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Repurposing Vermicide Ivermectin as Medicine in Oncology to Treat Cancer- The Silent but Accessible Role Player in Sustainable Innovation

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Abstract

Ivermectin (IVM) is an effective parasitic anti-drug that is used to treat neglected tropical diseases as onchocerciasis, helminthiasis, and scabies. Ivermectin has drawn considerable attention of the contemporary medical community due to its diverse pharmacological properties it has proved that itself is a highly effective anti-cancer drug, which has provoked an interest in its Ivermectin inhibits cancer cell replication, induces apoptosis, as well as changes the functioning of PI3K/Akt/mTOR, Wnt/-catenin, and STAT3 which leads to decreased angiogenesis and aggressiveness of tumors. Besides, it also boosts the effect of modern chemotherapy drugs existing in the market and lowers the danger of resistance. It is preclinical established that Ivermectin may have different anticancer mechanisms such as programmed cell death. Most of these studies were conducted in cells culture and animal models, which demonstrate the principle of ivermectin in cancer but still require further researches including clinical trials on humans to validate the potential effects of Ivermectin on cancer. As a result, although the laboratory findings indicate that Ivermectin can be used for the therapy of cancer, it is still early to use it as standard tumor treatment. More studies are required to describe the exact mechanism and confirming its efficacy and safety in oncological treatment is also relevant.

Keywords

Ivermectin, Repurposing, Vermicide, Cancer, Glioma, Cytotoxic, Oncology.

Introduction

Drug repurposing is a strategy that recognises new uses of chemical entities of drugs approved or investigated that are outside the original medical instruction. New treatments are mostly sought from prevailing items, but also compounds that have been adjourned, withdrawn or abandoned because they need not accomplished the anticipated performance in their main precise symptoms, or because better managements have been developed. This report confers the non-commercial institution of new cancer treatments using non-patent-based products based on both "hard-repurposing" (repositioning of non-cancer drugs for oncological usage) and "soft- repurposing" (add new re-tasking of cancer indications for recognized cancer drugs)[1].

- **Traditional Drug Discovery**: Encompasses discovering new drugs from scratch, starting with screening and going through widespread preclinical and clinical trials before reaching the market.
- **Drug Repurposing**: Utilizes already approved drugs, seeking new therapeutic uses, often reducing the time and cost required for development and approval.

The traditional drug discovery is a more time-consuming and costly process, starting from the identification of a lead compound to market approval, while drug repurposing leverages existing drugs to find new uses, potentially speeding up the development and approval process[2].

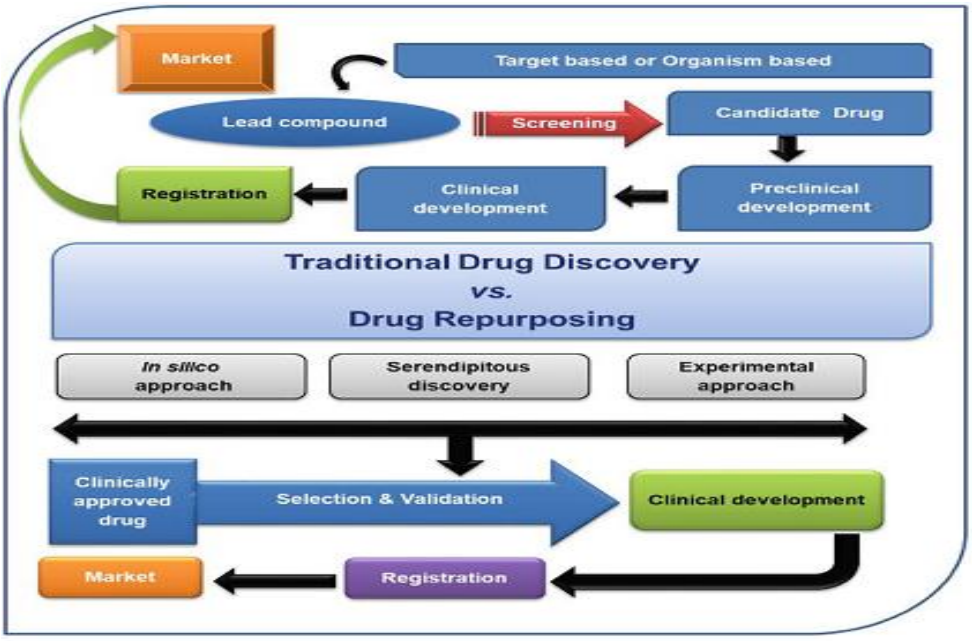

Figure 1.Traditional drug discovery vs drug repurposing

Cancer can arise when there occurs an uncontrolled replication/division of some types of cells in our body and defects in the genes that normally can slow down cell activity, like growth and division. It is those extra cells that fail to get "different signalling" which keeps on dividing to form tumours. More are being diagnosed with cancer and the rate of death from it being internationally is greater. For second place as the mortality cause in the Latin America and for the third place in the Ecuador as well it is ranked next. Based on statistics from the American Cancer Society (ACS), approximately 5.5 million women would develop cancer almost a decade later in 2030 which will bring the total deaths to 20 million women per year. A striking fact that stands out is why the rate of breast cancer is escalating alarmingly[3]. This is largely fueled due to increase in occurrence of factors such as physical inactivity, genetics, poor diet, obesity, and reproductive conditions, all of them can raise the risk for cancer. In accordance with the International Cancer Research Centre (IARC) established by the World Health Organization, it was found out that in Latin America account for 49% and 63% respectively of the deaths.

The concepts of on-target and off-target drug repurposing, detailing how a drug can be repositioned for new therapeutic indications. Both on-target and off-target repurposing explore different pathways to find new therapeutic uses for existing drugs, enhancing the efficiency and scope of drug development.

- **On-Target Repurposing**: Utilizes the same biological target but finds new therapeutic uses for the drug's action on that target.
- **Off-Target Repurposing**: Involves identifying new targets for the drug, leading to new therapeutic applications[4].

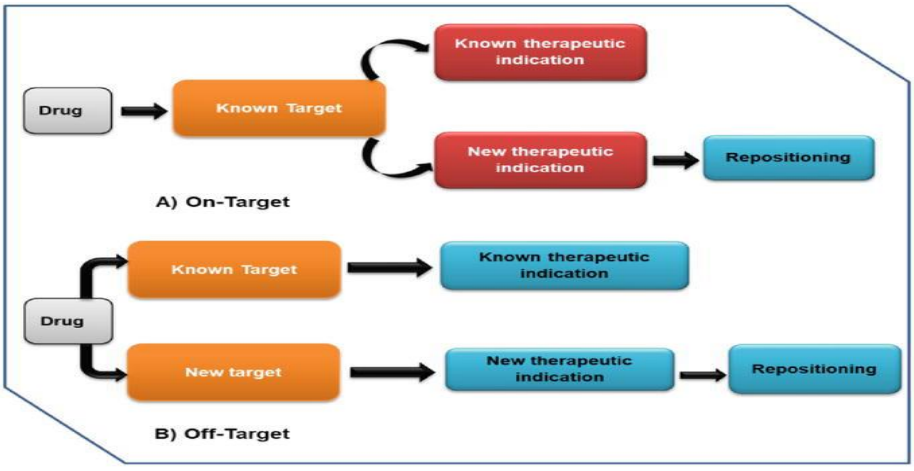

Figure 2. On-target and off-target strategies of drug repositioning.

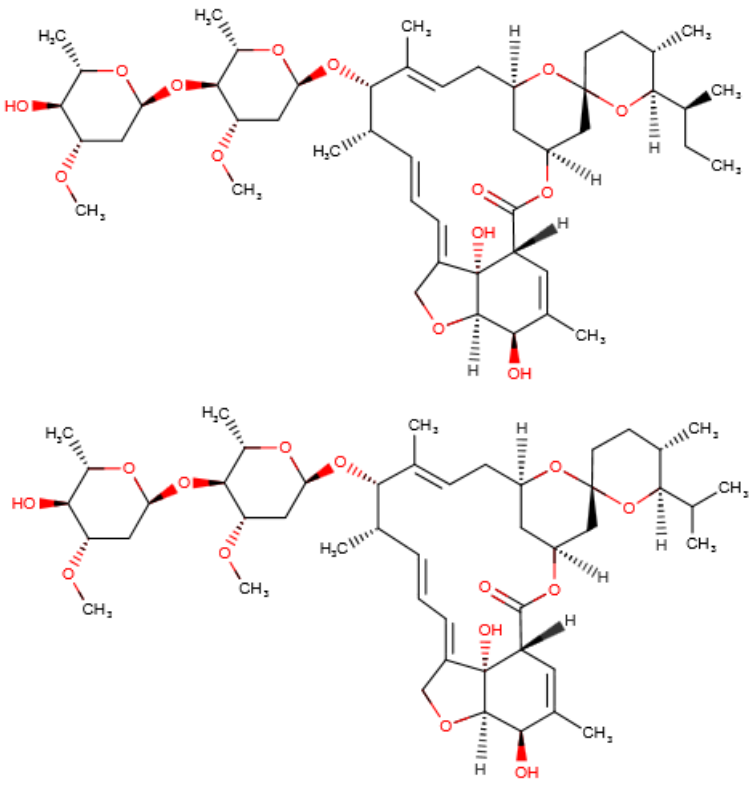

Figure 3.International Union of Pure and Applied Chemistry Name: (1*R*,4*S*,6*R*,10*E*,14*E*,16*E*,21*R*)-6'-butan-2-yl-21,24-dihydroxy-12-[(2*R*,4*S*,6*S*)-5-[(2*S*,4*S*,6*S*)-5-hydroxy-4-methoxy-6-methyloxan-2-yl]oxy-4-methoxy-6-methyloxan-2-yl]oxy-5',11,13,22-tetramethylspiro[3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene-6,2'-oxane]-2-one

Ivermectin is a 16-member macrolide antiparasitic drug produced from Vermectin, composed of 80% of 22.23-dihydroavermectin-B1a and 20% of 22.23-dihydroavermectin-B1b.Selamectin, doramectin, and moxidectin are present members of the Vermectin family, in addition to VIM, treatment effectively When the parasite stimulates the glutamate-gated chloride pathway, the gamma-aminobutyric acid (GABA) releases to destruct the nerve, causing a significant increase in chloride ions and neuronal hyperpolarization. Nevertheless, the IVM also shows an significant activity in conducting somatic muscle paralysis in the transmission of the body nerve which finishes the killing of parasites. Therefore, the IVM can be effective in treating malaria, trypanosomiasis, schistosomiasis, trichinosis, and leishmaniasis in addition to its antiviral properties. IVM inhibits multiple viruses, such as flaviviruses by blocking NS3 helicase function and dengue and HIV-1 viruses through additional mechanisms involving the stoppage of the transport of viral proteins and release of antiviral action, respectively. Recent studies indicate that, apart from this emergency aid

against the 2009 influenza pandemic, it has potential against SARS-CoV-2, which is responsible for the current 2020 global pandemic. On the one hand, it was also able to be involved in the therapy of asthma and neurological diseases development in clinical practice. It has been evidenced by the researchers lately that IVM is strongly anti-cancer property [5].

Drug repurposing, highlights both computational and experimental methods. Effective drug repurposing strategies often combine both in silico and experimental approaches to identify and validate new therapeutic uses for existing drugs. These approaches can significantly reduce the time and cost associated with traditional drug discovery processes by leveraging existing data and drug safety profiles.

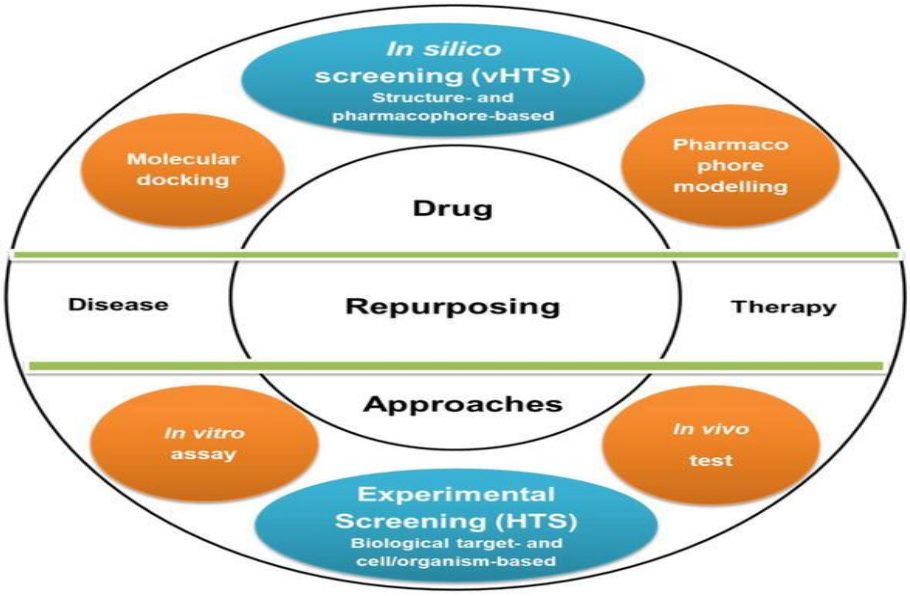

Figure 4. Computational and experimental methods

Drug repurposing is a systematic approach that leverages existing drugs for new therapeutic indications through a series of rigorous screening and validation phases. Utilizing phenotypic or computational data, the process identifies new targets or indications, followed by in silico, in vitro, and in vivo screenings. The candidate drug undergoes extensive pre-clinical and clinical trials to ensure safety and efficacy before receiving FDA approval [6]. This structured pathway enhances the potential of developing successful repurposed drugs, thereby optimizing drug discovery and reducing development timelines and costs.

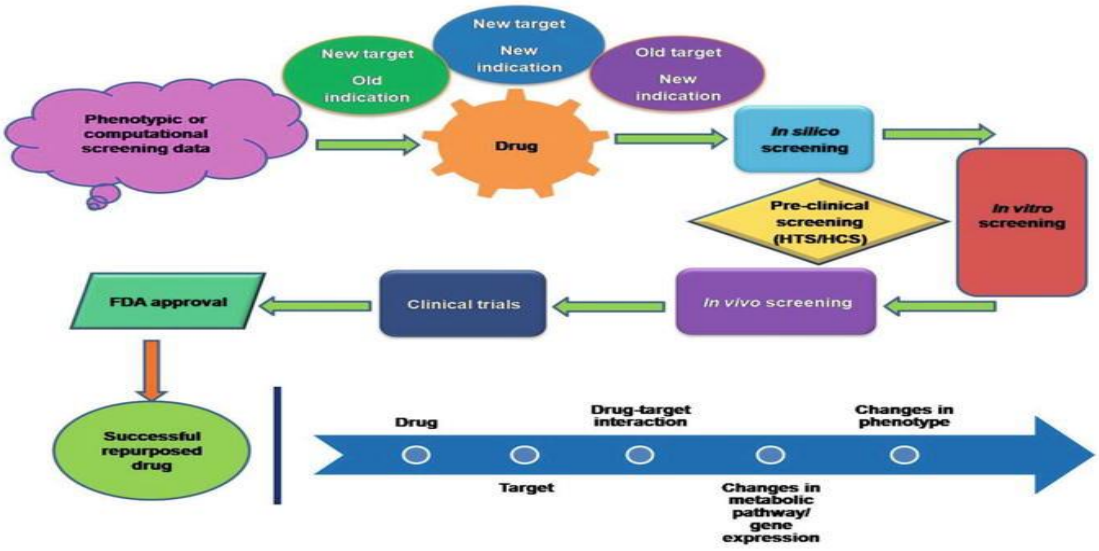

Figure 5.Sequential stages from initial screening to successful market approval

Recently ivermectin was discovered to control the growth of some cancer cell types by regulating a number of signaling pathways. It indicates that Ivermectin can be used as an anticancer drug. Since the 1996 discovery of IVM, which may antagonize multidrug resistance in TMDs (MDRs), important studies have begun exploring IVM as a new cancer treatment.

ROLE OF IVERMECTIN AGAINST CANCER CELLS

The pre-clinical studies have confirmed that ivermectin possesses cytotoxic effects especially on the cancer cell lines like breast, lung, intestine and prostate cancer. In addition, ivermectin was found to induce apoptosis, inhibit cell proliferation, and even reduce the size of cancer in animals which implies its therapeutic potential in cancer treatment. Ivermectin has a wide range of anti-cancer activities and this is achieved by causing changes in several cell pathways associated with cancers growth and metastasis. The research team found interaction of ivermectin with a variety of molecular targets in cancer cells, including ion channels, transporters as well as signalling proteins, destabilization of the progression of the cell cycle, DNA damage and inhibition of angiogenesis and metastasis. The restructuring of ivermectin as an anticancer drug is especially worth looking into because of its known human safety profile and its availability as a generic drug. Rather than the chemotherapeutic drugs commonly used, ivermectin, which has toxicities or side effects that restrain the dose, is

generally tolerated rather well even at a larger dose and, therefore, provides a promising choice for the combination therapy or treatment of cancer patients. It is more engaged in the study of the cancer-curing applications of ivermectin, in particular. Clinical studies are being done to investigate the security and effectiveness of using ivermectin or combined with other cancer drugs. If all goes well, repurposing ivermectin as a cytostatic drug will result in an inexpensive and widely available alternative to cancer treatment for ordinary cancer patients across the world, even in low resource communities where the traditional cancer treatment is not available [7].

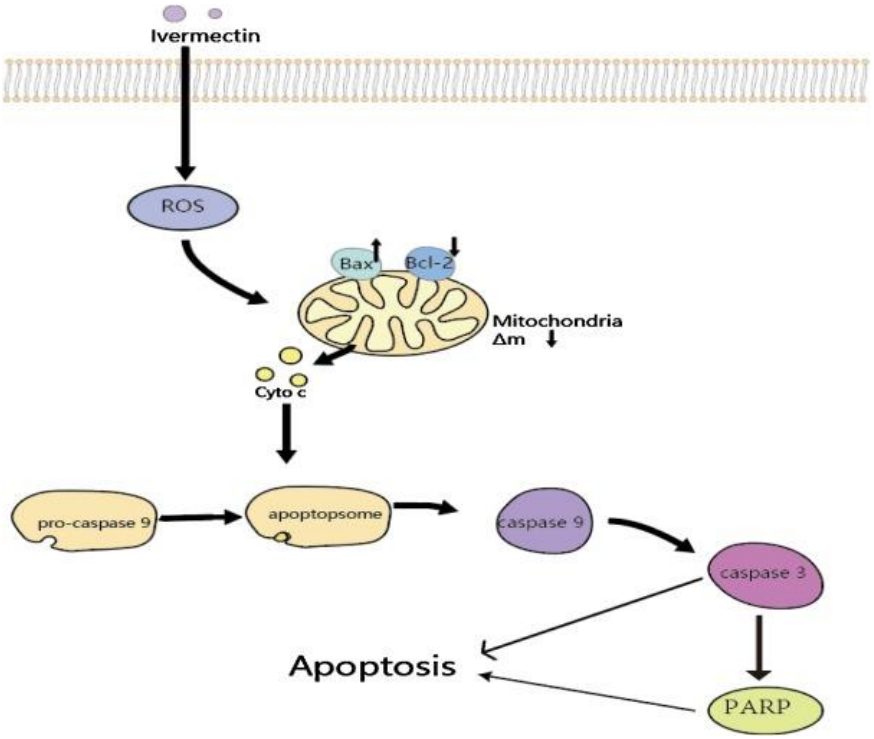

Figure 6.Mechanism of Ivermectin against cancer cells

MECHANISM OF IVERMECTIN AGAINST CANCER CELL

Ivermectin is a mechanism of action in tumours is diverse, with several mechanisms contributing to its anti-cancer activities. While the precise processes are still being investigated, research has provided insights into how ivermectin exhibits its anti-cancer activity:

2.1 Impede cancer cells proliferation: Ivermectin retards the multiplying of tumor cells through disturbing different vital biological processes including those, which are tissue growth dependent. Reportedly, it disturbs the cell cycle by stooping progression at different

stages such as G0/G1, S and G2/M preventing cells from growing or dividing into new ones. The administration of Ivermectin anti-mitosis and reduces accumulation of cancer cells via pathways which hamper cell cycle progression.

2.2 Induction of apoptosis: Cells that are damaged or abnormal are eliminated by apoptosis. Ivermectin is observed to stimulate cancer cells to undergo apoptosis through internal or external pathways. Activation of caspas, cytochrome c release from mitochondria, stimulation of apoptotic proteins, and DNA damage results in a domino of chemical reactions, which lead to cell death[8].

2.3 Autophagy Modulation: Autophagy is the mechanism which breaks down and recycles damaged proteins and organs to maintain the cellular homeostasis. The research has revealed that ivermectin affects phagocytosis in cancer cells by inducing it or inhibiting it depending on the environment of the cell. Disruption of autophagy of Ivermectin can obstruct the survival of cancer cells and elevate their chances of apoptosis or other forms of cell death.

2.4 Suppression of angiogenesis: Angiogenesis (growth of new blood vessels) allows oxygen and nutrients to support cancer progression and metastasis. Ivermectin had been demonstrated that it suppresses angiogenesis through all the signalling pathways targeting the signalling paths of VEGF, endothelial cell growth and migration. Ivermectin can block the synthesis of angiogenesis, thereby stopping the growth and transfer of tumours.

2.5 Cancer stem cell degradation: The cancer stem cells (CSCs) differentiate themselves by its capability to self-renew, which is why they are considered in the process of growth of tumor initiation and development, and also with resistance to treatment. It has been established that ivermectin targets CSCs by inducing differentiation, reducing self-renewal abilities, and making them more susceptible to radiation or chemotherapy. Ivermetcin killed the cancer stem cells that are the origin of cancer metastases and are responsible for tumour reoccurrence.

Ivermectin, by virtue of inhibiting cancer cells from proliferating, promotes apoptosis, modulates autophagy, suppresses angiogenesis and targets the cancer stem cells via a variety of complex processes, which work in combination to kill cancer cells. There is a need for more research to comprehensively comprehend the molecular events that govern the cure effect of ivermectin and optimize its ability for cancer treatment [9].

Materials and Methods

3.1. Breast cancer

Breast cancer is a tenacious malignancy which originates from breast epithelial cells by way of mutations together with diverse carcinogens. Breast cancer in women is the utmost common malignant ailments which, according to statistics occur more and more every year. An increasing amount MCF-7, MDA-MB-231 and MCF-10 (breast cancer cell lines) has been proven ineffective against IUMA treatment. This drug impairs the Akt/mTOR pathway, targets PAK1 in human breast cancer and enhances autophagy.

Moreover, Diao's studies reveled that Ivermectin would suppress growth of the CMT7364 and CIPp canine breast cancer cells by disrupting the cell cycle with no increase of apoptosis and that IVM mechanisms may be involved in the blocking of Wnt pathway. Molecular screening of TNBC identified IVM as a SIN3 interaction domain simulator that would specifically and efficiently disrupt the SID-pair A-helix2 interaction. Also, IVM has restored TNBC cell sensitivity by expressing EMT (Epithelial mesenchymal transition) related gene E-cadherin. Current research establishes that Ivermectin can increase the mortality rate by modulating the tumour cells subsects of micro environs of breast cancer. When microenvironment of the affected cells is stimulated at increased quantity of ATP outside the affected cells, Ivermectin increases the discharge of the HMGB1 (High-mobility box-1 protein) through P2 (1) Pannexin-1. On the contrary, the egression of a lot of HMGB1 to the extra cellular environs triggers immune lack and inflammatory reactions by means of the immune cell which hinders the progression of the tumour cells. IVM modifies tumour microenvironment and explains killing of immune cells [10].

3.2. Respiratory system cancer

Cancerous cells arising from the epithelium borders of the nasopharyngeal orifice are called carcinoma of the nasopharynx. The human herpes virus (Epstein-Barr virus: EBV) has a direct linkage with regional affairs which are evidently domestic (family-related). In a research concerning drugs that target neophelial cancers, the IVM could be used to in more than one way, the significant suppression of the development of the neophelial carcinoma in naked mice without affecting the normal thymus, however. Besides that, in vitro test IVM which had been proved effective treatments of the nasopharyngeal cancer cells by inhibiting the MAPK pathway through the suppression of PAK1 kinase activity. Nishio figured out that

after the treatment of IVM, there is a decrease in cell growth of H1299 lung cancer cells via YAP1[7]. The synergic deadly effect of the combination of IVM and erlotinib treatment was demonstrated by Nappi's study, which revealed that this effect is caused by disrupting EGFR signalling pathway in HCC827 lung cancer cells. IVM can work against EMT, and lead to the improvement of the lung cancer metastatic disorders.

3.3. Urinary system cancer

Renal cell cancer is the lethal urinary cancer that develops due to epithelial cells of the kidney tube. There is an average increase of two per cent in international severity, and treatment efficacy is believed to be insufficient. The Research indicates that IVM is a powerful antagonist of five different tumour cell lines but does not affect the multiplication of regular cells of kidney. This relationship might reflect the occurrence of mitochondrial defects.

Therefore, Ivermectin might considerable mitochondrial membrane Influential and block ATP production and mitochondrial respiration, as well. Animal studies with mitochondrial fuels like ALCAR and NAC as antioxidants reversed the inhibition produced by IVM. Immunohistochemical results from the tumor tissues after IVM treatment displayed a significant elevation of the mitochondrial stress marker HEL, which was consistent through the cell investigation. Prostate cancer is a type of malignant tumor originating on or after epithelial cells of the prostate gland and is only second the lung cancer amongst men in nations of Western countries. The study of Nappi found that IVM might improve the effect of estrogen drug Enzalutamide on cell line of LNCaP prostate cancer and overcome resistance to Docetaxel in PC3 prostate cancer cell line. Especially, The triple-negative sensitivity of breast cancer to estrogen drugs tamoxifen is equalized by Ivermectin. So IVM can be utilized in endocrine treatment. Additionally, IVM has exhibited anti-proliferative properties of DU145 prostate cell line of cancer [11].

3.4 Haematological cancer

Leukaemia as a malignant type and a hematopoietic stem cells dysregulated [disordered] blood cancer. During pharmacological screening of IVM the cells below the blood haemopoietic internal limit are selectively killed without causing damages to normal cells. The excessive influx of chloride molecules into the cells due to IVM effect cause cells to attain extreme hyperpolarization states and the efficient production of ROS. When it is combined with cytarabine and Danorubinic acid, IVM treatment of leukemia is highly effective and it was shown by Wang's experiments in particular that IVM actually causes

mitochondrial dysfunction and generation of reactive oxygen species in chronic myeloid leukemia K562 cells which in turn leads to significantly more apoptotic cell death [12].

3.5 Brain glioma

The most prevalent form of brain cancer is Glioma, impacting around 100,000 people globally with formidable destructive power. Glioma is characteristically represented by glioblastoma being a most aggressive and lethal type with such an average survival of 14 to 17 months. Research has shown that high dosage of IVM can bring on the apoptosis of human U87 and T98 G glioblastoma cells; the extent of the apoptosis that occurs in the cells is dependent upon the dose. This is due to enhanced mitochondrial dysfunction and oxidative stress. In turn, it has an effect on adrenal glands, adrenaline, cortisol, which sharply rise, In today's world, healthy eating has become more important than ever. With an increasing number of people facing chronic diseases like obesity, diabetes, and heart disorders, it is evident that our current dietary habits need Human brain endothelial microvascular cells mature and survive apoptosis following IVM exposure with the angiogenesis being significantly altered. Such outcomes demonstrate the presence of IVM and its ability reduces tumor growth and spreading of these malignancies. The mechanism of AVE depressed U251 and C6 glioma cells through Akt/mTOR pathway targeting were established by the given study.

The given case of gliomas, MiR-21 could modulate the Ras/MAPK pathway, amplifying the effect on both multiplication and incursion. The functioning of the DDX23 helicase alters the manifestation of miRNA-12. Ivermectin inhibits DDX23/miR-12 signalling path channel by regulating the DDX23 Helicase activity and suppressing cancerous bacterial expressions. By demonstrating that IVM can function as a RNA helicase inhibitor, this might give rise to a new treatment regime for tumors. Nonetheless, the application of IVM has fallen short in glioma treatment since it cannot pass the blood-brain barrier [13].

3.6. Digestive cancer

Gastric cancer is one among the world's greatest prevalent malignant tumors that leading causes of cancer-related mortality. Nearly one million people have been diagnosed with gastric cancer per year, across the globe. A 1999 specific study reported that growth and invasion of stomach cancer cells in vivo and in vitro can be considerably suppressed by GVBM, which is actually warning that YAP1 (yup associated protein 1) and MCNP1 and SH-

10-TC are prerequisites for the GVBM effect, however, MKN7 and MKN28 are not. Function of GVBM in humans basically is a cancer oncogene.

The investigation of Wnt pathway inhibitors demonstrated that Ivermectin could reduce growth of many tumour cells, including colorectal cancer cells CC14, CC36, DLD1 and Ls174T promote apoptosis by inhibiting Wnt signalling way. IVM therapy enhances expression of CSF-3 in DLD1 and cell lines of Ls174T which proves its capability to causes It has not yet been identified what precise molecular targets of the IVM are acting via this Wnt/-catenin pathway. Liver cancer is the IVth ranked source of cancer mortality factor globally. Carriers like B and H of HIV virus are responsible for about 80 per cent of all liver cancer cases while inhibiting the activation of yap1 in mice with spleen cancer leads to lower progression of hepatocellular carcinoma. The study by Intuyod was able to indicate that IVM suppressed the growth on of KKU214 cholangiocarcinoma cells through time and dose. IVM impeded the S-phase cell cycle by inducing cell apoptosis. Even though the IVM-resistant KKU214 cells were found to be sensitive to the drug which indicates that IVM is capable of treating chemotherapy

Result and Discussion

The efficacy of ivermectin remains extremely uncertain. Even so, the activity of ivermectin has been demonstrated to interrupt few cell practices that are important to cancer survival and growth, the generation of cell stress response and the inhibition of signals. In animal tumour models, numerous trials have demonstrated that ivermectin blocks tumour growth and improves life expectancy. It should be borne in mind that results of animal research are not necessarily human-applicable [14]. Ivermectin was proven to have anti-cancer properties on several cell lines in laboratory investigations. Cancers like breast, lung, and colon as well as others show these effects. However, how ivermectin works as an anticancer drug in humans is less understood clinically, but the results of laboratory and animal studies are promising. In clinical trials, it will be determined whether or not ivermectin is safe and effective against cancer, in particular [15]. As my fresh report indicates, the latest results of any clinical trial involving this purpose should also be examined. One advantage of the use of drugs like vermectin in cancer therapy is that they have been well studied for human safety in other settings. Though, the long-term clinical data of ivermectin as an anticancer drug should be examined broadly, including its tolerance and efficacy when combined with other cancer therapies.

Conclusion

Ivermectin shows a great promise as an anticancer drug, though it is only justified by the thorough research and clinical trials. In vitro research is very promising and has confirmed the “anticancer activities” of ivermectin. The in vitro studies dramatically show cancer cells inhibition of proliferation, induce apoptosis, and synergizes with conventional anticancer drugs. In addition, new clinical researches prove that the patients who receive ivermectin treatment report toward successful prognosis, underscoring strong evidence of the drug's efficacy profile and its ability to provide a cheap treatment option. The therapy schedule and drug combinations should be defined in a way that is safe and effective. In addition, the selection criteria for patients should be experimentally determined. In addition to all this, unearthing the specific molecular mechanisms exploited by ivermectin and developing clinically applicable biomarkers for the prognosis of response is an important step in translating ivermectin as a drug for the treatment of cancer. Although difficulties are still persistent in proving Ivermectin effects on cancer, the current data increase its role as an appropriate auxiliary to cancer treatment devices. The conducted studies devising a novel way of treatment should continue in order to create a co-dependency between academic, industrial and regulatory organizations for a better chance to improve clinically cancer patients. Investigative work and validation will empower ivermectin to be a new and cheaper therapy method for many different types of cancer which makes cancer patients worldwide envisage the bright future.

Traditionally, the dug repurposing has a long recorded history discovery of drug molecules particularly through serendipitous observations. In recent years, it has embarked a new avenue in the development of new therapies based upon existing/approved medicines. The strategic drug repositioning in a more systematic and rational way has brought innovation with the discovery of drug molecules with unknown therapeutic indications. As drug repositioning approach offers significant reduction in R&D costs, greater chances of success, shorter research time and lower investment risk, it has gained increasing market demands. Because these advantages are beneficial for discovery scientists, drug researchers, consumers and pharmaceutical companies, enabling the application of novel approaches of repositioning strategy in the drug discovery program for almost all human diseases. Moreover, the use of *in silico* techniques along with the application of structure-based drug design (SBDD) and pharmacophore modeling strategies and artificial intelligence (AI) technology can further accelerate the process of drug purposing in the drug discovery program. In the era of

precision medicine, the drug repositioning strategy has become very much useful to establish the unknown mechanism of action of drugs through exploration of novel disease/metabolic/signaling pathways, or off-targets and target-specific mechanisms/ genetic expression profile for even genetic disorders. Advancement in genomics have provided us with genomic and transcriptomic data in huge quantities using technologies like next generation sequencing, microarray data and transcriptomics, etc. Network biology and systems biology approaches may add additional benefits to unveil such novel mechanisms of actions with through insights into drug-target interaction profile at molecular/genetic level. For better drug repositioning, more in-depth understanding are required to be executed with integrated approaches between computational and experimental methods to ensure high success rates of repositioned drugs. However, drug repurposing can be successfully utilized in the discovery and development of new drugs with novel and effective therapeutic indications for human diseases.

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