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A Review on The Extraction Process and Activity of Curcumin on Diabetes Mellitus and Cancer

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Abstract:
Turmeric, or Curcuma Longa, is a natural product whose medicinal properties have been widely studied and a wide range of therapeutic effects in various diseases, including neurodegenerative, liver, kidney damage, cancer and diabetes have been linked mainly to its curcuminoid content. In recent decades Diabetes has become an alarming global health problem due to the increasing prevalence of diabetes. The people who suffer from this disease and the consequences for them are devastating. In this review article we review the current basic and clinical evidence on the potential of curcumin / curcuminoids for the treatment of diabetes mainly due to its hypoglycemic, antioxidant and anti-inflammatory properties. Action of curcumin or curcuminoids as a hypoglycemic agent or only as a healing aid improve metabolic profile and improve diabetes-related complications such as diabetes nephropathy and cardiopathy are discussed. Interactions between curcumin and conventional antidiabetic drugs could be investigated in the treatment of diabetes Curcumin has also been shown to be a mediator of chemoresistance and radioresistance. Anticancer effects have been observed in a number of clinical trials, mainly a natural chemopreventive agent in colon and pancreatic cancer, cervical neoplasia and Barrett's metaplasia. Something clinical studies in healthy volunteers have shown low bioavailability of curcumin, calling into question the use of curcumin alone food additive Our clinical experience with curcumin and the antimetabolite gemcitabine in patients with advanced pancreatic cancer resulted in an objective response in less than 10% of patients with a small effect on survival. However, the safety of this combination has been proven. The potent antiproliferative effects of curcumin, which interact with multiple intracellular signaling pathways, may enhance the antitumor effects of gemcitabine. The Preclinical data lead to various, but still few, clinical trials (some ongoing) that demonstrated the potential effectiveness of the drug. this treatment as a chemopreventive or chemotherapeutic agent. This review focuses on clinical evidence including our experience with curcumin as a chemopreventive and therapeutic agent and background results in vitro.

Keyword: Diabetis mellitus, Cancer, Curcunin, Extraction.

Introduction:

1.1 Curcumin:

Curcumin is the main component of the spice turmeric and is obtained from the rhizome of the East Indian plant Curcuma Longa. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hep thadiene 3,5-dione] is one of the most studied natural medicines in recent decades to its various properties. It is the

primary biologically active Curcuminoids from the herbaceous perennial plant Curcuma longa belongs to the ginger family (Zingiberaceae) native to Southeast Asia[1]. Turmeric contains a class of compounds known as curcuminoids, consisting of curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Root and rhizome (underground Curcuma long stem) is crushed and ground into a powder turmeric Turmeric powder is used worldwide as a spice and curry as the main ingredient. Curry contains ~2% curcumin, which was first identified in 1910 by Miłobędzka et al. In addition, curcumin is responsible for the yellow color spice, apart from most of the healing effects of turmeric[2].

Synonym:- Indian saffron, turmric,Haldi,

Colour:- Yellow or Brown Yellow

Odour:- Aromatic and Characteristics

Taste:- Slightly bitter

Biological Sourece:- *Curcuma longa*

Solubility:- Insoluble in Water, Soluble in chloroform.

Apart from being used as a flavoring and coloring agent in foods, turmeric has also be widely used as antioxidant, antiamyloid, antimicrobial, antitumor, immune response modulating and neuroprotective effects. Curcumin also had antidepressant properties by modulating the release of serotonin and dopamine. Therapeutic limitations of curcumin were good Known for a long time, low solubility, low stability, poor bioavailability, low penetration, rapid metabolism and targeting efficiency Curcumin has been used as a dietary supplement for centuries and is considered pharmacologically safe [2].

1.2 Diabetes Mellitus :

Diabetes is an indicator that occurs in people with high levels of blood glucose. These individuals are unable to metabolize glucose due to insulin secretion and/or dysfunction [3] [4]. Not only environmental and genetic factors are responsible diabetes, but also many other factors, including insufficient physical activity, excessive consumption of food and drink, obesity, stress and industrialization can affect development about diabetes [5]. Chronic hyperglycemia can cause other complications involving long-term damage, dysfunction and organ especially damages the eyes, kidneys, nerves, heart and blood vessels [6] [7]. Diabetes can be classified as type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes and other specific types diabetes T1D and T2D are the two main etiopathogenetic categories of diabetes [8], [9]. T1D is caused by an absolute deficiency of insulin secretion. T2D, a much more common category, is caused by a combination of insulin resistance and insufficient compensatory insulin secretory response [10][11]

Recent studies (2016) have shown hypolipidemic properties of ethanol extract of turmeric which can be used to treat hyperlipidemia. According to the authors, India is the diabetes capital and leads the world In 2007, there were approximately 40.9 million patients with diabetes and probably 69.9 million by 2025" [12]

1.3 Cancer:

Cancer is the leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 or nearly one in six deaths. The most common cancers are breast cancer (2.26 million cases), lung cancer

(2.21 million cases), colon and rectal cancer (1.93 million cases), and prostate cancer (1.41 million cases). About a third of cancer deaths are caused by tobacco, High body mass index, alcohol consumption, low fruit and vegetable consumption and low physical activity. [Data taken from WHO]
The most common treatments for breast cancer are chemotherapy and radiation therapy.[13] Side effects of chemotherapy and radiotherapy for patients include peripheral neuropathy, nausea, vomiting, fatigue, alopecia (hair loss), diarrhea and constipation, and the most dangerous is febrile neutropenia [14]. In addition, these treatments are relatively expensive; therefore, another option is to use traditional herbal medicine. Turmeric (Curcuma longa) is a medicinal plant traditionally used to treat various diseases such as eye disease, smallpox, indigestion, liver disease and itching. It is known to be anti-parasitic, anti-infective, anti-periodic, astringent, diuretic and tonic. Regular consumption of foods containing turmeric can reduce the risk of various diseases such as rheumatism, heart disease, tumors, cancer, Alzheimer's disease and other infectious diseases [15]. The active compounds of C. longa have antioxidant effects and stabilize damaged cells by providing free radicals with electrons.[16]. The 2,2-diphenyl-1-picrylhydrazyl hydrate (DPPH) assay is one method to evaluate the radical scavenging activity of antioxidants that is accurate, simple, and economical [17]. DPPH, which is stable at room temperature, is reduced in the presence of an antioxidant molecule to form a colorless (purple to yellow) compound [18][19].

Extraction Methods of Curcumin :

The structural properties and properties of curcumin can be the extraction method is affected. Traditional (Soxhlet extraction, hydrodistillation and soaking) and new technologies (ultrasonic extraction, microwave extraction extraction, high hydrostatic pressure extraction, supercritical liquid extraction, enzyme extraction, zone cleaning, and soaking methods) can be used to extract curcumin from turmeric roots [20].

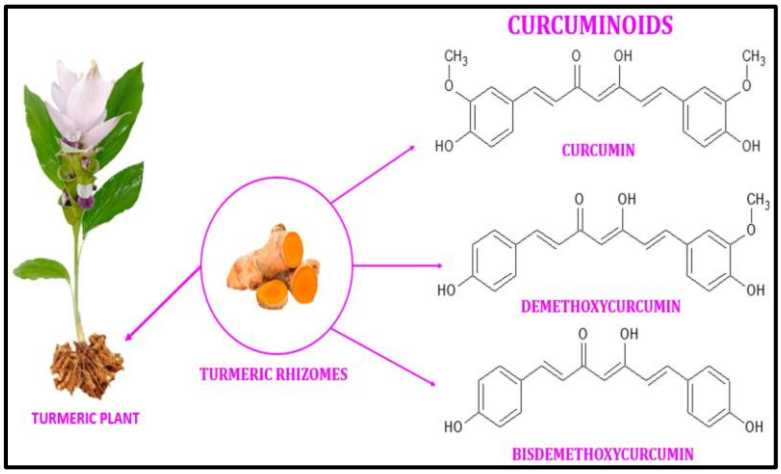


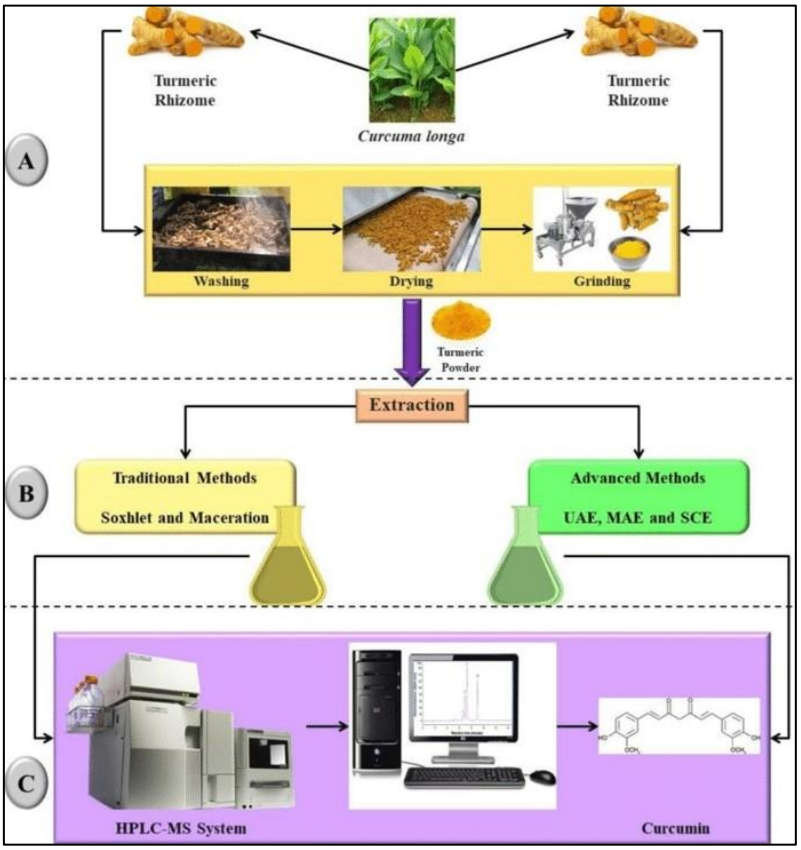
Fig 1: Active constituent of Curcumin

Traditional extraction methods have some limitations, such as the use of high temperature, which is not beneficial. For thermosensitive compounds using large volume organic solvent, long time and low extraction yield [21]. Expired Because of these disadvantages, researchers usually use other techniques which could include high mining efficiency and environmentally friendly technology [22].

Microwave extraction, ultrasonic extraction, supercritical fluid extraction (requires expensive instruments), pressurized fluid extraction and enzyme-assisted extraction extraction was described as common advanced methods for curcumin extraction [23][20].

Recent studies on curcumin extraction using new methods technologies have proven that new technologies are better extraction yield, shorter time and higher antioxidant activity [24]. Showed that high hydrostatic pressure is a promising method to achieve higher antioxidant activity of turmeric and they also found a higher concn the content of vanillin and ferulic acid in the extracts increases time A comparative study by Wakte et al [25]. reported that microwave extraction is more effective method for extracting curcumin from C. Longa With the help of Soxhlet, ultrasound and supercritical carbon dioxide extractions in terms of performance and time taken.d extraction extraction was described as common advanced methods for curcumin extraction [23] [20].

The extraction yield was reported in the same study in descending order as follows: microwave extraction (90.47%), ultrasonic extraction (71.42%), supercritical carbon dioxide extraction (69.36%) and Soxhlet extraction (2.1%). In addition, Liang et al.[26] also showed that ionic liquid-based microwave extraction is fast, an efficient and non-polluting method for curcumin extraction [11].



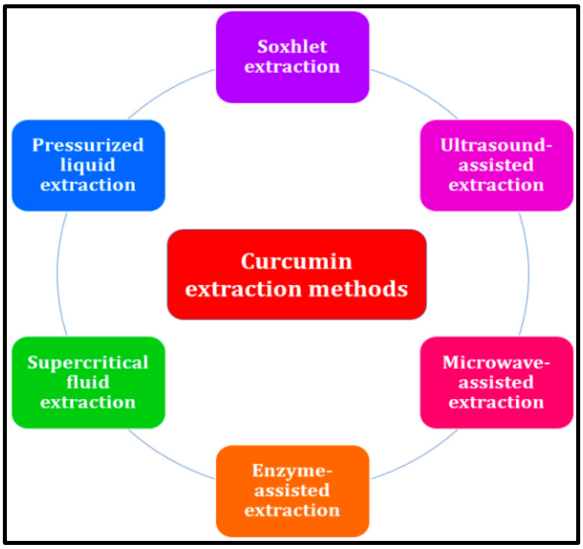


Fig 2: Methods of Extraction

Soxhlet Extraction:

In 1879, German chemist Franz Ritter von Soxhlet invented the Soxhlet extractor. extraction of lipids. Today, this device is also used for the extraction of bioactive compounds natural sources [27]. The experimental setup for Soxhletation consists of a heating chamber, a distillation flask, Soxhlet extractor and condenser. The dried sample is placed inside into a thimble and placed in a Soxhlet extractor. By heating the solvent in the distillation flask goes into vapor state.

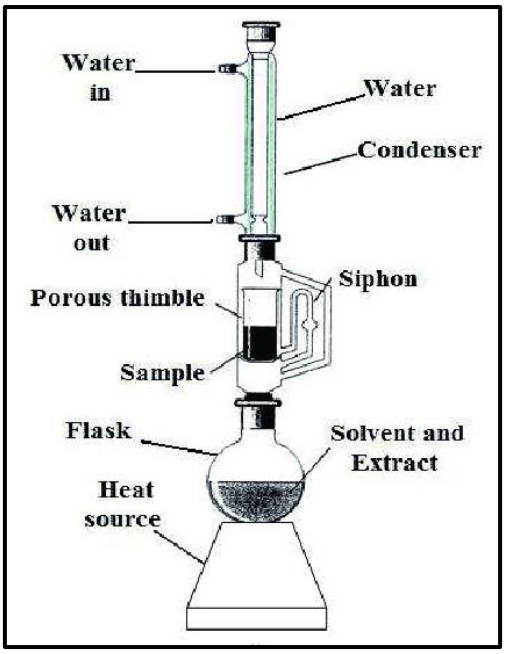


Fig.3 Soxhlet Extraction apparatus

It is then concentrated and reduced to liquid form I put my thimble on the vacuum cleaner. The solvent penetrates the cell wall of the solid sample and the compound of interest is extracted. When the solution volume reaches the extractor overflow level, the liquid is siphoned and returned to the distillation flask. The extraction cycle is repeated until the desired amount of the bioactive compound of interest is

reached concentration [28][29][30]. Soxhlet extraction is sometimes used today as a reference extraction method resulting in almost 100% curcumin extraction; however, it is a long process and requires high energy costs [31] [30]. Curcuminoids were extracted using the Soxhlet extraction method. Fresh rhizomes were cleaned, washed with deionized water. With water, cut and dried in the sun for a week and dried again in a hot air oven at 50ºC for six hours. They are dried rhizomes were cut into small pieces, ground with an electronic grinder. 6 g of the sample was taken in a thimble and placed in a Soxhlet apparatus; 250 ml of solvent were added and extracted at their boiling point for seven hours. The the solvents used were chloroform (BP = 61 ºC), methanol (BP = 65 ºC) and acetone (BP = 56.53 ºC) [32].

After the extraction was complete, the dark brown extract was cooled and concentrated using a rotary evaporator. This dried crude extract which turned black orange. Each raw turmeric sample was extracted an the corresponding method and performance were calculate [33][34].

$$\%of\ curcumin = \frac{\text{Dry wt of extracted curcumin}}{\text{Total } Wt\ of\ curcumin} \times 100$$

Ultrasound-Assisted Extraction:

Ultrasonically assisted extraction (UAE) is an environmentally friendly extraction technique. This method is based on the phenomenon of cavitation [35]. Ultrasound is defined such as sound waves with frequencies between 20 kHz and 100 MHz that cannot be detected with human ears [36]. Ultrasonic processing is widely used in industry and is called "green unique technology" because it contributes to environmental sustainability [37]. Depending on the amplitude and frequency of the sound waves [38], the mechanism can be heat or heat. In the case of a thermal mechanism, the energy is absorbed by the clock a hit with a sound wave turns into heat [36]; in the case of a thermal mechanism, the passage of sound waves causes the formation of liquids gas bubbles due to repeated cycles of compression and expansion [35]. Because In Brownian motion, bubbles accumulate energy and when they burst, they transfer it energy into the plant cell wall and the extraction medium, causing rupture intermolecular bonds between the compounds of interest and the solid matrix [31].

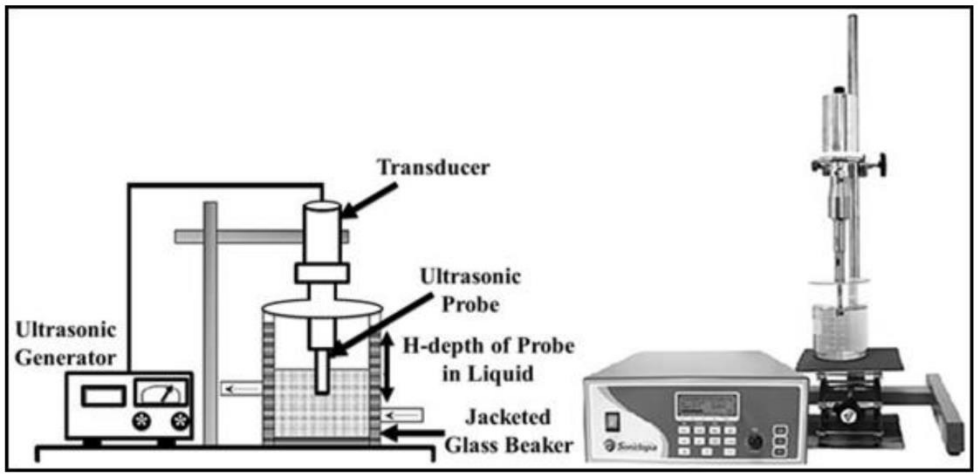


Fig 4: Ultrasound-Assisted Extraction Apparatus

This method is advantageous due to its short extraction time and low solvent and energy consumption consumption [39]. Wimonrut et al. using an extract yield of 160.3 mg/g was achieved ethanol as a

solvent using a solid to liquid ratio of 1:10, working with frequency 42 kHz using 240 W of input power and performing the stripping process for a period of time 40 min [40]. Shisath et al. studied the variation of different extraction parameters to find optimal conditions for ultrasonic extraction of curcumin. They found that the optimal extraction parameters are 40 ◦C, 1:30 solid/solvent ratio, average particle size 0.09, ultrasonic power 240 W, 22 kHz frequency and ethanol as the most suitable solvent. Use of optimal conditions the extraction yield was 73.18% in two hours compared to Soxhlet where the extraction yield was 100%, but the parameters were like temperature 78 ◦C and extraction time 14 h [31][30].

Solvent Extraction:

Solvent extraction is the continuous or mass transfer of the target compound into a polar or nonpolar extraction solvent [41]. The first step in this process involves a solvent, usually ethanol, methanol, penetrates the solid sample of the crushed plant, isopropanol or acetone; in the second step, the solute of interest is dissolved solvent and in the next step it is released again outside the solid matrix. The last step consists of a solution collection [42]. Solid matrix penetration and solvation phenomena migration occurs simultaneously until equilibrium is reached [41]. The solvent is removed by evaporation at the end of the process to obtain a high quality concentrated product [43][30] .

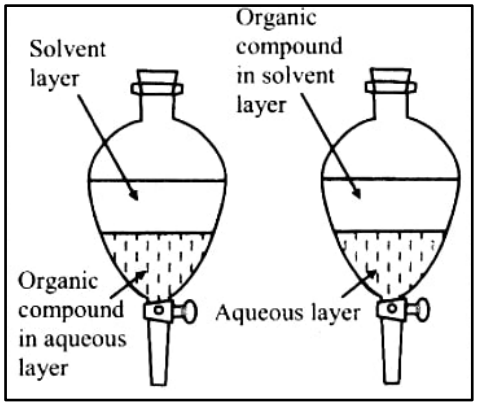


Fig 5: Solvent Extraction

Enzyme-Assisted Extraction:

This extraction method is based on hydrolytic enzymes that break down the polysaccharide polymers of the cell wall. Because the target metabolites also remain in the wall matrix hydrogen or hydrophobic bonds, they are thus released from the intracellular environment and cell wall [44].

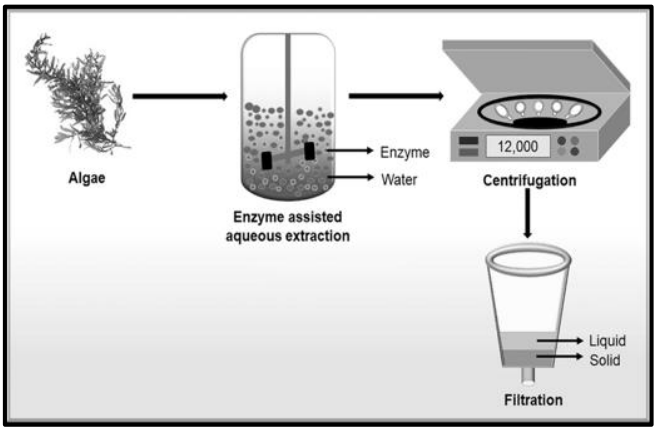


Fig 6: Enzyme-Assisted Extraction

Enzymes commonly used in this process are lipase, amylase, pectinase, amyloglucosidase, lactase and protease [45]. Factors affecting depreciation performance are pH, enzyme concentration, enzyme type, incubation time and temperature [44][46]. Although it is an ecological process, the long extraction time is a major disadvantage of this method [45][30].

Supercritical Fluid Extraction:

In supercritical fluid extraction (SFE), the temperature and pressure of the liquid are increased extractor above its critical points [47]. CO2 is often used as a solvent because it has a low critical temperature and odourless, colorless and non-toxic [48]. Removal process is divided into four stages: the first stage involves the diffusion of the supercritical liquid into the porous matrix of the sample; the second step is to balance the sample and solvent; the third step involves diffusion of the solute from the matrix; and the last step consists in recovery of the analytes by decompression [49].

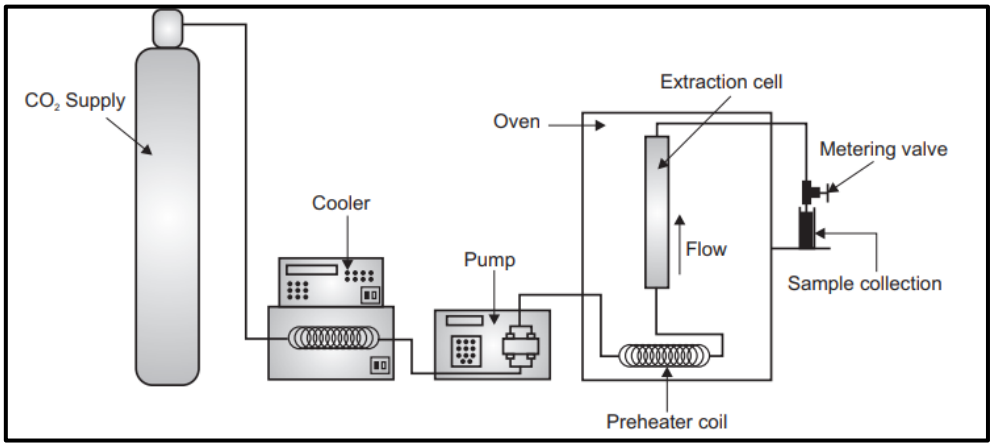


Fig 7: Supercritical Fluid Extraction

Removal process is divided into four stages: the first stage involves the diffusion of the supercritical liquid into the porous matrix of the sample; the second step is to balance the sample and solvent; the third step involves diffusion of the solute from the matrix; and the last step consists in recovery of the analytes by decompression [49]. Because of the low temperature, this method is suitable for thermally stable and easy extraction oxidized compounds [47]. Recently, Widmann et al. [50] obtained curcuminoids from SFE using carbon dioxide as solvent at constant temperature (75 ◦C) and pressure (425 bar). The flow rate was 0.5 kg/h for 1 hour. The maximum yield was 0.68-0.73% [50][30].

Pressurized Liquid Extraction:

Pressurized liquid extraction (PLE) is based on high temperature and pressure conditions that favor the desorption and dissolution of analytes in various solvents [51]. Water is one of the solvents that can be used in this process and can be kept liquid phase at temperatures between 100 and 374 ◦C and pressures high enough to obsd phase transitions [52]. As a result, the dielectric properties change, the propagation speed increases, the viscosity decreases and the surface tension decreases, so it acts the same as an organic solvent [47]. Hye-Lin Kwon and Myong-Soo Chung [53]. Investigated the extraction of demethoxycurcumin, bisdemethoxycurcumin and curcumin under different conditions including temperature (110-150 ◦C), time (1-10 min), pressure (5-100 bar), solid to solvent ratio, and mixing ratios of solvents. Before extraction, turmeric was dried with hot air and then cut to pieces. The sample was

stored at 4°C. After 1 g variable extraction was used the sample was added to a solvent containing 50% water and 50% ethanol. They found that the ideal extraction parameters were 135 ◦C, 5 min and a mixing ratio of 1:20 (w/v) for solid and solvent. In optimal conditions, the concentration of curcuminoids was 15.8%.

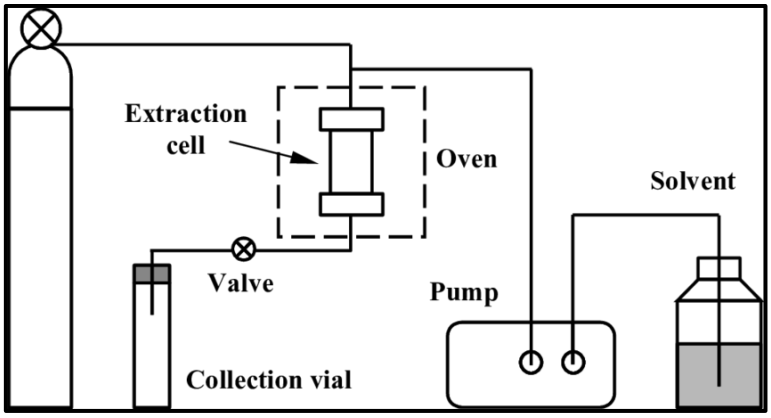


Fig 8: Pressurized Liquid Extraction

Another study compared the extraction time of curcumin using the PLE process using the Soxhlet extraction process. First, the rhizomes were seasoned very critically extraction with CO2. After this step, ethanol was used as a solvent in the PLE process, which was performed with a fixed extraction time of 20 min and independent variables pressure (100–300 bar) and temperature (60–77 ◦C). Optimal in terms of results extraction temperature and pressure were 60 ◦C and 100 bar, respectively. Come on with comparable extraction yields, PLE required three to six times less extraction time than Soxhlet extraction [54][30].

Bioavailability of Curcumin:

Bioavailability is defined as a certain fraction (percentage) of the taken dose of the drug that reaches the systemic circulation [23]. This is necessary in all cases of drug use that the active ingredient of the drug, known as "Pharmaceutically Active Compound" (CFA), able reach the body However, it is not enough for the active substance to enter to achieve a therapeutic effect the body The active ingredient must be available in the correct form of the dose in the area of the body where it must work. This area the body is called the "target area" [23]. The active substance must also reach the target area within a certain time into the frame and stay there for a certain amount of time. In this case, this as an intravenous injection when the drug is administered directly into the circulatory system, is bioavailability considered 100% [55]. Curcumin is characterized by poor solubility and poor absorption in free form in the digestive tract and its rapid biotransformation into inactive metabolites limits its use as a health promoting agent and dietary supplement. In recent years, several nanoformulation based methods have been developed to improve the utilization of curcumin in vitro and in vivo studies involving the use of adjuvants, stabilizers, conjugates/polymer conjugates, lipids/liposomes, hydro-/micro-/nanogels and nanoparticles [56]. Last experimental studies with nano- and micro-preparations of curcumin with very efficient absorption have shown that the level of active forms of curcumin in the blood [57]. Nanoformulations of curcumin may be possible used for many potential applications, including diabetes prevention, pain relief, and protection tissue [57][58]. The composition of curcumin consists of Liquid droplet

nanomicelles containing Gelucire® and Polysorbate 20 (BioCurc®) have the highest. bioavailability compared to absorption > 400 times of unformulated curcumin [59]38]. Hence nanotechnology can helpovercome the effectiveness of curcumin problems such as solubility, toxicity, rapid drug metabolism, degradation, and drug stability [56][11].

Therapeutic Activity of curcumin:

Anti Diabetic Activity:

Most of them referred to the use of curcumin as a glucose-regulating agent in rodent models(mostly in rats). The most commonly used models were alloxan, streptozotocin, streptozotocin, and nicotinamide-induced diabetes.

Curcumin was given to all to diabetic animals orally at different intervals. Blood glucose, hemoglobin (Hb) and glycosylated hemoglobin (HbA1C) concentrations an increase in insulin sensitivity was observed all models studied. Mechanisms of positive effects of curcumin in the case of diabetes, it can be explained, for example, by modulation on the activity of signaling molecules, transcription factors (such as TNF-α) and free fatty acid levels NF-κB, lipid peroxidase and inhibition of lysosomal enzymes [60]. Curcumin also has the ability to increase plasma insulin levels and sensitization lipoprotein lipase. The inhibitory effect on glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity leads to a decrease in blood glucose concentration [61]. Curcumin works as an anti-diabetic agent due to its anti-inflammatory and antioxidant properties, which can not only work. The activity of blood enzymes and factors, but also an increase β-islet glutathione levels and thus lowers it damage caused by oxidative stress [62]. Curcuminoids exerted antidiabetic effects, induced improving the lipid profile by reducing their oxidation in the pancreas, liver and aorta and improving post-diabetic brain complications in diabetics rats by stimulating antioxidant defenses mechanisms and reduction of mitochondrial dysfunction.

But the most effective anticancer, cardioprotective, neuroprotective and antidiabetic drug activity of the three natural curcuminoids (curcumin, DMC, BDMC) is carried out by the first compound. New synthetic curcumin analogs (C66 and B06) reduce TNF-α and NO synthesis and lower IL-1β, TNF-k, IL-6, IL-12 mRNA levels, COX-2 and iNOS [12].

Anticancer Activity:

The multiple functions of curcumin that affect a in a chemopreventive and directly therapeutic way, to show that it could be a potential anti-cancer drug. Although results were obtained in animal models, curcumin was shown to be active in several other in vitro models and doses are comparable to those used in humans. In vitro and in vivo studies have shown that curcumin inhibits carcinogenesis by affecting two key processes angiogenesis and tumor growth [63].

Turmeric and curcuminoids affect tumor angiogenesis through several interdependent processes [64]:

1. Action at level of transcription factors NF-κB, AP-1 (related inflammatory processes) and early growth response protein 1, which reduces IL-8 expression in the pancreas and head and cervical cancer cell lines and inhibits VEGF induction synthesis;
2. Inhibition of NO-mediated angiogenesis and iNOS;
3. Inhibition of COX-2 and 5-LOX;
4. Activity at levels of angiogenic factors: VEGF, the primary migration, sprouting, survival and proliferation factor during angiogenesis, and basic fibroblast growth factor; and

5. At the operational level ECM stability and cohesion, including downregulation of MMP-2 and MMP-9 and upregulation of tissue inhibitor metalloproteinase-1. Turmeric also inhibits release of angiogenic factors stored in the ECM [64][2].

Curcumin promotes cell death in a variety of animal and human cell lines, including leukemia, melanoma, and breast, lung, colon, kidney, ovary, and liver carcinomas [65]. It looks to be to function via caspase-dependent and independent (mitochondrial) pathways linked to the existence and p53 is not present. Certain studies have shown that curcumin demonstrates a biphasic activity on the proteasome, with Lower dosages result in activation, whereas greater amounts result in inhibition. Because proteasome inhibition causes apoptosis, and stimulation promotes cell survival, it is conceivable that curcumin Depending on the dose, this causes apoptosis or survival. Furthermore, turmeric at various dosages may influence the kind in terms of cell death: Low dosages cause oxidative stress [2].

Conclusion:

Food flavorin Curcuma longa rhizomes L. (turmeric) from the ginger family (Zingiberaceae) has been used for years in India and China a a useful remedy for many chronic diseases (most often diabetes). As shown, curcumin (diferuloylmethane), the active ingredient in turmeric, has significant antioxidant, anti-inflammatory and anti-cancer properties. Research (in vitro and in vivo) showed that curcumin can also inhibits the activity of some signaling molecules (such as transcription factors, various enzymes, such as protein kinases) and can be modulated in this way inflammatory process, gene expression and could possibly control the effectiveness of curcumin for the treatment of many organ diseases, mainly diabetes and its complications. However, in almost all the articles cited in this review are very poor the bioavailability of curcumin is emphasized. Due to fast metabolism and very low serum levels after oral administration. The modern use of curcumin is used as a curative agent agent absolutely impossible. Despite these difficulties recent studies have generated great interest in the valuable biology of scientists worldwide turmeric, especially curcumin and confirmed its important role in prevention and for the treatment of many specifically related disorders its antioxidant, anti-inflammatory and anti-cancer effects. In an age of increasing diabetes incidence, it is important to support treatment its complications because it reduces overall costs treat patients and improve their quality of life.

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