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Therapeutic Importance of Curcumin with a Special Emphasis on Mdr Cancer Cells and the Factors Influencing Pharmacodynamics

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ABSTRACT

Curcuma longa or turmeric is a plant that is used as a spice and as a natural remedy in many formulations from the Vedic age. Curcumin is the most important phytoconstituent present in turmeric with various pharmacological activities against neurological disorders, cardiovascular diseases, autoimmune disorders, metabolic disorders, cancer, inflammatory diseases and skin diseases. The present study reveals various pharmacological activities of curcumin with special emphasis on multidrug-resistant (MDR) cancer cells and their possible mechanism of action. The limiting factor of therapy using curcumin is its poor water solubility and less bioavailability. This review focuses on various formulations of curcumin with different additives and combination therapy of curcumin with conventional chemotherapy drugs. This will help to enhance its bioavailability and thereby be effective against various diseases including MDR cancer. This review is lighting to a treasure buried inside the soil with potential therapeutic activity and fewer side effects.

Keywords: curcumin, pharmacological activities, anticancer activity, multidrug-resistant cancer cells, formulations of curcumin, bioavailability enhancement.

INTRODUCTION

Turmeric was used as a functional food and as a home remedy for different diseases from the ancient period in India and was prepared from the plant *Curcuma longa* (Orellana-Paucar *et al.*, 2013). The medicinal values of turmeric have been known from the Vedic ages and are reported in ancient texts. The recent studies showed its real mechanism of action and its wide pharmacological activities. It has been widely used in Asian countries as a medicinal plant and as a spice due to its antimicrobial, antioxidant, anti-cancer, and anti-migraine actions. The anti-cancer activity of curcumin is due to its various mechanism of action on different target molecules (Schaffer *et al.*, 2011). Curcumin was one of the potential phytoconstituent that have been studied mostly against cancer because of its versatile therapeutic activity including anti-oxidant, anti-proliferative, apoptosis induction and anti-inflammatory activities. Even though cancer therapy developed drastically over the decade, there are numerous side effects of existing therapies and that is sighting to the hope for phytoconstituents for fighting cancer.

According to studies, there was a relationship between various food habits and carcinogenesis. It was proven by the studies in different ethnic groups. In the Asian population, some cancer such as prostate, breast, and gastrointestinal tract cancers had less prevalence because of their food habits or dietary intake of polyphenols from green tea (Khan and Mukhtar, 2008), quercetin from onions (Pan, Zheng and Ho, 2018), resveratrol from grapes (Rauf *et al.*, 2018), curcumin from turmeric (Unlu *et al.*, 2016), genistein-soy flavonoid (Farina *et al.*, 2006), etc. Phytochemicals show anti-cancer activity due to their multi-target mechanism of actions such as anti-proliferative and anti-mutagenic activities. So, they are considered a promising anticancer agent (Enrico, 2019).

Curcumin is a polyphenol compound evolved from the turmeric plant and the extensive research on this compound for the past 50 years indicates that curcumin can prevent (Cheng *et al.*,

2000) and treat cancer (Zoi *et al.*, 2021)The studies also provide shreds of evidence for suppression of initiation, promotion, and metastasis of tumors. Curcumin shows very little or no toxicity pharmacologically. Human clinical trials point that no dose-limiting toxicity when using doses up to 10 g /day. All this research indicates that curcumin has tremendous potential in cancer therapy. But functional food scientists feel difficulty because of the solubility and bioavailability issues of curcumin. The low solubility, higher degradability and low bioavailability of curcumin are the main problems associated with curcumin as a functional food (Tsuda, 2018)**.**

More than 100 compounds separated from turmeric to date and the main constituents of turmeric are curcuminoids like curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%), as well as volatile oils such as atlantone, turmerone, and zingiberene, other compounds like proteins, sugars, and resins. In these phytoconstituents, curcuminoids and turmerone have a vast variety of pharmacological actions (Hewlings and Kalman, 2017). Curcumin has profound medicinal values among the several natural remedies and that interested researchers to do further research on curcumin (Prasad and Tyagi, 2015). Curcumin exhibited a wide variety of actions like bactericidal, anti-inflammatory, antimicrobial, and anti-cancer activities (Grynkiewicz and Ślifirski, 2012; Faden *et al.*, 2016). Scientific research proved the greater efficacy of curcumin, to act against numerous diseases without side effects (Karlstetter *et al.*, 2011).

Curcumin showed potential activity as an anti-cancer agent by its activity of suppressing the tumour cell proliferation, downregulation of transcription factors like COX-2, NF-kB, Egr-1, AP-1, LOX, MMP-9, NOS, UPA, TNF, cyclin DI, chemokines, and cell surface adhesion molecules, down-regulate growth factor receptors (HER2 & EGFR); and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases, and protein serine/threonine kinases. All these factors point out the ability of curcumin against cancer cells. The activity of curcumin is suppressed by its bioavailability issues. Some of the formulations of curcumin available in the market show higher bioavailability and absorption. All this points to the scope for an effective therapeutic alternative for cancer with fewer side effects and higher potential (Aggarwal, Kumar and Bharti, 2003).

Chemo-resistance mainly occurs in clinical treatment, resulting in poor prognosis and recurrence of the disease. Alternative treatments like Chinese medicine light the new therapeutic modes to overcome chemo-resistance. It has been already demonstrated that MDR can be modulated by several plant secondary metabolites. Many cancer cells are resistant to chemotherapy and they are defective in apoptosis induction. The natural products which are based on non-apoptotic programmed cell death can be used as therapeutic agents for multi-drug resistant cancer and are considered a promising anti-cancer agent (Faden *et al.*, 2016).

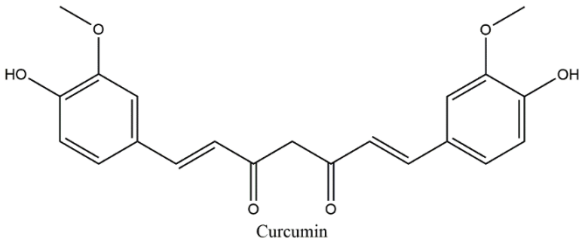

Figure 1: Structure of curcumin.

PHARMACOLOGICAL ACTIVITIES IN GENERAL

Neurodegenerative disorders

Malfunctioning of normal mechanisms of the central and peripheral nervous system leads to neurological disorders (Lavoie *et al.*, 2009). Examples of this include epilepsy, Parkinson's disease, Alzheimer's disease (AD), migraines, and traumatic disorders (Santos *et al.*, 2015). Lifestyle, serious cranial-cerebral injuries, cardiovascular diseases, and type-2 diabetes, etc can lead to the development of AD. The amyloidal cascade hypothesis is a prominent theory for AD development. But at the same time, over phosphorylation of tau protein is also important in the aetiology of this disease (Zhang *et al.*, 2012). The neuroprotective properties of turmeric have been proved by research (Tęcza and Żylińska, 2016).

Recent studies conducted *in vivo* indicate that in transgenic AD mouse models, curcumin by unknown mechanisms can minimize Aβ-related pathology (Kim *et al.*, 2005). Aβ binding can be enhanced by curcumin and avoiding the deposition of plaques and preventing cellular insults (Garcia-Alloza *et al.*, 2007). Decreasing the serum level of Aβ and attenuating microglial activation and the reduced inflammation in AD can rescue the distorted neuritis morphology near Aβ plaques by the curcumin (Tang *et al.*, 2018). Reduction of Tau protein processing and phosphorylation also have

been done by curcumin. In some studies, it is shown that α-synuclein aggregation can be modulated by curcumin (Sharma and Nehru, 2018). Parkinson disease is marked by the abnormal aggregation and accumulation of the α-synuclein. Because of this pharmacology of curcumin, it can be considered as a prominent drug in molecular target therapies of Parkinson's and other synucleopathies (Tripanichkul and Jaroensuppaperch, 2012).

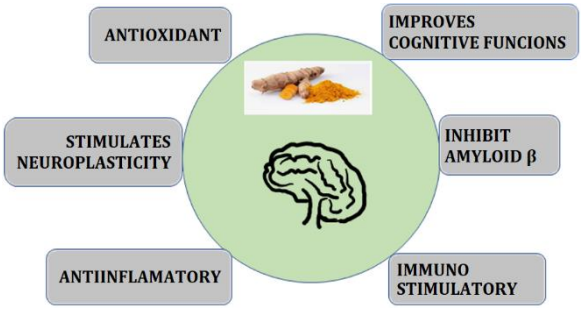

Figure 2. Activity of curcumin on neuro-degenerative diseases.

Curcumin can also improve locomotion, microglial activation (Hickey *et al.*, 2012), reduce Huntington's protein aggregation (Chongtham and Agrawal, 2016) and ameliorate disorder signs by the suppression of cell death (Sanmukhani *et al.*, 2014). In a study, depressive disorders were treated with curcumin and that treatment has been effective in improving mood swings (Lopresti *et al.*, 2014) and also altered the biomarkers present in the patients (Lee *et al.*, 2014). Curcumin showed activity on depression and it was proven that turmeric is the potential and safe compound for this disease (Lopresti *et al.*, 2015).

Cardiovascular diseases:

Cardiovascular diseases are the disease of the heart and the circulatory system supporting it, such as acute myocardial infarction, acute coronary syndrome, and dyslipidaemia. Curcumin can inhibit oxidative stress, inflammation, and apoptosis thereby exerting protective effects on the cardiovascular system. Curcumin influenced lipoprotein metabolism by reduction of triglycerides, LDL, and augmentation of HDL (Ganjali *et al.*, 2017). In a study in patients who are undergoing curcumin therapy, curcumin decreased cardiovascular risk factors such as coronary heart disease, triglyceride, LDL and VLDL with a considerable increase of HDL levels (Mirzabeigi *et al.*, 2015). The efficacy of phospholipidated curcumin showed that it can improve different pathophysiological features of Non-Alcoholic Fatty Liver Disease (NAFLD). This study shows that phospholipidated curcumin capsules with 100mg of curcumin for 8 days can reduce NAFLD severity (Panahi *et al.*, 2019). In another study, P300-HAT inhibitory effects and calcium(Ca) homeostasis of curcumin are studied and it was proven. Curcumin's anti-inflammatory activity have some effects on atrial arrhythmias and on correcting homeostasis and thereby prevention of some ventricular arrhythmias (Keihanian *et al.*, 2018).

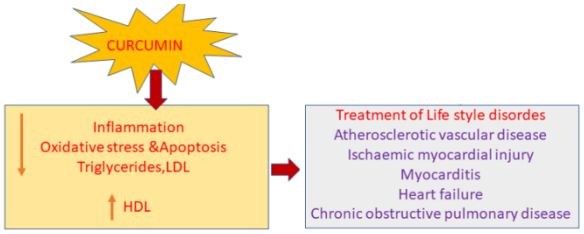

Figure 3 .Cardioprotective mechanisms of curcumin.

Autoimmune diseases

A disease in which the body was mistakenly attacked by its immune system was known as an auto-immune disease. Inflammatory bowel disease, arthritis, psoriasis, multiple sclerosis (MS), type-I diabetes mellitus, etc are common examples of autoimmune diseases (Funk *et al.*, 2006). Many kinds of research showed that the effectiveness of curcumin against autoimmune diseases (Xie *et al.*, 2009). The efficacy of well-characterized turmeric extracts for the treatment of arthritis at *in-vivo* conditions and clinical trials was shown that the inflammation was prevented (Panahi *et al.*, 2014).

The main characteristic of inflammatory bowel disease is gastrointestinal tract inflammation. Turmeric has potent activity against inflammation and in one study a pure preparation of curcumin was administered in an open-label study to five Crohn's disease patients and five with ulcerative colitis (UC) (Singla *et al.*, 2014). All UC and CD patients showed better results by using curcumin (Rudrappa and Bais, 2008).

Metabolic disorders like obesity and diabetes.

Curcumin was played an important action in the control of metabolic disorders like diabetes and obesity. In a study, curcumin extract was used for prevention of diabetes and the group treated with curcumin showed no development of diabetes. This study also showed the changes in the β-cell functions and also demonstrated that curcumin

intervention will be beneficial in a prediabetic population (Su, Wang and Chi, 2017).

Another research proved the pharmacological action of curcumin on glucose and lipid metabolism in Type-II diabetic rat models. By enhancing the sensitivity of insulin, curcumin can improve lipid and glucose metabolism. The FFA and TNF-α also decreased and this was also correlated with the curcumin mechanism to improve resistance to insulin (Chiu *et al.*, 2009). Curcumin also prevents kidney abnormalities due to diabetes (Alappat and Awad, 2010) and has an important role in regulating lipid metabolism (Holt, Katz and Kirshoff, 2005).

Anti-bacterial, anti-fungal and anti-viral activities.

Curcumin treatment reduced the pathogenicity of *P.aeroginosa, C. elegance, A.thaliana* infection models (Liu and Huang, 2012). Some studies showed that curcumin-loaded microemulsions can be used as an alternative treatment of *S.epidermidis* associated diseases and for acne vulgaris (Waghmare *et al.*, 2017). The aqueous extract of the drug showed anti-bacterial activity against *S.aureus, S.epidermidis,* etc (Rai *et al.*, 2008). Due to the potential of NF-κB inhibition of curcumin, it was showed effectiveness against *H.pylori* infections (Koosirirat *et al.*, 2010). The enhancement effect of curcumin against bacterial infection with *staphylococcus aureus* with several antibiotics was also studied and the results showed that curcumin increased the potency of antibiotics such as cefixime, vancomycin, cefotaxime, and tetracycline. But curcumin alone shows lesser activity when compared to combination therapy (Barthelemy *et al.*, 1998; Moghaddam *et al.*, 2009).

Various curcumin derivatives showed the significant inhibition of Tat transactivation of HIV1 (Barthelemy *et al.*, 1998). It has significant activity against HIV (Prasad and Tyagi, 2015)and the clear liquid soaps prepared using turmeric extract showed that it has physical and chemical stability and did not change the antimicrobial activity (Ungphaiboon *et al.*, 2005). The boron complexes of curcumin showed time-dependent inactivation of the proteases of HIV-1 and HIV-2 (Sui *et al.*, 1993). In another study, it was proven that the recruitment of RNA polymerase II was affected by curcumin (Kutluay *et al.*, 2008). In patients with liver diseases caused by HIV infection, curcumin extract can be used as a safe and effective medicine (Kim *et al.*, 2009). Curcumin can be used as a cytotoxic agent in cervical carcinoma developed by the infection of human papillomavirus, (Prusty and Das, 2005) by the regulation of AP-1 transcription factor (Foryst-Ludwig *et al.*, 2004; Divya and Pillai, 2006).

Anticancer activity

Curcumin showed activity against ovarian, uterine (Li *et al.*, 2014), breast (Liu and Ho, 2018), and cervical cancer (Ghasemi *et al.*, 2019). And also curcumin inhibits human prostate cancer stem cell proliferation (Liu *et al.*, 2017), *in vitro* invasion, and xenografts models (Rivera *et al.*, 2017). *In vitro* cell line studies showed the potential of curcumin to suppress tumour growth by inhibiting activator protein-1(Weber *et al.*, 2006), NF-kB (Ghasemi *et al.*, 2019), cyclooxygenase-2 (Handler *et al.*, 2007), nitric oxide synthase (Bengmark, 2006), MMP-9 (metalloproteinase-9) (Saja *et al.*, 2007) and STAT3 (signal transducer and activator of transcription - 3) (Saydmohammed, Joseph and Syed, 2010).

In the activation of cell cycle arrest, curcumin may serve as an effective agent against cancer cell proliferation (Peng *et al.*, 2014).On anti-human osteosarcoma, the effect of curcumin nanoparticles is studied and proved that curcumin-induced apoptosis cell death (Wang *et al.*, 2019). Curcumin exhibited cytotoxicity in Non-Small Cell Lung Cancer (NSCLC) and thereby curcumin is considered as an efficacious therapeutic agent for NSCLC (Hu *et al.*, 2018). Curcumin has significant action to inhibit the proliferation of a wide range of breast cancer cell lines (Tseng *et al.*, 2019) and is effective against leukaemia potentially (Kouhpeikar *et al.*, 2019).

MDR CANCER CELLS

The compounds present in spices possess potential therapeutic activities like anti-oxidant, anti-mutagenic, anti-inflammatory, and anticancer properties. In P- Glycoprotein (P-gp) mediated multi-drug resistant human cancer cells ERK1 and ERK2 activities are downregulated. ERK1 or ERK2 can be considered as a potential drug target for circumventing multi-drug-resistant human cancer cells. Control over metabolic regulation is the silver lining to correct pathway resistance in MDR tumour cells. Many mechanisms are causing multiple drug resistance, such as P-gp for decreased drug accumulation in intracellular space. In human MDR cancer, ABCB1/ P-gp mediated multidrug resistance involved several transduction pathways and transcription factors (Sui, Fan and Li, 2012).

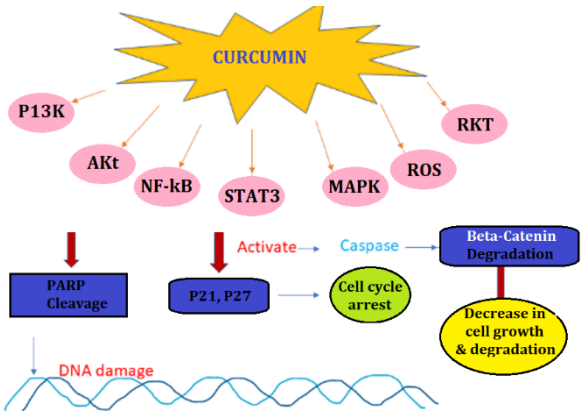

Figure 4: Various mechanisms of curcumin for tumour inhibition.

There was a different mechanism of action by phytochemicals for the prevention of cancer initiation and invasion by integrated signalling pathways in highly resistant multiple myeloma cells. A large group of proteins is involved in the control of metabolism and homeostasis pathways, such as the reaction related to metabolic generation, respiration, glycolysis and lipids, amino acids, and nucleic acid metabolisms. It was already reported in works of literature that the relationship between cancer chemoresistance and metabolic reprogramming in P-gp mediated multidrug resistance.

In hepatocellular carcinoma cells, extracellular signal-regulated kinase activities are down-regulated, so they are considered as potential drug targets of obstacles in MDR- HCC cells. MDR is a common barrier in cancer therapy. Nano delivery of medicine can make some changes in drug delivery, but the payload of drugs is low in nanocarriers than the conventional methods and thereby compromises the treatment outcomes (Mohammad *et al.*, 2019). Phytomedicine has a greater ability to delay the progression of cancer cells and thereby enhance the efficacy of anticancer agents (Yang *et al.*, 2011).

Curcumin effect on MDR cancer cells:

Bioactive constituents of natural products were contributed to reversing of multidrug resistance of cancer cells, improving the efficacy of already proven anticancer agents, and also reducing the side effects of chemotherapy. By blocking and downregulating the P-gp activity, curcumin rhizomes help to activate the sensitivity of doxorubicin and reverse the MCF-7 breast cancer cells resistance. In combination therapy, two or more therapeutic agents were used to enhance the therapeutic outcome. If the combination of therapeutic agents were used for cancer treatment, it will improve the outcome by synergistic activity or by reducing the multidrug resistance of cancer-treating agents. Meanwhile different varieties of phytochemicals are derived and used for cancer treatment due to their high potential and fewer side effects (Zhong *et al.*, 2018). In phytotherapy, the extracts are used for the treatment. In this, the secondary metabolites will not be single. A plant extract may contain numerous secondary metabolites such as phenols, terpenoids, alkaloids, etc. There are several hundreds of minor components present in phytomedicine, showing a wide variety of pharmacological actions. Because of this, there may be additive actions in the therapeutic potential of plant medicine. Therefore, we considered that synergy was the main reason for the positive impact of phytomedicine (Eid, El-Readi and Wink, 2012).

Curcumin suppresses ABC family transporters in cancer cells, including ABCA1, ABCB1, ABCC1, and ABCG2. Curcumin inhibits the mechanism of the P-gp/ABCB1 protein in cervical cancer cells by engaging with the P-gp binding site on the cell surface and by connecting with the P-gp active sites, resulting in a considerable reduction in the mechanism of this transporter. When these cells are treated with curcumin and vinblastine, vinblastine accumulates within the cells and thereby increasing the sensitivity of the cells (Limtrakul, Anuchapreeda and Buddhasukh, 2004; Zhang *et al.*, 2014).

Curcumin has been demonstrated to inhibit the activity of ABCG2 and increase the reactivity of tumour cells (Chearwae, Shukla, Limtrakul, & Ambudkar, 2006). Curcumin suppresses Bcl-2, MDR1 and BCR/ABL gene expression in these cells and enhancing doxorubicin efficiency by eliminating the resistance of cells (Misra and Sahoo, 2011). As a result, curcumin can be used in conjunction with other key chemotherapeutic drugs.

The prevention of DNA damage generated by anticancer medicines was another mechanism in the treatment of resistant cancer. Numerous studies show curcumin inhibits repair of DNA special enzymes and also causes the damage of DNA in various cell lines (Lu *et al.*, 2009; Rowe *et al.*, 2009) and 20 μM of curcumin reduces the expression of DNA damage–response genes (Lu *et al.*, 2009). According to other studies curcumin

produces DNA damage, modulates BRCA1, and keeps this in the cytoplasm in triple-negative breast cancer cells and causes apoptosis in these cells (Rowe *et al.*, 2009).

NF-kB produces antiapoptotic proteins and increases MDR production in cancer cells, resulting in cell survival and resistance (Xia *et al.*, 2018). Curcumin lowers the expression of genes controlled by NF-kB such as TNF, COX-2, IL-6, Bcl-2, and Bcl-xl in different cancer cells by inhibiting constitutive NF-kB activity and blocking NF-kB and DNA binding (Shishodia *et al.*, 2005). Downregulation of NF-kB in the presence of curcumin has been reported in cell lines by restriction of proliferation resulting in cellular accumulation in the G1 phase and S phase and thereby increasing cell sensitivity to medicines (Shishodia *et al.*, 2005; Meiyanto *et al.*, 2014).

In human head and neck squamous cell cancer cell lines, overexpression and continuous NF-kB activity have been found and curcumin has been shown to reduce the NF-kB by inhibiting IB-kinase (Aggarwal *et al.*, 2004). Curcumin also inhibits the PI3K/AKT pathway, which inhibits NF-kB expression. Suppression of NF-kB directly affects P53 activation, whereas inhibition of VEGF and COX-2 genes decreases cancer cells angiogenesis.

In mice with human gastric cancer xenografts, the combination of 5-fluorouracil and curcumin significantly lower tumour growth when compared to 5-FU alone. According to the findings, this will lower the levels of NF-kB and COX-2 proteins. Curcumin was recommended as a well-known natural chemical that decreased NF-kB activity and enhanced cancer cells treatment susceptibility (Mortezaee *et al.*, 2019). Curcumin also decreases the activity of cyclin D1 through NF-kB inhibition, found in squamous cell carcinoma of the neck and head (Aggarwal *et al.*, 2004).

BIOAVAILABILITY OF CURCUMIN:

Curcumin had some limiting factors such as low oral bioavailability and low aqueous solubility, which will hamper its application as a therapeutic agent. Different technologies are applied to overcome this problem and make curcumin more effective. In a study using A549- human lung cancer cell lines novel curcumin-loaded mixed micelles were prepared by using the solvent evaporation method to increase the oral bioavailability and cytotoxicity and the results revealed that a significant improvement in oral bioavailability and cytotoxic action of curcumin formulation as compared to curcumin. So curcumin micelles can be considered as important carrier systems for hydrophobic agents like curcumin with potential improvement in their oral bioavailability (Patil *et al.*, 2015).

The curcumin nanoparticle efficacy against paclitaxel-resistant ovarian cancer cells was studied. The results state that curcumin nanoparticles showed gentler and slow-release than free drug release. The P-gp content of the cell lines resistant to adriamycin was reduced significantly by the curcumin nanoparticles. Phospholipid nanoparticles with taxol and curcumin had improved the stability and solubility with the effect of a slow-release rate. Curcumin is also able to overcome the multidrug resistance of tumour cells by increasing the paclitaxel concentration in the tumour cells to improve the activity of this combination therapy (Z. Liu *et al.*, 2016).

Formulations of Curcumin with higher bioavailability.

The less bioavailability and a variety of pharmacological actions of curcumin lead to the invention of different formulations of curcumin with a variety of combinations including liposomes, microemulsions, phospholipid complexes, nanoparticles, and polymeric micelles. Studies show that there is a considerable increase in the bioavailability of curcumin in combinations. ETO-cur (Essential turmeric oils and curcumin) has increased around 7-8 times higher bioavailability than standard curcumin. *In vitro* and *in vivo* studies, it is showing the inhibition of growth of colon cancer cells. The anti-inflammatory property of the ETO-Cur combination is higher than standard curcumin (Toden *et al.*, 2017). The factors that limit curcumin's usefulness and effectiveness are low bioavailability due to its less water solubility and rapid metabolism of inactive metabolites. Because of its high oil solubility and degradability in alkali, many formulations have been developed to enhance its dispersibility and solubility in water to enhance its consequent bioefficacy. In this review, we consider the higher bioavailable formulations of curcumin and its pharmacological actions. Some of them are mentioned here.

Biocurcumax™ (BCM-95®)

It is a formulation in which curcumin is combined with turmerone, the essential oil of turmeric. The human bioavailability of curcumin is 6.9% higher than curcumin's raw form (Antony *et al.*, 2008).

Table I. Bioavailability enhanced formulations of curcumin.

Serial no	Formulation	Techniques to enhance bioavailability	RB Curcumin
1.	BCM-95® (Bio Curcumx®)	Turmeric oil	27 fold (Antony *et al.*, 2008).
2.	Curcumin C3 Complex®	Piperine	20 fold (Kaur, Invally and Chintamaneni, 2016).
3.	NovaSol® F	93% Tween-80, and 7% curcumin powder-liquid micelles.	185 fold (Ranjan *et al.*, 2012).
4.	Cavacurcumin®	Gama-Cyclodextrin	85 fold (Schiborr *et al.*, 2014).
5.	Meriva®	Microcrystalline cellulose/Lecithin	48 fold (Purpura *et al.*, 2018).
6.	CurcuWIN®	Cellulosic derivatives	136.3 fold (Cuomo *et al.*, 2011).
7.	Micronized Curcumin	Silicon dioxide/triacetin/Panadon	9 fold (Jäger *et al.*, 2014).
8.	CurcuminPro	Whey protein	100% (W. Liu *et al.*, 2016).
9.	CurQfen®	Galactomannan fiber	15.8 times (Im *et al.*, 2012).
10	Theracurcumin®	Ghatti gum/glycerine/Lipids/hydroxy methylcellulose	15.9 times (Sasaki *et al.*, 2011)
11.	MicroActive Curcumin	Cellulose/sodium algenate	9.7 times (Madhavi and Kagan, 2014)
12.	Longvida®	Docosahexaenoic acid/Lecithin/Stearic acid	100 % (Gota *et al.*, 2010)

Curcumin C3 Complex®

To enhance the oral absorption of curcumin, piperine is the bioavailability enhancer used in this formulation. Uridine diphosphate-glucuronosyltransferase improves the freely available curcumin in the blood. With piperine, curcumin is showing 20 fold higher bioavailability than unformulated curcumin (Kaur, Invally and Chintamaneni, 2016; Ranjan, Mohapatra and Das, 2020).

NovaSol® (micellar curcumin)

The solubility of certain drugs which is hydrophilic can be improved by forming micelles. Novasol is a drug that consists of curcumin powder and Tween-80. It shows 185 fold higher bioavailability than unformulated curcumin. The dissolution and absorption of the drug can be improved by the formation of liquid micelles(Schiborr *et al.*, 2014).

Cavacurmin®

It is a formulation based on γ-cyclodextrin. The bioavailability of the curcumin has been increased by 85 fold in comparison to unformulated curcumin. Up to the upper intestinal tract, cava curcumin is transported unchanged through the stomach, where human amylases works and curcumin molecules are absorbed and cyclodextrin molecules are hydrolyzed (Purpura *et al.*, 2018).

Meriva®

It is formulated by curcuminoids (18-20%) with microcrystalline cellulose and soy lecithin. When compared with an unformulated curcuminoid mixture Meriva has 29 fold higher absorption. Lecithin provides higher bioavailability of desmethoxy curcumin in Meriva (Cuomo *et al.*, 2011).

CurcuWin®

It is 136 times higher bioavailable than unformulated curcumin.CurcuWin is consists of 28%turmeric powder, polyvinyl pyrrolidine, cellulosic derivatives, and natural antioxidants (Jäger *et al.*, 2014).

Curcumin Pro

The whey protein encapsulation by spray drying method curcumin can improve its solubility. Around 100% increase in bioavailability is shown by this to prevent colon cancer. In different ratios, whey protein was used for nanoencapsulation such as 70:30, 50:50 and 35:65 to improve the bioavailability (W. Liu *et al.*, 2016).

CurQfen™

It is formulated by mixing up of turmeric powder with fenugreek soluble dietary fibres. The

amorphous formulation delivers colloidal curcumin slowly to increase absorption. When compared to the treatment outcome of unformulated curcumin the bioavailability of formulated curcumin is 15.8 times more. The slow release from non-digestible soluble fibres leads to protection from enzymatic degradation and that is to be the possible mechanism of action for higher bioavailability (Im *et al.*, 2012).

Theracurmin™

It is a preparation based on the colloidal nanoparticle. By the combined effect of improved solubility and reduced particle size, it is 16 times higher bioavailable than unformulated curcumin (Sasaki *et al.*, 2011).

MicroActive curcumin

Micro active curcumin is prepared by 25% curcuminoids in a sustained release matrix. It consists of 25% curcumin, 16.7% panadon, 58% triacetin and sprays dried in porous silicon dioxide. It has 9.7 times higher bioavailability when compared to unformulated curcumin (Madhavi and Kagan, 2014).

LongVida®

It is formulated by mixing soy lecithin with turmeric powder, which contains purified phospholipids, vegetable stearic acid, docosahexaenoic acid, ascorbic acid (vitamin C), 5 esters, etc. The studies show that in humans, relative bioavailability is approximately 100% higher (Gota *et al.*, 2010).

CONCLUSION

Curcuma longa or turmeric is a plant with an abundant treasure of medicinal values that should be selected for further research because of its proven activity against various diseases. The activity of curcumin against cardiovascular diseases, metabolic disorders, autoimmune disorders, and cancer shows a potent drug with fewer side effects. The higher therapeutic activity and lower bioavailability are the two contradictory points. So, to get the maximum benefits of curcumin as a potent drug, the formulations with maximum bioavailability should be studied and invented.

In this review article, we had gone through the various therapeutic activities of curcumin with a special emphasis on multi-drug resistant cancer cells, and different formulations of curcumin with higher bioavailability. The higher therapeutic efficacy of curcumin to reverse the multi-drug cancer cells are under study and the results light up to the possibility of combination therapy for cancer. The combination of phytoconstituents like curcumin with a conventional chemotherapeutic agent will make tremendous changes in the treatment outcome.

The lower bioavailability of curcumin can be improved by different additives like turmerone, piperine, quercetin etc. The major drawback of curcumin in clinical trials can be addressed with this and curcumin can be used as a better therapeutic agent for cancer prevention and treatment. This review paves the way for further studies on curcumin as an anti-cancer agent in multidrug-resistant cancer cells with higher water solubility and thereby higher bioavailability. Further studies should evolve to introduce curcumin and its higher bioavailability formulations as a potential therapeutic agent to treat multidrug-resistant cancer.

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