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A Comprehensive Review On Oxidative Stress Triggered Pathways In Colon Cancer

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ISSN PRINT 2319 1775 Online 2320 7876

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Abstract

Background: Colorectal cancer (CRC) is a global health concern with significant mortality rates. Lifestyle factors and heightened oxidative stress contribute to its development. CRC's genetic instability is driven by CpG island methylator phenotype (CIMP), chromosomal instability (CIN), and microsatellite instability (MSI) pathways, with oxidative stress playing a critical role. It disrupts DNA repair mechanisms, enhancing CRC development.

Main Body of the Abstract: Oxidative stress, stemming from reactive species like hydroxyl radicals, peroxynitrite, and superoxide anions, leads to DNA damage, mutagenesis, and genomic instability in CRC. The delicate balance between ROS production and antioxidant defenses tips towards oxidative stress, fostering cancer cell proliferation and DNA oxidation. Oxidative damage results in mutagenesis, carcinogenesis, and aging, with oxidative DNA damage observed as GC base pair changes. Reactive oxygen species (ROS) also play a significant role in CRC initiation, promotion, and progression. The JAK/STAT, PI3K/AKT, and COX pathways, disturbed by oxidative stress, are implicated in CRC pathogenesis. Redox-modifying drugs show promise in targeting CRC cell lines, exploiting their sensitivity to oxidative stress.

Short Conclusion: Oxidative stress is pivotal in CRC development and progression, affecting DNA integrity and signaling pathways. Understanding of the intricate

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

interplay between oxidative stress and colon cancer, offers valuable insights for future research and therapeutic strategies. Combining ROS modulators with chemotherapy could enhance CRC treatment outcomes, highlighting the significance of redox biology in CRC as a potential therapeutic target.

Keywords: Colorectal cancer; Oxidative stress; Reactive nitrogen/oxygen species; Signaling pathway; STAT/JAK pathway.

Background

Colorectal cancer (CRC) is a prevalent global malignancy with high mortality rates, affecting over 1.3 million people in 2012. Less developed regions have higher mortality rates (52.02%) compared to more advanced regions (47.98%).[1,2] Current therapies include chemotherapy and radiation, which have significant adverse effects. Consuming dietary prebiotics shows promise in improving glycemic indices, antioxidant status, immunomodulatory effects, cardiovascular disease risk, and lipid profile. Genetic instability plays a crucial role in sporadic colorectal cancer development.[3,4] Upregulation of "emergency enzymes" like LOX, COX-2, or iNOS contributes to elevated oxidative stress, leading to cancer formation. Chronic oxidative stress from various pathological situations may contribute to CRC. [5,6]

Main text

1. Colorectal Cancer's molecular basis

The regulation of colorectal cancer carcinogenesis is influenced by both genetic and epigenetic changes. The adenocarcinoma sequence was first documented in 1980, when the transformation of normal colorectal epithelium to an adenoma, then to a metastatic and invasive tumour, was discovered. In the genetic instability of CRC and its pathophysiology, three key pathways are implicated: CIMP (CpG island methylator phenotype), CIN (chromosomal instability), and MSI (microsatellite instability) pathways (Fig 1).[7]

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

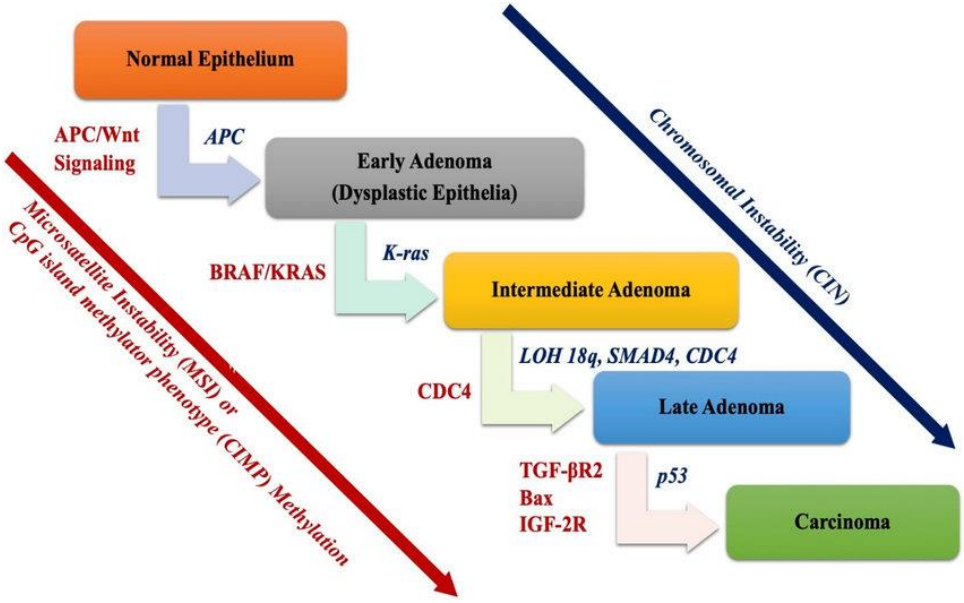

Figure 1. Colorectal cancer sequencing in a multistep genetic model. Three routes regulate the adenocarcinoma sequence.

2. Role of Oxidative Stress

A difference between the creation and buildup of reactive oxygen species in tissues and cells and a biological system's ability to detoxify these reactive compounds causes oxidative stress.[8] The incomplete reduction of oxygen produces ROS like hydroxyl radical, peroxynitrite and superoxide anion, which are normal energy metabolism byproducts. They are continually created in aerobic organisms from endogenous and external sources, including inflammatory cell activation, cytochrome P450 metabolism, mitochondria, and peroxisomes.[9] Inflammation, toxin exposure, smoking, stress caused by nutrition, metabolic disorders, dysbiosis, and lifestyle factors enhance reactive oxygen species production. Every day, one human cell is exposed to 1.5 × 105 oxidative attacks.[10] These reactive species can potentially react with biomolecules such as carbohydrates, proteins, nucleic acids, and lipids, disrupting cell function. Oxidation of pyrimidine and purine base, DNA strand breakage, and genetic instability may all occur from damage to the nucleotide sequence and DNA methylation changes, which may result in chromosomal aneuploidy and instability. The oxidative damage results in the initial stage of mutagenesis, carcinogenesis, and ageing. The GC base pair changes, observed by insertions, deletions, and base substitutions, are prevalent oxidative DNA damage induced by reactive oxygen species.[11]

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

DNA MSI (microsatellite instability), which leads to faulty DNA repair processes during replication, is another form of a mutation linked to oxidative stress and seen in CRC. MSI arises when mismatch repair (MMR) gene mutations in the germline or sporadic cause replication mistakes or instability in repetitive DNA sequences. Based on the proportion of loci that demonstrate instability, MSI is classed as low frequency (MSI - L) or high frequency (MSI - H). Oxidative stress has been shown to disrupt DNA repair processes, resulting in low-frequency microsatellite instability and CRC development in UC patients. Furthermore, ROS enhances the survival of cancer cell proliferation by encouraging oncogenic phenotypes through the activation of different transcription factors.[12]

Reactive oxygen species are a family of unique oxygen-containing molecules or oxygen chemical forms with much greater chemical activity than oxygen itself. When the production of ROS surpasses the antioxidant system's capacity to defend the cell, oxidative stress (OS) ensues.[13] The digestive tract, rich in microorganisms and the biggest endocrine and immunological organ, plays a significant role in stress responses like oxidative stress.[14] The nitric oxide free radical (NO) and the superoxide anion free radical (O_2) are the two primary endogenous RNS/ROS from which additional reactive free radicals such as peroxynitrite anion (ONOO), hydroxyl radical (HO), and hydrogen peroxide (H_2O_2) are produced.[15] In the digestive system, there are various sources of reactive oxygen species. Inside cells, H_2O_2 and ONOO are produced in aerobic metabolism as byproducts of mitochondrial respiration, cytochrome P450 detoxifying reactions, and neutrophil phagocytosis of bacteria granular materials soluble irritants have a large amount of ROS in the chronic inflammation process. [16]

Therapeutic selectivity is critical for developing effective anti-cancer drugs. Cancer cells are highly dependent on antioxidants for survival due to heightened oxidative stress, making them especially sensitive to exogenous ROS modifying agents. As a result, modifying tumour cells' endogenous redox states may cause selective tumor cell death. Many studies have used synthetic and natural reactive oxygen species-modulating drugs to treat colorectal cancer, as illustrated in table 1.

Table 1. Reactive oxygen species-inducing agents employed in cell lines generated from colorectal cancer

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Mechanisms	Compound	Cell Lines	Major Outcomes	References
ROS/TRAIL-dependent apoptosis	15dPGJ (2)	SW480, HCT116	↑CHOP, GRP78, XBP1	17
ROS-apoptosis	Betulinic acid	SW480, RKO	↓Sp, microRNA-27a, ZBTB10 gene	18
ROS-dependent apoptosis	5-FU	HT-29	↑Caspase-7, Src	19
ROS/DR-dependent apoptosis	Benzimidazole acridine derivative	SW480, HCT116	↑Caspase-3, -7, -8, -9, Bid, PARP; ↓Bcl-2	20
ROS/DR-dependent apoptosis	Capsazepine	HT-29, HCT116	↑Caspase-8, -9, Bax; ↓cFLIP, survivin	21
ER/ROS/caspase-dependent apoptosis	Andrographolide	COLO205, T84	↑Nrf2, GPx, PrX-6, LPO, TRX; ↓ΔΨm	22
ROS/ER/caspase-dependent apoptosis	HMF	HCT116	↑[Ca2+]i, Cyto c, BID, Bax; ↓Bcl-2	23
ROS/ER/caspase-dependent apoptosis	CLA	SW480	↑Phosphorylated eIF2α, mRNA, CHOP, Xbp1	24
DR/ROS/TRAIL-dependent apoptosis	Cardamonin	HCT116	↑Cleaved PARP, Bax, caspase-8, -9, -3; ↓cIAP-1, Bcl-2, XIAP, cFLIP,	25
ROS/DR-dependent apoptosis	Bakuchiol	HT-29, HCT116	↓Bcl-2, cFLIP, survivin, XIAP. ↑Caspase-3, -8, -9, PARP	26
ROS-autophagy	Bufalin	Caco-2, HT-29	↑LC3-II, ATG5, Beclin-1	27
DR/ROS-dependent apoptosis ROS/caspase-dependent apoptosis	Casticin	COLO205, SW480, HCT116, HT-29	↓ Bcl-xL, Bcl-2, XIAP, cFLIP; ↑ TRAP1 gene, G2/M phase arrest, CDKN1B gene; ↓ΔΨm, MMP-2, [Ca2+]i, CaMK4 gene, RKAR2B gene,	28, 29
Reactive oxygen species - autophagy, and apoptosis	Compound K	HCT116	↑ LC3-II, Caspase-3, -9ATG7, flux ATG6. ↓Bcl-2	30

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

ROS-apoptosis	Droxinostat	HT-29	↑ H4, Bax, Acetylated H3Puma, caspase-3; ↓HDAC3, 6, Bcl-xl, Bcl-2,	31
ROS/DR/caspase-dependent apoptosis	Hispidin	CMT-93, HCT116	↑p53, caspase-3, -8; Bax, ↓Bcl-2	32
Reactive oxygen species -dependent apoptosis and necrosis	Vitamin C	SW480, RKO	↓ VEGF, EGFR, c-Met, VEGFR1, Sp	33
Reactive oxygen species-apoptosis	Piperlongumine	HT-29, SW620	↑Cleaved Bax, PARP, caspase 3,	34

3. Colorectal Cancer and Oxidative Stress

With Western nations having the highest incidence rates, CRC is one of the most frequent malignancies globally.[35] Most CRC instances (70–80%) are thought to be sporadic. In contrast, around 15% of CRC cases are thought to be caused by inherited factors such as HNPCC (hereditary nonpolyposis CRC) and FAP (familial adenomatous polyposis).[36] Changes in global incidence rates and the migrant study's findings suggest that sporadic human colorectal cancer might be caused by a variety of environmental and lifestyle variables, including physical inactivity, food habits, and obesity.[37] The epithelial cells lining the gut are the source of colon cancer. These cells reproduce instantly and have a significant metabolic rate, identified as a possible contributor to enhanced DNA oxidation.[38] Compared to differentiated cells on the crypt's surface, cells in the lower crypt sections are more susceptible to hydrogen peroxide injury, according to a study on primary rat colonocytes.[39] As the colon's proliferating cells (stem cells and the cells that emerge from them) reside in the crypt's lowest part, this might point to increasing cells as potential colon carcinogenesis targets. The redox environment has been particularly sensitive to stem or progenitor cells. The redox environment plays a significant role in the gut mucosa in their self-renewal and differentiation. Because in the single-phase of the cell cycle, DNA exists as a single strand and as a template for the complement strand works in daughter cells, proliferating cells are particularly vulnerable to DNA damage. Damage to a single strand of DNA may result in various mutations in the daughter cell DNA that are not repairable.[39] DNA damage may cause cell cycle halt, transcription activation, signal transduction pathway activation, genomic instability, and replication mistakes, all linked to colon cancer. However, recent

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

data suggest that ROS production may play a vital part in all stages of carcinogenesis, including initiation, promotion, and progression.[40]

4. Apoptosis in Human Colon Cancer Is Induced by Emodin-Provoked Oxidative Stress

Emodin ("1, 3, 8-trihydroxy-6-methyl anthraquinone") is an anthraquinone found in traditional medicine products of China such as Polygonimuui multiflori radix, Polygoni cuspidati rhizoma et radix, and Rhei radix etrhizoma ("China Pharmacopoeia Committee, 2010"). Emodin inhibits and suppresses migration and cell proliferation and induces apoptosis, angiogenesis, and invasion, all of which are anti-cancer effects.[41, 42] Emodin has been shown to inhibit tumour development in tumour nude mice xenografts harbouring human colon cancer LS1034 cells and cause apoptosis in LS1034 cells in vitro.[43] HCT116 cells in human colon cancer, emodin inhibited phosphorylation of the VEGF receptor. Various studies have shown that emodin-induced apoptosis is partially reliant on ROS increase.[44] However, additional research into the molecular pathways of emodin-induced apoptosis in colorectal cancer cells is needed.

5. Changes in Signaling Pathways and Transcription Factors Caused by Oxidative Stress in CRC

Redox alterations of transcription factors and signalling pathways have been linked to CRC development in many studies. The PI3K/AKT, JAK (Janus kinases)/STAT (signal transducer and activator of transcription proteins), and Wnt/-catenin pathways are the three signalling pathways associated with CRC formation because of oxidative stress disturbance.[45, 46]

5.1 The different signalling Pathways

❖ **JAK/STAT pathway**

The JAK/STAT pathway is essential for the survival and development of CRC cells.[47] In recent research, Tang et al. found a link between colon cancer and the expression of JAK/STAT proteins in terms of clinical-stage, tumor infiltration depth, and lymph node metastasis. Therefore, JAK/STAT proteins were suggested as a diagnostic and prognostic marker for colon cancer.[48] STAT3 dimerization through oxidative modification of Cys253 stimulates the signalling pathway by translocating it to the nucleus.[49] As indicated by STAT3 impairment owing to S-glutathionylation in Cys328 and Cys542 residues[50], cysteine

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

modification may also block this pathway. Apart from thiol modulation, phosphorylation of the Tyr705 residue has been shown to activate STAT3, resulting in cyclinD1 upregulation and CRC cell apoptosis suppression.[51] Finally, it has been discovered that redox modification of the Cys797 residue in the EGFR (epidermal growth factor receptor) activates STAT.[52]

❖ **PI3K/AKT pathway**

Another major signalling pathway, PI3K/AKT, has been connected to CRC development.[53] In recent research, Ju et al. discovered a unique molecular relationship between redox stabilizing oncogenic signalling and metabolic adaption methods in CRC development. MTHFD2 (Methylenetetrahydrofolate dehydrogenase), an NADPH-generating enzyme, increased CRC cell proliferation and metastasis when MTHFD2 was transcriptionally activated by c-Myc through KRAS downstream effectors such as the ERK and PI3K/AKT pathways.[54] Several additional investigations back up this discovery, showing that ROS-mediated activation of PI3K/AKT is linked to the development of CRC.[55] For example, ROS-induced migration and invasion of CRC cells were seen when the PI3K-AKT-mTOR signalling pathway was activated. Furthermore, ROS-induced oxidation of Cys124 in PTEN activated PI3K signalling, resulting in CRC.[56] Moreover, EGFR is involved in PI3K activation and is susceptible to redox modification at the Cys797 position. By inhibiting Cys-dependent PTPs, H2O2 may enhance EGFR Tyr phosphorylation. The oxidation of Cys797 increased EGFR kinase activity.[57] Tyr phosphorylation, in turn, activates the PI3K/AKT and MAPK pathways downstream of the EGFR, which are critical for cell proliferation, invasion, and survival. Because of the oxidation of PTPs and EGFR, downstream signalling pathways are amplified.[58]

❖ **COX pathway**

CRC development has also been connected to the COX pathway, which catalyzes the rate-limiting step of PG production from arachidonic acid. Overexpression of the inducible isoform COX-2 has been linked to a poor prognosis in patients with CRC.[59] Simultaneously, its inhibition was linked to reduced tumorigenesis and metastatic potential in CRC and other malignancies.[60]. The precise relationship between COX-2 activation/suppression and ROS in CRC is unknown. COX-2 expression, on the other hand, has been linked to an increased degree of oxidative stress in several studies. When Tesei et al. used nitric oxide-releasing

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

non-steroidal anti-inflammatory medications (NO-NSAIDs) to treat human colon cancer cells, they found enhanced oxidative stress and elevated COX-2 expression.[61] Another research found that viral activation of COX-2 causes an increase in oxidative stress.[62] Another study found that arachidonic acid metabolism by COX-2 produces reactive oxygen species in human intestinal epithelial cells.[63] Inhibition of COX-2, on the other hand, has been linked to the development of oxidative stress. The inhibition of aldose reductase (AR), for example, decreased COX-2 levels, which led to enhanced proliferation of human colon cancer cells through the suppression of NF-B and protein kinase C (PKC).[64] Another fascinating study found that the quantity of ROS in the tumour environment might impact the level of COX-2. According to an earlier study, an increase in HT-29 proliferation was associated with increased COX-2 levels and vice versa. In an azoxymethane (AOM)-induced colon cancer model, pterostilbene (PS) therapy was linked to a decrease in oxidative markers NOS, COX-2, AR, and NF-B well as an increase in antioxidant glutathione reductase. This was also linked to a reduction in AOM-induced aberrant crypt foci (ACF), lymphoid nodules (LNs), and tumour growth.[65] To further understand the underlying molecular processes of COX-2 signalling in CRC, more research is needed.

- **MAPK pathway**

The Ras-mitogen-activated protein kinase (MAPK) pathway is also essential in CRC. Mutations in BRAF that cause cancer increase the level of MAPK constitutive activation, according to research, linked to CRC development. It's worth noting that KRAS, which is typically triggered by CRC mutations, is located upstream of BRAF. The MAPK signalling pathway enhances the phosphorylation and activation of CRC-related downstream genes. The activation of Ras by S-glutathionylation on Cys118 through higher levels of ROS was discovered in research.[66] According to Liu et al., the Wnt/ β-catenin and Notch signalling pathways are important in CRC cell proliferation, migration, and differentiation. They discovered that these pathways are redox-sensitive, and that NOX can modify them. These pathways are linked to maintaining gastrointestinal homeostasis under normal physiological settings. PTEN oxidation by NOX1 may affect the Wnt/-catenin pathway either directly or indirectly. Rac1 activation causes NOXO1 and NOXA1 to assemble with NOX1. The cysteine oxidation of nucleoredoxin (NRX) caused by NOX1 causes NRX to dissociate from the Axin-binding protein Dishevelled (Dvl). Dvl promotes CRC growth by blocking the

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

breakdown of the -catenin complex, which includes Axin, APC, and glycogen synthase kinase-3 (GSK-3) and facilitates -catenin accumulation.[67] When activated, GSK-3 phosphorylates -catenin, allowing it to be degraded by proteasomes. The phosphorylation of GSK-3 by AKT in, on the other hand, inactivates GSK-3 and targets it for proteasomal destruction. Because PTEN is a negative regulator of AKT, it may up-regulate GSK-3, increasing β-catenin breakdown and blocking Wnt signalling. As a result, PTEN may indirectly control Wnt signalling. Furthermore, through dephosphorylating phosphatidylinositol (3,4,5)-triphosphate (PIP3), which is generated by PI3K, PTEN inhibits the AKT signalling pathway. Through the overactivation of COX-2, HNE, a lipid peroxidation result of oxidative stress, has been demonstrated to increase angiogenesis in CRC. COX-2 has also been shown to stimulate the Wnt/ β-catenin signalling pathway by causing the loss of APC.[68]

The formation of new blood vessels or angiogenesis plays a role in tumour start, growth, and metastasis and is influenced by many variables, including vascular endothelial growth factors (VEGFs). The levels of VEGF and the activity of VEGFR are elevated in colorectal cancer and are linked to a poor prognosis. VEGF levels are high in the very early stages of colorectal neoplasia (adenoma); nevertheless, they are greatly enhanced in the later stages of cancer (metastatic setting). TP53 and KRAS mutations and COX-2 expression influence VEGF-VEGFR function, encouraging cancer development and migration.[69,70] Figure 2 depicts the molecular pathways involved in the aetiology of CRC.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

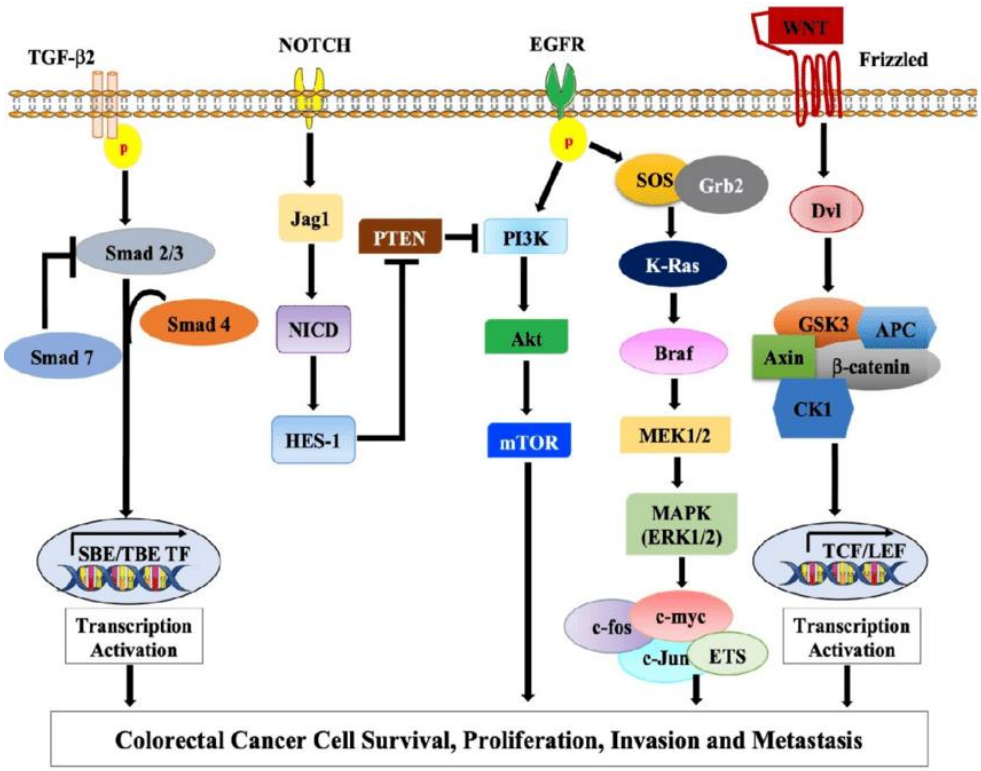

Figure 2. The molecular pathways involved in CRC pathogenesis are shown in this diagram [7].

6. Few studies by previous authors about colon cancer, as shown in the table 2.

Table 2. Few studies about colon cancer

Author	Studies or statement	References
Pathi et al. 2011	Reported "ethyl 2-((2,3-bis(nitrooxy)propyl) disulfanyl) benzoate (GT-094)", a new ROS-generating compound that contains NO moieties and NSAIDs (nonsteroidal anti-inflammatory drug). In CRC, GT-094 therapy caused an increase in apoptosis and an increase in reactive oxygen species, which were reduced with cotreatment with the antioxidant glutathione. By downregulating microRNA-27a, the medication also suppressed Sp1, Sp3, and Sp4 products of a regulated gene (miR-27a).	71
Wang et al.	Described Colon cancer metastasis mediated by NOX1 through the ADAM17 pathway.	72
Lim et al. 2014	Discovered that hispidin, a phenolic chemical, caused apoptosis in colon cancer cells via increasing ROS. In both human and rat colon cancer cells, this medication reduced cell viability. Furthermore, pre-treatment with the ROS scavenger NAC prevented hispidin-induced apoptosis.	31

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

O'Leary et al.	Found that colon cancer cell adhesion is enhanced by the NOX1-mediated redox signalling, which aids metastasis.	73
Agarwal et al. 2018	Stated that in HT-29 cells, cell cycle inhibitory effects and ROS-mediated apoptosis were comparably shown by the curcumin.	74
Ding et al., 2016	Supported that promoting ROS overload might be useful for developing novel anti-cancer treatments. For example, several anti-cancer medicines used by colorectal patients contribute to the production of reactive oxygen species.	75

Conclusions

ROS is abundant in CRC cells, as it is in other types of cancer, which help cells grow and divide. In advanced stages, CRC cells are also linked to redox adaptation, which helps cells stay alive and resist drugs. But more research needs to be done to fully recognize the redox biology of CRC in terms of how it starts, grows, and/or responds to treatment. Using redox modulation to take advantage of the fact that tumor cells have more oxidative stress than normal cells does have a huge chance of killing the tumor cells and leaving the normal cells alone. In preclinical models, a number of ROS enhancers that caused oxidative stress above the toxicity threshold showed promise as therapies for CRC cells. In fact, a combination of a ROS eliminator inhibitor and a ROS enhancer could be a good way to increase the amount of ROS in tumor cells and make them more toxic. An additional area of research to enhance treatment results in CRC might be the pattern of a redox's inhibitor adaption with conventional chemotherapeutics. As a result, it is plainly obvious from our explanation that the redox modulatory method may have significant effects on the therapy of CRC.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

List of abbreviations:

1. **CIMP:** CpG Island Methylator Phenotype
2. **CIN:** Chromosomal Instability
3. **COX-2:** Cyclooxygenase-2
4. **CRC:** Colorectal Cancer
5. **DNA:** Deoxyribonucleic Acid
6. **EGFR:** Epidermal Growth Factor Receptor
7. **FAP:** Familial Adenomatous Polyposis
8. **H2O2:** Hydrogen Peroxide
9. **HNPCC:** Hereditary Nonpolyposis Colorectal Cancer
10. **HO:** Hydroxyl Radical
11. **iNOS:** Inducible Nitric Oxide Synthase
12. **LOX:** Lipoxygenase
13. **MAPK:** Mitogen-Activated Protein Kinase
14. **MMR:** Mismatch Repair
15. **MSI:** Microsatellite Instability
16. **NO:** Nitric Oxide
17. **ONOO:** Peroxynitrite Anion
18. **OS:** Oxidative Stress
19. **PTEN:** Phosphatase and Tensin Homolog
20. **ROS:** Reactive Oxygen Species
21. **RNS:** Reactive Nitrogen Species
22. **UC:** Ulcerative Colitis
23. **VEGF:** Vascular Endothelial Growth Factor
24. **VEGFR:** VEGF Receptor

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

ISSN PRINT 2319 1775 Online 2320 7876

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Not applicable

Availability of data and material

The article and its supplementary files include the datasets that this one used to draw its conclusions

Competing Interests

The author declares that they have no competing interests.

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Authors' contributions

1. **V Brahmaiah:**

Conceived the idea and design of the review, Made the final draft of the review, performed data analysis, synthesized information and organized the review and reviewed and provided input for data analysis and synthesis.

2. **BY Kavitha:**

Assisted in the literature search, Contributed to data collection.

3. **G Deepthi Reddy:**

Assisted in the literature search, Contributed to data collection.

4. **Dr G Deepika:**

Reviewed and provided input for data analysis and synthesis.

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ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

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