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Original Research Article

Recent Advances of Curcumin in the Treatment of Various Allied Disorders

Muzamil Muzaffar[1], Arifa Hassan[2], Mohd Rafi Reshi[3*], Saman Anees[4], Maaz Naqvi[5*]

[1]Department of Physiology, Govt. Medical College Kathua, J & K, India
[2]Department of Physiology, Govt. Medical College Udhampur, J & K, India
[3]Department of Pharmacology, Govt. Medical College Kathua, J & K, India
[4]Department of Amraze Niswan Wa Atfal, SUMER, Jamia Hamdard, New Delhi, India
[5]Department of Pharmacology, Hamdard Institute of Medical Sciences and Research, New Delhi, India

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Corresponding author: Dr. Mohd Rafi Reshi
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Abstract:

The Indian plant Curcuma longa L., popularly known as turmeric, produces curcumin, also known as curcuminoid. The main curcuminoids included in turmeric (Curcuma longa L.) rhizome include dihydrocurcumin, tetrahydrocurcumin, curcumin, bis-demethoxycurcumin, and demethoxycurcumin. Curcumin also contains anti-inflammatory, antioxidant, pro-apoptotic, anti-proliferative, antiparasitic, chemopreventive, chemotherapeutic, antinociceptive, preeclampsia, and antimalarial effects. The two major categories of pharmacologically potent secondary metabolites present in turmeric rhizome are curcuminoids and essential oil. Curcuminoids are isolated from turmeric rhizomes by using both conventional and modern extraction methods. Soxhlet extraction and maceration are two conventional extraction methods. Due to inadequate small intestine absorption, rapid liver metabolism, and rapid systemic clearance, curcumin has a low bioavailability in humans. The vast majority of curcumin consumed orally is removed through the faeces, with only a small, absorbed fraction of curcumin changing the metabolism.

Keywords: Curcumin, Isolation, Pharmacology.

Introduction

Curcumin, also known as curcuminoid, was initially found in the aromatic rhizome of the Indian plant Curcuma longa L, a member of the ginger family (Zingiberaceae), in 1870. It is a common food ingredient and natural food colouring in Asia. It is a spice that transforms the structure, flavour, and appearance of food. Curry is the spice that effectively utilises turmeric rhizome powder.

Curcumin, commonly known as Natural Yellow, is referred to as an ecological dye when used as a food colouring. Dihydrocurcumin, tetra hydrocurcumin, curcumin, bis- demethoxy curcumin, and demethoxycurcumin are the primary curcuminoids found in turmeric (Curcuma longa L.) rhizome. Some of the health benefits of curcumin include immune system management, cardiovascular and vascular protection, and neuroprotection [1]. Curcumin is used to treat bruises, amenorrhea, hysteria, rheumatic pain, and chest flank pain, according to the Pharmacopoeia of China. It should be emphasised that curcumin, one of turmeric's main active ingredients, has pharmacological properties.

A naturally occurring substance with significant in vitro therapeutic promise is curcumin, a yellow-orange pigment first discovered from turmeric two centuries ago. It has been utilized for ages in both traditional Chinese medicine and Ayurvedic medicine.

Due to its capacity to affect a variety of signaling molecules, the polyphenol curcumin has been revealed to have pleiotropic properties. In addition to being utilized as a wound-healing agent, curcumin also has anti-inflammatory, antioxidant, pro-apoptotic, chemopreventive, chemotherapeutic, antinociceptive, anti-proliferative, antiparasitic, and antimalarial properties. In recent years, the study of curcumin and its pharmacological effects has gained importance [2].

Isolation of Curcumin from Turmeric Rhizome and Methods of Identification

Curcuminoids and essential oil are the two main groups of pharmacologically active secondary metabolites found in turmeric rhizome. The majority of turmeric's biological action is attributed

to its curcuminoids, which include curcumin, demethoxycurcumin, and bis-demethoxycurcumin. Use of both traditional and contemporary extraction techniques results in the isolation of curcuminoids from turmeric rhizomes. Two traditional extraction techniques include soxhlet extraction and maceration. Ultrasound extraction, enzyme-assisted extraction, microwave extraction, supercritical fluid extraction, and pressured fluid extraction are some of the contemporary techniques for extracting curcuminoids [2].

Alcohol, dichloromethane, ethyl acetate, isopropanol, methanol, n-butanol, and acetone are the solvents that are most frequently employed to extract curcuminoid compounds. Due to its high solubilization ability, acetone was utilized by Sahne et al. in both traditional and non-conventional extraction procedures. Several organic solvents for curcumin extraction were explored in the paper by Muthukumar et al. The results of the study demonstrate that acetone is the best extraction solvent. A traditional analytical method for isolating curcumin from the extraction mixture is thin-layer chromatography (TLC). The extract's curcumin content is measured using high-performance liquid chromatography (HPLC). Following extraction, the organic solvents are taken out of the extract by vacuum evaporating it. After being dissolved in methanol, the residue (oleoresin) is analyzed using HPLC.

The process of extraction is what determines the yield and stability of curcumin (Sahne et al) examined the extraction of curcumin from the turmeric rhizome using a number of cutting-edge techniques, and the outcomes were compared with those of Soxhlet extraction, the most widely used reference technique. The results demonstrated that the yield of curcumin extracted using the Soxhlet method (6.9%) was much greater than the yields of curcumin extracted using ultrasound (3.92%), microwaves (3.72%), and enzymes (4.1%). Modern extraction techniques don't have the same high extraction yields as the Soxhlet method, but they have other advantages, such as low temperature, quick extraction times, and the use of relatively little solvent.

The work by Naksuriya et al looked at the kinetic degradation of curcumin from a natural mixture of curcuminoids in various settings (pH, temperature, and solvent dielectric constant), as well as the deterioration of pure curcumin under specified parameters. The kinetics of curcumin degradation was investigated using a standard medium composed of a 50:50 (v/v) mixture of aqueous buffer and methanol. The outcomes demonstrated that a first order reaction took place in the pure curcumin contained in the curcuminoid mixture as it degraded. The rate of curcumin degradation rises as pH, temperature, and the medium's dielectric constant rise. In an aqueous buffer with a pH of 8.0, curcumin degraded quickly at a constant rate of 0.28 hours per hour, resulting in a half-life (t1/2) of 2.5 hours. In a solution of phosphate buffer and methanol, curcumin that was combined with curcuminoids to form methoxypoly (ethylene glycol)-b-(N-(2-benzoyloxypropyl) methacrylamide) polymer micelles was around 300–500 times more stable than pure curcumin.

A promising method for stabilizing curcumin and creating formulations suited for additional pharmacological and clinical trials is the incorporation of curcumin into polymer micelles. Natural deep eutectic solvents made from organic acids and sugars were investigated by Liu et al for their effectiveness in extracting curcuminoids. When using a solvent with a ratio of citric acid and glucose 1:1 and 15% water, higher extraction yields were obtained when compared to the conventional extraction solvents under ideal conditions (the temperature was 50 C, the solid and liquid components were 0.1/10 g/mL, and the extraction time was 30 min). Since the suggested process is sustainable and good for the environment, it is a great substitute for obtaining natural pigments.

The volatile oil of turmeric dissolves curcumin during the separation and purification of curcuminoids from oleoresin, which interferes with the process of recrystallization. Curcuminoids were tested for selective recrystallization using a variety of organic solvents and their mixtures. The most effective solvent for recrystallization in the purification of curcuminoids was a mixture of isopropyl alcohol and hexane (1:1.5, v/v). The purity of the curcumin was improved to 99.45% w/w in the recrystallized powder, compared to the raw curcuminoid powder's total curcumin concentration of 76.82% w/w [3].

Physico-Chemical Properties of Curcumin

Curcumin, also known as diferuloylmethane or 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a key component of turmeric (up to 5%), a well-known traditional spice. It is a lipophilic molecule that is soluble in ethanol, dimethylsulfoxide, and acetone but insoluble in water, acidic solutions, and neutral solutions. Using organic solvents, curcumin can be extracted from turmeric rhizomes. Curcumin has the chemical formula C21H20O6 and a molecular weight of 368.38 g/mol. Curcumin has a melting point of 183 ^{o}C. Due to the presence of -diketone in its molecular structure, curcumin is a tautomeric molecule and exhibits diketo/keto-enol tautomerism.

Both cis and trans versions of the diketo tautomer are possible. The equilibrium of keto-enols in curcumin is greatly influenced by solvent polarity, pH, and temperature. Contrarily, the ratio of

curcumin's keto and enol tautomers has a significant impact on its pharmacological activities. Using the aid of modern quantum chemical computations and ultraviolet-visible (UV-VIS) spectroscopy, Manolova et al. investigated the tautomerism of curcumin in binary mixes of ethanol and water. The outcomes demonstrate that ethanol solely contains the enol-keto tautomer.

The diketo tautomeric form is given a new spectral range that appears after the addition of water. In the 90:10 (v/v) mixtures of water and ethanol, the diketo form predominates. Quantum chemical simulations demonstrate that water molecules stabilize the diketo tautomer by generating stable complexes, which accounts for the observed equilibrium shift. Kawano et al. used liquid chromatography/mass spectrometry to analyze the keto-enol tautomers of curcumin. The results of the study indicate that the major form in solution (water/acetonitrile) is the enol form. Curcumin occurs as an enol in both the solid state and solution in nonpolar solvents (carbon tetrachloride). Curcumin in solution form is unstable. In the basic solution, the color changes from an intense yellow to a dark crimson [4].

The Metabolism of Curcumin

At a dose of 12 g/day, curcumin has a poor bioavailability in humans due to poor small intestine absorption, quick liver metabolism, and quick systemic elimination. While a tiny, absorbed portion of curcumin is altered metabolically, the majority of curcumin taken orally is eliminated through the feces. There are two stages to curcumin's metabolism.

In enterocytes and hepatocytes, the reduction occurs in the first phase in the presence of reductases. Dihydrocurcumin, Tetrahydrocurcumin, Hexahydrocurcumin, and Octahydrocurcumin (Hexahydrocurcuminol) are the reduction product. Alcohol dehydrogenase, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductase, and an undiscovered microsomal enzyme are among the enzymes that catalyze the curcumin reduction reaction.

The enzyme for curcumin reduction was isolated from Escherichia coli and described in the study by Hassaninasab et al. It was discovered that a purified enzyme reduced curcumin in two processes, first converting it into the intermediate compound dihydrocurcumin and then into the final compound tetrahydrocurcumin, both of which were dependent on NADPH [5]. In vivo and in vitro, glucuronic acid and sulfate are easily attached to curcumin and its reduced metabolites. In the presence of glucuronyl transferase and sulfotransferase, respectively, glucuronidation and sulfation processes occur. In the liver and intestines of rats and people, curcumin undergoes glucuronidation and sulfation. A percentage of curcumin administered orally to humans is absorbed and detected in the plasma as a water-soluble glucuronide and sulfate conjugate. In humans and the intestines of rats, curcumin is sulfated by human phenol sulfotransferase 1A1 (SULT1A1) and human phenol sulfotransferase 1A3 (SULT1A3), while curcumin is glucuronidated by uridine diphosphate-glucuronosyltransferase (UGT).

When curcumin is reduced or conjugated, new species are created that have a lesser capacity than curcumin to suppress the production of cyclooxygenase-2 (COX-2). Hexahydrocurcuminol is inert, whereas tetrahydrocurcumin, hexahydrocurcumin, and curcumin sulfate exhibit lower suppression of prostaglandin E2.

Other than tetrahydrocurcumin, the biological activity of curcumin metabolites is dramatically diminished. Piperine, which prevents glucuronidation, curcumin in liposomes, curcumin nanoparticles, curcumin phospholipid complexes, and structural curcumin analogues are all utilized to increase curcumin's bioavailability.

Pharmacology property

Turmeric has the following qualities, according to the "Tang Materia Medica" and "Compendium of Materia Medica" records: it is spicy, bitter, warm, and related with the treatment of spleen and liver functions.

In China, the primary therapeutic goal of curcumin is to increase blood circulation and prevent blood hemostasis. Broadly speaking, the treatment of cardiovascular disorders and immunomodulation are two common uses of turmeric/curcuminoid in Chinese medicinal therapy. It has also been demonstrated to lessen menstruation pain.

According to the Pharmacopoeia of the People's Republic of China, curcumin/turmeric is used to treat bruising, amenorrhea, hysteria, rheumatic pain, and chest flank pain. It should be noted that curcumin, a key active component of turmeric, has pharmacological effects.

Recent studies have shown that curcumin has pharmacological actions against hyperlipidemia, diabetes, tumors, inflammation, fibrosis, viruses, and oxidation as well as acting as a free radical scavenger. Curcumin's medical properties aren't fully covered here (Figure 1) [6]

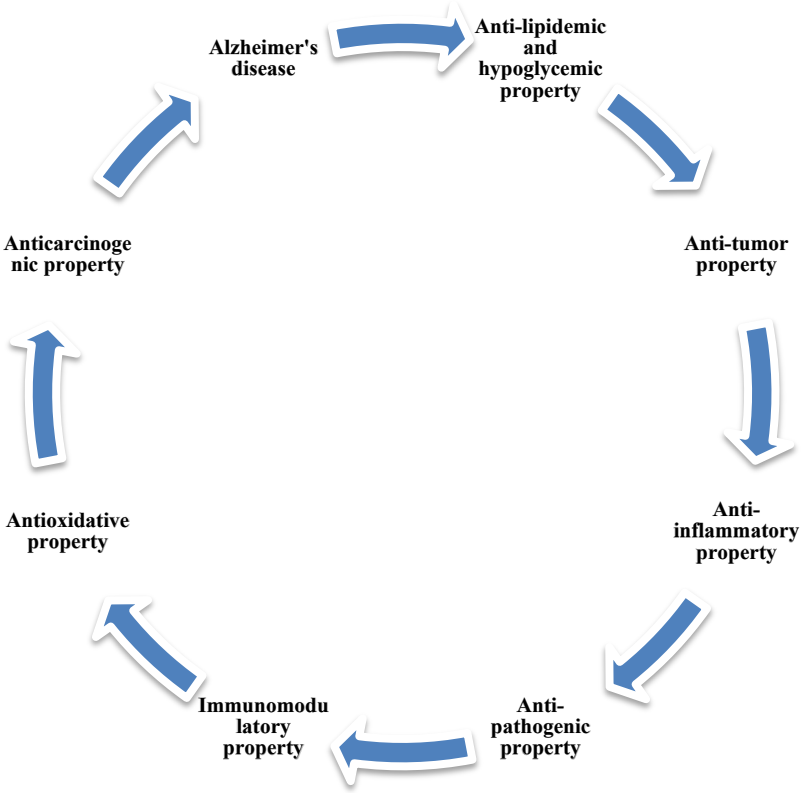

Figure 1: Pharmacological activity

Anti-lipidemic and hypoglycemic property

When compared to the untreated control group, many preclinical and clinical studies showed that feeding turmeric extract or curcumin to hyperlipidemia model animals induced by high-glucose diet resulted in significant reductions in total cholesterol, free fatty acids, and triglycerides in plasma; particularly in triglycerides, which returned to close to normal levels. Curcumin also lessens the symptoms of non-alcoholic fatty liver disease and excessive drinking [7,8].

Type 2 diabetes (T2DM), a diverse and chronic metabolic disease that is characterized by a rise in blood glucose levels brought on by insulin resistance in target tissues and/or by dysfunctional pancreatic beta-cells, accounts for about 90% of all cases of diabetes. Curcumin dramatically lowers glycated hemoglobin (HbA1c) and fasting blood sugar levels, according to preclinical investigations on animal models and clinical experiment findings for T2DM (fasting plasma glucose).

Curcumin efficiently reduces levels of aminotransferase (AST), low-density lipoprotein cholesterol (LDL-C), and triglycerides while improving fasting blood sugar and insulin resistance (HOMA-IR), as well as body weight. The activities of glucose transporters on the cell membranes of enterocytes in the intestine and of carbohydrate-digesting enzymes in the gastro-intestinal tract can also be inhibited by curcumin treatments, indicating that curcumin inhibits carbohydrate digestion and absorption and reduces the range of blood glucose fluctuations after food intake [9-11].

Now, our focus has shifted to using computational biology to virtually screen curcuminoids for many anti-diabetic targets. Table 1 displays the binding affinities of curcuminoids with numerous molecular targets or proteins associated with diabetes. In 2D and 3D conformational structures, the interactions of amino acid residues at the binding sites of diverse target proteins are also shown. It is necessary to conduct additional bioassays to confirm whether there is a higher interaction between the curcumin derivative on the target protein and a high efficacy of anti-diabetic for a particular enzyme or molecule to meet the demand of lowering blood glucose. Curcuminoids have varying affinities with different amino acid residues in various target proteins via a variety of bonds, such as hydrogen bonds. Curcumin administration, it turns out, has a positive effect on metabolic syndrome. Although curcumin can be taken alone or in combination with other anti-diabetic and anti-lipidemic medications, further clinical research is still required to confirm these claims.

Anti-inflammatory property

Interleukin-4 (IL-4), IL-6, IL-8, and tumor necrosis factor alpha (TNF-) are pro-inflammatory

cytokines that are produced and secreted by tissues, and curcumin suppresses and controls these processes. On the other hand, curcumin can boost the production of anti-inflammatory cytokines including IL-10 and soluble intercellular adhesion molecule1 (sCAM-1). Curcumin has been shown in preclinical investigations to lessen animal skin inflammation as well as to prevent or lessen inflammation of the respiratory system brought on by viral or bacterial infections. Curcumin therapy has been shown in clinical trials to reduce osteoarthritis-related pain symptoms, reduce tissue inflammation, and postpone the loss of articular cartilage, all of which benefit the patient's mobility and quality of life. In addition, curcumin reverses the effects of histamine, nicotine, acetylcholine, serotonin, barium chloride, and nicotine on the inhibition of intestinal peristalsis.

Anti-pathogenic property

Several studies have shown that turmeric and curcumin extracts prevent the development of germs. Both gram-positive and gram-negative bacteria, including those that frequently cause infectious disorders in humans, such as Staphylococcus aureus, Streptococcus pneumoniae, Salmonella, Escherichia coli, and Helicobacter pylori, are susceptible to the antibacterial actions of curcumin. Curcumin can act on PI3K/AKT, NFB, TNF-, and TGF-1 pathways to attenuate the toxicity of LPS on sepsis in preclinical and clinical studies for sepsis treatment, i.e. systemic bacterial infections. Curcumin also exerts the protective role in the lungs, liver, and kidneys while reducing the aftereffects of tissue fibrosis after sepsis Moreover, the volatile oils in turmeric extract have antifungal effects on candidiasis, which is the cause of urogenital and intestinal infections in people [12].

Immunomodulatory property

Curcumin therapy can boost endogenous immune activity to attack foreign pathogens or cancer cells, minimize excessive inflammation and allergy activation, and promote immune component cell activation in the management of immunological modulation. Surprisingly, curcumin can inhibit inflammatory pathways such as NF-B, MAPKs, JAKs/STATs, -catenin, and the Notch-1 pathway by controlling the expression and secretion of pro-inflammatory cytokines like IL-1, TNF-, IL-2, IL-6, and IL-10. Curcumin can be used to treat autoimmune illnesses including lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, psoriasis, etc. in clinical management. Treatment with curcumin can boost cellular immune-reactive T lymphocytes and help the body fight foreign infections and endogenous cancer cells. Curcumin can prevent cancer cell proliferation or induce cancer cell apoptosis, according to in vitro and in vivo research [13].

Antioxidative property

Curcumin has a strong antioxidant potential that is 2.75 times greater than that of vitamin C and 1.6 times greater than that of vitamin E because to its chemical makeup. In addition to acting as a natural free radical scavenger, curcumin encourages the body's production of the antioxidant glutathione (GSH), which shields cells and tissues from free radical damage. Curcumin can boost the activity of superoxidase dismutase (SOD), as well as raise GSH levels in cells and serum, according to in vitro cell and animal studies. When body organs or tissues experience ischemia as a result of a temporary disruption in blood flow, as in stroke, myocardial infarction, surgery, organ transplantation, etc., as in preclinical investigations and clinical trials. These ischemic re-perfused tissues frequently release too many free radicals after blood flow have been restored, leading to oxidative stress and damage. By scavenging free radicals, curcumin administration can lessen the harm done to tissue cells by free radicals, which also lessens the harm done by excessive tissue inflammation.

Anti-tumor & Anticarcinogenic property

Using curcumin lowers the number of cell mutations brought on by carcinogen exposure and triggers the body's anti-tumor reactions. In order to obliterate tumors, curcumin can enhance recruited natural killer cells and activate tumor microglia in a manner similar to M1. By the inhibition of NF-B, COX-2, CD-31, VEGF, and IL-8 as well as matrix metalloproteinase (MMP)-9, curcumin can prevent the proliferation of cancer cells. In vitro and in vivo studies have shown that curcumin, an extract from turmeric, can stop the growth of cancer cells in the digestive, urinary, and reproductive systems, as well as in the head and neck, lung, and head and neck systems. The chronic latent condition known as oral submucosal fibrosis, which is strongly linked to oral cancer, causes the oral mucosa and deep tissues to harden. It can also spread to the throat or esophagus, impairing one's ability to swallow and pronounce words. Curcumin is clearly a medication that can prevent, decrease, and improve oral mucosal fibrosis in clinical management. Increases in vitamin C and E levels in serum and saliva can improve an organism's antioxidative properties, while decreases in malonaldehyde and 8-hydroxydeoxyguanosine (8-OHdG) can lessen oxidative stress. Curcumin is utilized in clinical tumor therapies as an adjuvant or supplement to chemotherapy or nuclear therapy to lessen postoperative adverse responses, although this use still has to be clinically validated [14-16].

In-depth studies on curcumin's (and/or its analogues') anticarcinogenic efficacy was conducted in a number of labs. Initiation,

promotion, and progression are the three distinct but linked stages that make up the process of carcinogenesis. Damage to tissue caused by oxidative and inflammatory processes is crucial in the development of cancer. Curcumin, a strong anti-inflammatory and antioxidant, may prevent cancer by inhibiting the growth of tumors. Moreover, it stops cancer cells in the S, G2/M cell cycle phase and promotes apoptosis in a variety of different cell types, including human bladder cancer cells. It participates in a variety of signaling pathways, some of which have recently been reviewed. These pathways include reducing COX-2 expression and inhibiting signaling through NF-B, which controls the expression of many genes, including COX-2, the enzyme that causes inflammation and malignant transformation. On the basis of these pathways, curcumin is being tested for its ability to prevent colon cancer.

Many cell-regulating proteins, including the mitogen-activated protein (MAP) cascade, interact with curcumin as well. Because it directly inhibits v-Src, less Shc, cortactin, and focal adhesion kinase are phosphorylated (FAK). Moreover, curcumin directly reduces FAK activity. Because to the loss of Src-mediated cell motility, invasion and metastasis may be significantly impacted. In addition to its other qualities, curcumin has been shown to have potent inhibitory effects on various cytochrome P-450s, phenol sulphotransferase, and glutathione S-transferases. A number of disorders, such as cancer and atherosclerosis, depend on angiogenesis, which is the development of new blood vessels from an already-existing vascular network. Angiopoietins (Ang 1 and Ang 2), vascular endothelial growth factor (VEGF), and fibroblast growth factor (bFGF)-induced angiogenesis are all inhibited by curcumin, which has an antiangiogenic effect (reviewed by Dulak). Cancer and illnesses that cause bone inflammation both accelerate bone resorption. It is well known that curcumin inhibits bone resorption and stimulates cell death. As a result, its usage has been encouraged in cases of cancer and bone inflammation [17].

The majority of the in vitro data demonstrating curcumin's anti-tumor efficacy were collected. Major cancer targets such as the prostate, colon, and lung are being clinically studied for curcumin's potential as a chemoprotective drug (reviewed by Manson et al.). The results from the in vivo and in vitro experiments should be supported by additional epidemiological and clinical trials involving large populations.

Alzheimer's disease

Curcumin has been studied against Alzheimer's due to its anti-inflammatory and antioxidant properties. Metal chelation, which may lessen amyloid aggregation or oxidative neurotoxicity, is a different mechanism for these effects. Metals are accumulated in the brains of people with Alzheimer's disease and can cause Abeta aggregation and toxicity. Desferrioxamine and clioquinol, two chelators, have shown anti-disease Alzheimer's properties. See the review by Calabrese et al. [18] for a more thorough discussion of the application of phytochemicals (including curcumin) in Alzheimer's disease.

Pre-eclampsia disorder

One of the recent study conducted that curcumin have beneficial effect in LPS induced preeclampsia. Curcumin has some beneficial effect to reduce some biochemical markers and histological examination of liver & kidney. It contains some constituents that can be used for different markers of preeclampsia [1]. In a different study, it was shown that curcumin reduced the PE-like phenotype in a rat model that was brought on by the administration of LPS to GD 5. The outcomes showed that curcumin reduced proteinuria and hypertension. Additionally, the LPS induced insufficient trophoblast invasion and SA remodelling were enhanced by the curcumin. Following curcumin treatment, the LPS-induced kidney functional and morphologic damages were reduced. Additionally, it was discovered that giving curcumin repaired the weight loss that LPS-induced in foetal animals [19]. So more research required to be conducted in future for this plant.

Conclusion

Natural substance curcumin has received much research and has demonstrated tremendous in vitro and in vivo medicinal potential. In addition to being utilised as a wound-healing agent, curcumin also exhibits anti-inflammatory, antioxidant, antiviral, chemopreventive, chemotherapeutic, antinociceptive, antiproliferative, antiparasitic, and antimalarial properties. Curcumin has a low bioavailability in humans due to inadequate small intestine absorption, quick metabolism, and rapid systemic clearance. It can be used to treat new problems in the future or stop preeclampsia from occurring.

Author's contribution

Muzamil Muzaffar contributed full manuscript, literature, study plan and design. Arifa Hassan also takes part in this manuscript making. Final correction of manuscript was done by Mohd Rafi Reshi, Saman Anees and Maaz Naqvi. Most of the work we have done equally. The final review article was approved by authors.

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