JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/34910

SHORT REVIEW

The Role of Curcumin in Gastric Carcinoma by Modulating the Immune System and its SAR

Akshay Kumar[1], Chandana Majee[1*], Rupa Mazumder[1], Ruchi Sharma[1], Avijit Mazumder[1] , Rashmi Mishra[2] and Pankaj Wadhwa[3]

[1]Department of Pharmaceutical Chemistry, Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida – 201306, Uttar Pradesh, India; cmchandana1@gmail.com

[2]Department of Biotechnology, Noida Institute of Engineering and Technology, Greater Noida – 201306, Uttar Pradesh, India

[3]Lovely Professional University, Jalandhar - Delhi, Grand Trunk Rd, Phagwara – 144001, Punjab, India

Abstract

The second most prevalent cancer in the world and the fifth most common malignant tumour is gastric carcinoma. It is thought that several factors, including genetics, epigenetics, and environmental impacts, contribute to the development of gastric cancer. One of the main pathogenic variables associated with stomach cancer risk has been identified as inflammation. There are currently few methods to treat the gastric carcinoma. Therefore, an alternative plan is urgently needed. Explaining the importance of curcumin derived from *Curcuma longa* Linn. in stomach cancer is the goal of this review. According to recent research, Curcumin (CUR) has a great effect against stomach mucosal injury brought on by non-steroidal anti-inflammatory medicines, gastric mucosal injury in rats, stress haemorrhage, and Helicobacter pylori infection. In this review article, we have discussed the chemistry of CUR, the role of CUR in immunomodulation, and gastric cancer. We have also highlighted the various signalling pathway of gastric cancer where CUR work. By controlling miRNAs on gastric cancer and other relevant signal pathways, CUR exhibits notable anti-inflammatory and anti-cancer properties. In future there are more research work will be done on CUR.

Keywords: Curcumin, Immune-Modulation, Gastric Carcinoma, Structure-activity Relationship, Signalling Pathways

1. Introduction

Gastric cancer is the main factor contributing to high mortality rates and a poor prognosis[1]. The treatment of gastric cancer has not greatly changed despite recent advances in diagnosis and therapy. Low rates of survival and the vast majority of cases of stomach cancer are fatal[2]. Due to their chemo-prevention abilities, natural products such as green tea, resveratrol[3], vitamins, and functional meals like probiotics and prebiotics may be helpful[4]. CUR, a natural cancer-preventing drug, has drawn more interest since it can stop tumour growth. Studies on animal models of breast, oesophageal, stomach, and colon cancer have demonstrated that CUR decreases inflammation and carcinogenesis[5]. This natural chemo-preventive medication, which possesses antioxidants, anti-tumour, and antiproliferative characteristics, was made using the rhizomes of Curcuma species[6]. CUR has been utilised for centuries in Asian countries, yet there is no evidence that it is toxic or has any side effects[7]. Because of CUR's pharmacological safety, efficacy, and affordability as well as the fact that there is no dose-limiting toxicity, many researchers have been inspired to continue studying it[8]. Through a variety of biological mechanisms, including angiogenesis, invasion, apoptosis[9,10], mutagenicity[11], cell cycle regulation[12], and tumorigenesis[13], CUR may inhibit the excessive growth of human gastric carcinoma cells. CUR has also shown strong chemo sensitization by inhibiting NF-κB (nuclear transcription factor κB)

*Author for correspondence

Article Received on: 31.08.2023 Revised on: 16.09.2023 Accepted on: 28.09.2023

in human gastric cancer cells (SGC7901 and AGS)[14]. In numerous studies, the synergistic impact of CUR and 5-fluorouracil, a chemotherapeutic medication, has also been confirmed. Wei *et al*., concluded that long-term CUR ingestion might be advantageous for curing gastric carcinoma, especially when combined with 5-FU[15,16]. In future trends, much research is required to determine the compound's potential involvement in preventing and/or treating gastric carcinoma, even though the majority of its mechanisms have already been examined[17].

2. Role of Immune Modulation in Gastric Cancer

Cancer treatments that rely on the immune system of the body to defend the disease-causing tumour cells are known as cancer immunotherapy[18]. To modify the immunological response to a desired extent. These procedures make use of medications that alter immune system function, prevent tumour-induced immunologic tolerance, or both[19]. Inducing tumour-specific immunological memory may result in long-term tumour shrinkage or prevent cancer patients from relapsing, which makes this situation particularly noteworthy[20]. Based on the location (e.g., in peripheral blood, lymphoid organs, or inside the tumour microenvironment) and the kind of immune response (e.g., cytotoxic T lymphocytes or regulatory T cells), myeloid-derived suppressor cells[21] and regulatory T cells employ a variety of suppressive mechanisms to inhibit anti-tumour responses[22]. Plant-based products have shown the ability to fight cancer through a variety of biological mechanisms, including immune system modulation. It has been demonstrated that medicinal plants' immunomodulatory capabilities inhibit the development of cancer cells[23]. This process involves a variety of immune cell types, particularly cytotoxic T cells[24], natural killer cells[25], and cytokines like tumour necrosis factor-α and chemokines[26]. According to reports from many parts of the world, medicinal herbs like *Glycyrrhiza glabra*[27], *Uncaria tomentosa*[28], *Camellia sinensis*[29], *Panax ginseng*[30], *Prunus armenaica* (apricot)[31], *Allium sativum*[32], *Arctium lappa*[33], and *Curcuma longa* have a significant potential to treat cancer[34]. Fascinating research results have revealed that the primary components of these plants that are responsible for the anticancer effects are bioactive immunomodulators. There are lots of phytoconstituents such as Ajoene[35], arctigenin[36], beta-carotene[37], CUR, ginseng[38], epigallocatechin-3-gallate[39], glabridin[40], quinic acid and so on have a prominent immunomodulatory effect. From the various studies, it was observed that one of the key active compounds of Curcuma species, CUR, has a well-known powerful immunomodulating and antioxidant[41].

2.1 Source, Physicochemical Property, and Pharmacological Importance of CUR

A natural substance called curcumin was present in the rhizome of the plant known as turmeric *Curcuma longa* Linn.[42] and also prepared synthetically by various methods. The plant was initially cultivated, according to information from current studies, in subtropical and tropical parts of the globe, notably India, Indonesia, and Thailand[43]. Due to its striking orange-yellow hue, turmeric powder, which is commonly used as a spice (as a flavouring and coloured element for curries) and in mustards, is referred to as "Golden spice"[44].

There are various methods to extract the CUR from rhizomes of *Curcuma longa* Linn. such as maceration, soxhlet extraction, steam distillation, and solvent extraction. In general hexane, acetone, and alcohol are used to extract the active ingredients from powder drugs[45]. The scientific name for CUR (as per IUPAC) is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It is a hydrophobic phenolic compound. CUR (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin are three main chemical compounds that belong to the "curcuminoid" family. Turmeric's chemical components and pharmacological effects are generally attributed to curcuminoids, which are predominantly composed of roughly 77% CUR and related derivatives, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC), with quantitative compositions of about 3% and 17%, respectively[46]. The physiochemical and biological properties of CUR and CUR derivatives are depicted in Tables 1 and 2.

2.2 Chemistry and SAR of CUR

CUR is composed of two phenyl rings having methoxyl and hydroxyl groups. A seven-carbon keto-enol system

Table 1. Physicochemical properties of CUR and its derivatives

S. No.	Compounds and Derivatives	Molecular Formula	Molecular wt.	Melting Point	Solubility	Log P value	References
1.	Curcumin	$C_{21}H_{20}O_6$	368.4 g/mol	183°C	DMSO	3.03	46
2.	Demethoxycurcumin (DMC)	$C_{20}H_{18}O_5$	338.3 g/mol	168**°C**	DMSO	3.18	57
3.	Bisdemethoxycurcumin (BDMC)	$C_{19}H_{16}O_4$	308.3 g/mol	232.8°C	Ethanol, DMSO	3.12	58
4.	Tetrahydrocurcumin	$C_{21}H_{24}O_6$	372.4 g/mol	97°C	DMF	3.51	59
5.	1,7-bis(4-ethyloxy-1-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione	$C_{25}H_{28}O_6$	424.4 g/mol	298°C	DMSO	4.23	56
6.	1,7-bis(4-butyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione	C29H36O6	480.85 g/mol	298°C	DMSO	5.68	56

Table 2. Pharmacological importance of CUR and its derivatives

S. No.	Compounds Names	Pharmacological Activity	References
1.	Curcumin	Hypocholesterolemic, Antithrombotic, Carminative, Antihepatotoxic, Antirheumatic, diuretic, Hypotensive, Larvicidal, Antiviral, insecticidal, Antidiabetic Antityrosinase, Antioxidant, Antiprotozoal, Antimicrobial, Anti-inflammatory, Antiproliferative, Antimalarial, Antitumor, Dyslipidemia, Gastric difficulties, Arthritis, and Hepatic diseases	47-50
2.	Demethoxycurcumin (DMC)	Antioxidant activity and Anti-angiogenic activity	51
3.	Bisdemethoxycurcumin (BDMC)	Acetylcholinesterase inhibition activity**,** Anti-metastasis activity and Anti-diabetic and anti-inflammatory activity	52-54
4.	Tetrahydrocurcumin	Anti-inflammatory activity	55
5.	1,7-bis(4-ethyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione	Photodynamic cancer therapy	56
6.	1,7-bis(4-butyloxy-1-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione	Photodynamic cancer therapy	56

(C7) connects the two phenyl rings[60]. Although CUR is a naturally occurring molecule, most of its derivatives are produced when acetylacetone aryl-aldehydes combine. With the use of this assembly method, several chemical analogues can be produced, including compounds that have alkyl replacements attached to the linker's C7 moiety's central carbon[61]. According to a SAR study of CUR derivatives, a coplanar proton donor group and a -diketone moiety are required for the antiandrogenic action that is used to treat cancer[62]. The activity and a combination of the NF-κB and STAT3. Due to their elevated methoxylation levels, moderate hydrogenation levels, and unsaturated diketone moiety, several of the modified curcuminoids exhibit greater anti-inflammatory and anticancer effects than CUR. The heptadiene moiety and the hydrogenation level are changed when the essential radical of curcuminoid is ortho-methoxy substituted. Several hydrogenated CUR derivatives outperformed the original CUR substitute in a comparison study of CUR and its derivatives' antioxidant properties. Tetrahydro CUR (THC), as opposed to dihydro CUR (DHC) and unmodified CUR, for instance, showed stronger antioxidant activity[63]. Apoptosis could not be induced by THC, a non-electrophilic variant of CUR, since it does not block the STAT3 signalling pathway. This suggests that CUR's electrophilic properties play a role in blocking the STAT3 signalling system during anticancer therapy[64]. Metal ions Cu^{2+}, Ni^{2+}, and Zn^{2+} have been utilized to construct metallo-curcumin-conjugated DNA complexes, which improve the solubility of CUR and its ability to connect to DNA. Along with improved antibacterial action, these compounds also showed substantial toxicity to a variety of prostate cancer cell

lines[65]. Curcuminoids exhibit anti-inflammatory, anti-cancer, and antioxidant properties. The chelating activity of the diketone moiety is principally responsible for this. Figure 1 illustrates the SAR for CUR.

However, from various studies, it was observed that there was no clear link between antioxidant activity and the prevention of tumour growth via NF-κB in the previous research studies of 72 distinct CUR derivatives[63]. It was observed that the methoxy group was detached from its proton acceptor-diketone molecule, and the O-methoxy replacement of CUR improved its antioxidant activity[66].

3. Immunomodulatory Effect of CUR

The dysfunction of inflammatory pathways seems to be a typical factor in the emergence of cancer, according to a wealth of research[67]. In reaction to inflammation, the body produces more pro-inflammatory substances like cytokines, reactive oxygen species (ROS), cyclooxygenase (COX-2), nuclear factor κB (NF-κB), protein kinase B (AKT), and activator protein 1 (AP1)[68] and signal transducer and activator of transcription 3 (STAT3), which in turn causes the onset and progression of cancer[69]. When CUR acts with different immunological mediators, it can exercise its immunomodulatory potential, which gives it its anticancer properties[70].

The nuclear component κB is a transcription factor that promotes inflammation and regulates the expression of a wide range of proteins, such as the interleukin IL-1, IL-2, and interferon, which are involved in several cell signalling pathways linked to the development of cancer and inflammation[71]. Phosphorylated NF-κB, which places to DNA and phosphorylates NF-κB, initiates the transcription of oncogenes, causing cellular death and starting the expansion of cells and angiogenesis. CUR decreases NF-κB property by blocking I.B kinase (I-B) phosphorylation and decreasing the activity of NF-κB p65 nuclear alterations[72]. CUR is believed to have anticancer properties in a wide variety of in vitro functions via inhibiting the AP-1 and NF-κB proteins[73]. In numerous animal models, CUR has been investigated

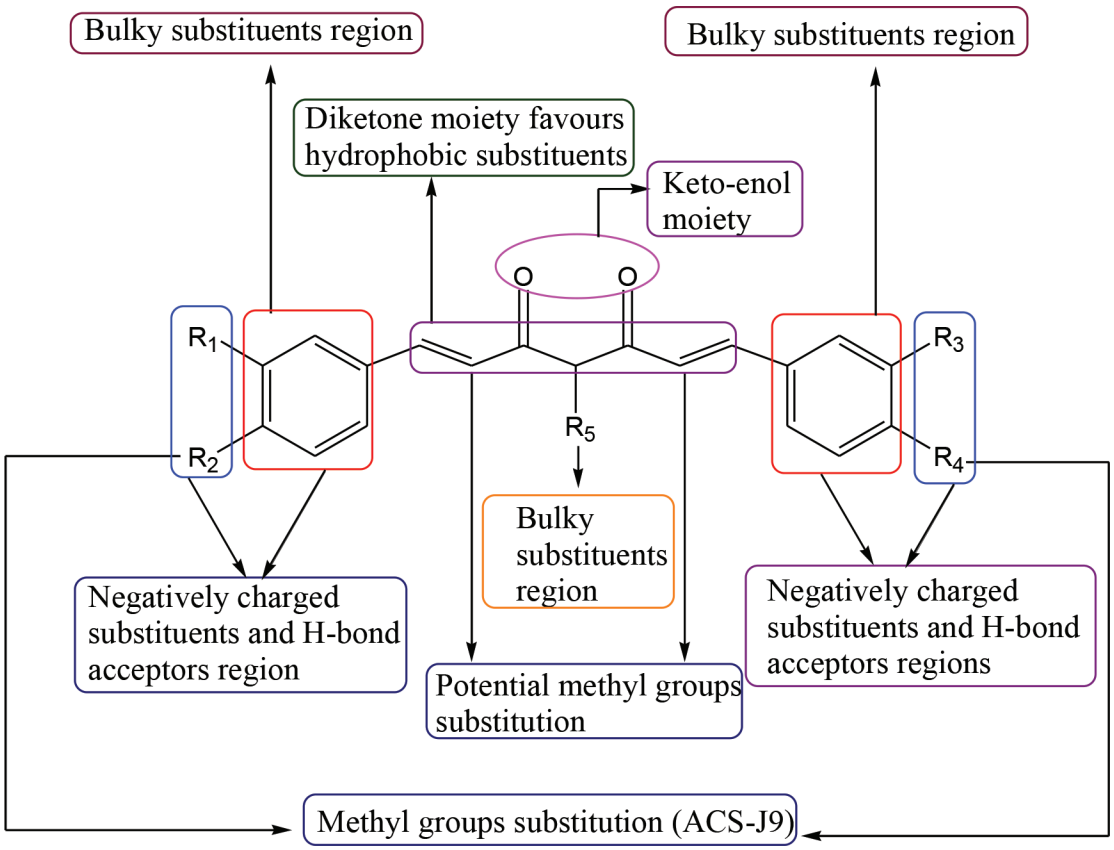

Figure 1. SAR of CUR.

for the treatment of several cancers, including those of stomach cancer, breast cancer, hepatic cancer, pancreatic cancer, prostate cancer, and colon cancer[74].

Human astroglioma cells exposed to TPA exhibited decreased PKC activity, as well as pro-angiogenic AP-1 and MMP975 expression and It also prevented LnCap prostate cancer cells from proliferating when hydrogen peroxide was present by inhibiting the AP-1 transcription factor[75]. CUR effectively reduced NF-κB activation brought on by a variety of stressors, including phorbol ester, TNF, and hydrogen peroxide[76]. Other researchers later demonstrated that CUR inhibited IKKα and IKKβ, which are kinases in the NF-κB pathway[77]. According to reports, CUR activates PPAR-γ and stops Moser cells from growing. This stops the expression of cyclin D1 and EGFR genes as a result[78]. In multiple myeloma cells, interleukin IL-6-induced STAT3 phosphorylation and subsequent STAT3 nuclear translocation were demonstrated to be inhibited by CUR[79], Through inhibition of the JAK/STAT3 pathway, CUR also reduced cell growth and triggered dose-dependent caspase-dependent death[80]. CUR inhibited osteosarcoma cell proliferation, invasion and migration, and promoted apoptosis via inhibiting the Wnt/β-catenin pathway[81]. The activation of p38 MAPK and the production of caspase-3 were the mechanisms by which CUR triggered neutrophil apoptosis[82]. Poly ADP-ribose polymerase (PARP), a specific substrate for caspase-3, may hydrolyze in response to the action of caspase-3[83]. CUR dramatically boosted the expression of caspase-3 and cleaved PARP, as demonstrated by Xia Xue *et al*[84]. These results suggested that CUR might induce apoptosis in the SGC-7901 cells. TNF- has been shown to play a role in the formation, extension, and metastasis of malignancies. Monocyte adhesion to endothelial cells in the vascular system was inhibited by CUR pre-treatment[85]. Apoptosis can be induced and tumour cell viability can be dramatically reduced by CUR in vitro, according to recent reports. Wnt3a, LRP6, p-LRP6, b-catenin, p-b-catenin, C-myc, and survivin have all been demonstrated to be inhibited by CUR[86]. This process is depicted in Figure 2.

4. Role of CUR in Gastric Cancer

CUR can prevent tumour development in Gastric Cancer (GC) cells in experimental investigations. As shown in Figure 3, CUR may impact GC development via several different mechanisms. It's interesting to note that in a co-culture setup, CUR inhibited colony formation, and cell proliferation, and decreased interleukin (IL)-6 secretion by MDSCs (Myeloid-derived suppressor cells)[87]. Apoptosis can be induced and tumour cell viability can be dramatically reduced by CUR, according to a recent investigation. It has been demonstrated that CUR can survive while inhibiting Wnt3a, LRP6, p-LRP6, b-catenin, b-catenin, and p-b-catenin[88]. Zinc finger proteins (ZNFs), involved in this process, regulate mostly number of genes associated with carcinogenesis, tumorigenesis, and tumour growth. The transcription element in ZNF139, a component of this family, is linked to the development of GC. ZNF139 may be in charge of upregulating MDR1 and MRP1 expression, which results in resistance to many therapeutic methods[89]. CUR suppresses GC proliferation as well as expansion both in vitro and in vivo by downregulating ZNF139, Bcl-2, and survivin[87].

CUR may also inhibit the NF-κB pathway through its impact on (The inhibitor of nuclear factor-kappa kinase subunit) IκK and regulation of various genes involved with cell growth and survival, such as IL-6, B-cell lymphoma-2 (Bcl-2), MMP-9, cyclin D1, and COX-2[90]. IkK is prevented by CUR from phosphorylating and degrading IκBα, which inhibits NF-B from entering the nucleus to initiate translation by keeping it connected to IκBα in the cytoplasm. Along with reducing NF-B activation, CUR also has an impact that inhibits other inflammatory pathways[91].

According to past research, CUR and its counterpart may have anti-cancer properties in models of stomach cancers. CUR may inhibit the extension, invasion, and angiogenesis of stomach malignant cells by several biological mechanisms, including cell death, mutagenicity, and regulation of the cell cycle[92]. Additionally, CUR dramatically decreased nuclear transcription factor κB (NF-κB) in the stomach cancerous cells SGC7901 and AGS, indicating strong chemosensitization[93]. Additionally, numerous studies have demonstrated the favourable outcomes of combining CUR with the chemotherapy drug 5-fluorouracil[94].

4.1 Effect of CUR on the Regulation of miRNAs on Gastric Carcinoma

CUR minimized the H_2O_2-induced oxygen species by dropping MDA levels, raising the gene expression

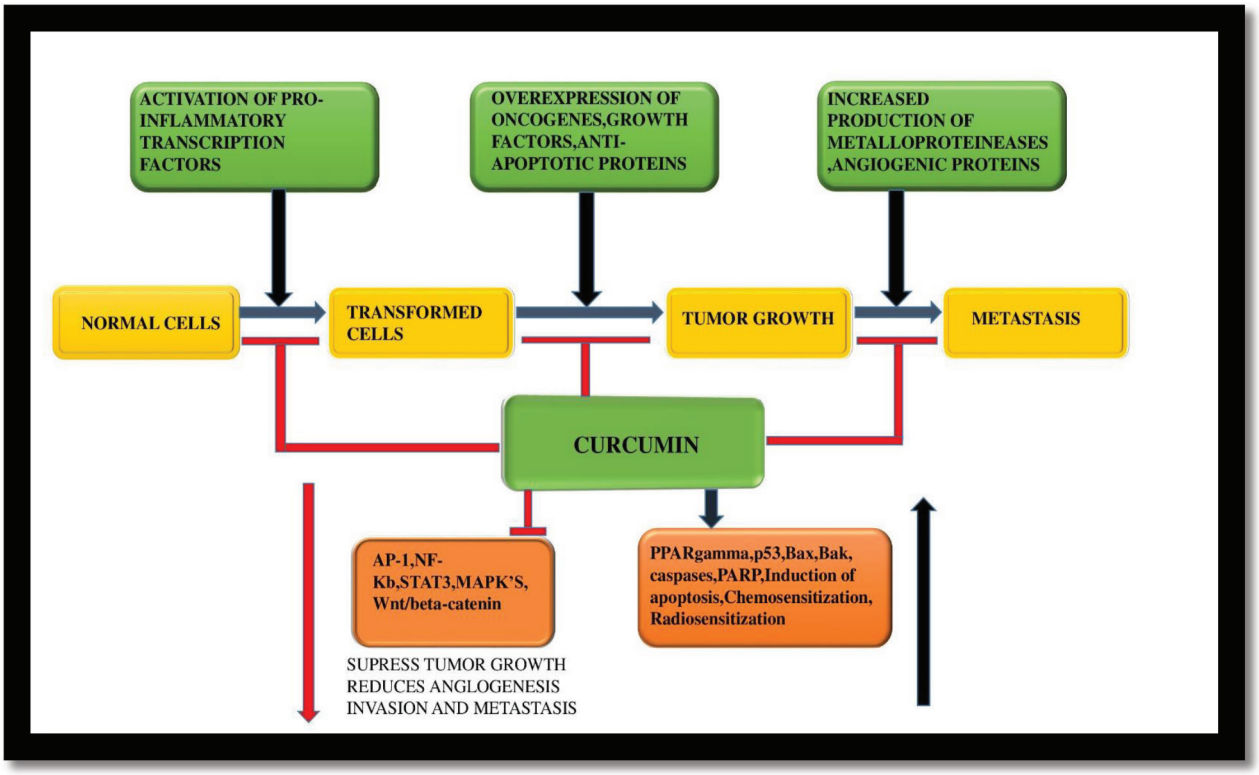

Figure 2. Immunomodulatory effect of CUR.

of Cu/Zn-SOD, Mn-SOD, GPX-1, and GPX-4, and improving the level of SOD and CAT activity[95]. CUR reduced oxidative stress brought on by H_2O_2, damage to the intestinal epithelial obstacle, and mitochondrial damage[96]. Oxidative stress (OS) is the term used to describe a rise in the intracellular concentration of ROS brought on by an increase in oxidant factors or a reduction in the body's capability to produce antioxidant defences[97]. Hydrogen peroxide (H_2O_2), superoxide anion (O2-), and hydroxyl radicals (OH) are by-products of aerobic metabolism[98]. As was already mentioned, CUR has great antioxidant properties[99]. Recent research has shown that the oncogene miR-21 typically increases and functions as a tumour suppressor in a variety of cancers. Previous research has demonstrated that the miR-21/PTEN/Akt molecular route is compulsory for the growth of gastric cancer and that miR-21 expression is greater in gastric tumour cells. Evidence suggests that suppressors of miR-21 greatly reduce stomach cancer cells' proliferative abilities, migration, formation of colonies, and invasion. The previous study's findings showed that gastric cancer cells have higher levels of miR-21 and that the miR-21/PTEN/Akt molecular route is compulsory for the development of gastric cancer. Evidence suggests that suppressors of miR-21 significantly decrease the ability of stomach tumour cells to boost, form colonies, migrate, and invade. According to a recent study, CUR treatment reduced the levels of miR-21 and p-Akt while enhancing the pattern of the PTEN protein in MGC-803 cells[100].

4.2 CUR on Gastric Carcinoma Cells through the Shh and Wnt Signalling Pathways

The sonic hedgehog (Shh) signalling system is crucial for embryonic growth, maintaining adult tissues, and oncogenesis[101]. The Shh signals are subsequently transmitted by a protein present in the cytoplasmic complex down of Smo, which includes the fusion inhibitor (Sufu), kinin (Kif7), and GliFL. Our research data explains that CUR prevented the addition and migration of malignant gliomas by blocking the Shh signalling system, which in turn reduced the exodus of SGC-7901 cells. In SGC-7901 cells, CUR decreased the expression of Gli1, Shh, and Foxm1 in the Shh signalling

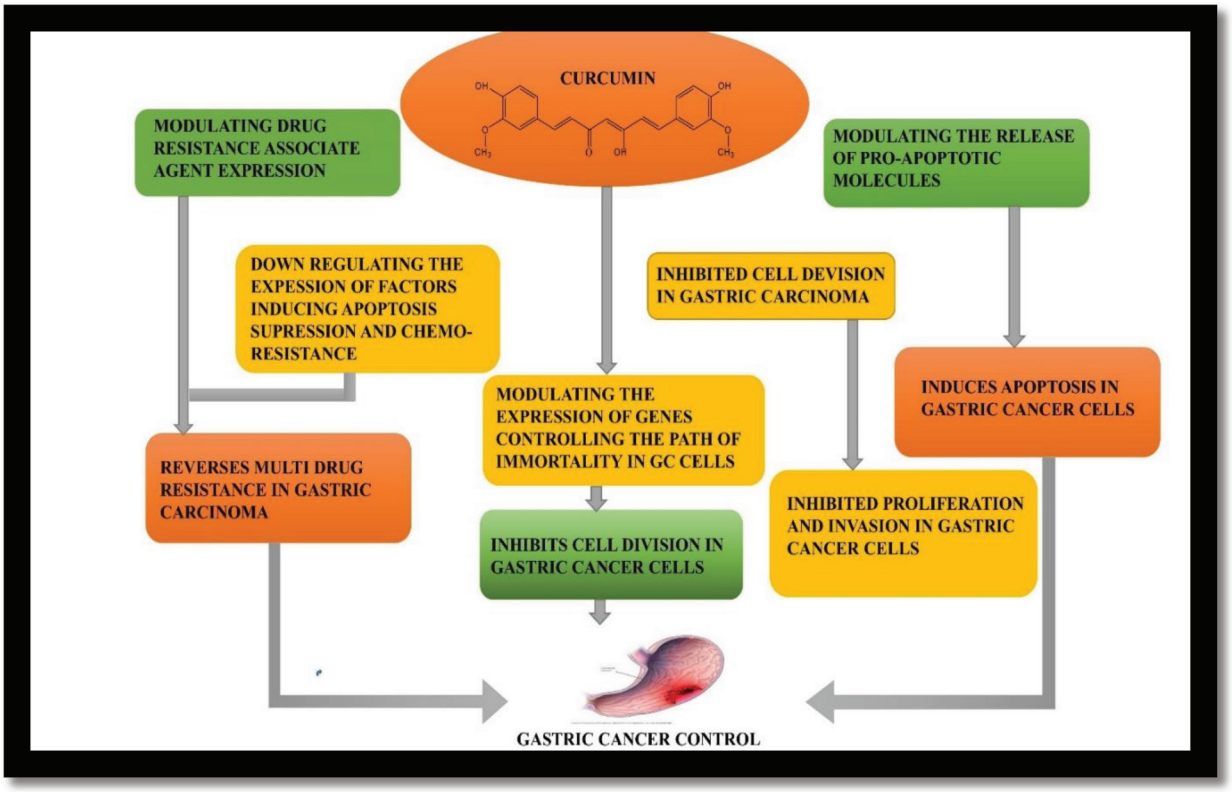

Figure 3. GC progression through several mechanisms affected by CUR.

circuit as well as -catenin and -catenin in the Wnt signalling route[102]. According to several research, Shh signalling is essential for the development of tumours[103]. Poor tumour differentiation and prognoses are linked to high Gli1 and Ptch expression levels, and Shh is typically activated in advanced gastric adenocarcinomas. The prognostic indicator for the development of stomach cancer is sonic hedgehog overexpression[104].

The capacity of preliminary gastric carcinoma to control tumour angiogenesis, invasion, and anti-apoptotic activity of the cell. The activity and a combination of the STAT3 and NF-κB signalling pathways powerfully control the association between gastric malignancies and circulation cells. An in-depth examination of the pathways and variables that affect NF-κB and STAT3 in cancer of the stomach could open up novel possibilities for both prevention and treatment[105].

5. Conclusion

Gastric carcinoma is a malignant tumour of the stomach, often associated with chronic inflammation. CUR's ability to regulate the immune system makes it an effective candidate for the treatment of ulcers and cancer of the stomach. By altering the immune system, CUR has an impact on gastritis and stomach cancer. Natural killer cells, also known as NK cells, and cytotoxic T lymphocyte activity may be raised to trigger the demise of cancer cells. The synthesis of inflammatory cytokines that are anti-inflammatory like interleukin-10 (IL-10) is also boosted by the SAR of CUR, helping in lowering inflammation and fostering tissue healing. It is a good option for further study and development as a therapeutic intervention for these illnesses on account of its anti-inflammatory, anticancer, and immune-enhancing properties. To completely understand the mode of action of CUR and determine the ideal dose, treatment, and possible combination therapies, additional in-depth preclinical and clinical investigations are needed. CUR may open up novel avenues for avoiding and therapy cancer of the stomach with additional research.

6. Acknowledgments

The facilities and support for this investigation were given kindly by Dr. O. P. Agrawal, Chairman of the

NIET, Gr. Noida U.P., India, and Dr. Nima Agrawal, the Managing Director of NIET, Gr. Noida U.P., India.

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