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Drug repurposing in the management of colorectal cancer: An emerging therapeutic strategy

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ABSTRACT :

Colorectal cancer, which has a high incidence all over the world, continues to be a serious health burden. Effective illness management is still hampered by the use of traditional treatments including surgery, chemotherapy, and targeted therapeutics, which have side effects, are expensive, and have resistance. One possible tactic to fight resistance is drug repurposing. Drug repurposing—the process of finding novel therapeutic applications for already-approved medications—has been a popular and affordable oncology therapy in recent years. Since patients with metastatic colorectal cancer typically share risk factors for other chronic diseases and are therefore frequently receiving incidental therapy with these medications, drug repurposing may present new therapeutic alternatives. Through mechanisms like autophagy inhibition, angiogenesis suppression, apoptosis induction, and regulation of oncogenic signaling pathways, a number of non-oncological medications, such as chloroquine, mebendazole, nitroglycerin, riluzole, and antiretroviral medicines, have demonstrated encouraging anti-CRC benefits. The therapeutic potential of these medications in the therapy of colorectal cancer is covered in this review, along with their prospective use as a supplement to multimodal treatment approaches.

KEY WORDS: Colorectal cancer, drug repurposing, chloroquine, mebendazole, nitroglycerin, riluzole, antiretroviral drugs.

INTRODUCTION:

Decades ago, colorectal cancer was rarely discovered. Colorectal cancer (CRC), which ranks second in terms of cancer-related fatalities, is thought to be the third most frequent kind of cancer among individuals of all ages and genders globally. It causes 9.4% of all fatalities. Over 1.1 million people receive a CRC diagnosis each year, and the illness claims the lives of over 600,000 people.

By utilizing current safety and pharmacokinetic data, drug repurposing—the act of finding new uses for licensed non-cancer medications—offers a productive and economical way to speed up the development of CRC therapeutics. Five such medicines with strong anticancer potential in colorectal cancer are highlighted by an increasing body of evidence:

1. Chloroquine is the antimalarial drug, it prevents late-stage autophagy. Chloroquine makes CRC cells more sensitive to chemoradiotherapy and to 5-fluorouracil plus radiation in hypoxic conditions, which dramatically lowers clonogenic survival, according to in vitro studies, especially in HCT-116 and HT-29 cells [14,13].

2. Mebendazole, an anthelmintic with preclinical anticancer efficacy in CRC models, inhibits β-tubulin polymerization, triggers apoptosis via Bcl-2/Bax modulation, and has anti-angiogenic qualities [19].

3. Nitro-glycerine improves treatment response in hypoxic tumor microenvironments by reducing tumor hypoxia, a major mechanism underlying chemoradiotherapy resistance, through nitric oxide donation [20].

4. Antiretroviral drugs, like nelfinavir, inhibit the PI3K/Akt pathway and cause the unfolded protein response and ER stress, which causes autophagy and apoptosis. These effects have been confirmed in early clinical trials and on a variety of cancer cell lines, including colorectal cancer [5,6].

5. Riluzole Originally used to treat ALS, riluzole inhibits glutamate signaling and alters the oxidative balance in tumor cells, which impairs proliferation and increases apoptosis in CRC settings [12]. Each agent will be examined in detail in this review, along with its molecular mechanisms, preclinical and clinical studies in colorectal cancer, and translational potential.

The review highlights how drug repurposing could expand therapeutic horizons in CRC care by focusing on these five repurposed medications.

Repurposing approved drugs in colon cancer:

This approach is gaining momentum due to its cost effective, faster development of time, and already established safety profiles. Several challenges in traditional drug development such as high attrition rates, long timelines and expensive R&D to make repurposing an attractive alternative. (4)

FIGURE 1. approved drugs repurposed for colorectal cancer therapy

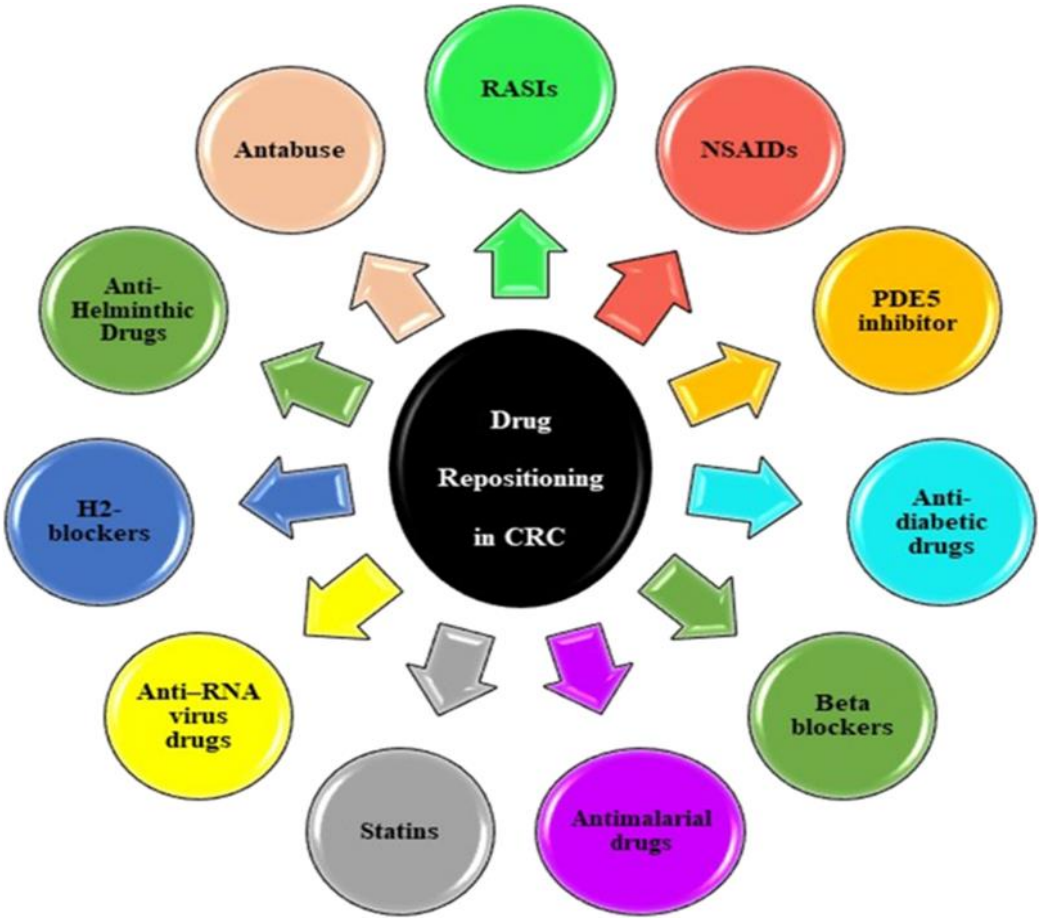

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Table 1. Treatment of different stages in CRC (3):

Stages of CRC	Treatment Modalities	5-year survival rate
Stage 1	Endoscopic or surgical excision of the pedunculated malignant polyp and surrounding lymph nodes.	90%
Stage 2	Surgery, in isolation, deemphasizes the necessity of adjuvant chemotherapy unless there are notable high-risk attributes evident.	75%
Stage 3	Adjuvant chemotherapy in addition to surgery.	60%
Stage 4	The therapies available include chemotherapy, tailored therapy, immunotherapy, surgery, radiation, ablation, and stenting.	3%

1.Chloroquine

Chloroquine, which has been used as an antimalarial agent for generations, came into prominence once again in oncology by its capability to modulate autophagy, the cellular survival response often hijacked by the cancer cells [13]. In the case of colorectal cancer (CRC), the tumor cells are known to induce autophagy in response to hypoxia, chemotherapy, and radiotherapy. By suppressing the late phase of autophagy, chloroquine inhibits this adaptive response and sensitizes the CRC cells to therapy [9].

Preclinical studies have demonstrated that chloroquine sensitizes CRC cells to 5-fluorouracil (5-FU) and oxaliplatin, thereby enhancing the efficacy of standard chemotherapy. Moreover, chloroquine has been shown to reduce tumor hypoxia and affect the tumor microenvironment by inhibiting angiogenesis and altering immune responses. These actions collectively contribute to reduced tumor progression and metastasis

Apart from the inhibition of autophagy, chloroquine also has anti-inflammatory and immunomodulatory actions, which potentially contribute to the suppression of pro-tumorigenic signaling pathways in CRC. Clinical trials in the early phase are already examining the combination of chloroquine and standard chemotherapy to assess its safety and therapeutic value in advanced CRC patients.

Overall, chloroquine represents a promising repurposed agent in CRC management by overcoming drug resistance, sensitizing tumors to therapy, and modulating the tumor microenvironment [17].

2.Mebendazole

Traditionally an anthelmintic, the benzimidazole derivative, mebendazole, has demonstrated significant promise in oncology and specifically in the malignancy of the colon and rectum (CRC). By virtue of its binding to β-tubulin and inhibition of polymerization of the microtubules, it obtains its anticancer activity. This causes quickly multiplying tumor cells to apoptose and reduce the production of mitotic spindles [1].

Reports state that mebendazole suppresses angiogenesis of CRC models by the inhibition of vascular endothelial growth factor (VEGF) signaling. By inhibiting the vascularization of tumors, the effect decreases the supply of the nutrients to the cancer cells. Mebendazole is also a strong candidate for combination therapy as it can induce the enhancement of the cytotoxic action of usual chemotherapeutic agents such as oxaliplatin and 5-fluorouracil (5-FU) [11].

Notably, mebendazole has also demonstrated the potential to inhibit key oncogenic signaling pathways commonly aberrant in CRC, including MAPK, Wnt/β-catenin, and hedgehog. Mebendazole is of particular interest for clinical translation to low-resource environments, owing to its outstanding safety profile, affordability, and oral availability.

Although there are currently few clinical trials, preclinical data strongly suggests that mebendazole should be further evaluated as a multi-targeted repurposing drug in CRC therapy [4].

3.Nitroglycerin

Recently, nitroglycerin, a well-known vasodilator used to treat heart failure and angina, has drawn interest from oncologists as a possible medication repurposing candidate. Its function as a nitric oxide (NO) donor, which affects several pathways related to tumor growth, angiogenesis, and drug resistance, is principally responsible for its anticancer effects.

Tumor hypoxia contributes importantly to resistance to therapy and poor outcome in human CRC. Hypoxia-induced survival of the tumor can be relaxed by nitroglycerin through the release of NO, which decreases the activity of hypoxia-inducible factor-1α (HIF-1α).

This sensitizes the cancer cells to chemotherapeutic agents like oxaliplatin and 5-fluorouracil (5-FU) [22].

Additionally, nitroglycerin has been reported to enhance immune surveillance by modulating tumor-associated macrophages and improving cytotoxic T-cell activity. It also possesses anti-angiogenic properties through the inhibition of pro-angiogenic signaling, thereby reducing tumor vascularization [15].

Clinical trials in additional malignancies, including non-small cell lung carcinoma (NSCLC), have established that nitroglycerin can enhance therapeutic effectiveness when administered in conjunction with chemotherapy. Indirect CRC-specific clinical evidence is scarce, but the mechanistic justification overwhelmingly justifies its consideration as an adjuvant therapy in the management of CRC.

Because of its cost-effectiveness, availability, and demonstrated safety profile, nitroglycerin presents the possibility of a repurposed adjunct therapy to penetrate hypoxia-induced resistance of colorectal cancer [8].

4.Riluzole (ALS Agent)

Riluzole, an FDA approved drug approved for amyotrophic lateral sclerosis (ALS) treatment, has been recently proposed as a novel anticancer compound, also for colorectal cancer (CRC). Glutamate signaling, which is important for tumor growth, survival and metastasis, is a critical target for its anticancer action [16].

The glutamate metabotropic receptor (mGluR1) pathway has also been demonstrated to be utilised by colorectal cancer cells to enhance cell growth and resistance to apoptosis. Riluzole works by suppressing glutamate release and antagonizing the downstream signaling of MAPK/ERK and PI3K/AKT, leading to the suppression of the viability of the tumor cell [18].

Riluzole has been reported to promote CRC cell cycle arrest in G2/M and apoptosis in preclinical studies. Furthermore, riluzole exhibits an inhibition of metastatic properties through the modulation of the randomized movement and cancer cell intrusion. Crucially, moreover, it acts in synergy with common chemotherapeutic agents, e.g., oxaliplatin and irinotecan, thus increasing chemotherapy-induced cytotoxicity and bypassing resistance phenomena.
Beyond direct tumor inhibition, riluzole may also modulate the tumor microenvironment, particularly by affecting oxidative stress and immune responses. These combined effects make riluzole a strong candidate for repositioning in CRC, especially as an adjuvant to current chemotherapeutic regimens.
While clinical evidence in CRC remains limited, early findings from other solid tumors, such as melanoma, support the rationale for advancing riluzole into CRC-specific clinical trials [10].

5.Antiretroviral drugs in CRC

The antiretroviral drugs, which were first developed to treat HIV infection, showed the possibility of the treatment of oncological disorders due to their action in cell proliferation, apoptosis, and immunomodulating action. PIs, lopinavir, ritonavir, and saquinavir, and the reverse transcriptase inhibitors, zidovudine, are among the agents evaluated for anticancer action, even the CRC [23].
One of the main mechanisms involves the inhibition of Akt signaling, a pathway often upregulated in CRC and associated with chemotherapy resistance. For example, ritonavir has been reported to block Akt phosphorylation, resulting in increased apoptosis and reduced cancer cell survival. Similarly, protease inhibitors impair NF-κB activity, leading to suppression of inflammatory and pro-survival signaling that supports CRC progression.
Additionally, antiretroviral drugs can disrupt proteasome function, inhibit angiogenesis, and reduce tumor cell invasion. Preclinical studies indicate that combining PIs with chemotherapeutic agents like 5-fluorouracil (5-FU) enhances cytotoxicity and overcomes drug resistance [7].
Interestingly, these agents may also improve immune surveillance by restoring T-cell function, which is often compromised in CRC patients. This immunomodulatory effect could further support their use as adjuncts to standard chemotherapy or immunotherapy.
Regardless of the dearth of clinical trials conducted directly in CRC, evidence from the other malignancies such as Kaposi's sarcoma and prostate cancer confirms the anticancer action of antiretroviral drugs. Due to their proven safety profiles, cost-effectiveness, and availability, they are strong candidates of the drug repurposing in CRC [2].

Future prospectives

Drug repurposing demonstrated significant promise in colorectal cancer (CRC) management by identifying new therapeutic roles for well-established agents such as chloroquine, mebendazole, nitroglycerin, riluzole, and antiretroviral drugs. However, several future directions can further strengthen this strategy:

- **Integration with precision medicine:** Personalized repurposing strategies are possible through advances in genomics, proteomics, and metabolomics. Molecular signature-based stratification of the CRC patient population will improve the efficacy of drugs while keeping the toxicity low (5).
- **Combinatorial therapies:** Repurposed agents can also be used in combination with traditional chemotherapeutic agents, immunotherapy, or targeted therapy to evade resistance and rescue patient prognosis. For instance, the combination of autophagy inhibitors such as chloroquine and checkpoint agents may boost the immune response in CRC (1).
- **Computational modelling and machine intelligence :** Network pharmacology and machine learning can potentially minimize the time required to find new repurposing candidates by computationally predicting the drug–target interactions and synergy (13).
- **Overcoming clinical trial barriers:** Designing adaptive and basket clinical trials specifically for repurposed agents in CRC will provide robust evidence for regulatory approval and clinical translation (21).

Conclusion

Drug Repurposing of drugs offers a novel and effective strategy in the management of colorectal cancer, filling the void of the existing therapies. Drugs like chloroquine, mebendazole, nitroglycerin, riluzole, and antiretrovirals offer novel mechanisms of action through targeting of survival processes of the cancer, angiogenesis, and resistance. Future clinical trials and investigations are needed to validate their use in the management of CRC and define their position among the existing therapeutic schemes.

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