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Review Article

Curcumin Potential and Problems in Pancreatic Cancer

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ABSTRACT

Curcumin, a diferuloylmethane and derivative of turmeric is one of the well-described and profoundly investigated phytochemicals, which has been utilized since old occasions for the treatment of different illnesses. Several in-vitro, in-vivo and human studies have examined the underlying molecular mechanism by which curcumin may intercede chemotherapy and anticancer effects including pancreatic cancer. Curcumin can inhibit of pancreatic malignancy through the modulation of multiple molecular targets such as transcription factors (NF-kB, STAT3, b-catenin, and AP-1), growth factors (EGF, PDGF, and VEGF), enzymes (COX-2, iNOS, and MMPs), kinases (cyclin D1, CDKs, Akt, PKC, and AMPK), inflammatory cytokines (TNF, MCP, IL-1, and IL-6), upregulation of proapoptotic (Bax, Bad, and Bak) and downregulation of antiapoptotic proteins (Bcl2 and BclxL). A number of in-vivo studies and clinical trials have shown that curcumin is safe and well tolerated even at very high doses but curcumin's efficacy is hindered by low bioavailability and rapid elimination from the body. Different factors contributing to the low bioavailability include low plasma level, tissue distribution, rapid metabolism, and elimination from the body. Even though, curcumin poor absorption and low systemic bioavailability limit its translation into clinics, some of the methods for its use can be approached to enhance the absorption and achieve a therapeutic level of curcumin. Recent clinical trials suggest a potential role for curcumin regarding pancreatic cancer therapy.

Keywords: Curcumin; Cell signaling; Bioavailability; Absorption; Half-life and cancer

INTRODUCTION

Cancer is a complex cluster of diseases represented with an abnormal increase in cell proliferation. The promotion and development of this disorder is an evolutionary phenomenon mediated by the regular changes in genetic and epigenetic setup of a cell. These kind of genetic mutations causes disruption of the cell cycle, boost regulatory proteins which activate cell proliferation, and decrease the function of proteins that normally inhibit cell proliferation [1]. It is known that cancer arises because of sequential mutations in oncogenes and truncations or deletions in the coding sequences of tumor suppressor genes. Two genomic mutation types such as Chromosomal Instability (CIN) and Microsatellite Instability (MIS) contribute to the development of various cancers. CIN leads to anomalous separation of chromosomes followed by abnormal DNA structure, while MIS is related to loss of function of tumor suppressor and/or DNA repair genes that code a number of regulatory proteins involved in DNA base pair mismatches during the S phase of DNA replication in dividing cells [2]. Cancer is alarming public health issue around the globe, and it is estimated that cancer is the cause's one in 4 deaths in the United States. According to American Cancer Society, it has been estimated that a total of 1,806,590 (893,660 men and 912,930 women) new cancer cases and 606,520 deaths (321,160 men and 285,360 women) due to cancer are expected to occur in the United States in 2020 [3]. In the recent decade, large increase in the expenses of medical care, combined with the restricted viability of single objective malignant treatment therapies, has encouraged the importance of naturally occurring phytochemicals in plants for use in the prevention of human disorders including cancer.

Chemically curcumin is a bis-□, □-unsaturated □-diketone constituent of the dried ground rhizome of the perennial herb turmeric, Curcuma longa, which is a member of the Zingeberaceae family (Figure 1) [4].

Although comparatively pure curcumin has been used in some experimental studies, most studies have used either a mixture of curcuminoids or turmeric, commercial grade turmeric contains 80% curcumin, 18% demethoxycurcumin, and 2% bis-demethoxycurcumin. It possesses limited solubility in water but is

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completely soluble in ethanol or dimethylsulfoxide [5]. Essential oils such as a-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%), and sesquiterpenes (53%) have been isolated from the turmeric rhizome by steam distillation. At the cellular level, curcumin exists in equilibrium with its enol tautomer, and bis-keto forms [6]. The bis-keto form of curcumin dominates in acidic and neutral aqueous solutions, as well as in cell membranes due to the heptadienone linkage between the two methoxyphenol rings, which is occupied with a highly activated carbon atom [7]. There is compelling evidence that curcumin undergoes glucuronidation and sulfation that leads to the formation of tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol, while the minor metabolites included dihydroferulic acid and ferulic acid [5,7]. Poor absorption and low bioavailability of curcumin hinder its anticancer benefits. Recently, several techniques have been developed to increase its absorption and overcome poor bioavailability.

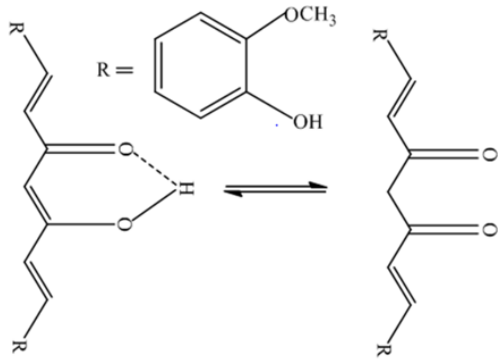

Figure 1: Bis-α, β-unsaturated β-diketone.

Surgical resection and chemotherapy (gemcitabine) has been used as a main strategy for the prevention and treatment of pancreatic cancer. Chemotherapy has been associated with harmful effects and poor prognosis of other diseases. Curcumin mediates the modulation of enzymes, growth factors and their receptors, as well as cytokines and various kinase proteins which control cell proliferation and cell cycle progression. Curcumin can inhibit pancreatic cell lines (MIA PaCa2, MPanc-96, BxPC3, Panc1, and AsPC1) by blocking survival pathways and inducing apoptosis [6,8]. The optimized daily intake of curcumin is 0-1 mg/kg body weight according to the Food and Agriculture Organization and the World Health Organization, and it has been demonstrated in clinical studies that it is nontoxic and well tolerated, even at doses as high as 12 g/day [9].

The present review focuses on the recently published in-vitro, in-vivo animal studies and human clinical trials regarding the curcumin treatment with future implication methods for the enhancement of curcumin half-life and bioavailability in pancreatic cancer.

CURCUMIN MOLECULAR MECHANISM IN PANCREATIC CANCER

Pancreatic cancer is a major cause of cancer related mortalities and 7th leading cause of cancer-related deaths in men and women. It is estimated that a total of 57,600 (30,400 men and 27,200 women) new cases and 47,050 (24,640 men and 22,410 women) deaths related to pancreatic cancer will occur in the United States in 2020 [3]. Globally, 458,918 new cases of pancreatic cancer have been reported in 2018, and 355,317 new cases are estimated to occur until 2040. Curcumin decreased the expression of NF□B-downstream targets such as cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and interleukins (IL-8) (Figure 2).

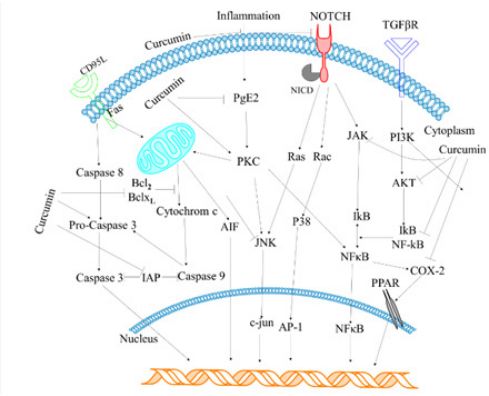

Figure 2: Pancreatic cancer promotion, development and chemoresistance.

This down regulation of inflammatory signaling results in the inhibition of cell cycle followed by the induction of apoptosis in human pancreatic cells [10]. Curcumin synergistically potentiates the growth inhibitory and pro-apoptotic effects of celecoxib in pancreatic adenocarcinoma cells through inhibition of COX-2 [11]. In line with this, curcumin induced pancreatic cell growth inhibition and apoptosis is associated with the inhibitors of apoptosis and Notch-1 signaling pathway, which downregulates NF□B expression [12]. Curcumin also decreased COX-2, EGFR, and phosphorylated extracellular signal-regulated kinases (p-Erk1/2) expression levels in a dose-dependent manner. Concomitant treatment of curcumin with gemcitabine enhanced its cytotoxic effects against pancreatic adenocarcinoma cell lines through the downregulation of COX-2 and Erk1/2 [13]. In addition, curcumin treatment significantly arrested the proliferation of BxPC-3 human pancreatic cancer cells in the G2/M phase through increased phosphorylation of Ataxia Telangiectasia Mutated (ATM) and Chk1, while concurrently decreasing the expression of cyclin B1 and Cdk1 [14]. In-vitro studies have shown that curcumin analogue 3,4-di□uorobenzylidene curcumin (CDF) has increased accumulation rate in the pancreas as compared to normal curcumin [15]. But this particular accumulation of CDF induces harmful effects in pancreatic cancer cell lines as well as in resistant phenotypes. A highly active derivative of curcumin, 3,4-difluorobenzylidene curcumin (CDF) was formulated in dendrimer based nano-formulation for targeted treatment of CD44 overexpressing pancreatic cancer [16]. Poly (amidoamine) PAMAM dendrimers are branched nanoparticles with cationic surface charge making it highly toxic for both cancer and healthy cells. The CD44 targeting hyaluronic acid (HA) is coupled to (PAMAM) dendrimer and the resulting HA-PAMAM conjugate was loaded with CDF. The hyalorunate residue increases the drug uptake by facilitating the dendrimer entry into cancer cell through CD 44 receptor mediated endocytosis [17]. Compared with PAMAM alone, the HA-PAMAM dendrimer showed 1.42 times higher CDF encapsulation and doubled the drug release time. The in vitro MTT assays using AsPC-1 cells showed significantly better IC50 of HA-PAMAM-CDF than free CDF, 580 ± 1.55 nM and 975 ± 3.42 nM respectively [17]. Previous studies have also confirmed the therapeutic potential of curcuminoids and nanomicelles preparation for the treatment of pancreatic cancers [16,18].

In another study, liposomal curcumin (40 mg/kg) was intravenously administered to female athymic nu/nu mice for 20 days. Liposomal curcumin suppressed pancreatic carcinoma growth, possibly by

decreasing expression of CD31, VEGF, COX-2 and IL-8 [19]. Clinical trials addressing the effect of orally administered curcumin and piperine in human patients with tropical pancreatitis resulted in reduced erythrocyte MDA levels with significant increases in glutathione (GSH) levels in the curcumin treated group. Oral administration of curcumin (8 g) to pancreatic cancer patients decreased the expression of NF□B, COX-2, and phosphorylated Signal Transducer and Activator of Transcription 3 (STAT3) [19,20].

In a clinical trial, curcumin (8 g) was orally administered to 25 patients per day for 2 months. Circulating curcumin was detected as the glucuronide and sulfate conjugate forms, albeit at low steady-state levels, suggesting poor oral bioavailability. Despite this poor bioavailability, two patients showed clinical biological activity and one had ongoing stable disease for more than 18 months [21]. In this study, one patient showed marked tumor regression accompanied by significant increases in levels of serum cytokines such as IL-6, IL-8, IL-10, and IL-1 receptor antagonists. To overcome this issue, new curcumin analogs Theracurcumin, a nanoparticle-based curcumin has been developed for efficient drug delivery system [22]. In a phase I clinical trial, Theracurcumin (200-400 mg oral/daily) was given to 16 patients with PC resistant to gemcitabine-based chemotherapy [23]. The results have confirmed that high concentration of Theracurmin has no side effects in concomitant administration with gemcitabine-based chemotherapy. These findings demonstrate that orally administered curcumin is well-tolerated and has biological activity in some patients with pancreatic cancer.

CURCUMIN BIOAVAILABILITY IMPROVEMENT TECHNIQUES

Even though a huge literature showing the anticancer properties and biological role of curcumin, but its therapeutic efficacy is hindered and limited by low systemic bioavailability, poor absorption and rapid elimination from the body. Several studies have reported low serum levels of curcumin following oral administration at a dose of 2 g/kg to rats. A maximum serum concentration of 1.35 ± 0.23 μg/mL was observed at time 0.83 h, whereas in humans the same dose of curcumin resulted in very low (0.006 ± 0.005 μg/mL at 1 h) serum levels [24]. Furthermore, curcumin metabolites have not been detected in the blood or the urine but only in the feces, indicating the decrease levels of curcumin in the blood [24].

Different techniques have been practiced improving the bioavailability or therapeutic effect of curcumin in the treatment and prevention of pancreatic cancers. The use of adjuvants such as piperine together with curcumin can increase its delivery, distribution and bioavailability up to 2000% [5], making it applicable to cancer treatment by suppressing the hepatic and intestinal glucuronidation of curcumin. Several studies have also shown that phospholipid complexes of curcumin also enhanced systemic bioavailability. The curcumin phytosome preparation Meriva®, which contains soy phosphatidylcholine has better bioavailability than curcumin. The effect of Meriva® examined the absorption of a curcuminoid mixture and Meriva® in a randomized, double-blind, crossover human study [25]. They found that the total curcuminoid absorption was about 29-fold higher for the Meriva® mixture than the unformulated curcuminoid mixture. Furthermore, the phospholipid formulation increased the absorption of demethoxylated curcuminoids much more than that of curcumin [25]. Recently, in a phase II clinical trial, Meriva® and gemcitabine were given to 52 (13 locally advanced and 31 metastatic) pancreatic cancer patients. were suitable for primary endpoint evaluation. Curcumin phospholipid complex has shown remarkable therapeutic effect with low toxicity (neutropenia, 38.6%; anemia, 6.8%) in pancreatic cancer [26]. Another study reported focusing on the safety of combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy (1000 mg/m2 on day 1 and 8) and (60 mg/m2 of S-1 orally for 14 consecutive days every 3 weeks) in 21 patients with gemcitabine-resistant pancreatic cancer, the patients were shown no dose-limiting toxicities in the phase I study, suggesting that oral curcumin 8 g/day is safe and feasible in patients with pancreatic cancer [27,28].

CURCUMIN NANOFORMULATIONS

The phytosome and liposome technology create intermolecular bonding between individual polyphenol molecules, with one or more molecules of the phospholipid, phosphatidylcholine. Molecular imaging suggests that PC molecules enwrap each polyphenol; upon oral intake, the amphipathic PC molecules likely "usher" the polyphenol through the intestinal epithelial cell outer membrane, subsequently accessing the bloodstream [29,30]. The bioavailability of the curcumin phytosome preparation (Meriva®, from Indena SpA) has been tested in rats. The rats were fasted overnight and the curcumin complex was administered by oral gavage at 360 mg/kg body weight, in either phytosome or nonphytosome form. The phytosome preparation displayed superior curcumin plasma absorption from the first 30 min. In this study, the liver also accumulated significantly more curcumin from the phytosome as compared to the nonphytosome [30]. Liposomes differ from phytosomes in the sense that they are aggregates of hundreds of phospholipid molecules into a spherule, within which other molecules are compartmentalized, but not specifically bonded. A micelles and phospholipid complex improved the intestinal absorption of curcumin and enhanced its bioavailability. Curcumin has been successfully loaded on human serum albumin nanoparticles and showed remarkable anti-tumor activity against human pancreatic cancer cells [31]. The HSA is an optimal choice for nanoparticle carrier due to its low toxicity and immunogenicity. The albumin bound nanoparticle preparation has advantage over surfactant free or polymeric materials [29,31]. The curcumin-albumin nanoparticles CCM-HSA-NPs are formulated using albumin bound nanoparticle technology yielding spherical particles 130-150 nm in size. These nanoparticles have 300 folds higher water solubility and 5.5-fold increased endothelial binding as compared to free curcumin. In vivo studies of human pancreatic cells-induced xenograft models revealed up to 78% reduction in tumor size after 10 days treatment with 20 mg/kg dose of nanocurcumin [17,24,29]. Nanoparticle-based drug delivery approaches have the potential for rendering hydrophobic agents like curcumin in overcoming poor bioavailability. However, very limited studies were made and the complete mechanism regarding the nanoparticle-mediated curcumin delivery system is still unknown.

DISCUSSION AND CONCLUSION

To develop curcumin into a preventive or therapeutic drug, it is important to consider the dose levels which elicit desirable/undesirable effects. Nevertheless, due its proven efficacy over centuries of use and demonstrated safety in several human studies, it should be translated to clinics for the treatment and prevention of cancers. Several preclinical studies have demonstrated that

curcumin, a naturally occurring polyphenolic compound, has anticancer effects against different types of cancer, including PC, by modulating many molecular targets. On the basis of these results, several researchers tested the anticancer effects of curcumin in clinical trials, trying to overcome the poor bioavailability of this agent, which limited its clinical application. New bioavailable forms of curcumin have been developed and the results from clinical trials on patients with pancreatic cancer suggest that these agents could represent promising new treatments for pancreatic cancer, although more clinical studies will be still needed.

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