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IVERMECTIN AS A POTENTIAL DRUG IN INHIBITING COLORECTAL CANCER CELL GROWTH

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ABSTRACT

Colorectal cancer (CRC) ranked as the third most frequently occurring cancer, with an estimation of 1 to 2 million new cases occurring globally every year. The high mortality rate of CRC is due to the failure of current treatment options, at present the CRC treatment mainly adopts surgery combined with radiotherapy, targeted therapy and chemotherapy. A dihydro derivative of avermectin also known as ivermectin firstly introduced in agriculture and veterinary sector, but soon it was used for the treatment of onchocerciasis and parasitic infections in humans. Ivermectin also possess certain cancer related epigenetic deregulators such as SIN3A and SIN3B, which potentially effect the cancer population. In colorectal cancer, the ivermectin cause death of certain cell lines that include SW1116 and SW480 through modulating some pathways including WNT-T cell factor or by dysfunction the mitochondria. Ivermectin affects the proliferation and growth of CRCs by playing several roles that includes functioning as an RNA helicase, activating the chlorine channel activator and as an inducer of oxidative stress. There are number of studies that have proven the

antitumor effect of ivermectin. However, despite such promising results in several studies that showed that ivermectin could be used in the treatment of colorectal cancer and other cancerous treatment the passage of this drug through blood-brain hurdle could be a common problem that should be considered in future.

Keywords: Colorectal cancer, Multidrug Resistance, Parasitic infection

1. INTRODUCTION

One of the common types of cancer that occur worldwide is colorectal cancer that occurs in colon and rectum, often referred as colon cancer. It is ranked as the third most frequently occurring cancer, with an estimation of 1 to 2 million new cases occurring globally every year.In 2018 it was one of the second leading cause of cancer related deaths with an estimation of 881 000 deaths globally **[1]**. Ivermectin is a derivative of the 16-membered macrolide compound abamectin, which was first widely used in clinical practice as an antiparasitic drug.

Furthermore, studies have shown that ivermectin has an inhibitory effect on various tumour cells and could be a potential broad-spectrum antitumor drug. Ivermectin is the most sensitive to breast cancer cells MDA-MB-231, MDA-MB-468, MCF-7, and ovarian SKOV-3, while it is the least sensitive to prostate cancer cell line DU145.

2. Molecular pathogenesis of CRCs:

Most of the colorectal cancers (CRCs) arise from a neoplastic lesion often called as polyps, after 10 to 15 years these polyps become mature and progress to CRCs. In studies, it is believed that CRC originate from the stem cell, which take genetic and epigenetic alterations resulting in activation of oncogenes and inactivation of tumor suppressor genes **[2]**. For the initiation and maintenance of tumor cells stem cells are important and depending on the genetic and epigenetic events, the CRC development can occur through three pathways that are:

1. Through Serrated Neoplasia
2. Through Microsatellite Instability (Lynch Syndrome)
3. Through Adenoma-Carcinoma

In 70-90% cases the CRC development occur through the adenoma-carcinoma, in which the earliest stage is called stage 0 during which the cancer cell are only in mucosa and inner lining of the colon and rectum. The stage 1 to 4 is classified depending upon the development of disease, at the start the cells proliferation is restricted only to one site but with the time when the cells acquire the malignant characteristics, they are called adenocarcinomas **[3]**. The development of CRC as in most of the cancers is potentiated through mutation in specific

gene, these mutation can occur in tumor suppressor genes or the genes involved in DNA repair. The mutation can inhibit the apoptotic mechanism that can result in uncontrolled proliferation of cancerous cells.

3. Current treatments of CRC:

The high mortality rate of CRC is due to the failure of current treatment options, at present the CRC treatment mainly adopts surgery combined with radiotherapy, targeted therapy and chemotherapy. The surgery can be used during the early stages of cancer and of all the CRCs 20% are treated at the early stage. In a patient with metastatic CRC the resistance to first line chemotherapy is created due to lack of information of molecular mechanism and heterogeneity of the metastatic cancerous cells. The treatment of CRC is done using the multimodal approach and depend upon the characteristics of the tumor and patient. But prior to defining the treatment of CRC patient it is important to first evaluate the presence or absence of metastatic cells, presence of biomarkers and also the assessment of patients age **[4]**.

4. Ivermectin as a potential anticancer Drug:

Ivermectin is a drug approved by the US food and drug administration (FDA) for the treatment of parasitic infections. But based on the assumptions of WNT-TCF signaling pathway that is involved in many diseases including the CRC. According to Melotti et al., the ivermectin was a blockage to the response of WNT-TCF responses in colon tumor cells. In another study, it was observed that ivermectin was effective in reversing the drug tumor in two solid tumor lines that are HCT-8 CRC cells and MCF-7 breast cancer cells. Despite these effective results, the passage of this drug through blood-brain barrier is a common problem **[5]**.

5. Ivermectin role in different cancers:

Table 1: Role of Ivermectin

Cancer type	Role of Ivermectin	Reference
Breast cancer	**Studies have shown that ivermectin in breast cancer regulate he microenvironment which can cause the death of tumor cells. The high level of ATP along with tumor microenvironment the ivermectin enhance the release of pannexin-1, which is a high mobility group protein (HMGB1). This HMGB1 promotes the cell immunogenic death of cancerous cell.**	**[6]**
Digestive system cancer (CRC)	**According to studies in digestive system cancer or CRC the ivermectin inhibit the proliferation of multiple cancer cells including the CC14, DLD1 and Ls174 which are the colorectal cancer cell lines. It also blocks the Wnt path and promotes apoptosis**	**[7]**
Urinary system cancer	**In urinary system cancer the Ivermectin stops the division of five renal cells that are carcinoma cell lines without affecting the normal kidney cells by dysfunction the mitochondria.**	**[8]**
Reproductive system cancer	**The proliferation in the various ovarian cells is inhibited by the ivermectin. The inhibition of PAK1 kinase is responsible for inhibiting the division of cells in the ovarian cancerous cells. IVM could impede the cell cycle and initiate cell apoptosis through a KPNB1-subordinate system in ovarian malignancy.**	**[9]**

6. Apoptosis induced by Ivermectin:

Ivermectin induces the programmed cell death also known as apoptosis in different tumor cells including the CRC cells. Mainly the apoptosis is regulated by the genes to maintain the cell stability by eliminating the worn out or old cells. Invermectin induces the apoptosis in two ways that are **[10]**.

1. Mitochondrial pathway/ Endogenous endoplasmic reticulum stress
2. Exogenous death receptor pathway

The recent studies conducted showed that ivermectin induce the apoptosis through mitochondrial pathway, it was observed that with the intervention of ivermectin the mitochondria potential was decreased and release of chromatin c was detected. In addition, the ivermectin upregulated the protein bax and downregulated the anti-apoptotic protein BCL-2 this resulted din change of balance among the apoptosis related proteins **[11]**.

7. Autophagy induced by Ivermectin:

Autophagy is the programmed cell death that is induced by the lysosomes, this process involves the elimination of superfluous and damaged organelles in the cell to maintain homeostasis. Autophagy is regarded as the double-edged sword in tumor development, as sometimes the autophagy help the tumor cells from radiotherapy and chemotherapy and on the other hand sometimes it increase the sensitivity of tumor cells towards the radiotherapy **[12]**. Overall it is observed that the specific environment of the tumor cell usually determine the fate of autophagy process. In recent studies, it is observed that the intervention of ivermectin increases the autophagy flux, as seen in the case of breast cancer where ivermectin intervene with the cancer cell lines MCF-7 and MDA-MB-231 and increase the autophagy flux. The ivermectin increased the expression of certain autophagy proteins such as LC3, Bclin1, Atg5 and certain autophagosomes is also observed **[13]**. This showed that the ivermectin exhibit the antitumor effect through the autophagy pathway.

8. Effect of Ivermectin as anti-cancerous drug on colorectal cancer cells (CRC):

8.1 Change in morphology of CRCs:

In a study the effect of ivermectin on the morphology of colorectal cancer cell was observed. The colorectal cancer cells SW1116 and SW480 was treated with different concentration of ivermectin and the morphological changes were observed under the optical microscope. There was a significant change in the morphology of the CRC after certain time, in SW480 the increase in concentration of ivermectin the cells became more and more spare, especially the cells of 20μm size became rounded and shrink in their size was

observed. The cells of SW1116 were more sensitive to the ivermectin concentration; with the increased concentration, the cells were shredded. Thus, the study showed that in colorectal cancer, the ivermectin could promote the death of cancer cells and the effectiveness depends upon the dose of ivermectin **[14]**.

8.2 Change in the proliferation rate of CRCs:

In a study to investigate the impact of ivermectin on the multiplication of colorectal malignancy cells, we utilized various groupings of ivermectin (0, 2.5, 5, 10, 15, 20, and 30 µm) to culture colorectal disease cells SW480 and SW1116, the cell viability of SW480 and SW1116 cells diminished depending on the dose concentration by ivermectin treatment (Dose, D: $p < 0.01$). Besides, ivermectin repressed SW480 and SW1116 cell suitability in a periodic manner (Time, T: $p < 0.01$). Thus, the result showed that ivermectin was responsible for decrease in the proliferation rate of colorectal cancerous cell depending upon the dose concentration and time **[14]**.

8.3 Change in mitochondrial ROS generation in CRCs:

The effect of ivermectin on the mitochondrial ROS level and intracellular level of ROS is important to determine as the ROS exposure at high level can result in the oxidative damage of mitochondria and very acute level of ROS could inactivate the iron-sulfur centers of electron transport chain **[15]**. In a study, to determine this level SW1116 cell of CRC treated with ivermectin, it was observed that with the increase in the concentration of ivermectin the ROS content was increased in total and of mitochondria. This increase was also dose dependent; this showed that ivermectin could be possible used against the tumor cells of colorectal cancer that with the increased dose could cause the oxidation of mitochondria cause the death of tumor cell **[14]**.

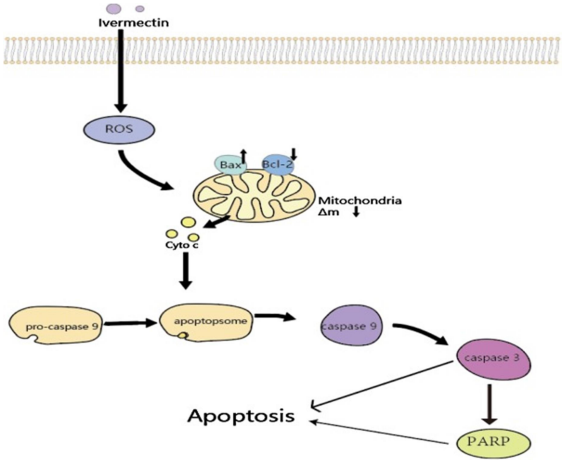

Figure 1: Ivermectin induced mitochondria-mediated apoptosis [16]

9. CONCLUSION

Thus the results showed that the ivermectin effectively inhibit the colorectal cancerous cells but depends upon the concentration and time. The mechanism adopted by the ivermectin can be mitochondria dysfunction or inhibition of HSP27. Despite such promising results in several studies that showed that ivermectin could be used in the treatment of colorectal cancer and other cancerous treatment but the passage of this drug through blood-brain hurdle could be a common problem that should be considered in future.

The table below shows the mechanism adopted by the ivermectin drug to treat different cancer types including the colorectal cancer.

Table 2: Mechanism adopted by the ivermectin drug

Mechanism	Cancer type	Reference
Inhibit Wnt pathway	Breast cancer, Colorectal cancer	[17]
Inhibit MAPK pathway	Nasopharyngeal carcinoma, Melanoma	[18]
Inhibit HSP27	Prostate cancer, Lung cancer Colorectal cancer	[19]
Induce mitochondrial dysfunction	Colorectal Cancer	[11]
Inhibit p-glycoproteinand MDR protein	Colorectal cancer, Breast cancerLeukemia	[20]
Inhibit PAK1 protein	Breast cancer, Ovarian cancer, Nasopharyngeal carcinoma, Melanoma	[21]

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Conflicts of Interest

The authors declare no conflict of interest

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