lead to carcinogenesis. On the basis of various studies, it was confirmed that a high dose of curcumin leads to various forms of carcinoma in mice and rats, that is, lung cancer, thyroid gland follicular cell hyperplasia, hepatocellular adenomas, small intestine adenomas, ulcers, inflammation, etc. (Burgos-Morón et al., 2010)

In recent studies, curcumin was found to behave like an active iron chelator in vivo. The observations show iron deficiency anaemia in mice fed with a poor iron diet. (Burgos-Morón et al., 2010). Enzymes like Cytochrome P450, UDP-Glucuronosyltransferase, Glutathione-s-transferase plays a vital role in drug metabolism. Curcumin was found to inhibit these enzymes, leads to an increase of the concentration of a drug, which are metabolized through these enzymes. A high concentration of these drugs may lead to various toxic effects. (Burgos-Morón et al., 2010). Curcumin is considered as safe for short term periods of treatment up to the dose of 8g per day. But this dose is not completely harmless. In some cases, it may cause diarrhoea, nausea and shows an increase in serum alkaline phosphatase and lactate dehydrogenase. (Burgos-Morón et al., 2010)

**Analysis**

Various ayurvedic drugs and cosmetics formulations containing curcumin are available in the market. Hence, it becomes necessary that suitable methods of analysis should be developed to confirm the label claims. Various varieties of turmeric are also available, which contains a variable amount of curcumin in them. Therefore, the possibility of its adulteration by standard rhizomes cannot be ruled out. Some of the researchers tried to analyse the curcumin with different methods like Pawar performed TLC for the identification (Pawar et al., 2014) Kiran Sharma et al. established a method for UV spectrometric method for curcumin using double beam UV visible spectrophotometer. Fugita et al. recorded the DSC curve of commercial and crystalline curcumin using thermal analysis system model Q-10 (Fugita et al., 2012) and Masek et al. performed the TG-DTA analysis of commercial and crystalline curcumin by taking 5mg of each sample in an alumina crucible, (Fugita et al., 2012) Shaik et al., observed the XRD pattern of curcumin with Cu source of radiation, a voltage of 40 kV and 25 mA. The scanning was done at an angle of 3°≤2θ ≤40° and at 2°/min scan rate, Pawar et al.and Jeevana...
et al. performed FTIR (Pawar et al., 2014; Lavanya and Jyothi, 2016) Coorey et al. examined the curcumin sample by plasma desorption, laser-induced, electro spray ionization-time of flight mass analysis. Wisut et al. established a method for the estimation of curcuminoids by the HPLC technique. The sample solution was prepared using acetonitrile. (Wichitnithad et al., 2009) Official methods of analysis of curcumin are also available in the ayurvedic pharmacopoeia. (The Ayurvedic Pharmacopoeia of India, 2016)

CONCLUSIONS

The ongoing research in curcumin shows that it has anti-oxidant, anti-inflammatory, anti-microbial, anti-tumour, anti-diabetic activities. It is well tolerated in the human body with negligible side effects/toxic effects. The ongoing research on the molecules shows that its benefits can be further exploited in modern medicine if its aqueous solubility could be enhanced and its degradation in the intestine could be minimized.

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Conflict of Interest

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REFERENCES

Aggarwal, B. B., Gupta, S. C., Sung, B. 2013. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. British Journal of Pharmacology, 169(8):1672–1692.

Anand, P., Kunnumakkara, A. B., Newman, R. A., Aggarwal, B. B. 2007. Bioavailability of Curcumin: Problems and Promises. Molecular Pharmaceutics, 4(6):807–818.

Budhwar, V., Vikas, Y., Manjusha, C. 2018. Cyclodextrin Complexes: An approach to improve the physicochemical properties of drugs and applications of cyclodextrin complexes. Asian Journal of Pharmaceutics, 12(2):394–409.

Burgos-Morón, E., Calderón-Montaño, J. M., Salvador, J., Robles, A., López-Lázaro, M. 2010. The dark side of curcumin. International Journal of Cancer, 126(7):NA–NA.

Cui, J., Yu, B., Zhao, Y., Zhu, W., Li, H., Lou, H., Zhai, G. 2009. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. International Journal of Pharmaceutics, 371(1-2):148–155.

Fugita, R. A., Gálico, & Bannach, G. D. 2012. Thermal behaviour of Curcumin. Brazilian Journal of Thermal Analysis, 1(1):19–23.

Gordon, O. N., Luis, P. B., Schneider, C. 2015. Unraveling curcumin degradation: autoxidation proceeds through spiro epoxide and vinyl ether intermediates en route to the main bicyclopentadione. Journal of Biological Chemistry, 290(8):4817–4828.

Heger, M., van Golen, R. F., Broekgaarden, M., Michel, M. C. 2014. The Molecular Basis for the Pharmacokinetics and Pharmacodynamics of Curcumin and Its Metabolites in Relation to Cancer. Pharmacological Reviews, 66(1):222–307.

Hewlings, S., Kalman, D. 2017. Curcumin: A Review of Its Effects on Human Health. Foods, 6(10):92–92.

Kole, P. L., Jadhav, H., Nagappa, A. 2005. The cosmetic potential of herbal extracts. Natural product radiance, 4(4):315–321.

Lavanya, M., Jyothi, B. 2016. Performance Analysis of 5-Phase Multi-level Inverter Using Carrier Based PWM Technique.

Liu, W., Zhai, Y., Heng, X., Che, F. Y., Zhai, G. 2016. The oral bioavailability of curcumin: problems and advancements. Journal of Drug Targeting, 24(8):694–702.

Ma, G., Wang, Z., Du, G. 2018. Preparation and properties of stearic acid–acetanilide eutectic mixture/expanded graphite composite phase-change material for thermal energy storage. Energy Technology, 6(1):153–160.

Maradana, M. R., Thomas, R., O’Sullivan, B. J. 2013. Targeted delivery of curcumin for treating type 2 diabetes.

Nimiya, Y., Wang, W., Du, Z., Sukamtoh, E., Zhu, J., Decker, E., Zhang, G. 2016. Redox modulation of curcumin stability: Redox active antioxidants increase chemical stability of curcumin.

Pawar, H., Karde, M., Mehra, K. 2014. Phytochemical evaluation and curcumin content determination of turmeric rhizomes collected from Bhandara District of Maharashtra (India). Medicinal Chemistry, 4(8):588–591.

Prasad, S., Tyagi, A. K., Aggarwal, B. B. 2014. Recent Developments in Delivery, Bioavailability, Absorp-
tion and Metabolism of Curcumin: the Golden Pig-
ment from Golden Spice. Cancer Research and
Treatment, 46(1):2–18.

Rahmani, A. H., Zohairy, M. A. A., Aly, S. M., Khan,
M. A. 2014. Curcumin: A Potential Candidate
in Prevention of Cancer via Modulation of Molec-
ular Pathways. BioMed Research International,
2014(9):1–15.

Ravichandran, R. 2013. Studies on Dissolution
Behaviour of Nanoparticulate Curcumin Formu-
lation. Advances in Nanoparticles, 02(01):51–59.

Ravindranath, V., Chandrasekhara, N. 1980. Absorp-
tion and tissue distribution of curcumin in rats.
Toxicology, 16(3):259–265.

Sanidad, K. Z., Sukamtoh, E., Xiao, H., McClements,
D. J., Zhang, G. 2019. Curcumin: Recent Advances
in the Development of Strategies to Improve Oral
Bioavailability.

Shen, L., Ji, H. F. 2012. The pharmacology of cur-
cumin: is it the degradation products? Trends in
molecular medicine, 18(3):138–144.

The Ayurvedic Pharmacopoeia of India 2016. Ghazi-
abad: Pharmacopoeia Commission For Indian
Medicine & Homoeopathy. Government of India
ministry of health and family welfare department of
Ayush, 1(1):60–61.

Vareed, S. K., Kakarala, M., Ruffin, M. T., Crowell,
J. A., Normolle, D. P., Djuric, Z., Brenner, D. E. 2008.
Pharmacokinetics of Curcumin Conjugate Metabo-
lites in Healthy Human Subjects.

Wang, Y. J., Pan, M. H., Cheng, A. L., Lin, J. K.
1997. Stability of curcumin in buffer solutions and
the characterization of its degradation products.
Journal of pharmaceutical and biomedical analysis,
15(12):2024–2033.

Wichitnithad, W., Jongaroonngamsang, N., Pum-
mangura, S., Rojsitthisak, P. 2009. A simple iso-
cratic HPLC method for the simultaneous deter-
mination of curcuminoids in commercial turmeric
extracts. Phytochemical Analysis, 20(4):314–319.