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# EXERCISE-INDUCED CHEMOPREVENTION: SEROTONIN INHIBITS NF-B SIGNALLING AXIS TO COUNTERACT COLON CANCER

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**Abstract**

Serotonin is an important neuroregulatory and secreted during the exercise. Its function in the regulation of the body is not entirely understood. According to recent research, it reduces inflammation. Prolonged inflammation is a contributing factor to the high prevalence of colon cancer in the community. KB cells were used to assess the anti-inflammatory properties of serotonin in a colon cancer model. DMEM was used to cultivate KB cells, and the MTT assay was used to measure the IC50. RT-PCR was used to measure Bax, TNF-α, NF-κ, and IL-6 (at 50 and 100 µg/ml < IC50). Docking analysis using NF-κB (PDB: 5T8O) and serotonin (CID 5202) was performed using Schrodinger. The findings were statistically assessed and expressed as mean +/- standard deviation. In KB cells, serotonin significantly inhibited proliferation (IC50: 225±3.1). It elevated TNF-α expression while downregulating the expression of Bax, NF-κ, and IL-6. Two hydrogen bonds (ASP53 and ALA54, respectively) hold serotonin to NF-κB. Through the inhibition of NF-B pathways in KB cells, the current study demonstrated the strong anti-cancer potential of serotonin.

**Keywords:** Colon Cancer, Serotonin, Inflammatory Pathway, Good Health and Well-Being, Sustainable Development.

## INTRODUCTION

Serotonin, a neurotransmitter primarily known for its role in regulating mood and behavior, has been discovered to exert significant effects on various physiological processes, including immune response and inflammation (1). Its presence within the tumor microenvironment suggests a potential link between neural regulation and tumour development (2). The NF-κB (Nuclear Factor-Kappa B) signalling pathway is a critical regulator of inflammation, immunity, and cell survival. Dysregulation of this pathway has been implicated in various cancers, including colon cancer, where NF-B promotes tumor cell proliferation, survival, and resistance to apoptosis (3). Serotonin has been recognized for its anti-inflammatory properties, mediated through its interaction with specific receptors on immune cells. Activation of these receptors can lead to the downregulation of pro-inflammatory cytokines and chemokines, subsequently influencing the tumor microenvironment's inflammatory milieu (4). The serotonin receptors, particularly 5-HT7, have been found to modulate NF-κB activity. Activation of the 5-HT7 receptor has been shown to suppress NF-κB signalling and, leading to decreased expression of key pro-inflammatory and pro-tumorigenic genes. Recent studies have demonstrated that elevated serotonin levels in the tumor microenvironment correlate with improved prognosis and reduced tumor growth in colon cancer (5). This effect is attributed to the inhibition of NF-κB signaling, which subsequently hinders tumor progression. Serotonin not only acts directly on immune cells but also indirectly affects cancer cells. By altering the tumor microenvironment and immune response, serotonin creates an unfavorable condition for cancer cells to

thrive, possibly by inhibiting their ability to evade immune surveillance (6). The gut-brain axis, a bidirectional communication system between the gastrointestinal tract and the central nervous system, plays a pivotal role in transmitting signals from the gut to the brain. Serotonin, as a key player in this axis, can influence immune responses and inflammation within the colon, impacting the development and progression of colon cancer (7). Harnessing the potential of serotonin and its interaction with the NF-κB signaling axis could offer innovative therapeutic avenues for colon cancer treatment. Targeting serotonin receptors or enhancing serotonin levels within the tumor microenvironment might be explored as adjuvant therapies to conventional treatments. Combinatorial approaches that integrate serotonin-targeted interventions with existing therapies could lead to enhanced treatment outcomes (8). By simultaneously targeting multiple pathways, these strategies might achieve synergistic effects against colon cancer progression. Translating the discoveries about serotonin's role in blocking colon cancer into clinical applications requires further investigation. To confirm the safety and effectiveness of targeting serotonin receptors to modify the NF-B pathway in patients with colon cancer, preclinical models and clinical trials are required (9). It has been established that physical activity has a strong correlation with preventing the development of several chronic illnesses, including human malignancies. Numerous clinical trials and meta-analyses demonstrated that exercise significantly lowers the risk of colorectal cancer (CRC) (10). CRC is a highly prevalent kind of cancer affecting a vast number of people. Its prognosis gets better every day, and by 2035, 2.5 million people are expected to have it. In particular, colon cancer is highly risky in the population since it is typically exacerbated by a number of lifestyle changes. Many populations change the way they eat, relying mostly on foods high in fat. The risk of colon cancer was elevated by a high intake of red meat, drinks, diets high in sugar, and a low use of vegetables in food preparations (11). Furthermore, smoking, drinking hot beverages, and leading a sedentary lifestyle all directly contribute to chronic disease by prolonging inflammation. Oxidative stress, inflammation, and metabolic dysfunction are caused by those metabolic alterations (12). The mechanistic signalling in these physiological networks is complicated, making colon cancer a difficult disease to treat. The three most popular treatments for colon cancer are chemotherapy, surgery, and radiation therapy; however, these approaches are typically limited by a number of related issues, including side effects and tumour recurrence (13). Treatments for these patients appear to be futile in terms of survival because the majority of the time the diagnosis is made at the stage of metastasis. Conversely, it has been demonstrated that physical training and exercise can either prevent or decrease the growth of certain cancer types, such as prostate, lung, oesophagus, pancreatic, proximal and distal colon, endometrial, breast, and prostrate cancer (14). Exercise and related secreting substances substantiate inflammation and inhibit cancer signalling pathways, which disrupt the growth of malignancies. Exercise reduces mitogenic signals, according to a number of studies using various animal models. Exercise suppresses the genes that suppress tumour growth and increases p53 expression. In a mouse model of breast cancer, exercise also decreased the amounts of hyperphosphorylated retinoblastoma protein (15).

Exercise causes the release of serotonin (SA), a type of neurotransmitter that is regulated by both central and peripheral brain cells. It also contributes to the chemical homeostasis of the nervous system and is an essential signalling molecule for motor neurons, memory processing, and other relevant cognitive functions (16). Humans

are vulnerable and have symptoms that are similar to those of depression. According to recent studies, serotonin has a commendable role in tailored characteristics that impact the development of cancer (17). Furthermore, serotonin is present in some amounts in malignant cells, and an increase in serotonin concentration slows down the proliferation of these cells. Additionally, it decreased the formation of tumours and angiogenesis linked to chronic stress. DNA is owned by mitochondria, which also control the energy currency of the cell (adenosine triphosphates, or ATPs) and are capable of organising Reactive Oxygen Species (ROS) and the inflammatory, apoptotic, and anti-apoptotic pathways they are linked to (18). Chemotherapeutic medicines that specifically target mitochondria essentially alter the expression of Bax/Bcl-2 and modulate the membrane potential of the organelles (Mitochondrial Transmembrane Potential, MTP). One gene that promotes inflammation is NF-κB (Nuclear-Factor–kappa-B), and when it is overexpressed, the Bax/Bcl2 ratio decreases, which promotes the progression of cancer. Through the expression of TNF-α (tumour necrosis factor α) and interleukin-6, NF-κB favourably contributes to the progression of cancer. In cells of many cancer types, such as lung, prostate, and breast cancer, serotonin suppressed NF-κB (19). This study examined the potential use of serotonin, an anti-inflammatory, as a substitute drug for the treatment of colon cancer (20).

## MATERIALS AND METHODS

### Cell Viability Assay – MTT Assay

The vitality of the KB cell (purchased from National Centre for Cell Sciences, Pune, India) under serotonin therapy was evaluated using the MTT technique. To improve cell adhesion, 103/well were grown in DMEM (10% FBS, 1% pen-strip) and incubated for 24 hours at 37°C with 5% CO2. The experiment was started with 80% confluency (0, 50, 100, 250, and 500 µg/ml, serotonin) in DMSO (0.1% as maximum). After 48 hours, the vitality of the cells was assessed in comparison to the untreated cells (21). IC50 was computed by use of the probit technique. Utilising a prior technique, the protein denaturation (in vitro) experiment was completed (22).

### RT- PCR Reaction

TRIzol reagent (TaKaRa Bio, Dalian, China) was used to treat KB cells after they had been exposed to serotonin for 48 hours in order to extract total RNA from them. A Prime Script RT Reagent Kit was utilised to reverse-transcribe cDNA. A Mx3005P Real-Time PCR System was used for the amplification. (Agilent, CA, USA), and the Q-PCR experiment was conducted in accordance with the kit's instructions. Using the 2CT approach, the relative mRNA expression levels of each gene were normalised to the RNA of GAPDH. Invitrogen, a company situated in Shanghai, China, produced the primers (23).

### Molecular Docking Analysis

The structures of NF-kB (PDB: 5T8O) and serotonin (Pubchem with CID 681) were obtained. To optimise the ligand and prepare the epik states, Schrodinger software suite was utilised. The extra precision approach (XP) was used for the docking, and the glide score (kcal/mol) was determined.

### Statistical Analysis

One Way/Two Way ANOVA (Bonferroni post hoc test or Newmann Keuls post hoc test) was used to confirm the significant value.

## RESULTS AND DISCUSSION

Persistent inflammation is one of the main causes of cancer development. Its role in the initiation and progression of colon cancers has been well studied. In KB cells, serotonin reduced the consequences of inflammation. Serotonin increased the expression of Bax on KB cells while decreasing the expression of inflammatory genes such TNF-, NF-B, and p38 (24).

### Effect of Serotonin on Cell Viability

Using the MTT assay, the cytotoxic effect of serotonin was investigated. For the experiment, a variety of concentrations were used, including 0, 50, 100, 250, and 500 g/ml (25). In contrast to controls, the results demonstrated that serotonin exhibited dose-dependent cytotoxicity with KB cells (Figure 1). The IC50 values of doxorubicin and serotonin were 252±3.1 and 128.98±1.56, respectively. 50 and 100 g/ml of the pro- and anti-inflammatory genes, respectively, were used to express them.

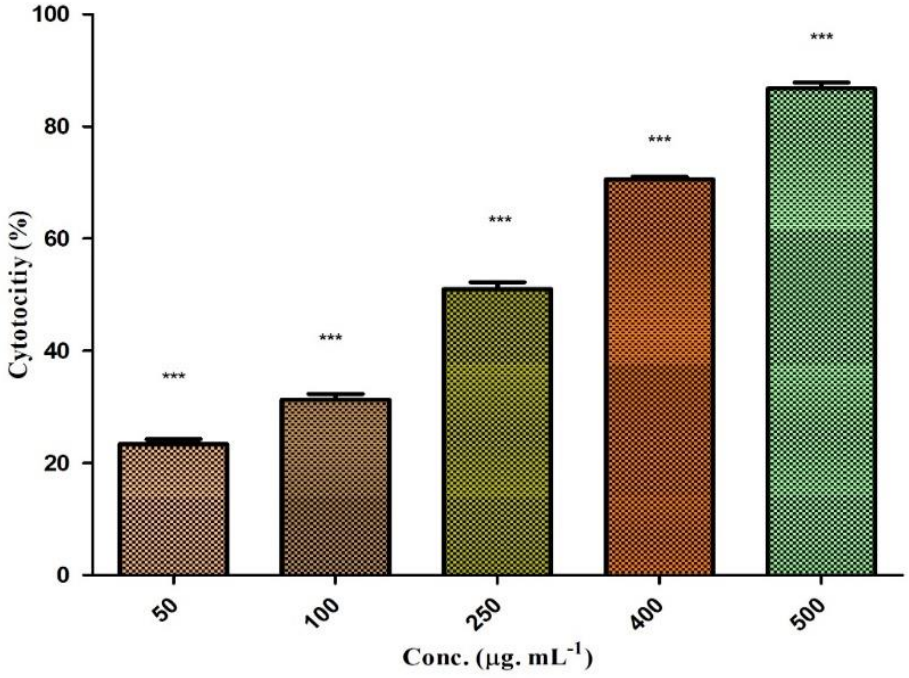


**Figure 1: Effect of Doxorubicin, Serotonin on KB cells. Different Concentration (50- 500µg/mL) of Respective Drugs Treated with KB cells for MTT Assay**. (Two Way Anova – Bonferroni post hoc test) with p value if p < 0.05 ---*, p< 0.005 ...**, p< 0.001-----***).

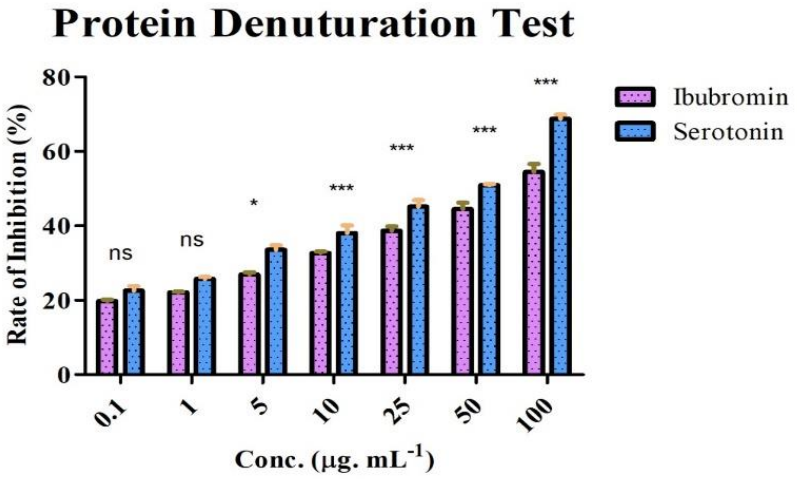


**Figure 2: Protein denaturation Test.** (Two Way Anova – Bonferroni post hoc test) with p value if p < 0.05 ---*, p< 0.005 ...**, p< 0.001-----***).

**Serotonin Inhibited Bax Expression on KB Cells**

Bax expression on serotonin-treated KB cells was assessed by qPCR. Two concentrations—50 and 100 g/ml—were selected for the investigation based on the IC50. At 100 g/ml, serotonin reduces the expression of Bax in KB cells. The Bax decrease was higher at 100 g/ml than it was at 50 g/ml. Consequently, the reduction in Bax expression in response to serotonin therapy is dose-dependent. As a result, the increased gene expression was dose-dependent (Figure 2).

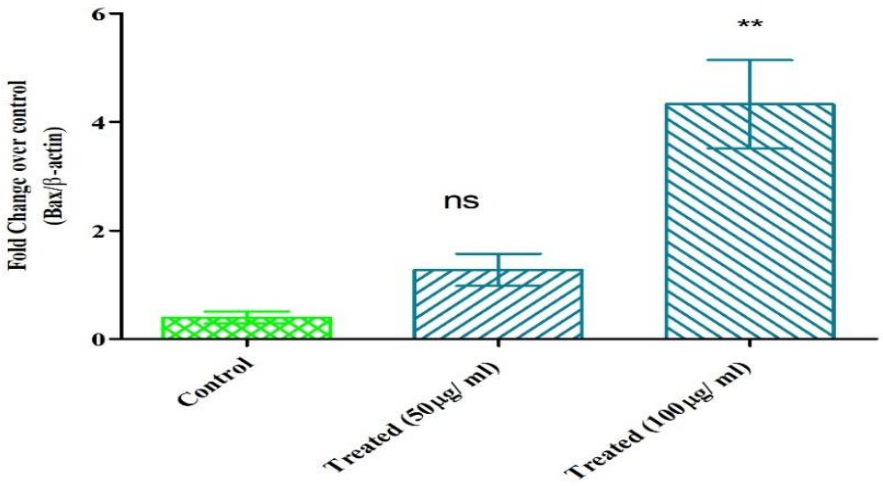


**Figure 3: Serotonin Inhibited the Expression of Bax on KB.** The X axis displays the drug concentration (log), the Y axis displays the fold change over control, and the yellow line represents control. Bax expression at 100µg/mL, a higher concentration. (One Way Anova – Newmann Keuls post hoc test) with a non-significant ns and a p value of p< 0.005.

**Serotonin Reduced the Expression of NF-κB mRNA in the KB Cells.**

The ratio of NF-B in serotonin-treated KB cells was investigated using qPCR. There was a dose-dependent alteration in the expression. At a 50 g/ml dose, serotonin significantly reduced NF-B expression in comparison to the control (Figure 4).

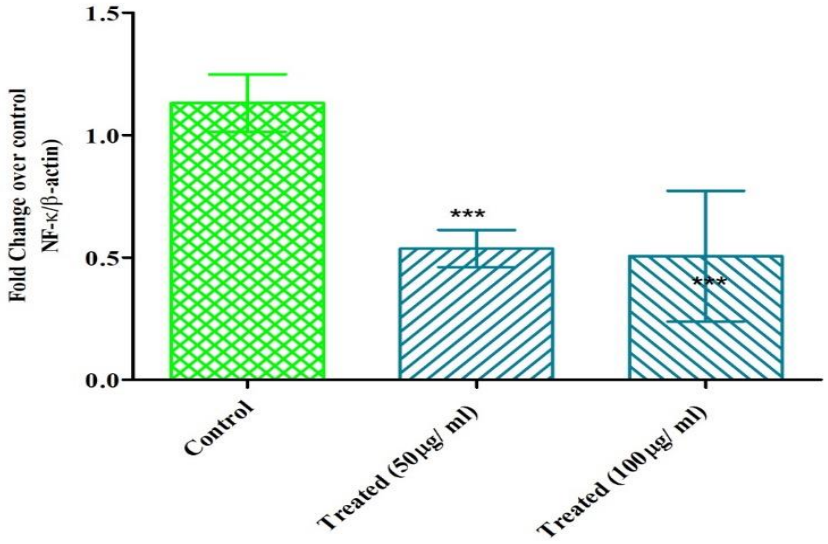


**Figure 4: Effect of Serotonin the Expression of NF-κB mRNA on KB Cells.**

The drug concentration (log) is plotted on the X axis, and the fold change relative to the control is plotted on the Y axis.

According to our findings, serotonin reduced inflammation by suppressing pro-inflammatory indicators such BCl-2 and NF-κB. In the meantime, it induced a dose-dependent rise in TGF-α expression.

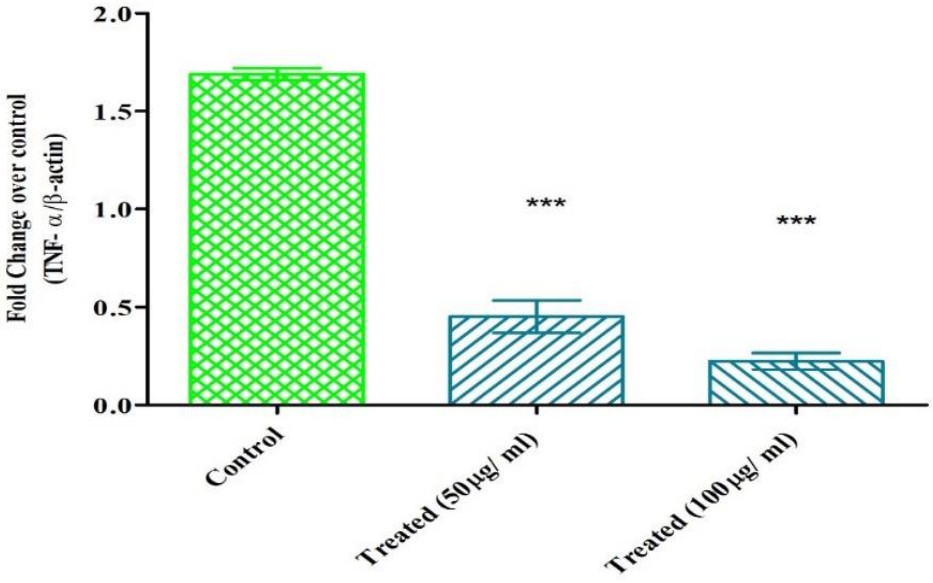


**Figure 5: Serotonin Reduced the Expression of TNF-α mRNA on KB Cells.** The Y axis shows the fold change over control, and the X axis shows the medication concentration (log). At 100 µg/ml, there was a statistically significant decrease in TNF-α expression as compared to the control.

## Molecular Docking

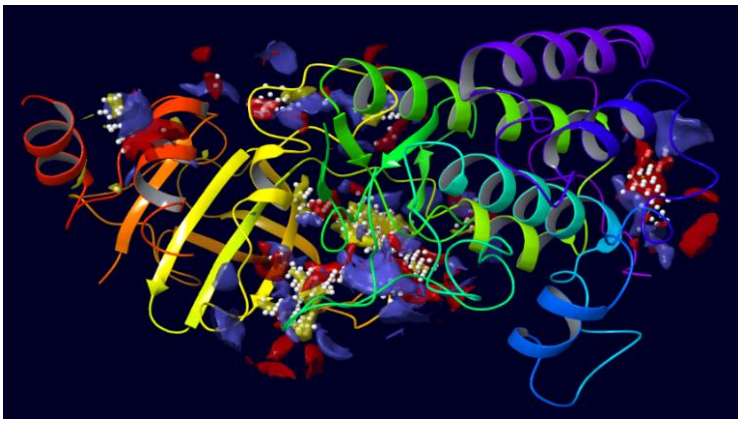

**Figure 6: Structure of NF- κB, (PDB – 5T80).** In order to analyse its protein-ligand binding characteristics, it was docked with serotonin.

The PDB databank was used to obtain the protein structure (PDB: 5T8O) of the imidazolbenzoxepin molecule connected to murine NF-kappaB (Figure 5). Using the protein wizard to optimise the protein structure, the binding site detector was used to find the binding sites within the protein (27–29). A key idea in the hunt for new drugs is the validation and alignment of the ligand-inhibitor combination at the active or docking site. Figures 7 and 8 present the findings of this study, which made use of Schrodinger docking software. The actual binding free energy of the NF-B-dopamine complex was found to be -2.456 kcal/mol (Figure 6). Figure 7 shows the relevant docking energy attitude. Two intramolecular hydron bonds were generated by dopamine and NF-κB (Figure.7a). Using the LigPlot+ tool and the BIOVIA DS Visualizer, we further examined whether intermolecular interactions exist in protein-ligand complexes (Figure. 7b-c). Aspartic acid (ASP55) and alanine (ALA54) allowed dopamine to create two hydrogen bonds with NF-κB, respectively.

| Row | In | Title | Stars | | RMS Derivative-OPLS3e | tautomer probability | Ionization Penalty | State Penalty | Tot Q | flags | docking score | XP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | glide-dock_XP_1_pv (6) | | | | | | | | | | |
| 1 | | sitemap_1_protein | ☆☆☆ | 0 | 0.076 | | | | | | | |
| 2 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -7.116 | |
| 3 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -5.185 | |
| 4 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -4.388 | |
| 5 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.918 | |
| 6 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.884 | |
| | | glide-dock_XP_2_pv (4) | | | | | | | | | | |
| 7 | | sitemap_1_protein | ☆☆☆ | 0 | 0.076 | | | | | | | |
| 8 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -5.641 | |
| 9 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.064 | |
| 10 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -2.988 | |
| | | glide-dock_XP_3_pv (6) | | | | | | | | | | |
| 11 | | sitemap_1_protein | ☆☆☆ | 0 | 0.076 | | | | | | | |
| 12 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -4.252 | |
| 13 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -4.216 | |
| 14 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -4.066 | |
| 15 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.891 | |
| 16 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -1.978 | |
| | | glide-dock_XP_4_pv (6) | | | | | | | | | | |
| 17 | | sitemap_1_protein | ☆☆☆ | 0 | 0.076 | | | | | | | |
| 18 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.504 | |
| 19 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.245 | |
| 20 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.106 | |
| 21 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.050 | |
| 22 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | 0.307 | |
| | 1 | glide-dock_XP_5_pv (6) | | | | | | | | | | |
| 23 | | sitemap_1_protein | ☆☆☆ | 0 | 0.076 | | | | | | | |
| 24 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -4.578 | |
| 25 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.744 | |
| 26 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.409 | |
| 27 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.279 | |
| 28 | | seratonin | ☆☆☆ | | | 1.000 | 0.0024 | 0.0000 | 1 | 0 | -3.236 | |

**Figure 7: Binding Efficiency of Serotonin with NF- κB**

## DISCUSSION

Researchers are now considering the serotonin pathway as a possible target for anticancer medications due to data linking the influence of serotonin and cancer. Repurposing serotoninergic medications can be very beneficial to patients (30). Exercise is one of the easiest ways to raise serotonin levels in tissues. However, considering the abundance of information relating DA to both cancer and non-tumor cells inside the tumour microenvironment, a thorough investigation of the possible uses of this therapeutic approach in cancer treatment is necessary (31).

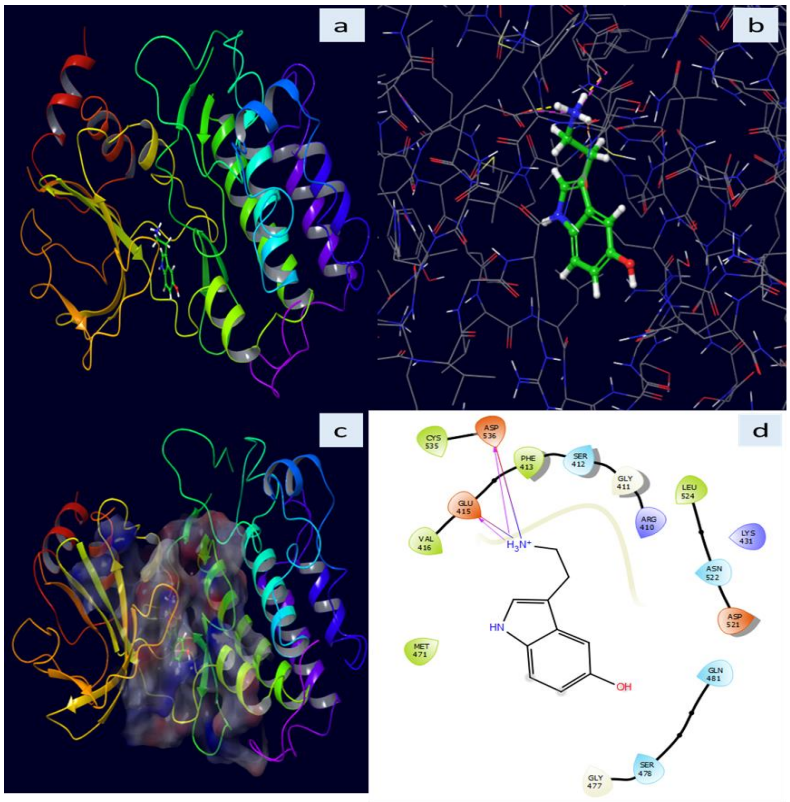


**Figure 8: Molecular Binding of Serotonin with NF- κB**

Protein structural conformance – ligand binding (a). Serotonin binding resulted in the creation of electrostatic clouds (b). View of the ligand within the protein (c). Hydrogen bond formation (d). We found good evidence for the anti-cancer activity of serotonin via the inhibition of NF-B in KB, colon cancer cells, summing the prior empirical investigations on the reciprocal interaction between serotonin and colon cancer cells (32). Serotonin lowered pro-inflammatory markers in comparison to the control group. Elevations in extracellular serotonin have been linked to inflammation, NF-B activation, and certain intracellular targets that could be utilised to find novel targets in colon cancer cells for effective treatment strategies (33). Our findings support the findings of the earlier research. Prolonged inflammation causes the immune cells to release a large amount of inflammatory cytokines, including TNF-α, IL-1, and IL-6. In the past, we demonstrated that serotonin supported BCl-2 in A549 lung cancer cells. In cancerous areas, serotonin has shown a strong anti-inflammatory effect. Numerous biochemical processes have been discovered previously. It increased the efficacy of the pancreatic cancer treatment (34). It inhibited PKA/p38 signalling, reduced cAMP, and activated the DRD4 receptor. DRD4 is a member of the DRD1–DRD5 dopamine family receptors. Consequently, it also stopped tumor-associated

macrophage activity. Serotonin suppresses NF-B by activating DRD2, DRD3, DRD4, and DRD5 receptors. DRD2 activation was shown to lower the risk of gastric cancer in an earlier study. However, Kline et al. (2018) showed that DRD2 deletion in colon cancer has a different mechanism and has no impact on features.

## CONCLUSION

Furthermore, our results suggest that dopamine may be an endogenous bioactive chemical with anti-inflammatory properties, suggesting that it could be employed as a treatment for pathological illnesses produced by inflammation through the NF-κB signal, including malignant colon cancer.

**Competing Interests:** The authors declare no competing interests declared.

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