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Mini Review

An Update on Role of Curcumin in Colorectal Cancer-A Minireview

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Abstract

Earlier we had reviewed the part of curcumin as an anti-oxidant, anti-inflammatory, neuro shielding, anticancer, hapatoprotecting, as well as cardio shielding actions. Further its bioavailability issues, bio effectiveness as well as safety parameters along with quality properties of Curcumin were further tackled, besides its role in PCOS. Here we tried to concentrate on the part of curcumin in Colorectal cancer (CRC). Diffusion of curcumin takes place via the cell membrane into the cell membrane endoplasmic reticulum (ER), mitochondria along with nucleus where its anti-oxidant characteristics get impacted. Hence its utilization has been recommended regarding chemopreventive, antimetastatic along with anti-angiogenic uses. Thus we conducted a minireview review on role on CRC with the utilization of search engines like PubMed, google scholar, web of science, Cochrane library from 1995 till date in 2022 with the utilization of MeSH terms like Curcumin; antioxidant actions; other anti-inflammatory actions; anti angiogenic actions; CRC; chemopreventive actions; ER stress; familial adenomatous polyposis (FAP); *in vivo* studies in animal models; *in vitro* studies. We found 2500 articles but selected only 53 articles for this review with the journals constraints of upto 50 references. No meta-analysis was done. *In vitro* studies conducted on human colon cancer cell lines illustrated that Curcumin hampered growth via cell cycle arrest at the G2/M along with G1 phase, besides crosstalk with numerous molecular targets. *In vivo* studies were conducted in mice having inflammatory along with genetic CRC in animal models possessing a chemopreventive action. regarding enhancement of bioavailability, it has been correlated with small particles that escalate its absorption on oral delivery with great outcomes in both inflammation as well as carcinogenesis. Furthermore curcumin utilization has been done in dietary formulation for CRC chemoprevention. These illustrated that *in vivo* along with *in vitro* anti carcinogenic characteristics in inflammatory along with genetic CRC.A synergestic action was pointed on utilization of unique dosages of the component that was lesser in contrast to experimentally utilized for single component. Thus with favourable actions in animal models, good scope of their working in humans preclinical studies.

Keywords: Curcumin; CRC; Animal Models; Apoptosis; Cellular Culture

Introduction

Curcumin represents a yellow phytochemical obtained from the plant Curcuma longa (turmeric) rhizome, a plant akin to ginger [1]. It is a natural phenolic pigment possessing a classical yellow colour. Its solubility is good in acetic acid, ketone, alkali as well as chloroform, whereas it is insoluble in water, acidic along with neutral pH [2]. In view of its hydrophobic characteristics it possesses the capacity of diffusion via the cell membrane into the endoplasmic reticulum (ER), mitochondria along with nucleus, with it having the capacity of acting in all the 3 areas [3]. Curcumin utilization is normally done in the form of an element for dietary supplementation, as a constituent of cosmetics, escalate flavours of foods, besides beverages in particular in South along with Southeast Asia. Nevertheless, curcumin is acknowledged to possess antioxidant

characteristic, hence its utilization has been recommended regarding chemopreventive, antimetastatic along with anti-angiogenic uses [4].

Colorectal cancer (CRC) is one of the maximum spread tumors all over the world besides is believed to be the 2nd commonest etiology amongst cancer patients [5]. The height of cancer incidence of CRC in Western countries might be correlated with alterations in the lifestyle, specifically in dietary habits swing might reason it out [6]. Actually, the generation of Colon cancer gets markedly impacted by environmental factors, noticeably, carcinogenesis of the Gastrointestinal Tract (GIT). From this angle a diet with abundance of polyunsaturated chain fatty acids (PUFA's), along with red meat, besides lesser vegetables have been is believed to be the main risk factors for the formation of CRC [7]. In view of this modulating constituent of diet can be utilized in the form of an approach regarding chemical avoidance of the initiation of CRC as well as curcumin might be a good food component. Actually, it has been pointed to work in the form of an anti carcinogenesis substance for different tumors inclusive of, prostate, pancreatic, Breast, stomach, liver carcinoma along with leukaemia [8]. Mechanistically epithelial apoptosis induction is the mode maximum evaluated [9]. Actually, it has been illustrated in cancer cells that curcumin can facilitate the generation of proteins correlated with proapoptotic events along with could crosstalk with the pathways of inflammation- correlated programmed death [10].

Utilization of curcumin in chemoprevention as well as complementary treatment of CRC is attractive. The review here tries to outline the association amongst studies that evaluated correlation of curcumin along with CRC *in vitro* models as well as human trials.

In vitro studies: the action of curcumin on Colon cancer Cell lines

It has been illustrated that curcumin possess the capacity of avoidance of CRC growth by blockade of cell cycle along with augmentation of apoptosis. *in vitro* studies conducted on various human Colon cancer Cell lines, revealed that curcumin hampered cell growth by crosstalk amongst numerous molecular targets, hence modulating various unique signalling pathways. In the human Colon cancer Cell lines, HCT-16, apoptosis Moseniak., *et al.* [11]., illustrated that curcumin hampered cell proliferation by cell cycle arrest at the G2/M phase along with partly in the G1phase [11]. Furthermore Lim., *et al.* [12], observed that curcumin negatively controlled cyclinD1 along with lead to induction of block in the G1phase in the same cancer cell lines. Cyclin D1 is acknowledged to possess the capacity of binding both CDK4 as well as CDK6, hence generating an active complex that phosphorylates Rb protein in Ser 780 along with controls the transit from G1to S phase in the form of end result [13]. Kim along with Lee [14] in a study revealed that curcumin hampered cell proliferation of HCT-16 via inducing transcription factor Reactive oxygen species (ROS) production besides downregulation of Rb E2F4, as well as correlated genes, like cyclin A, p21 along with p27 [14]. A study by Watson., *et al.* [15], regarding curcumin cytotoxicity on HCT-16 besides HT29 cell lines documented that a sequential in addition to dose-based hampering of cell proliferation was found on upregulation of p53 [15].

Thus one of major modes implicated in curcumin's blockade of cell growth is via apoptosis induction. Such events require numerous molecular targets inclusive of cyclooxygenase-2 (COX-2), transcription factors like [nuclear factor κB (NFκB) as well as β-catenin), Bcl2 family members (Bcl2, Bax, along with Bcl-xL), death receptors [DR (death receptor5] DR 5as well as Fas), protease enzymes (caspase3 as well as caspase8) besides ROS.

Escalated COX-2 expression has been observed in numerous tumors inclusive of CRC. Enhancement of COX-2 expression was found in 77% of patients of CRC in contrast to normal surroundings, mucosa. Greater Illustration validated that curcumin downregulated COX-2 expression in CRC [16]. Furthermore curcumin had an antiapoptotic impact on HT29 Colon cancer cell lines via COX-2 along with apoptotic correlated pAKTkinase decrease as well as by escalated pAMP protein kinase (AMPK) signalling pathway [17].

Considerable evaluation of NFκB has been done in view of its implication in CRC [18]. Regarding this curcumin possesses the capacity of reduction of expression of NFκB in CRC cells. Collect as well as Campbell [19] detailed that curcumin facilitated apoptosis in HCT-16Cell line via hampering NFκB [19].

Transcription factor β-catenin possesses a key part in the pathogenesis of CRC basically in view of APC in activation along with β-catenin mutations. Both events facilitate nuclear accrual of β-catenin besides β-catenin transcription of numerous oncogenes. β-catenin works in the form of crucial effector of the well acknowledged Wnt signalling in the nucleus besides inherent structural

constituent of cadherin dependent adherens junctions. Narayan., *et al.* [20], illustrated that curcumin on Colon cancer cell hampered the Wnt/β-catenin signaling pathway by repressing expression of c-myc along with induction of caspase3modulated cleavage of β-catenin, E cadherin as well as APC. All of these events are correlated with apoptosis along with G2/M phase arrest in HCT-16 Colon cancer cells [20]. Lastly Park., *et al.* [21], evaluated SW480 along with HCT-16 Colon cancer Cell lines documented that curcumin hampered the β-catenin/Tcf signaling via reduction of quantities of nuclear β-catenin along with Tcf protein [21].

Numerous cancer histotypes inclusive of CRC have been correlated with a dysfunctional expression of Bcl2 family members. That curcumin facilitates Bax expression besides decreasing Bcl2 quantities in Colon adenocarcinoma phosphorylation throughout at Ser15 along with activation of p53 [22]. Escalated Bax expression might impact Bcl2: Bax or Bcl-xL ratio, hence guiding the neoplastic cells towards apoptosis. Curcumin induction of Bcl2 hampering as well as upregulation of Bax expression has been revealed in other cancer cell lines as well like HCT-16 [22], along with COLO205.

Death receptors like DR 5 as well as Fas, possess a key part in the transfer of signals from the cellular membrane to the cytoplasmic signaling pathways. That curcumin possesses the capacity of upregulating DR 5 protein has been documented, a receptor that is foundational for apoptosis in HCT-16 cells HT29 Colon cancer cells. Moreover, curcumin was invented for stimulating activation caspase 8, an event which starts Fas modulated apoptotic pathways [23]. Pro caspase 8 forms with Fas ligand, a complex that is a part of a component of Death induced signaling complex (DISC), hence resulting in activation of caspase 8 by reciprocal splitting along with facilitating caspase 3, caspase 7 along with Bid.

Curcumin facilitates its cytotoxic actions by generating ROS. Despite Curcumin is a robust forager of free radicals, proof exists that they possess the capacity of facilitating the formation of free radicals hence probably. Curcumin has been observed to stimulate apoptosis by escalating the generation of ROS, thus stimulating Oxidative reactions along with breakdown of mitochondrial membrane in CRC cancer cells.

In summary the modes of anti-cancer actions of Curcumin might be numerous that result in reduction of cell growth along with apoptosis. These total studies pointed to utilization of this information for translation of this *in vitro* information to *in vivo.*

In vivo studies: the action of curcumin on Colorectal cancer (CRC) in animal models

Perkins., *et al.* [24], in 2002 illustrated in an animal model that consumption of Curcumin at 0.2% that was equivalent to 300mg/kg, caused avoidance of generation of adenoma. Adenomas that were Small besides those of medium size possessed greater sensitivity to the chemopreventive action of curcumin. The decrease in the adenoma quantities was more obvious in the central as well as lower parts of the intestinal Tract, utilization ofC75BL/6J/Min/+ (Apc Min/+) mice for a model that mimicked human familial adenomatous polyposis (FAP). A standardized diet with abundance of curcumin at quantities of 0.1%,0.2% as well as 0.5% x 15weeks. At0.1%, amount no action of curcumin was illustrated, while with 0.2% as well as 0.5% a significant decrease in intestinal tumor no's took place by 39% as well as 40% respectively. Subsequently Park., *et al.* [25], detailed positive outcomes of this [25].

Furthermore, McFaden., *et al.* [26], has utilized a model commonly used for assessment of generation of colitis correlated- CRC. Utilization of particular pathogen free wild kind (WK) 129/Sv Av as well as germ free interleukin-10 (IL-) 10--/-mice. Initiating from 10wks of age WK or IL-10-/-mice were administered a weekly intraperitoneal injections of azoxymethane (AOM) or saline x6weeks along with concomitant diet supplemented with curcumin. They illustrated practically complete elimination of CRC load in IL-10KO/AOM mice. Apparently these chemopreventive actions were indirectly correlated with the normalizing actions of curcumin on Colonic microbial flora greater than its anti-inflammatory action. Intriguingly, this study pointed to the characteristic of rectification of the healthy homeostasis of the gut along with microbial -host association. Nevertheless, all the transgenic mice who had AOM, as well as received curcumin had demise, while just 50%of controls died. Moreover, mice in receipt of curcumin had a tendency of lesser consumption that was associated with weight reduction. However, curcumin totally avoided body weight reduction in IL-10-/-mice in receipt of AOM, without a variation from WK mice in receipt of AOM. This process might have influenced their AOM consumption, action along with microbial constituents. In addition to that no polypoidal lesions were seen in the WK mice in receipt of AOM that had received curcumin. Lastly normalization of the β-catenin expression pattern in the colonocytes. Noticeably, the 2 separate housing kinds (IL-10KO along with WK mice) ensured difficulty in contrasting the outcomes despite treatment of the2 with the utilization of akin protocol.

Epigenetic mutations are of considerable interest in their part regarding carcinogenesis. DNA methylation is a frequent epigenetic mode correlated with abnormal gene expression in cancer. A great association with the dietary factors are correlated with epigenetic modifications. Regarding this Guo., *et al.* [27], evaluated the DNA methylome along with transcriptome changes as well as cancer avoidance of curcumin in colitis correlated- CRC in mice. C75BL/6wild kind (WK) mice had AOM chemical treatment along

with dextran sulfate sodium (DSS). Feeding with a particular diet possessing curcumin from 5wks of age till the experiment was over. Reduction in methylation was seen. In addition to that curcumin ameliorated shortening of colon secondary to fibrosis as a result of inflammation of long duration. Observation of adenoma or adenocarcinoma was not there in the mice having AOM/DSS curcumin in contrast to the animal consuming a standardized diet [27].

Curcumin possesses low water solubility along with bioavailability in view of the extreme situations of the intestinal Tract. To get over these limitations, it has been recently correlated with substances/small particles aiding in transportation besides escalating absorption. In view of this, Han *et al.* [28], attempted orally administrable nanotherapeutic by combination of water-soluble curcumin along with 7ethyl 10hydroxycampothecin (SN 38), an active metabolite of irinotecan. They evaluated the actions of this formulation regarding inflammatory bowel disease (IBD) along with CRC in a mouse model. In contrast to monotherapy, curcumin with SN 38 nanoparticles possessed a synergistic advantageous action on intestinal inflammation. These actions might have been secondary to the synergistic actions of curcumin - SN 38 instead of improvement in drug absorption. Astonishingly, oral delivery of this combined formulation possessed greater efficacy over parenteral delivery. The disease activity index, body weight reduction, stool consistency, along with intestinal bleeding in addition to mortality were decreased by curcumin - SN 38. Concomitantly, the tumor numbers/mouse along with size besides diameter were considerably decreased, along with histological evaluation showed that most polypoidal lesions were adenomas with low grade dysplasia. Curcumin - SN 38 hampered the propagation of CRC, working on cell cycle as well as apoptosis. Actually, cyclinD1 along withD3 were significantly downregulated besides proapoptotic proteins (cleaved versions of caspase3,7,9, along cleaved poly adipose ribose polymerase (PARP) upregulated with curcumin along with SN 38. Lastly decreased expression of anti-apoptotic protein Bcl2 was observed.

The major modes by which curcumin causes avoidance of CRC is depicted in (Figure 1) [29] in animal models.

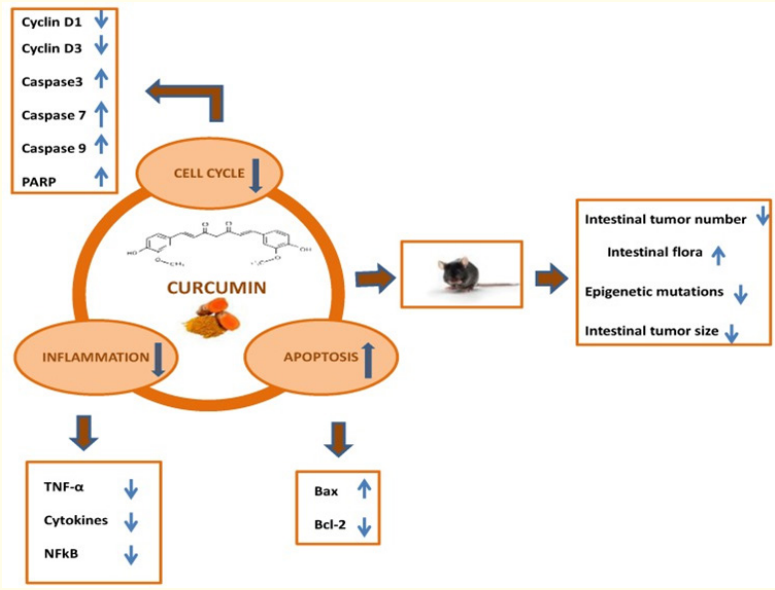

Figure 1: Courtesy ref no-29-Summary of induction of apoptosis by curcumin in colorectal cancer (CRC). Curcumin induces apoptosis in CRC through multiple target molecules and associated signaling pathways. Curcumin inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and cyclooxygenase-2 (COX-2), down-regulates transcription factor β-catenin and activating protein-1 (AP-1), suppresses anti-apoptotic proteins and increase reactive oxygen species (ROS), superoxide dismutase (SOD), and pro-apoptotic proteins and also up-regulates Fas and death receptor 5 (DR5) receptor. Molecules in red represents the main targets of apoptosis while molecules in black are the downstream targets of the molecules labelled in red.

Curcumin actions in the form of constituents of dietary formulation of plant origin

Numerous molecules obtained from plants have been detailed for obtaining an action in decreasing the initiation of intestinal cancer, specifically in animal models. Omit inflammation Silymarin possesses the capacity of inhibiting carcinogenesis by antioxidant as well as estrogen receptor-beta (ER beta) agonist functions [30]. In addition to that boswellic acid along with in particular acetyl-11 keto -beta- boswellic acid (AKBA) are components of gum resin of *Boswelliaserrata* along with believed to be attractive for avoidance of gut carcinogenesis.

Depending on the probability regarding a phytochemical combination possesses the capacity of impacting advantageous actions, whose provision was made by a single substance. The action of each constituent of nutritional combination of Silymarin, AKBA as well as curcumin was contrasted *In vitro* with the full mixture of cultured cancer Cell proliferation (DLD-1). Every component demonstrated an antiproliferative action cultured Colonic cancer Cell in contrast to control samples. Furthermore, the actions of 3 the mixture of the constituents was far superior in contrast to single or double combination [31].

Followed by that the nutritional formulation whose enrichment had been carried out was evaluated for inflammation correlated CRC in an AOM/DSS animal model [31].

Anti-inflammatory along with chemopreventive actions were determined by the lesion numbers, their sizes as well as determination of histological inflammation, dysplastic besides neoplastic regions. Additionally, proinflammatory cytokine mRNA molecular pattern ER-β along with bromodeoxyuridine immunohistochemistry (IHC), as well as terminal deoxynucleotidyl transferase biotin-d UTP nick end labelling (TUNEL) Immunofluorescence labeling were conducted. In case of enrichment, yet not standardized formulation avoided the shortening of the colon (a cornerstone for inflammation of long duration). Furthermore, with the dietary formulation reduction of the polypoidal lesion numbers, sizes, histological inflammation score, proinflammatory cytokine mRNA expression along with the numbers of low-grade dysplasia (LGD) as well as high grade dysplasia (HGD) regions. Lastly CRC was seen in 69.6% of the standardized in addition to23.5% of the ones with enrichment nutritional formulations whose consumption was done by animals. Greater ER-β expression was observed in LGD besides escalated apoptosis in LGD. With the well acknowledged Anticancer actions of ER-β, this study pointed that LGD might reflect the checking of neoplastic evolution along with the ER-β agonist functions of the supplemented formulation might facilitate apoptosis, hence reduction of propagation to carcinoma. Actually, the simultaneous escalated TUNEL expression documented in LGD pointed towards a direct association amongst ER-β along with apoptosis. These outcomes agreed with the earlier work of group of Ieraldi., *et al.* [29], namely the colocation of ER-β as well as caspase3, a well appreciate clear marker of apoptosis [32]. Moreover, the epithelial cell migration was seen in the normal epithelium from the base of the crypt to the top of the villi for the assessment of this dietary formulation in the normal physiological event. The observation regarding epithelial migration in case of normal tissue was more rapid enrichment group in contrast to the standardized diet group that pointed to a decreased cellular half-life, thus reduction of the time of exposure to DNA generating cells to risk of mutation. Actually, the decreased cellular half-life resulted in exaggerated turnover, hence to an earlier cellular demise, that in all processes which avoid the tumor growth as well as accrual of DNA mutations which facilitate Carcinogenesis. The chemopreventive actions of the same dietary formulation was further evaluated in Apc Min/+mice. in contrast to the standardized diet, the enrichment diet group decreased the full along with average polypoidal lesion numbers as well as regions of LGD along with CRC. Additionally, a significant reduction in the size of the polyp took place in the enrichment diet group (Figure 2). The ER-β protein illustrated that a considerable signal was correlated with the dietary supplementation, along with normal mucosa, cleaved caspase3 illustrated a greater robust signal in the enrichment diet grp in contrast to standardized diet. This outcome validated the robust correlation amongst ER-β along with apoptosis. The expression of Cyclin D1 (namely a marker of cell proliferation) was greater in standardized diet than the enrichment diet grp of normal as well as polypoid tissue. Epithelial migration in case of normal tissue illustrated a design akin to that in AOM/DSS animal models. The actions of dietary formulation consumption apparently was modulated by the decreased epithelial proliferation, escalated apoptosis, in addition to aggravated villous cell renewing with a decreased risk of DNA mutations.

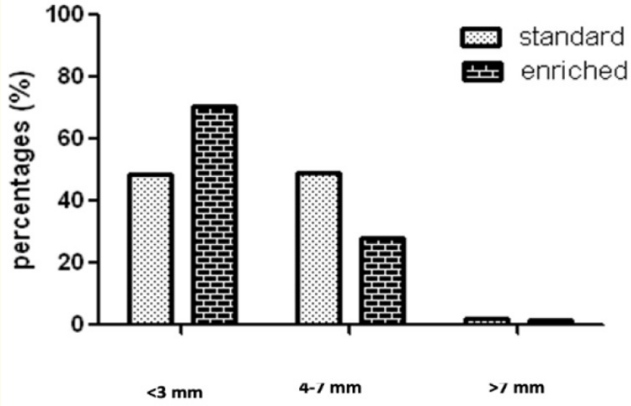

Figure 2: Courtesy ref no-29-Percentage of small (<3 mm), intermediate (3-7 mm) and large (>7 mm) polypoid lesions in ApcMin/+ mice assuming standard or enriched diet. Statistical analysis (Chi square for trend, $p < 0.001$).

These studies pointed that utilization of a combination of various phytochemicals in CRC chemoprevention in animal models. The benefit of the mixture is apparently correlated with the synergistic actions pointed by the dosage utilization of the nutritional constituents which in turn out to be lesser that the once utilized in the Single *in vivo* experiments in the same animal models [24,33].

Human Clinical studies

Assessment of Curcumin has been performed in early preclinical studies for analysis of the maximum tolerated dosages. Actually, it has been acknowledged regarding greater dosages of curcumin or its continued exposure might result in hepatobiliary inimical actions by interference with the cholecystokinin signaling.

Storka A., *et al.* [34], analyzed the safety of curcumin at dosages varying from 10-400mg/m^2. The maximum tolerated dosages were the liposomal curcumin in 120mg/m^2, besides resulted in the avoidance of mean red blood cells volume in the blood, usually seen at greater dosages.

Other preclinical studies that were attempting to find if subsequent to curcumin consumption, certain of its metabolites (curcuminoids) might be observed in epithelial tissues. Like echinocytes in a group of of26 individuals ingesting 2.35g daily for 14 days, curcuminoids were found in 28/35 biopsy samples, hence validated that curcumin absorption in addition to binding to colonocytes [35].

Furthermore assessment of curcumin has been performed in healthy individuals for assessment of conferring protection against Oxidative stress (OS). Regarding this it was illustrated that a dosage of 3.6g daily possessed the capacity of decreasing DNA adducts on colon biopsy samples [29]. Akin to that its administration was made in smokers at 2-4 g daily doses for 30 days, demonstrating that just higher doses possessed the capacity of reduction of numbers of abnormal crypt foci in the colon [29]. Nevertheless, the same study could not illustrate a decrease of epithelial proliferation index by Ki67.

Moreover, Cruz-Correa M., *et al.* [36], for illustration of its applications in familial adenomatous reduction polyposis (FAP) delivered a mixture of curcumin 480mg as well as quercetin 20mgt. i. d for6mths, followed by endoscopic demonstration of 60% of reduction of polyp numbers along with 50% decrease of polyp sizes. Subsequently Cruz-Correa M., *et al.* [37], in case of a randomized placebo-controlled trial, evaluated a greater dosage of curcumin (1500mg b.d) for a year in44 in patients with FAP [65]. Astonishingly, no variation in polyp numbers along with sizes amongst placebo as well as curcumin was observed. Moreover, a case report [38], in a patient with 54 polyps at index colonoscopy with all the genetic investigation negative regarding genetic polyposis illustrated intriguingly that subsequent to approximately 40 polyps surgical elimination, administration of 400mg curcuminfor3mths followed by silibinin. Following 2yrs just3 polyps were picked up at the follow up colonoscopy.

Lastly utilization of curcumin has been performed in the form of adjunctive treat men regarding advanced Colorectal cancer with attractive outcomes. Like patients going via FOLFOX regimen got randomized to 2g curcumin daily or no supplementation for12 cycles [39]. This phase IIa open labelled randomized control trial illustrated that an enhancement of overall survival in curcumin group, in spite of no enhancement of quality of life (QOL) or neuro toxicity was seen. An akin study in continuing [40], here inoperable Colorectal cancer (CUFOX) would be randomized to curcumin vs placebo besides FOLFOX regimen. Here different curcumin dosages varying from 0.5-2g daily would get utilized. Lastly, a phase I study in a small group of patients with metastatic Colorectal cancer who ingested liposomal curcumin (300mg/m twice weekly for8wks) did not demonstrate any antitumor action in decreasing cancer size as per RECIST criteria [41]. Thus, in conclusions the studies analyzed did not yield unequivocal outcomes. Nevertheless, probability of negative outcomes were seen in extreme situations like in patients with advanced cancer along with patients with greater genetic load (like FAP individuals). Hence probably this phytochemical could not have enough robust impact of getting over these situations. Thus, as a sequel study conducted in individuals possessing the collective risks of CRC with the idea of validating the action on pre-cancerous lesions could add greater intriguing conclusions.

Inimical actions of curcumin

Detailed assessment of inimical actions of curcumin have been attempted. Turmeric extracts along with curcumin have not demonstrated any main toxic actions on administration to rodents. Furthermore, no mutagenic or genotoxic actions were seen in case of pregnant animals [29]. Five randomized control trials detailed inimical actions of curcumin. Rehmani., *et al.* [42], illustrated that 2 patients generated concomitant abdominal pain as well as nausea, another one only had abdominal pain. Amin., *et al.* [43], illustrated certain adverse actions like nausea in addition to dyspepsia, despite no detailing of the full numbers of patients experiencing the same. Cheungsamarn., *et al.* [44], revealed these curcumin correlated- Inimical actions in 4 patients; constipation (2), hot flashes (1) as well as nausea in 1 more Nevertheless., In the last study mild diarrhea in 2 patients, while in the placebo group vertigo, itching, constipation besides hot flashes in 1 each. Selvi., *et al.* [45], observed mild diarrhea in 2 patients.

Twelve systematic reviews documented adverse actions clubbed as mild as well as akin to a placebo.

The commonest ones being abdominal pain, nausea as well as dyspepsia.

Intriguingly Medina-Caliz., *et al.* [46] in an assessment of herbal along with dietary supplementation were implicated in 4% (32subjects) of the full 856 drug induced liver damages. These kinds of processes took place more commonly in younger pregnant women that were correlated with the hepatocellular damage accompanied with escalated transaminase quantities. Herbal along with dietary supplements were implicated in greater robust damage in contrast to those seen with other kinds of drug induced liver damages. Furthermore the recurrence of liver dysfunction was more probably following secondary repeat exposures. Imam., *et al.* [47], by chance detailed a case report of hepatocellular damage that got induction in a 78 yr old woman presenting with jaundice with latent period of a mth [78]. Laboratory investigations could not observe any etiology of hepatitis. The Roussel Uclaff Causality Assessment Method (RUCAM) score was 6 pointing to a probable correlation. Peak quantities of alanine amino transferase (ALT) as well as aspartate amino transferase (AST) were greater than 20-fold of the upper limit. A 50% decrease was observed in a wk of the supplements omission, whereas reverting of transaminase quantities was observed in 42days.No rechallenge was attempted. Hence in conclusions apparently curcumin is safe, however studies in children along with adolescents or pregnant women, along with trials concentrating on nano formulations are essential to finish validating its security.

Role of Human CRC patient- derived organoids (PDO)

Human CRC patient- derived organoids (PDO) are robust ex vivo platforms for direct evaluation of the influence of molecular changes along with treatment on tumor cell proliferation, differentiation, reaction to chemotherapy, tumor microenvironment cross-talk along with other aspects of CRC biology. Studies implicating next generation sequencing have illustrated that CRC is a considerably heterogenous disease with numerous unique subtypes. PDOs reflect an attractive newer technology for evaluation of CRC In view of their capacity of precise recollecting their source tumor along with hence ensuring reproducibility of heterogeneity. Hence Ding., *et al.* [48], reviewed the state of art for PDOs in the assessment of cancer stem cells (CSC's) along with cancer stem cells niche. Concentration of research are gaining insight regarding applicability

of CRC correlated paracrine signaling, besides crosstalk amongst CRC as well as tumor microenvironment along with recapitulating CRC induced resistance to chemotherapies along with targeted therapies. Lastly they outlined the present observations, besides isolation in addition to validation of CRC targets along with their probability of utilization in individualized medicine (see figure 3).

Further Oio A., *et al.* [49], summarized how curcumin impacted its antiproliferative action against Colon cancer Cell lines *in vitro* along with *in vivo* by different modes inclusive of intrinsic as well as extrinsic apoptotic signaling pathways (see figure 4 and 5), halting of the expression cell cycle besides activation of autophagy.

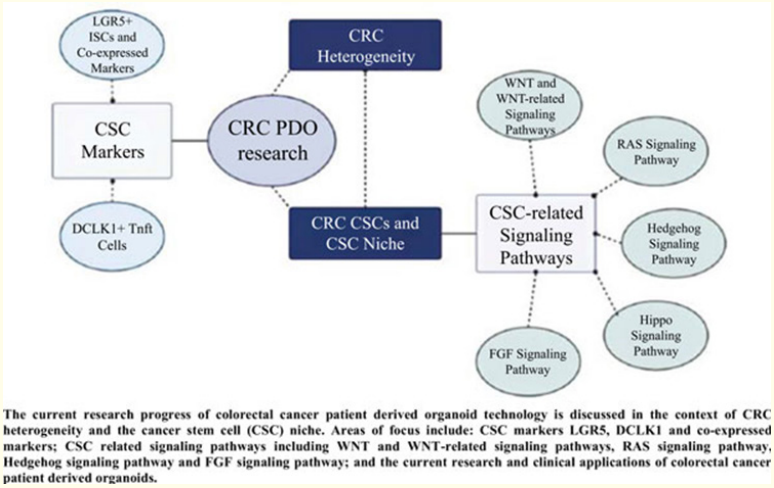

Figure 3: Courtesy ref no-48-Graphical abstract.

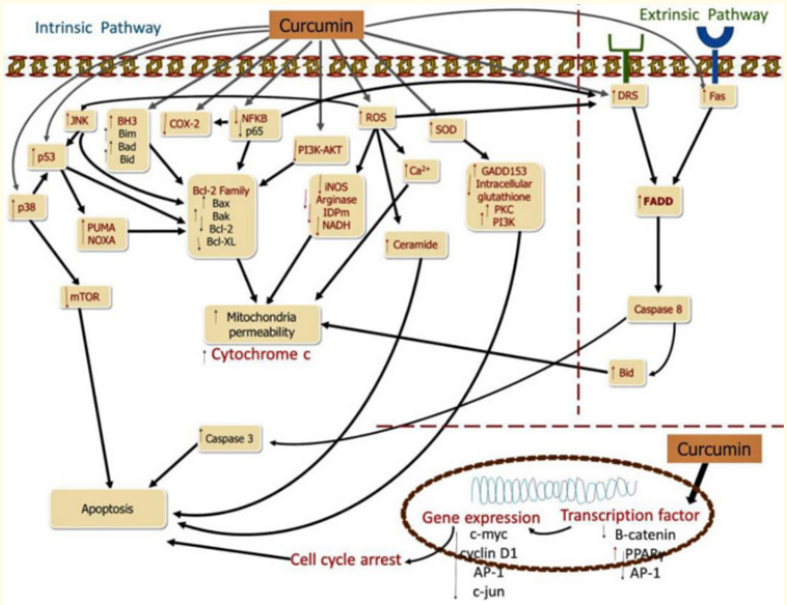

Figure 4: Courtesy ref no-49- Curcumin induces apoptosis in CRC.

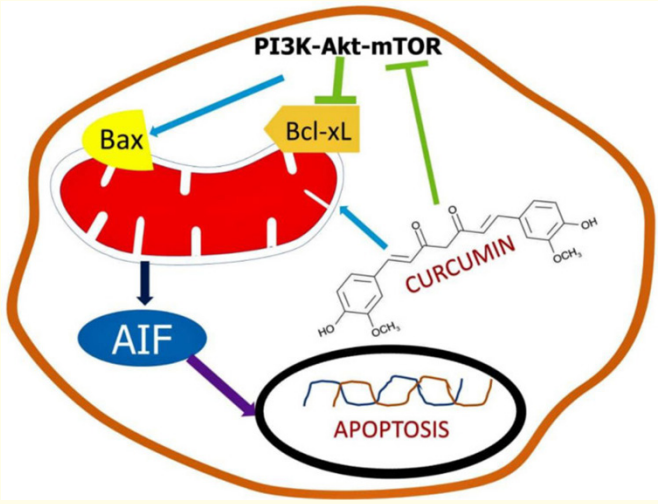

Figure 5: Courtesy ref no-49- Curcumin induces apoptosis in CRC.

Curcumin possesses anti-angiogenesis action. They further emphasized on the key part of curcumin in CRC chemoprevention [49].

Conclusions

Earlier we had reviewed the part of curcumin as an antioxidant, anti-inflammatory, neuro shielding, anticancer, hepatoprotection, as well as cardio shielding actions. Further its bioavailability issues, bio effectiveness as well as safety parameters along with quality properties of Curcumin were further tackled, besides its role in PCOS [50,51]. Here we have concentrated on the part of curcumin as an anticancer agent. It has been validated in numerous ways that curcumin is a substance of plant origin that possesses the capacity of avoidance of CRC. Probability of various modes being implicated in curcumin's anti CRC actions have been illustrated in studies conducted in *in vitro* along with *in vivo* animal models inclusive of intrinsic as well as extrinsic apoptotic signaling pathways. Furthermore, proof exists of clinical advantages in mice having inflammatory along with genetic CRC. Curcumin has been delivered by itself or combined with substances or particles which aid in transportation besides escalating its absorption on oral administration. Moreover utilization of curcumin has been made as constituent of dietary formulations containing agents of plant origin that. This characteristic gives favourable anticipation in humans. However no definite proof exists regarding feasibility of translation of outcomes obtained on cultured cells or animal models in human. Actually, occasional human clinical studies are present, besides have illustrated contradictory outcomes. Moreover, queries with regards to dosage, bioavailability, ideal indication as well as probability of toxicity requires clarification in further studies with bigger sample sizes.

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