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Review

Multiple strategies with the synergistic approach for addressing colorectal cancer

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ABSTRACT

Cancer treatment is improving widely over time, but finding a proper defender to beat them seems like a distant dream. The quest for identification and discovery of drugs with an effective action is still a vital work. The role of a membrane protein called P-glycoprotein, which functions as garbage chute that efflux the waste, xenobiotics, and toxins out of the cancer cells acts as a major reason behind the therapeutic failure of most chemotherapeutic drugs. In this review, we mainly focused on a multiple strategies by employing 5-Fluorouracil, curcumin, and lipids in Nano formulation for the possible treatment of colorectal cancer and its metastasis. Eventually, multidrug resistance and angiogenesis can be altered and it would be helpful in colorectal cancer targeting.We have depicted the possible way for the depletion of colorectal cancer cells without disturbing the normal cells. The concept of focusing on multiple pathways for marking the colorectal cancer cells could help in activating one among the pathways if the other one fails. The activity of the 5-Fluorouracil can be enhanced with the help of curcumin which acts as a chemosensitizer, chemotherapeutic agent, and even for altering the resistance. As we eat to survive, so do the cancer cells. The cancer cells utilize the energy source to stay alive and survive. Fatty acids can be used as the energy source and this concept can be employed for targeting the colorectal cancer cells and also for altering the resistant part.

1. Introduction

Cancer is a fractioned condition associated with abnormal cell growth along with the abrupt potential to spread or migrate to other body parts [1]. In contrast, there are few tumors called benign tumor which does not spread. Unhealthy food habits and sedentary lifestyles increase the risk of cancer and cancer-related death [2]. There are more than 100 types of cancer and the name starts from the place where cancer originates. The spread of cancer to other parts of the body is known as metastasis and once cancer starts to spread then the chances of recovery and the success rate of conventional therapy are also reduced [3]. In this review, we mainly focus on colorectal cancer and the approaches for its management.

Colorectal cancer usually attacks the large intestine and usually starts as a polyp in the intestinal walls. Colorectal cancer is the major cause of cancer-causing death in the United States [4]. Colorectal cancer can affect both men and women equally but when compared to women, men are mostly affected with the same, and it is the second most affected

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cancer after lung cancer [5]. The complication when we are focusing on colorectal cancer is that the signs and symptoms cannot be easily detected and the worrying signs and symptoms are mostly recognized at the later stages where the metastasis would have started and the survival rate becomes10–15% [6]. One of the major and most commonly seen symptoms of colorectal cancer is blood in the stool and pain while passing the bowel which is followed by inflammation and pain in the abdomen [7]. Noticing the tumor location in the colon, the adenoma or polyp is mainly observed in the area where the blood supply comes into the bowel wall, which in turn has diverse implications in research and therapy [8]. The development of cancer takes 5–10 years, and the spread is mainly to the blood and lymphatic system. The liver is the common part for the spread of metastatic cancer as the blood flows directly to the liver followed by lungs and bones [9].

For classifying colon cancer, the American Joined Committee of cancer introduced a staging system. T,N, and M depict the cancer growth areas. The growth area for the primary tumor is described as T Score, cancer growth near the colon or lymph node as N score, and spread to distant sites as M score. Apart from these there are five stages of colon cancer, numbered as 0,1,2,3, and 4 respectively [10,11].

Stage 0: This cancer is also considered an in-situ carcinoma of the colon. It is not invaded into the bowel walls and grown beyond the first layer [12]. The main drawback in this stage is that signs and symptoms are not explored more. If diagnosed conventional therapy is not needed once it is removed completely using endoscopic polypectomy [13].

Stage 1: the invasion of cancer to the second or third layer of the colon wall and the furthermore not detected into the nearby or distinct sites [14].

Stage 2: the invasion of cancer to the fourth layer of the colon wall and the furthermore not detected into the nearby or distinct sites [15].

Stage 3: Initiation of the spread of cancer to the nearby lymph nodes and the formation of tumor deposits where there is a formation of a secondary tumor [16].

Stage 4: The spread of the tumor to the distant organs such as lungs and liver, the metastasis had begun and the survival rate is reduced to 10–15% [17].

World health organization indicated that across the globe 1 in 6 deaths is mainly because of cancer [18]. In 2020, the statistics of colon cancer are at a rate with 36,257 patients, with a crude rate of 2.6, where the cumulative risk is around 1 in 298, whereas that of rectal cancer is 36,900 patients were affected with a crude rate of 2.6 and cumulative risk of around 1 in 295 [19]. Previous mortality and surveillance report shows that the cases of colorectal cancer are mainly seen in the age group above 50, but from 1990 it is noted that the cases of colorectal cancer are also reported in the age group below 50. Around 18,000 patients were detected with colorectal cancer in the age group below 50 in the year 2020 when reports were taken in the United States [20].

In this review,we have mainly focused on the mechanistic approach for the depletion of the cancer cells using multiple strategies. The first-line drug of choice for the treatment of colorectal cancer is 5- Fluorouracil, but it comes up along with various failures on the clinical side [21]. This criterion is managed by employing a combination strategy with curcumin, where its chemotherapeutic and chemosensitizing aspect can help to minimize the failure and besides the resistant part as well [22]. The lipids used in this concept can help to overcome the multidrug resistance-related issues and also hacking the cancer cells. This multiple strategic plans helps to achieve a better success rate for the management of colorectal cancer in a safely and effectively [23]. The approach for accomplishing this role is explained in detail in this review.

2. Conventional treatment modalities

The stages of the cancer are from 0 to 4, where stage 4 cancer requires more expansion conferring with our assumption [24]. Not all the tumors are identical. Some patients will develop metastasis restricted to the liver only maybe others have it in lymph nodes. So for this reason, a different treatment modality should be followed which may be necessarily a combination of surgery and chemotherapy in distinct sequencing. We feel that based on our hypothesis, we would be able to develop a formulation approach and a therapeutic modality that could be able to predict patients out comes in a better way both safely and effectively. Cancer treatment mainly includes surgery which involves the complete removal of cancer, radio or chemotherapy that kills the cells left behind, immune therapy, hormonal therapy, and targeted therapy, tailored for the individual type of cancer are sometimes used [25]. Sometimes this treatment can be effective but 100% cure cannot be assured. So a better option should be established that can be used for different types of cancer safely and effectively. The complications in the conventional method of treatment include fatigue, GI toxicity, radiation therapy- mutagenic, nausea, hair loss, loss of appetite, and vomiting [26].

The use of natural products for the treatment of cancer is gaining prominence. World Health Organization (WHO) evaluated that around 80% of the population across the globe relies on natural products of plant-based origin as the medicine for primary healthcare [27]. Moreover, the use of natural products is considered to be safe, more natural, holistic, and symptomatic- relief (pain and nausea). Indian scenario follows the use of natural ingredients for the treatment of cancer by targeting naturally derived peptides such as the use of necrotic peptides, apoptotic peptides, angiogenic peptides, functional blocking peptides, and immune-stimulatory peptides with the ability to activate tumor regression [28,29]. The Indian Americans pioneering the cancer research focusing on herbal extracts on January 11 2011 with the study on curcumin [30]. A dose of 12 g of curcumin was orally administered for 3 months and found to inhibit the cell proliferation with no side effects in the animals [31]. Foreign scenario: for the usage of natural products for cancer care, they reported with the study on curcumin (diferuloyl methane), the active compound in the spice turmeric, has the potential of an anti-proliferator activity on a variety of cancer cell lines and can directly induce cancer cell apoptosis. Bharat Aggarwal, Professor of cancer medicine, at Texas University researched the activity of turmeric on cancer [32]. People who consume plant-based food products are less likely to die from cancer or heart-related disorders [33]. As the pain in association with the conventional treatment methods, as it mainly includes the use of injections, it is being depicted that 89% of the people prefer to have oral dosage form as compared to injections [34].

3. Why it is hard to cure cancer?

There are some problems associated with colorectal cancer research that scientists need to solve.

A better way of study to cancer is needed as most cancer studies are carried out with the use of human cancer cells cultured in the lab [35]. This cell describes cancer genetics but lacks complexity when considered with the developed organism. This is the major reason where most of the newly developed drugs fail when it comes to the real picture in clinical trials [36].

Genetic mutation of cells in different parts of cancer can result in developing into unique subclones. This makes the cancer treatment more complicated since the drug which works on one clone fails to react with other subclones [37].

The dynamic interconnected ecosystem-like nature of cancer cells leads to failure in the therapy [38]. This is the phenomenon where cancer cells can communicate and invade nearby healthy cells. They can utilize the normal cells to produce blood vessels to feed them and for the removal of waste materials. This action can even extend to the immune

system to suppress its function, making it unrecognized, and from destroying or immunizing the cancer cells [39].

Cancer stem cell eradication, the formation of cancer stem cells is rare, but it comes with a special property of contributing resistance to chemo and radiotherapy [40]. The complete eradication of cancer stem cells is required if we have to follow any kind of treatment modalities [41]. If we leave behind a single residue it can also lead to the growth and development of newer ones.

Targeting these stubborn cancer cells is another issue, although if this problem is solved [42]. These cancer cells are masters in adopting, adjusting their cellular and molecular characterization receiving under stress. The cancer cells can be bombarded by chemo or radiotherapy because some can create a protective shield and change the expression of the gene [43].

Malignant cancer cells are usually complex that can adapt and evolve constantly. To fight for them, we need an expert system that can match their complexity and control and as the better treatment option adjusts as the cancer changes. The oral dosage form is having better patient compliance as compared to that of injections, but they are limited due to idiosyncratic physiochemical properties, and biological barriers like gastrointestinal instability, and pre systemic metabolism [44].

The molecular basis of drug resistance in the case of cancer drugs is complex and in turn, elevates the enzyme level that aids in neutralizing the anti-cancer drugs [45]. The major reason behind this is the over-expression of the P-gp belonging to the family of MDR transporters, which modulates the efflux pump mechanism for the transport of the chemotherapeutic agents out of the cells thereby depleting the inter-cellular drug dose, down to the level of lethal threshold. The cellular factors answerable for attaining the sub-therapeutic concentration within the cancer cells are associated with an increase in drug efflux, DNA repair, drug metabolism, apoptotic machinery, and lack of apoptotic machinery [46]. The conventional chemotherapeutic regimen can only kill the drug-sensitive cells where the drug resistance cells or the cells which show mild expression for MDR is left behind. If these cells are left behind or untreated, they can even spread adversely causing damage to the other tissues within [47].

4. Challenges for multi-drug resistance

Resistance is a phenomenon where the cells in our body efflux the foreign particles that enter into the cells. It is a kind of natural defense mechanism in our body, where the body cells protect us from the invaders [48]. The same mechanism happens inside the cancer cells as well. The cancer cells resist themselves and efflux entry of the drugs which in turn have an adverse effect of reducing the therapeutic concentration of drugs inside the cells and ultimately results in the failure of the therapeutic regimen. The cancer cells show resistance to a broad spectrum of drugs belonging to their family [49]. Not only the cancer cells, almost all the cells in our body show resistance to the drug which is the major issue while focusing on various treatment strategies. The causes of resistance can be divided into two categories, intrinsic resistance, and acquired resistance. If the cancer cells developed intrinsic resistance then the cancer cells do not respond to the anticancer treatment at all or become sensitive to some of the drugs over the course of therapy [50]. In the Multidrug resistance protein family, the major reason for resistance created in the colorectal cancer cells is associated with the action of P-glycoprotein (P-gp). In colorectal cancer cells, the activity and function of P-gp are predominantly expressed. Colorectal cancer cells are insensitive to most of the anticancer drugs from the beginning of therapy; this is called intrinsic resistance [51].

5. P-gp emanation and its concept

In Multidrug-resistant colorectal cancer cells, an increase in the level of P-glycoprotein is observed, which is proven to be functional as an energy-dependent drug efflux pump with widerange of specificity for the toxicity of hydrophobic drugs [52]. Orally administered drugs that are P-gp substrates are less absorbed and show less physiological action as the expression of P-gp is found in the entire region of the gastrointestinal tract. The gut flora composition, the time of the day, sakidian factors, dietary, inflammation factors, and also stress regulate the expression of P-gp. P-gp reduces the bioavailability and distribution of most of the cytotoxic drugs and reduces the efficacy of colorectal cancer treatment also known as Phase III detoxification, which means detoxifying the cells in a non-specific manner [53]. The efflux mechanism mostly confines on the quantity of the P-gp present in the cancer cells or cell membrane. Mostly the P-gp expression is mainly observed in the colorectal cancer cells than in colorectal cells [54]. The over-expression of P-gp in the intestinal region,makes the chemotherapeutic drugs as its substrate and act on the absorption pathway. Hence the therapeutic concentration and the bioavailability of the drugs are not attained inside the cancer cells, on the other hand, the concentration of the drugs on the plasma and blood will attain its supratherapeutic and toxic level leading to toxicity to the normal cells [55]. The chemotherapeutic agents, xenobiotics, and toxic substances act as substrates. The infiltration of the substrate into the P-gp is through the inner leaflet of the membrane or the protein cytoplasmic side [56]. Adenosine triphosphate (ATP) approaches to the cytoplasmic front of the P-gp, following with its binding, hydrolysis of ATP appears to follow the throwing out of the substrate to efflux out of the cell. The excretion of the substrate occurs with the discharge of the phosphate the molecular ATP. A new molecule gets attached to the ATP secondary binding site, which results in the release of adenosine diphosphate (ADP). The reaction will proceed with the release and hydrolysis of ADP and phosphate molecule to transplant the protein [57].

6. Beating the action of P-gp on colorectal cancer cells

Overcoming the P-gp and inhibiting its action is one of the major criteria to be undergone for effective delivery of the drug to colorectal cancer cells. The action of the P-gp should be mimicked in such a way that it will not disrupt the natural defense mechanism of the body [58]. If the action of the P-gp is reversed then the whole body mechanism will be collapsed and it can even lead to more adverse effects in our body. For altering the activity of P-gp, the inhibitors of P-gp are mainly developed. The action exhibited by the P-gp is mainly by two mechanisms, i) driving to the extracellular membrane leaflet or ii) attachment to the P-gp protein molecule before getting detached [59]. The P-gp inhibitors are classified into first-generation, second-generation, and third-generation inhibitors. The molecules belonging to these classes are mainly chemical motifs that show less efficacy and more toxicity-related issues, this advised the scientists to focus on the use of natural ingredients for the management of P-gp activity which would be more safe and effective [60].

7. 5-FU and its substantial effect on P-gp

5-fluorouracil (5-FU) is an analog of fluoropyrimidine and the mechanism of action is via inactivating thymidylate synthase (TS) and repair of DNA by incorporating its metabolites directly into DNA and RNA of tumor cells [61]. The use of 5-FU is already proven as first-line therapy for the treatment of various cancer including colorectal cancer.5-FU has shown to be somewhat finite due to its limited success, toxicity, and its associated adverse effects [62]. The use of the 5-FU is challenging when focused on the clinical side due to its poor selectivity and side effects such as mucositis, myelosuppression, emesis, nausea, and hand-foot syndrome. The poor biopharmaceutical characteristics such as poor absorption, short biological half-life (10–20 min), and rapid catabolism make the 5-FU regimen more challenging. Treatment of colorectal cancer with 5-FU is challenging as 15–20% of the patients developed resistance towards this drug and also showed a 50–60% of recurrence rate [63]. 5-FU is used alone or in combination with other drugs for the treatment of cancer or with anti-epidermal growth factor

agents or anti-angiogenic agents. But when focused on clinical approach, its use is limited because of dose-related toxic effects, and mainly due to the multidrug resistance issues, related to the TS over-expression [64], cyclooxygenase-2 (COX-2) [65], nuclear transcription factors [66] (NF-kB), insulin-like growth factor 1 receptors [67] (IGF-1), human epithelial growth factor receptor [68,69] (EGFR) and multidrug resistance gene 1 encoding transporter P-glycoprotein (P-gp), etc. The activation of NF-kB is by stimulating the bacterial products, inflammatory cytokines, phorbolesters, reactive oxygen species, and other molecules via degradation and phosphorylation of IKB kinase followed by the stimulation of NF-kB, which enhances the transcription of genes to be targeted [70]. Various studies have depicted that NF-kB is the extensive downstream ramify for chemoresistance in various conventional therapy and activation of NF-kB was also elicited with multidrug resistance development. Further, NF-kB determines the expression of various gene products such as COX-2, BCLxl, Bcl-2, P^{53}, cyclin D1, and Fas, which is associated with apoptosis and carcinogenesis of cancer cells [71]. When 5-FU is exposed to cancer cells for a longer period, results in the activation and expression of Bcl-2, Bax, and P^{53}dysregulation leads to activation of MDR proteins. COX-2 is an inducible enzyme and its overexpression results in the progression of various cancers including colon cancer. HER2, EGFR belongs to the family of human epidermal growth factor receptor mediate the proliferation, migration, invasion, and differentiation of tumor target through various signaling pathways and become an important trigger for anticancer drugs. For the progression and development of cancer cells, IGF-IR insulin-like growth factor 1 receptor, a transcription membrane glycoprotein, with the efficacy of tyrosine kinase is associated [72,73]. The abnormalities in the action of HER2, EGFR, and IGF-IR can be associated with the progression of MDR. Activation of P-gp has a leading role in the activity of MDR. Some reports elicit that the therapeutic activity of 5-FU is enhanced with the increase in dose [74]. But with the increase in the dose, the cytotoxicity is increased to the normal cells gradually rising with unwanted side effects. To overcome these effects a combination strategy can be adopted with other chemotherapeutic agents and opt for various mechanistic activities [75].

8. Speed of the cancer and its cure using your grocery store ingredient

Cancer is considered as a disease where normal cells are converted into atypically dividing cells; when it is allowed untreated it can migrate to other body parts and become dreadful [76]. Though various conventional treatment modalities are available, the recovery rate is reducing drastically as 30–80% of patients are developing resistance. Mostly the patients are turning towards the natural remedies due to the adverse effects of the conventional methods and cost of the therapy [77]. Nature has the remedy for almost all the disorders in this world. Flavonoids are the natural ingredient that can be used for the prevention, treatment, and management of cancer safely and effectively. One more advantage of using flavonoids in nature's perspective is the less contamination of the environment [78]. Flavonoids are used for the therapeutic management of cancer as a chemosensitizer and chemotherapeutic agent. Flavonoids can also act as a natural P-gp inhibitor, due to the adverse effects and the side effects of first, second, and third-generation inhibitors; the flavonoids which are the fourth generation of P-gp inhibitors are mostly used [79]. Contemporary research proposed that curcumin, a polyphenolic compound, a major non-toxic compound found in turmeric, can be advised to be used in enhancing the sensitivity of cancer cells to chemotherapeutic agents by inhibiting the pathway that results in the chemoresistance development in cancer cells.

Curcumin is a flavonoid proven with chemotherapeutic and chemosensitizing effects. The ability of the curcumin to get absorbed at the lower part of the Gastrointestinal tract made it a good candidate for the treatment of colorectal cancer [80].

9. The ability of the kitchen ingredient; curcumin against colorectal cancer

Curcumin [1,7bis (4-hydroxy-3- Methoxyphenyl) 1,6- heptadiene-3,5 dione, $C_{21}H_{20}O_6$, M Wgt: 368.37 g/mol] is naturally available from the roots of the plant belonging to the family Zingiberaceae [81]. For centuries these plants and their major metabolite curcumin is used as a food additive. Curcumin is a potent candidate for the treatment of various disorders such as cardiovascular events, anti-rheumatism, liver disorder, anticancer agents, and also as antioxidant and anti-inflammatory agents [82]. The action of curcumin is potent for the treatment and therapeutic modulation of various cancer such as colorectal, gastric, liver, lung, prostate, esophageal, breast, and leukemia in preclinical and clinical studies. Curcumin can act as a radio or chemosensitizer in most cancer cells can inhibit angiogenesis and act as a P-gp inhibitor which is a promising approach for the treatment of colorectal cancer [83]. But the oral administration of turmeric or curcumin can't help in meeting its therapeutic index as the body rapidly breaks down these molecules into its metabolites [84].

Curcumin possesses anticancer activities intimately associated with a mechanistic approach such as proliferation, development, invasion, transformation, angiogenesis, and metastasis by affecting cytokinesis, transcription factors, tumor necrosis factors (TNF), reactive oxygen species (ROS), NF-kB, COX-2, signal transducer and activator of transcription (STAT), matrix metalloproteinase (MMPs), and protein kinase B (Akt),etc [85].

The role of curcumin for reversing the activity of multidrug resistance and multidrug resistance protein was proven, by involving in various mechanisms including apoptosis induction, anti-proliferation, suppression of epithelial-mesenchymal transition (EMT), and blocking cell cycle arrest of cancer cells [86]. The action of curcumin for reversing the MDR is by inhibiting P-gp and also by promoting the activation of caspase-3. P13k/Akt/ mToR, as one of the principle cell signal pathways, can involve proliferation, metastasis, survival, and mortality and is generally stimulated in cancer cells. Its stimulation is normally associated with the activation and development of MDR in cancer cells [87]. P13k activation can convert phosphatidylinositol 4,5-bisphosphate (PIP2) into Phosphatidylinositol 3,4,5-triphosphate (PIP3) to phosphorylate Akt and promote activation of Akt- mediation of downstream targets along with tuberous sclerosis complex-2 (TSC2) Bcl-2 family membranes, and mouse double minute 2 homolog (MdM2) [88]. Moreover, PTEN can negatively regulate the process by PIP3 dephosphorylation to inhibit the action of P13K/Akt/MTOR signaling pathway [89]. Studies depict that curcumin can inhibit the P-gp expression via deactivating P13K/Akt/Nf-kB signaling pathway for reversing the MDR. Cells experiencing an epithelial-mesenchymal transition (EMT) exhibit a comparable aspect to cancer stem cells (CSCs) with a similar phenotype of drug resistance [90]. Curcumin has the potential to modulate EMT for regulating MDR. The activity of STAT3 was detected during cancer cell progression. The activity of curcumin and its analogs by inhibiting the expression of STAT3 and finally reversing MDR were also reported [91].

Curcumin can be used as a cell proliferation inhibitor, have pro-apoptotic activity, inhibit angiogenesis, COX-2, carcinogenesis, down-regulation of Epidermal growth factor receptor-2, and transcription factor NF-kB, including AP-1 inhibitor [92]. The potency of curcumin came up with the publication of 12,595 papers between 1924 and 2018, in this 37% focused mainly on cancer.

10. 5-FU, curcumin and its synergistic activity: a battle front

In addition, reports also came up with the synergistic effect of curcumin as a chemosensitizer, chemotherapeutic agent and also can overcome MDR issues by reducing the toxicity, and improve the anticancer efficacy of drugs such as 5-FU (routinely used in patients with colorectal cancer), paclitaxel, gemcitabine, doxorubicin, oxaliplatin, cisplatin, and so on [93]. When curcumin is combined with other

anticancer agents, it won't increase the toxicity of synergistic ones thus making it a good candidate for combination therapy.Curcumin when given in combination with 5-FU, enhances the chemosensitivity of the first-line chemotherapeutic agent (5-FU) for colorectal cancer by targeting Src, NF-kB, and NF-NB dependent regulated gene products. When observed in high-density culture, curcumin used alone or in a 5-FU combination can eminently inhibit the formation of colonoscopy, induce apoptosis, inhibit proliferation, down-regulated colon cancer cell markers in MMR deficient 5-FU resistant cells [94].

11. Fuel for the hungry cancer cells

Hungry cancer cells require energy sources for meeting their nutritional demand, and as cellular building blocks for their growth, division, and metabolism changes. Monoacylglycerollipase (MAL) organizes the networking of fatty acid that develops pathogenesis of cancer [95]. MAL is mainly unregulated in primary tumors and aggressive cancer cells. MAL regulates the metabolism of fatty acids and maintains tumor signaling, which holds with the pathogenicity of cancer. The cancer cells can be called the molecular factory that plays an important role in the uptake of lipids [96]. The cancer cells shift from catabolism to anabolism, to produce a higher amount of lipids that are required for the irrigorous proliferation and metabolism. MAL is well organized in primary tumor cells and aggressive human cancer cells which have the capability to fatty acid network regulation in oncogenic signaling lipase hence promoting the invasion, migration, in vivo tumor growth, and survival of the cancer cells [97].

Lipid droplets (LD) are organelles that concentrate neutral lipids mostly di-asoglycol and tri-asoglycol and widely activate metabolic homeostasis. For signaling purposes also the lipid droplets are available. The lipids that are synthesized in the cytoplasm can be relocated to the endoplasmic reticulum and can be stored in lipid droplets [98]. In the cancer cells due to their higher energy need, the lipids are released by lipase as free fatty acids and can enter into the beta-oxidation cycle. The hydrolysis of triacylglycerol (TAG) reserved in the LD compartments brings as a convenient energy source in conditions like cancer and even during fasting. For complete lipolysis to occur, three enzymatic reactions are required. TAG is converted into fatty acid and then into glycerol [99]. In the first step, adipocyte triglyceride lipase (ATGL) hydrolyzes TAG into diacylglycerol and fatty acid, in the second step with the use of hormone-sensitive lipase act on diacylglycerol, in the third step is catalyzed by monoacylglycerol lipase. The steps involved are illustrated in Fig. 1. Owing to their biological role diversity, the contribution of lipids to the different tumor biology aspects such as a source of energy, growth, and redox homeostasis, and besides for the cancer dissemination to form distant metastasis is remarkable. Even for the higher proliferation of cancer cells, the use of lipids as building blocks for the biological membranes is also noticed. Due to the less ordered inner structure, maximum lipids are generally recommended as safe (GRAS Category), hence have low toxicity-related issues [100].

(a) Cleavage of fatty acids from phospholipid pro-drugs and glyceride within the GI tract using a hydrolytic enzyme (Phospholipase and lipase) results in the formation of lysophospholipids and di-glycerides are integrated into altered pathways that exist for dietary lipid classification.
(b) When mono-glyceride pro-drug is once absorbed by enterocytes, they are exposed to re-esterification to form triglycerides like pro-drug.
(c) Simple lipophilic pro-drugs (typically ethers and esters) are once absorbed cohort with lipid lipophilic converted domains where preferentially pro-drug subdivided into the triglyceride core during the point at which the triglycerides are assembled into chylomicrons.

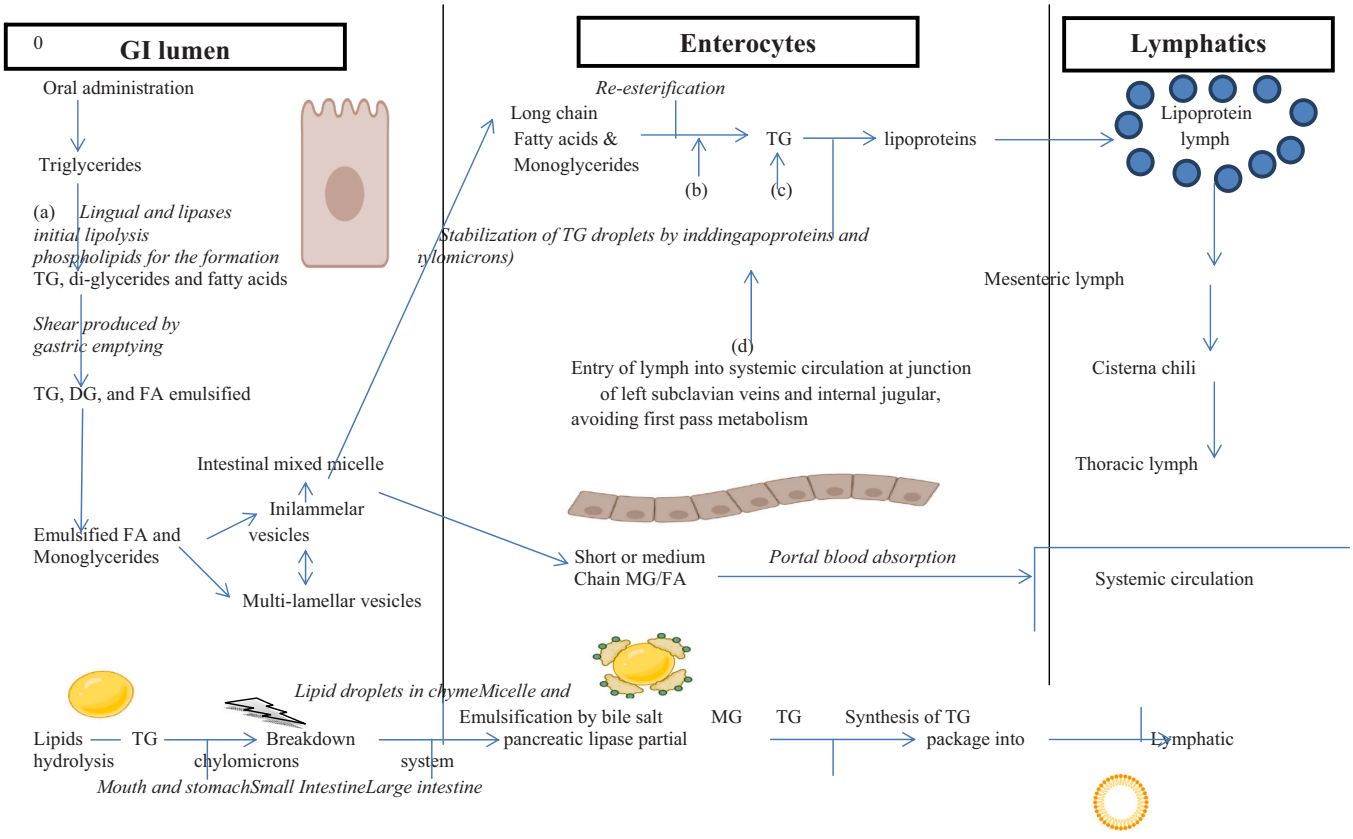

Fig. 1. Diagrammatic representation regarding the sequential process in lipid digestion and absorption through portal blood and intestinal lymphatics. The concept is based on pro-drug on various design approaches to different pathways before pro-drug transport.

(d) Phospholipids pro-drug accomplices with lymph lipoproteins at the junction of the point where natural apoproteins and phospholipids are supplemented as stabilizing agents to developing lipoprotein surface.

The fate of the lipids in our body is also represented through Fig. 1.

12. Lipid conjugates a chemistry based strategy

Triglycerides are usually assembled by linking the fatty acids with glycerol using ester linkage. Research strategies are developed by replacing the second position fatty acyl group with the drug molecule for taking the preference of TG metabolic pathway generally termed as triglycerides deacylation-reacylation pathway [101]. In this pathway, the hydrolysis of TG will take place to 2-monoglycerides and free fatty acid in the lumen of the gastrointestinal tract. This is then followed by the absorption of monoglycerides in the enterocytes, then reacylated to produce triglycerides [102]. Incorporation of triglycerides into lipoproteins takes place followed by its accumulation in the lymphatic system. The drugs conjugated to glycerides can take advantage to improve their absorption, enhance targeting to the lymphatic system, and it can even be helpful in cancer metastasis (since the studies reported that the metastasis of colorectal cancer is mainly through the lymph nodes) [103].

To reduce the toxicity of 5-FU, and improve therapeutic efficacy, 5-FU pro-drug can be synthesized, this can be prepared by conjugating 5-FU with lipids with a chemical linkage [104].

Regarding the dysregulated metabolic pathway, the lipogenic phenotype development or heightened de novo lipid biosynthesis has been pointed to play a leading role in cancer. Fatty acid synthase (FAS) is the primary enzyme involved in the de novo pathway which in turn FAS will act as a biomarker for cancer [105].

13. Lymphatic absorption of orally administered prodrug

The access of the orally administered drug to the systemic circulation is through the portal blood or via the intestinal lymphatic system transport. The effect on systemic circulation and limit on the amount of drug absorbed portal route depends on the hepatic first-pass metabolism [106]. The effect of lipophilic compounds in their interaction and association with enterocyte-derived lymph lipoprotein became relatively important for the absorption and transport through lymphatic route became important in quantitative drug transport pathway. The pivotal modulation of lymphatics as an integral part of the immune system, and precisely as a pipeline for the propagation of metastasis from severe solid tumors, have accomplished targeted delivery to lymphatics exceptionally attractive [107]. For a drug to get transported through the lymph node, primarily its high lipophilicity should be maintained. The log P value should be higher than 5. Ingested lipids dispersion into a coarse emulsion with high surface area, (like the nanoparticles) will increase the intestinal absorption. The mechanism behind the uptake of lipids products across the apical membrane of enterocytes can be through active or passive transport [108].

Inside the enterocytes, 2 monoglycerides and fatty acids are involved in severe lipid processing pathways. Rule of thumb illustrates that long chain and medium-chain fatty acids are resynthesized in enterocytes without going into the portal blood supply [109]. However, they follow the*denovo* pathway, where the synthetic part is illustrated in Fig. 2.

Lipophilic pro-drug targeting to the lymphatic transport pathway, after administrating orally will pass through simple amide or ester linkages to form a straight-chain or cyclic alkyl group. This strategy can be used for the drug targeting the lymphatic tissue and is phenomenal for the treatment of cancer [110].

14. The utility of lipid pro-drug for lymphatic delivery

To characterize fully the lymphatic absorption of the pro-drug administered orally, the necessity to study on animal model is very crucial [111]. Where the GIT physiology is comparable with humans, postprandial response differentiation can be observed and utilization of human-relevant sized dosage form is possible. It is the traditional method which was followed when the mesenteric lymph duct-cannulated rats are used to identify the impact of different formulation and also to determine the role of lipophilicity of pro-drug and pro-drug lipid transport. The triple-cannulated dog model is also available for the determination of pre and postprandial administration

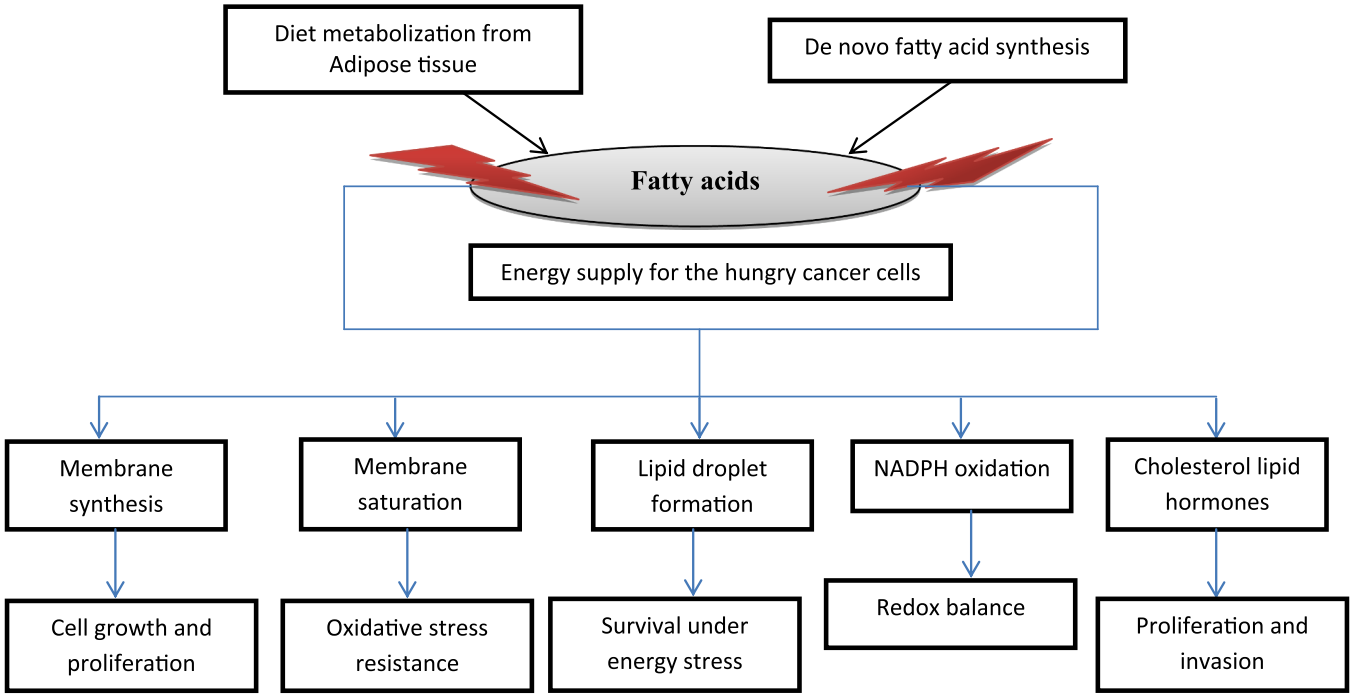

Fig. 2. Depicts the pathway and the mechanistic approach of fatty acid on cancer cells.

and transport of series of compounds [112].

15. A deal of nanoparticles on cancer cells

The main activity of the passive tumor specific drug delivery can be accomplished depending on the physiological and morphological difference between the cancer cells and normal ones. The use of the Nano-lipid carriers for cancer therapy can result in better features like higher drug loading capacity, good compatibility, high drug loading capacity, the feasibility of scaling up, and provide a controlled drug release [113]. By following the path of leaky vasculature of the cancer cells, otherwise called as EPR (enhanced permeation and retention) effect, aids the nanoemulsion and the molecules to easily influx into the extracellular space, where the undeveloped lymphatic drainage in the cancer cells, will never allow getting effluxed. Nanoparticles are used widely for the formulation and development of anti-infective, anti-cancer, and anti-inflammatory drugs [114]. The size range of the nanoparticles is from 1 to 100 nm. Types of nanoparticles include solid lipid, liposomes, micelle, metals, polymers, dendrimers, and quantum dots. The nanoparticles assemble are mostly multi-layered and its coating helps to overcome the problems related to solubility, stability, and specificity [115]. The problems associated with the macromolecules such as cell toxicity, low specificity, cellular uptake, and high dose can be reverted by using the nanoparticle-based approach and on the other hand, the issues related to MDR and P-gp efflux can also be altered. By accomplishing all these strategies, the therapeutic value of the drug can also be enhanced [116]. The size of the nanoparticles generally < 100 nm can impart inherent stealth. The lipophilic property of the drug makes it easy to get entrapped and for the formulation into nanoparticles. The conjugation of the parent first-line chemotherapeutic agent and the flavonoid with a lipid, in turn, increases the lipophilicity of the drug which helps in enhancing the entrapment efficiency while formulating into nanodroplets. The positive charge of the nanoemulsion system helps in interacting with the surface of the negative charge of cancer cells. This helps in the effective delivery of the nanoparticles onto the surface of the cancer cells [117]. No reports came up with the adverse effect or toxic effects of the nanoparticles after administered in 2D human and in-vivo [118]. These are proven with an evidential report that the toxicity-related issues are not much seen and do not produce any effects on the brain, heart, lungs, or kidney. A contradiction report came that accumulation of nanoparticles was seen in the body parts like liver and spleen [119]. This is mainly due to fact that these two organs are mainly involved in the filtration of blood. This accumulation part also adds an advantage to our hypothesis as the metastasis of colorectal cancer mainly occurs to the liver and lymph nodes [120]. From the evidential report on the study of nanoparticles, the drug moiety embedded in the nanoparticles shown with the potent anticancer property as compared to that of the drug motif given alone.

16. Concept on using dual lipids

Rapidly dividing cancer cells need more energy for growth and development. The use of the dual lipid concept, one in the conjugation part and the other in the formulation part can act as an effective energy source for the hungry cancer cells [121]. The lipids or fatty acids used in the synthesis part are for accomplishing the prodrug approach, and the conjugation of a hydrophilic and lipophilic drug. On the other hand with the use of the lipids in the formulation part mostly as a Nano droplet is involved in the concept of following the EPR effect, cancer cell targeting, energy source, and the ability to overcome the MDR in cancer cells [122]. The mechanistic action plan of this multiple strategic plans is depicted in Fig. 3.

17. Bulletin ideas for targeting colorectal region

Colon-specific drug delivery can be of pro-drug/ azo-polymer system, pH-dependent, pressure-dependent, and microbial triggered system. With our concept we are combining the use of the three approaches, one is the prodrug approach, and the other is the pH-dependent approach, following the concept of the microbial trigger system [123]. With the use of the lipid conjugation, the prodrug approach can be applied and the coating of the oral dosage form (tablets or spheroids) with the pH-dependent polymer, the concept of the delivery to the colorectal region can be accomplished to an extent [124]. For example with the use of the pectin as the pH-sensitive polymer, and also as a microbial triggering agent, the property of pectin by providing high strength of mucoadhesion on the large intestine compared to that of large intestine mucosa [125]. The digestion of pectin mainly is accomplished with the help of pectinolytic enzyme along with the influx of water into the core, pressure built up by cross-linked polyvinylpyrrolidone to the substances near to the core or matrix, accelerate the drug release into the colon.

18. Limitations

1. Conjugation of the drugs is challenging. The conjugates should be made after checking out the compatibility and related issues. Two types of conjugates are mainly possible, physical method or chemical

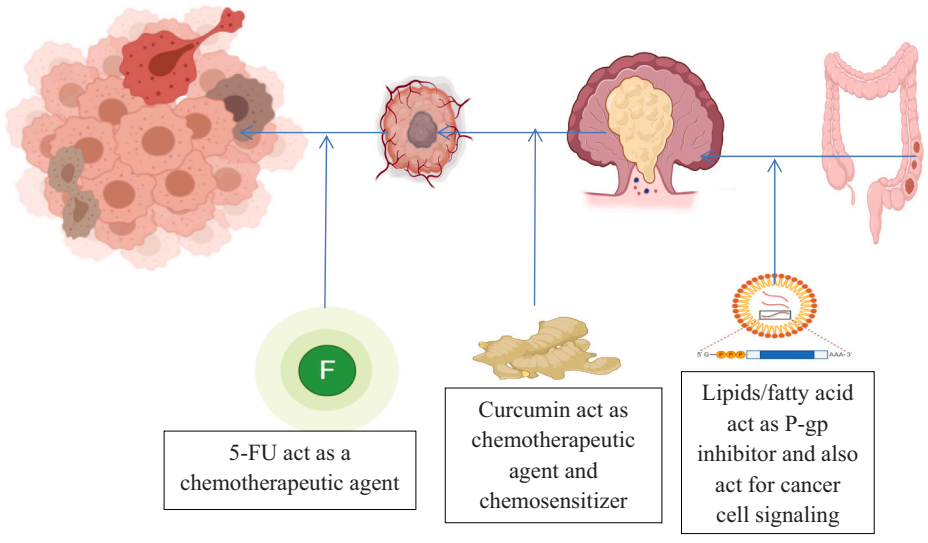

Fig. 3. Represents the multiple strategies involved with the action of the 5-Fluorouracil, lipids, and curcumin for the management of colorectal cancer.

method. For following the chemical synthesis method, the linkage of the bond is crucial, where the protocol development for the conjugation between 5-Fluorouracil, lipid, and curcumin is challenging.
2. The solubility-related issues are the other issue that needs to be considered. Screening of the oils and the surfactants is also a major criterion
3. Most of the research plans succeed when considered from the preclinical point of view but mostly fail in the clinical perspective.

A detailed explanation regarding the concept is described in Table 1, and the concept behind this is illustrated in Fig. 4.

19. The state of cancer, are we close to cure?

Innovations in the field of cancer treatment aim to consign notably some issues which typically interfere with the clinical and therapeutic problems in association with the health care professional are perspective [126]. These include tumor reoccurrence after treatment, unwanted side effects, surgery, or aggressive cancer that are resilient to a broad range of anti-cancer drugs. The research work based on cancer research mainly focuses on improving the absorption, solubility, bioavailability, and metabolism of conventional anticancer drugs [127]. They mostly manage these issues by mucoadhesion, targeted delivery, controlled release, enhance cellular uptake, and improved stability. Anticancer efficacy also depends on the quantity of drug-loaded. The major problem associated with the discovery plan is that most of the drugs fail when studies with in-vivo models and considering clinical trials [128]. The recent trend studies on 3D models of cell culture help to resemble the in-vitro and in-vivo reports [129]. To a greater extent, pharmacokinetics and bio distribution studies should also be considered. The issues involved in cell line studies are the effect of drugs on cell line response differs likewise in the patients [130]. The concept of combination therapy is good as its focuses on different cancer pathways. The combination strategy is well versed used as it put forward a synergistic approach also. This combination strategy can in turn reduce the toxicity-related issues and also improve the efficacy. The natural combination with conventional therapy is also a better approach to be considered as far as any compatibility issues are developed. Nature has the cure for the diseases which are developed in nature and can treat the lives on this globe. Better management of the effect of natural ingredients can help to eradicate the culprit, cancer from life.

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CrediT authorship contribution statement

Chenmala Karthika: Data curation, Writing - original draft; **Balaji Hari**: Data curation, Writing - original draft; **Md. Habibur Rahman**: Writing - original draft; **Rokeya Akter:** Writing - review & editing; **Ghadeer M. Albadrani**: Writing - review & editing; **Amany A. Sayed**: Writing - review & editing; **Muhammad Furqan Akhtar**: Writing - review & editing; **Agnieszka Najda**: Writing - review & editing;

Table 1
Mechanistic approach behind the choice of the drugs and concept.

SL. No	Mechanistic approach	Function	Mechanism of action	Critical concepts	Alternative approach
1.	5-Fluorouracil (5-FU)	First line treatment for colorectal cancer, used alone or in combination with other agents, side effects, chemo resistance, reoccurrence, these limitations needs an urgent need to be addressed	Anti-epidermal growth factor and anti-angiogenic agent.	15% of resistance is observed and 50–60% tumor reoccurrence	5-FU is the first line drug commonly used drug for the treatment of colon cancer hence the resistance part associated with it is mainly focused
2.	Flavonoid-Curcumin	Curcumin act as chemotherapeutic agent, angiogenesis, apoptosis and also as a P-gp inhibitor	Absorption in colorectal region. Synergistic activity on combination with 5-FU.	Solubility and compatibility related issue should be taken into consideration.	Selection of different flavonoid such as luteolin, quercetin, resveratrol or leutiolin.
3.	Lipid	Bypass first pass metabolism, cell signaling, conjugation, lymphatic absorption and metastasis	Denovo synthesis, absorption of lipids through lymph nodes, energy source for the hungry cancer cells. The lipids can help in conjugating a hydrophilic and hydrophobic drugs	There is a contradiction that some lipids are carcinogenic in nature, according to the properties of lipids the selection of the lipids have to be made.	Lipids can be replaced with protein, carbohydrate or amino acid
4.	Chemical Conjugation	Compatibility related issues, solubility profile and pro drug approach	Increase the solubility, pharmacokinetic and pharmacodynamics profile of drug combination, increase the drug loading capacity and reduces the toxicity	Determination of scheme for the synthesis part is difficult	If chemical conjugation is not possible then we focus with physical conjugation method.
5.	Nano formulation	The loading of conjugate into Nano formulation, bypass first pass effect, EPR effect, P-gp inhibitor, cell signaling, metastasis	Oils are lipids, where circulated mainly through the lymphatic system hence can be used effectively in metastatic stage of cancer, particle size enhances the permeation and retention time, lipids can be used for the cancer cell signaling and lipids are used as P-gp inhibitor	Stability related issues	Active targeting with dendrimers or monoclonal anti-bodies
6.	Oral administration	Patient convenience	Taken through oral dosage form like capsules or tablets	Unpredictable oral bioavailability	If the oral route of administration is challenging then can be given through rectal route
7.	Coating with pH sensitive polymer	For colon specific drug release	Depending on the pH release pattern the outer coating material will degrade.	Degradation of the polymer can be possible, organ specific effect can't be attained	If pH sensitive polymer is not appropriate then temperature sensitive polymers can be designed which are specifically target at colorectal region or coating can be made with aptamers.

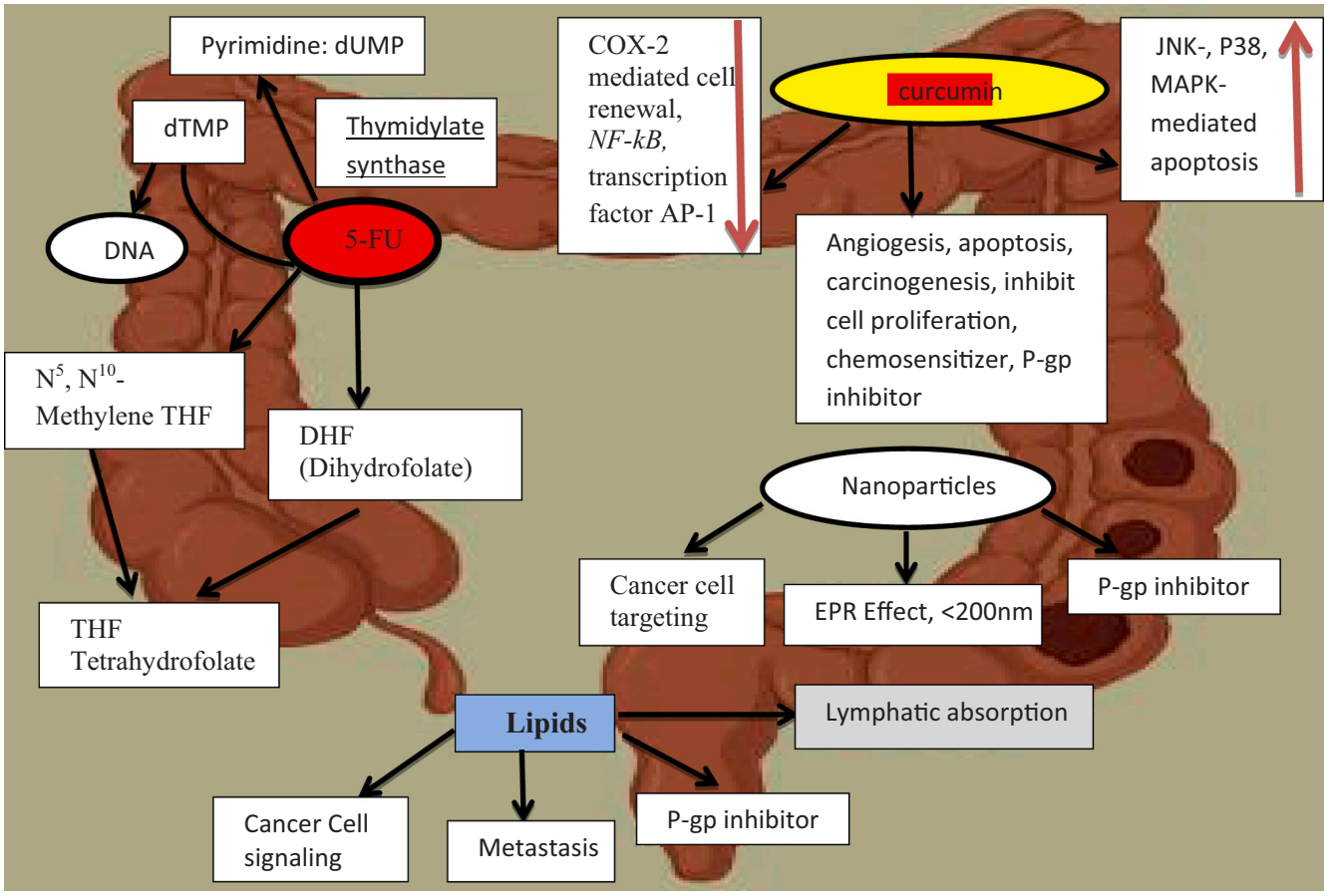

Fig. 4. Concept behind the multifactorial approach for the management of colorectal cancer.

Mohamed M. Abdel-Daim: Conceptualization, Supervision.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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