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REPURPOSING OF THIORIDAZINE AS ANTICANCER AGENT: AN OVERVIEW

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ABSTRACT

Thioridazine was an antipsychotic drug which was widely used to treat schizophrenia and psychosis but had been abandoned due to its cardio-toxic effect including arrhythmia. Some years back, it was analyzed that the patients under its treatment showed significantly lower risk of getting cancer (-1.04%). The study for various types of cancer including Glioblastoma, Hepatocellular carcinoma, Breast Cancer, Gastric cancer, Esophageal Cancer, Colon Cancer with on-going experiments has been practiced. The prevalence and dose-dependent effect was also studied for investigating the adverse drug effects as well as any toxicological conditions. Thioridazine has been used as a combination adjuvant alongside many drugs. The clinical results were reported with its mechanism and the pharmacology as well. In this review, we summarize the recent studies on anticancer activities of Thioridazine and studies for further advancements.

Keywords *– Thioridazine, Glioblastoma, Hepatocellular carcinoma, Breast Cancer, Gastric cancer, Esophageal Cancer.*

1. INTRODUCTION

Cancer is a major public health problem and one of the leading contributors to the global disease burden. The high cost of development of new drugs and the increasingly severe burden of cancer globally have led to increased interest in the search and development of novel, affordable anti-neoplastic medications.[1]

Antipsychotic drugs have a long history of clinical use and tolerable safety; they have been used as good targets for drug repurposing. Being used for various psychiatric diseases for decades, antipsychotic drugs are now reported to have potent anti-cancer properties against a wide variety of malignancies in addition to their antipsychotic effects [2,3]

Psychiatric medications are also promising as a new generation of cancer chemotherapies. Several epidemiological studies have reported that patients with schizophrenia who are receiving anti-psychotic drugs have a lower cancer incidence than the general population, suggesting that psychiatric medications might have positive effects on some human cancers. Decreased incidences of prostate, colon, and rectal cancers were observed in patients receiving schizophrenia drugs [4-7]

Thioridazine (10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine) is an antipsychotic agent and was previously used in the treatment of mental disorders like psychosis and schizophrenia but was demarcated due to product insufficiencies and newer, better product manufacturing.

Although, a first-generation drug, the repurposing of this compound threw a light upon its varied activities like that of anti-inflammatory, anti-tubercular, antimicrobial, anti-proliferative activities. These activities prove to be a boon in the oncological studies. Thus, various experimental analysis and cell mapping techniques have deduced thioridazine to be a promising anticancer agent.

In this article, various activities of thioridazine or a combination therapy along with its mechanism of action in different types of cancer are reviewed.

2. ACTIVITIES SHOWN BY THIORIDAZINE

2.1. Antimicrobial: Thioridazine has significantly been identified for its antibacterial resistance property. It extensively inhibits bacterial efflux pumps thus accumulating noxious substances in cellular body. This causes ultra-structural changes in the cell envelope, resulting in bacterial lysis. [8-10]

2.2. Anti-proliferative: The proliferative action of any cell can be inhibited by either bringing about changes in the cell cycle or by auto-destruction, i.e., apoptosis. There is an increase in time of G1 sub-phases resulting into nuclear fragmentation- thus discontinuing the re-growth of the cell. Thioridazine shows this extension or arrest of G1 phase and thus acts as anti-proliferative agent. [11,12]

2.3. Antioxidant: As soon as any mechanism is hampered, the compensatory mechanisms are activated. One such example is of oxidative stress. This induced stress is down regulated by certain enzymes like superoxide dismutase and Relative Oxygen Species (ROS). Thioridazine helps in elevating SOD activity and thus ultimately raising ROS, thus protecting the cell. [13,14]

2.4. Apoptosis induction: Thioridazine shows its pharmacological effect on PI3K/AKT pathway. It inhibits the activation of this pathway, thus giving a cellular modification. This produces Annexin-V positive cells indicating occurrence of apoptosis and at times autophagy. [15-17]

3. EFFECT OF THIORIDAZINE ON VARIOUS CANCER CELLS

Various analytical and clinical data compilations have shown positive effects of Thioridazine in several types of cancers. The autophagy inducing, multi-drug-resistance reversing as well as apoptosis activating properties of the drug immensely accelerates the recovery rate. Thioridazine is thus clinically under observations for the treatment of many tumors such as glioblastoma, melanoma, breast cancer, esophageal cancer, gastric cancer, colon cancer, etc. In further studies, its effective actions on stem cells in some of the carcinomas also paved a different path to make future advancements in the repurposing.

3.1. Glioblastoma

Glioblastoma is one of the most fatal cancer with an even lesser life expectancy. Repurposing of anti-psychotic agents was a preferential choice because of its efficacy in crossing the Blood Brain Barrier (BBB). Thioridazine, a phenothiazine derivative, proved to be more advantageous over others as far as the cell mapping obliges to the in-screening method.

Cheng, HW., Liang, YH., et al studied the effect of Thioridazine on antiglioblastoma and anticancer stem cell agent using public gene expression data. It was evaluated by various methodologies on human glioblastoma GBM8401 and U87MG cells. It was observed that Thioridazine showed potential of inducing autophagy activity indicated by elevation of LC3-II cells and caspase

enzymes along with c-PARP inducing apoptosis at different concentrations respectively. The PI3K/AKT pathway were down regulated, thus maintaining the cell stability. It also happened to show activity on glial stem cells. Recently, thioridazine decreased protein expression of Translationally Controlled Tumor Protein (TCTP). It is interesting to know that pharmacology of the interaction may be a complementary reaction to each other. That is, it can be a conversion of autophagy into apoptosis. Also, the fact remains that the DRD2 activity remains isolated from any of the pathway. Clinical studies done on xenograft mice also indicated autophagy induced gene expression confirming its therapeutic utility.[18]

Johannessen T.C, Hasan M.M. performed a genome-wide RNA interference (RNAi) lethality screen to establish a functional gene signature for TMZ sensitivity in human GBM cells. By this approach they identified several potential pharmacological sensitizers to TMZ, where the most potent drug was the established antipsychotic agent Thioridazine, which significantly improved TMZ sensitivity while not demonstrating any significant toxicity alone. the specific chemosensitizing effect of Thioridazine is mediated by impairing autophagy, thereby preventing adaptive metabolic alterations associated with TMZ resistance. Moreover, they demonstrate that Thioridazine inhibits late-stage autophagy by impairing fusion between autophagosomes and lysosomes. Thioridazine in combination with TMZ significantly inhibits brain tumor growth in vivo, demonstrating the potential clinical benefits of compounds targeting the autophagy-lysosome pathway. [19]

Schwab S.G., Sarnow K., et al. designed and synthesized new compounds based on Thioridazines tricyclic structure, and to determine their therapeutic potential. Fourteen compounds were synthesized where variations were made within the tricyclic side chains. The newly synthesized compounds were screened for therapeutic efficacy with or without TMZ using a WST-1 cell viability assay as well as a real-time imaging system (IncuCyte). Tests were performed on both monolayer cell cultures, as well as on glioma stem cell spheroids (GSC). The therapeutic effects were also studied on human astrocytes (NHA) as well as on rat brain organoids (BO). Annexin V/propidium iodide (PI) double staining followed by flow cytometric analysis was performed after 48 hours of treatment. Following an extensive screening, they identified two novel compound that at concentrations of 4 and 9.5 µM showed a strong cytotoxicity on GBM cell lines. both compounds induce apoptosis in the GBM cells.[20]

Although thioridazine shows a bright prospect for repurposing, its cytotoxicity implies huge incompatibility. For this, a combination through isoprenoid biosynthetic pathway was analyzed. It resulted such that the pathway may be perturbed to sensitize cells, its products are not sufficient to protect GBM cells from the cytotoxic effects of thioridazine.[20]

3.2. Hepatocellular carcinoma

Due to in-acquaintance of screening techniques, there is a high possibility that hepatic cancer may undergo last stage diagnosis, thus treatment is provided mostly in worsened stage. In such a type of cancer, it is observed that a combination therapy shows drastic changes in the proliferative action of the cells.

El-Sayed Ibrahim, N., Morsy, et al. Observed synergistic effect of Nisin- an antimicrobial agent and thioridazine. The induction of apoptosis can be a result of inhibitory actions shown by thioridazine on PI3K/AKT pathway. Thus, cell proliferation was exhibited along with decreased expression of genes seen in the assay. During cancerous stage of patient, the ROS levels might take a hike, this is often compensated by cancer cells by absorbing oxygen in it therein arousing oxidative stress crisis. When such a crisis occurs in hepatic cells, SIRT1/NRF2 signaling pathway is activated. At normal times, this pathway helps in protecting the cells from oxidative stress. However, in cancerous conditions, without knowing specificity of cell, this pathway becomes fatal. This pathway was observed to inhibited by Thioridazine.

The autophagy induction, antimicrobial activity, inhibition of angiogenesis and metastasis thus, simultaneously help in the cancer cell autophagy makes thioridazine along with nisin a good potential to be a future aspect to look at.[21]

Shu-lin M., Bu-yunM. et al. studied Killing Effects of Thioridazine on Liver Cancer Stem Cell The suspension culture was used to enrich cancer stem cells in vitro to test killing effect of THO on liver cancer stem cell. Liver cancer cells that cultured in suspension medium are detected similarly to liver cancer stem cells in many aspects, including embryonic transcription factors dependence, drug resistance and cell cycle arrest; which show that it significantly upregulated the expression of phosphorylated STAT3, NANOG and XIAP, and decreased expression of albumin proteins. The cytotoxicity of THO on liver cancer stem cells were evaluated by MTT, Western blotting and flow cytometry assay. The results indicate that THO can significantly inhibit the proliferation of liver cancer stem cells and induce caspase-dependent apoptosis; but weakly to liver cancer cells. However, the combination of THO and doxorubicin hydrochloride (DOX) could more significantly inhibit the proliferation of liver cancer stem cells and cancer cells similarly. The results show that THO has a specific strong killing effect on liver cancer stem cells, and may bring new hope for future clinical treatment of liver cancer [22]

3.3. Breast Cancer

Now-a-days, there are frequent cases reported about breast cancer. Though there is effectiveness in the advancement of the treatment, it was widely observed that there was recurrence after its treatment in initial stages.

Jin X, Zou B, et al. studied the effect of Codelivery of thioridazine and doxorubicin using nanoparticles for effective breast cancer therapy. Doxorubicin- an anthrax-cycline antibiotic, prototype drug used in cancerous conditions, proved to show a synergistic effect with Thioridazine. It was strategized in such a way that it maximized anticancer activity and minimized its drug resistance.

The analysis proceeded with the applications of nano-particle technology which enhanced drug permeability and retention of the drug in cancerous cells. methoxy poly(ethylene glycol)-poly(L-lactic acid) (MPEG-PLA) , an amphiphilic drug, is most widely used in the treatment due to its biodegradation ability and permeation rate as well as clearance rate. The cytotoxic effects were observed on C26, 4T1, and HEK293 cell lines. What was remarkably observed was its IC50 value, which was quite low, thus reducing the adverse activity of thioridazine as well as doxorubicin.[23]

3.4. Gastric cancer

Gastric cancer is rather asymptomatic more than being non-specific symptoms at an early stage, and thus a huge accord of patients presents with late-stage disease at the time of primary diagnosis thus ensuring a poor prognostic report. Gastric cancer treatment includes all the most prevalent techniques of chemotherapy, radiation and medication. However, current drugs are forfeited due to low efficacy and the high rate of patients at the late stage of gastric cancer. Thus, the development of novel drugs for gastric cancer therapy has been need of the hour. It was further discovered that thioridazine may induce anti-neoplastic pluripotent stem cell ability, without any interference with normal pluripotent stem cells.

Chemo-resistance is a major limitation for gastric cancer therapy and thus a remedy has to be discovered at its earliest. Research studied indicated that thioridazine is capable to reverse the chemo-resistance of cancer cells. It is observed that when in combination with verapamil, thioridazine's synergistic activity gives a greater benefit of precision.

Mu J., Xu H., studied antitumor effect of thioridazine in gastric cancer. Thioridazine sought out for the cytotoxic effects on NCI-N87 and AGS cells in a dose-dependent manner, as well as inhibited the colony formation ability of the NCI-N87 and AGS cells. Thioridazine treatment induced DNA fragmentation, increased the levels of sub-G1 phase cells, indicating the occurrence of apoptosis. Moreover, thioridazine induced gastric cancer cell apoptosis in a caspase-dependent manner, as shown by a decrease in the precursors to reverse the cytotoxic effect of thioridazine. It was revealed that thioridazine induced gastric cancer cell

apoptosis with the help of mitochondrial pathway. In addition, thioridazine also used in pretreatment has inhibited the growth of NCI-N87 cell-derived tumors.

The anti-Cancer Stem Cells (CSC) ability of thioridazine was found to have an influence on cyclin and cyclin-dependent kinase (CDK) in correlation with the cell cycle and cell growth. Besides, thioridazine has inhibited the PI3K/Akt pathway, which plays a crucial role in CSCs. Thus, thioridazine may elicit its anti-CSC capacity by preventing the exclusion of small molecules out of CSCs and by inhibiting the Wnt and PI3K/Akt pathways in CSCs. However, this needs to be confirmed by further experiments. Thioridazine was shown to have anti-gastric cancer ability both in vitro and in vivo in the present study, yet whether it has an effect on gastric CSCs has not been detected. Studies are needed to isolate gastric CSCs and to assess the effects of thioridazine on gastric CSCs.

Therefore, thioridazine possesses anti-gastric cancer ability through in vitro and in vivo experiments, suggesting thioridazine as a potential drug in gastric cancer therapy.[23]

3.5. Esophageal Cancer

Radiotherapy is an important form of nonsurgical management of Esophageal Squamous Cell Carcinoma (ESCC). Unfortunately, there seems no effect on patients with unrespectable, re-current, or metastatic ESCC. Induced apoptosis undergoing radiotherapy is the major pathway in treatment of esophageal cancer. The recruitment of apoptosis is a prominent zone makes it a hallmark of cancer, and thus induces resistance to radiotherapy. Therefore, agents that inhibit apoptosis may be a newly strategized for antagonizing cancer resistance to radiotherapy.[24]

Li H., Juan L., Xia L et al revealed that thioridazine induces apoptosis by targeting the PI3K-Akt-mTOR pathway. Induction of the PI3K-Akt-mTOR pathway has been studied as it contributes to resistance of esophageal cancer to many more common classes of chemotherapeutic agents. Therefore, thioridazine is currently considered as a potential anticancer drug in chemotherapy or radiotherapy.

Thioridazine combined radiation therapy can inhibit proliferation of ECA-109 and TE-1 cells by inducing a G0/G1 phase cell cycle arrest. Cyclin D1 and cyclin-dependent kinase 4 (CDK4) have been reported to be involved in the regulation of cell proliferation by mediating the G1 to S phase transition. It was also found that combination treatment decreased the expression of CDK4 and cyclinD1 in both esophagus cancer cells compared with thioridazine and irradiation treatment alone, indicating that thioridazine can be used as an enhancer in the irradiation-mediated cell suppression through cell cycle arrest.

To affirm the anti-tumor effect of combination therapy with thioridazine and irradiation in vitro, the combination therapy showed similar effect, i.e., as high efficacy as shown in xenograft model. Tumor volume was preferentially reduced in the combination group after the treatment, and survival rate had also been much longer than in the control group. Thus, it results that thioridazine is a promising candidate for radiotherapy sensitization in ESCC treatment.[24]

3.6. Colon Cancer

Colon cancer is quite probably a most widespread cancer along worldwide. The multidrug resistance towards anticancer agents has been an obstruction for more years than one would consider it to be in spite of all the transitions brought about in colon cancer chemotherapy. Thus, overcoming this hiatus via targeting cancer stem cells (CSC) had been the major phenomenon to improve the therapy treatment as well as the response. Overcoming drug resistance and targeting CSCs are key for the improvement of chemotherapy response. Therefore, the development of novelty with efficacious drugs for colon cancer has been urgently required.

Zhang, C., Gong, P.et al revealed that Thioridazine has the capability to reduce viability of CSCs from colon cancer cells (HCT116) and follow the mechanism of apoptosis of CSCs via the mitochondrial pathway. The anticancer effect of thioridazine was duly observed via in-vivo mouse models, but down the road, with some clinical trials- the cancer patients were also being experimented to understand its mechanism. It was reported that mitochondrial membrane potential was down regulated during thioridazine induced apoptosis, thus giving a clue for pathway. Thioridazine has a potentially induced CSC differentiation to overcome neoplastic self-renewal and forcibly make the CSCs to enter the normal cellular cycle.

Thioridazine has a potential to reduce proliferation, decrease invasion and activate apoptosis of CSCs thus depleting its viability. Although the clinical studies have to be further evaluated, the results are promising to work upon.[25]

Chen T., Hu Y. et al used thioridazine (THZ) in a combination with loratadine (LOR) to target gastrointestinal tumor, with the aim of investigating whether combined therapy was superior to monotherapy in its antitumor effects. The antiproliferative effects on CT26.WT and MFC cells were analyzed using cell-counting kit-8 assay, and synergistic effect was assessed by combination index. Annexin V and propidium iodide staining indicated the combination therapy was able to induce apoptosis and that this may be mediated via caspase-3, -9 and poly (ADP-ribose) polymerase (PARP). Antitumor activity was also evaluated in CT26.WT xenografts in BALB/c mice. Furthermore, combination therapy was able to successfully inhibit the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin signaling pathway. These findings suggest that the combination therapy with THZ and LOR may provide a promising therapy for gastrointestinal cancer [26]

3.7. Ovarian cancer

Thioridazine is an identified DR2 blocker, has anti-neoplastic activity in a variety of cancer cells. Ovarian cancer cells over-express DR2 therefore blocking DR2 may be a novel treatment strategy for ovarian cancer. Surgical debulking combined with chemotherapy is the standard therapeutic strategy. However, the relapse rate is high, primarily due to the development of chemotherapy resistance therefore exploration of novel modalities was needed.[27]

Yong M., Yu T et al Studied the effect of thioridazine on ovarian cancer cells. A2780 and SKOV3 human ovarian cancer cell lines were studied by seeding into a 96-well plate at a density of 1×104 cells/well, followed by thioridazine treatment with increasing doses (5, 10, 15, 20 and 25 μm) for 24 h at 37°C. Cell viability was determined by performing a Tetrazolium assay for various time periods (6, 12 and 24 h). The morphological changes and the protein expression related to the DR2, apoptosis and autophagy were detected. Detection of apoptosis was done by using Annexin V. To be noted that concentration that produced significant cell inhibition was determined to be 15 μM. Morphological changes observed included cellular rounding, vacuolation and detachment. Western blotting indicated that the expression of DR2 in SKOV3 and A2780 was down regulated following the treatment with 15 μM thioridazine. Flow cytometry analysis revealed a higher percentage of apoptotic cells following a 24-h thioridazine treatment. Apoptosis was confirmed with the activation of caspase 3 and the subsequent production of cleaved caspase-3, which was detected by western blot analysis expression. Levels of LC3 (a marker of autophagy) and P62 (a substrate of autophagy) were evaluated. LC3-II was significantly up-regulated in a dose and time dependent manner observed in the two cell lines following treatment with 0, 5, 10 and 15 μm thioridazine for 0, 6, 12 and 24 h. Results indicated that thioridazine induces autophagy, which may be a pro-survival mechanism associated with thioridazine-induced cytotoxicity in ovarian cancer cells. The present study demonstrated that thioridazine inhibited the expression of p-Nrf2, and suggested that it may be a potential adjuvant for cisplatin therapy. A previous study demonstrated that the co-delivery of thioridazine and doxorubicin (DOX) using polymeric micelles eradicated cancer cells and DOX-resistant cancer stem cells. It could hence be said that Thioridazine is a very promising drug in ovarian cancer treatment.[28]

3.8. Lung Cancer

Yue H., Huang D., et al used different dosage of thioridazine to test its effect on lung cancer stem cells sphere formation. The response of lung cancer stem cells to chemotherapy drug with thioridazine treatment was measured. The cell cycle distribution of lung cancer stem cells after thioridazine treatment was detected. The in vivo inhibitory effect of thioridazine was also measured. We found that thioridazine could dramatically inhibit sphere formation of lung cancer stem cells. It sensitized the LCSCs to chemotherapeutic drugs 5-FU and cisplatin. Thioridazine altered the cell cycle distribution of LCSCs and decreased the proportion of G0 phase cells in lung cancer stem cells. Thioridazine inhibited lung cancer stem cells-initiated tumors growth in vivo. This study showed that thioridazine could inhibit lung cancer stem cells in vitro and in vivo.[29]

Jiani S., Buyun M., et al. Utilized Thioridazine to treat lung cancer stem-like cells (A549 sphere cells) and its cytotoxic effect and mechanism were evaluated in vitro and in vivo. TDZ elicited cytotoxicity in A549 sphere cells and inhibited their proliferation in a dose-dependent pattern. A549 sphere cells treated with TDZ showed nuclear fragmentation, increased G0/G1 phase distribution, positive Annexin V staining, and a change in the expression of caspase family and cell cycle-associated proteins. These results suggest the induction of caspase-dependent apoptosis and cell cycle arrest. In addition, TDZ treatment resulted in significant inhibitory effect on mice xenografts established by A549 sphere cells. TDZ repressed growth of lung cancer stem-like cells in vitro and in vivo, indicating its potential application in targeting lung cancer stem-like cells.[30]

4. ADVERSE EFFECTS ASSOCIATED WITH THIORIDAZINE

Thioridazine proves to be a promising compound, be its individual activity or be its combination- synergistic cancer therapy, it has a wide-ranged potential to be an anticancer agent.[31] But certain discrepancies have to be dilute when considering the practicality of the therapy in the discussion. For example, the ant proliferative activity of thioridazine has been observed at high doses in some cancers, which increases its side effect profile.[32] Such pharmacokinetic properties should be taken into account accordingly.

Also, the adversities observed that of Thioridazine as antipsychotic agent- like difficulty breathing, swelling of face, lips, tongue, or throat, chewing, lip smacking, frowning, tongue movement, blinking or eye movement, tremor, drooling, trouble swallowing, etc. are retained and thus should be taken into consideration. [33-37]

5. DISCUSSION

Thioridazine is a first generation, phenothiazine derivative, antipsychotic drug which has been a prominent name in the Drug repurposing industry. Throughout the years of research and data analysis as well as newer version of the techniques and machineries, it has narrowed down the search path of finding an efficacious use in a different manner. Along with being an anti-inflammatory, antimicrobial, anti-tubercular and antioxidant agent, it has been observed to have far more advancements in anti-neoplastism. With such a broad spectrum of scope, the drug is being thoroughly studied and any refurbishments needed are brought into light. Though mechanism of action is still in grey area, it still needs more data to conclude.

In Glioblastoma, although the action of thioridazine provides certain clearance of its action, there is ambiguity in the pathway of mechanism followed. Although, it is theoretically possible to consider thioridazine, the practicality is still a constant hurdle because of its dose dependent activity and thus ultimate exhibition of its actions. The anti-proliferative action is seen in high doses but when compared to autophagy induction and apoptosis they are relatively low. Thus, to avoid cytotoxic elements the drug combination of isoprenoid biosynthetic pathway inhibitors was proposed with liposomal properties such as Lovastatin, Zoledronate, etc.., but it was not a stable solution for this.[38]

In Hepatocellular carcinoma, there is a synergism of two drugs observed. It is also seen that the when individually given, both the drugs, Nisin and Thioridazine, might not be as useful when given in a combined dose. The mechanism of actions is as well a series of combination starting with its antiproliferative action via inhibiting the PI3K/AKT pathway, autophagy and apoptosis induction resulting into decreased viability of cancer-causing cells. The blockage of compensatory mechanism becomes necessary in oxidative stress, endoplasmic reticulum stress, etc. [39]

In Breast cancer, the newer use of technologies including nano-particles stimulates the multi drug resistance reversing activity of Thioridazine and Doxorubicin elevated potentially increasing its drug repurposing to greater extent.[40]

There is a high profile of Thioridazine with respect to its viability for treatment of gastric cancer. The major advantage is chemo-resistant therapy being compensated. Thioridazine has showed its activity via mitochondrial pathway thus facilitating diagnosis via mitochondrial membrane potential alteration method. However, its antitumor activity on gastric cancer has never been revealed.

In Esophageal cancer, it acts on Cyclin D1, and cyclin Dependent kinase4 which have been involved in regulation of G1 phase, thus contributing proliferative action. Thioridazine thus easily compensates this mechanism through irradiation induced apoptosis.[41]

In Ovarian cancer, as a potential DR2 blocker, its pro-survival mechanism being to induce autophagy in ovarian cancer cell, it also has shown significant effects in experiments where 15 µM drug is administered which is tolerable by humans. Hence, with further studies and research it can be an anti-cancer drug for ovarian cancer.[42]

The clinical trials of colon cancer treatment via thioridazine are positive to make out the cancer suppression activity shown by the drug in cancer patients. This signifies the understanding of cancer stem cells being down regulated with the help of mitochondrial pathway. Future reports may assure its dose-dependency and its regulation.[43]

6. CONCLUSION

Drug repurposing has brought many known drugs into limelight due to its newly found therapeutic activity. Similar is observed in thioridazine, being a drug with several properties and thus useful for various purposes. There remain certain drawbacks because of no up-to-date/ complete data and a probable a smaller number of experimental analogues along with the newer technologies and innovation to get familiarized with. Thus, a wide-variety of useful properties along with a good, effective dose as well as combination is what makes Thioridazine a great potential for future aspect of being an anti-cancer agent.

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