

The Problem

Many chemotherapeutic agents exhibit dose-limiting toxicities. Therefore, there is increasing interest in identifying compounds that may increase the sensitivity of cancer cells to conventional chemotherapeutic agents, thus reducing chemotherapeutic-related toxicity

2. Interaction of BioBran with Chemotherapy Drugs

BioBran is known by several names, including Rice Bran Arabinoxylan Compound (RBAC), MGN-3, and ImunoBran. These are all the same ingredient extracted from rice bran utilizing enzymes from shiitake mushroom mycelia. which possesses immunomodulatory function.

3. BioBran has Chemo-sensitizing Effects

Results:

1. Treatment with BioBran increased susceptibility of BCCs to DNR as compared to BCCs treated with DNR alone.
2. The chemo-sensitizing effect of BioBran was associated with increased accumulation of DNR in cancer cells.

Conclusion:

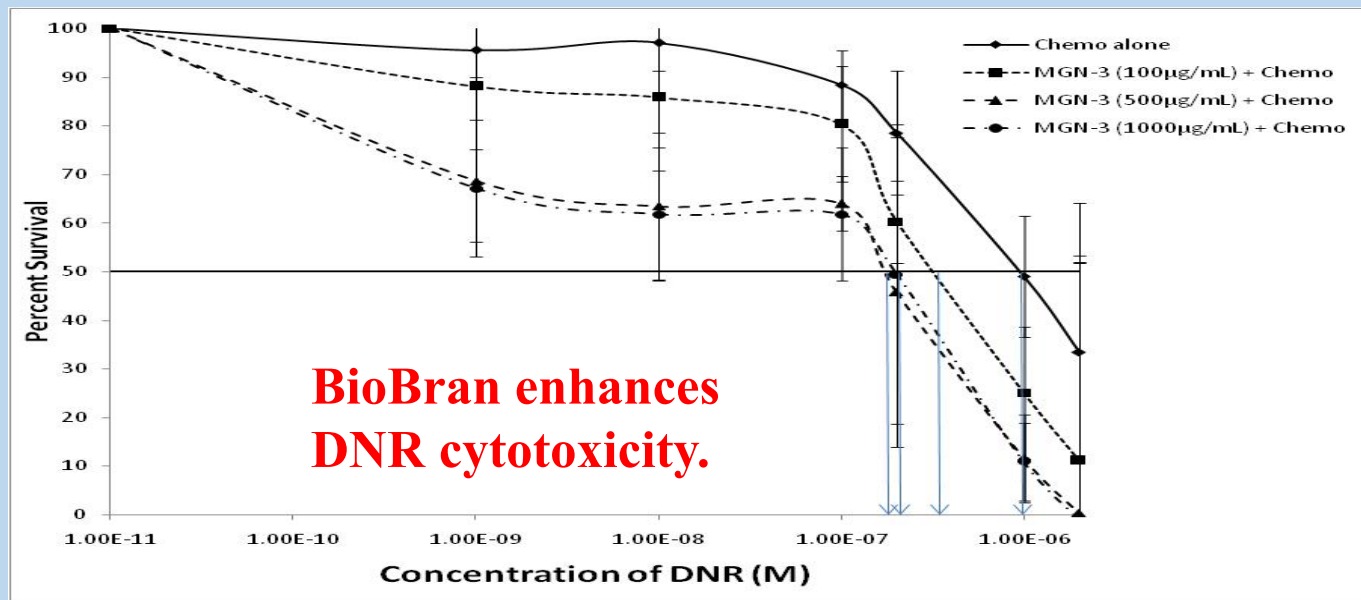
BioBran is an effective chemo-sensitizer, and may have a possibility to reduce the dosage of chemotherapeutic agents against cancer patients

Source: MGN-3/Biobran modified arabinoxylan from rice bran, sensitizes human breast cancer cells to chemotherapeutic agent, daunorubicin, Sastry Gollapudi ,Mamdooh Ghoneum, *Cancer Detection and Prevention* 2008

4. Effects of BioBran on The Sensitivity of MCF-7 to DNR

MCF-7 cells were co-cultured with DNR at different concentrations with or without BioBran for three days.

⇒ The cell survival rate and the IC₅₀ value, which is the 50% inhibitory concentration, were determined.



Source: MGN-3/BioBran modified arabinoside from rice bran, sensitizes human breast cancer cells to chemotherapeutic agent, daunorubicin, Sastry Gollapudi, Mamdooh Ghoneum, *Cancer Detection and Prevention* 2008

BioBran = ImunoBran

5. Paclitaxel

Paclitaxel injection is used to treat advanced cancer of the ovaries, breast, prostate, non-small cell lung cancer, esophageal, melanoma, and Kaposi sarcoma. It is an antimitotic agent that blocks cancer cell growth by stopping cell division, resulting in cell death (apoptosis).

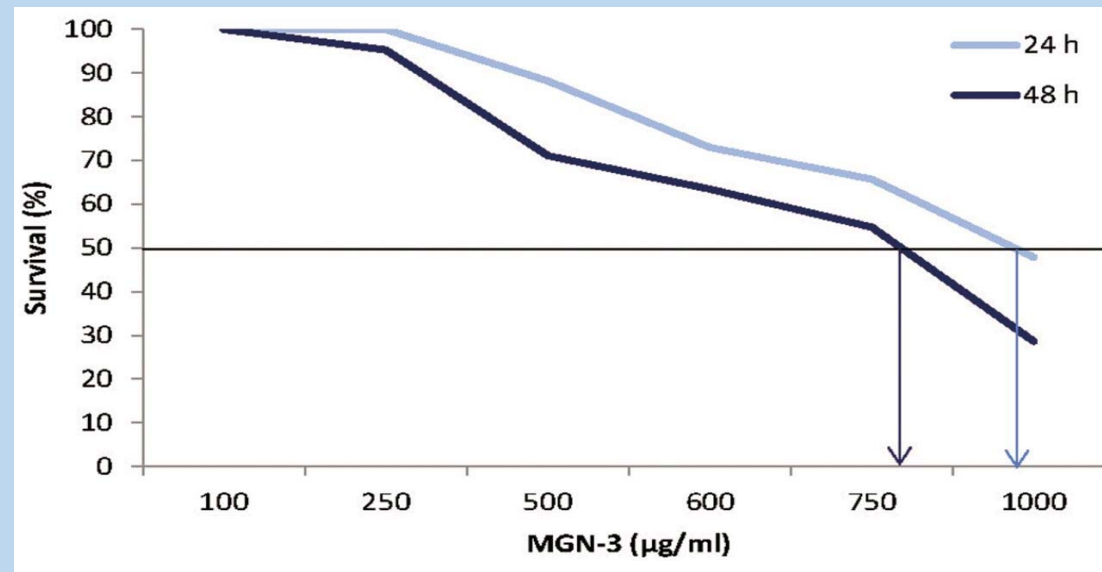
6. Side Effects of Paclitaxel

Nausea, vomiting, diarrhea, mouth sores, muscle/joint pain, numbness/tingling/burning of the hands/feet, flushing, dizziness, or drowsiness may occur. If any of these effects persist or worsen, the doctor should promptly be notified. Temporary hair loss may also occur.

7. Other Side Effects of Paclitaxel

- blurred vision
- burning, numbness, tingling, or painful sensations
- confusion
- cough or hoarseness with fever or chills shortness of breath
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- lower back or side pain
- painful or difficult urination
- redness of the face, neck, arms, and occasionally, upper chest
- skin rash or itching, petechia
- sore throat; ulcers, sores, or white spots in the mouth
- unusual bleeding or bruising
- unusual tiredness or weakness; weakness in the arms, hands, legs, or feet
- bradycardia
- black or tarry stools

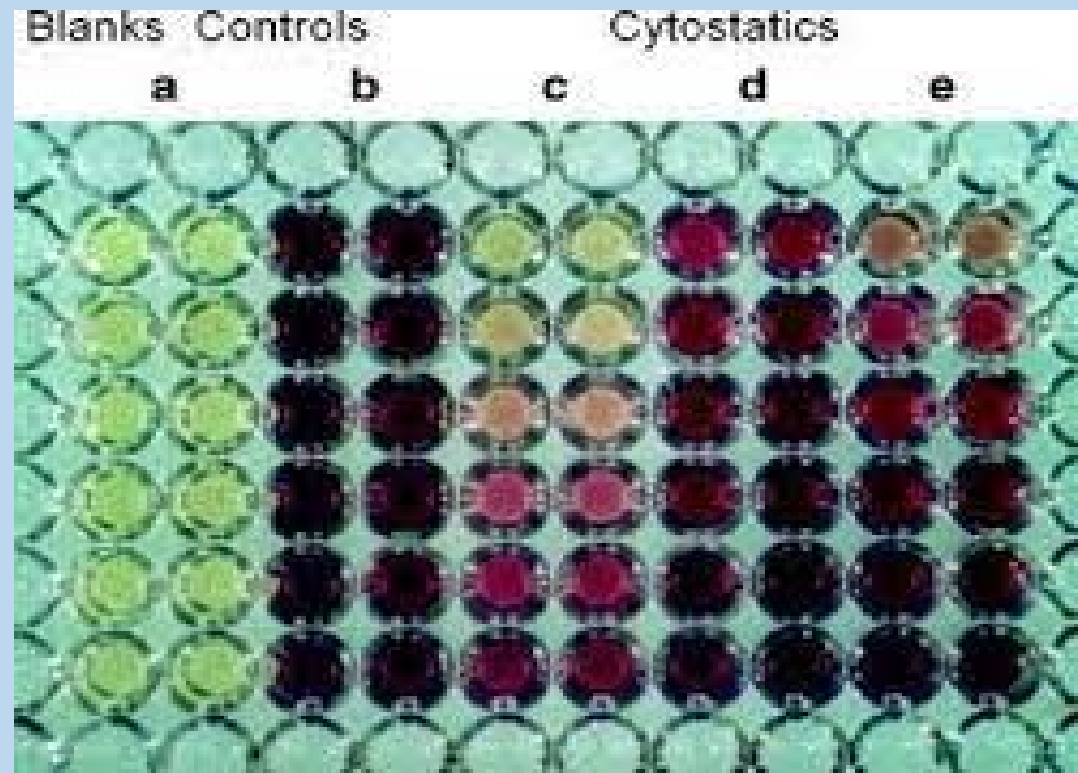
8. BioBran alone reduces the survival rate of MCF-7 cells. Using MTT assay method, MCF-7 cells were incubated with MGN-3 (100-1000 $\mu\text{g/ml}$) for 24 and 48 h. The half-maximal inhibitory concentration (IC_{50}) is indicated by arrows.



Treatment with BioBran resulted in a decrease in the percentage of viable cancer cells at 24 h. The IC_{50} value was 1000 $\mu\text{g/ml}$. The cytotoxic effect became more remarkable at 48 h, where the IC_{50} value was approximately 800 $\mu\text{g/ml}$.

9. The MTT Assay

The MTT assay is used to determine the cellular viability or metabolic activity in microcapsules. It is based on the ability of metabolically active cells to transform a water-soluble dye into an insoluble formazan by dehydrogenases in active mitochondria of living cells to estimate the number of viable cells.

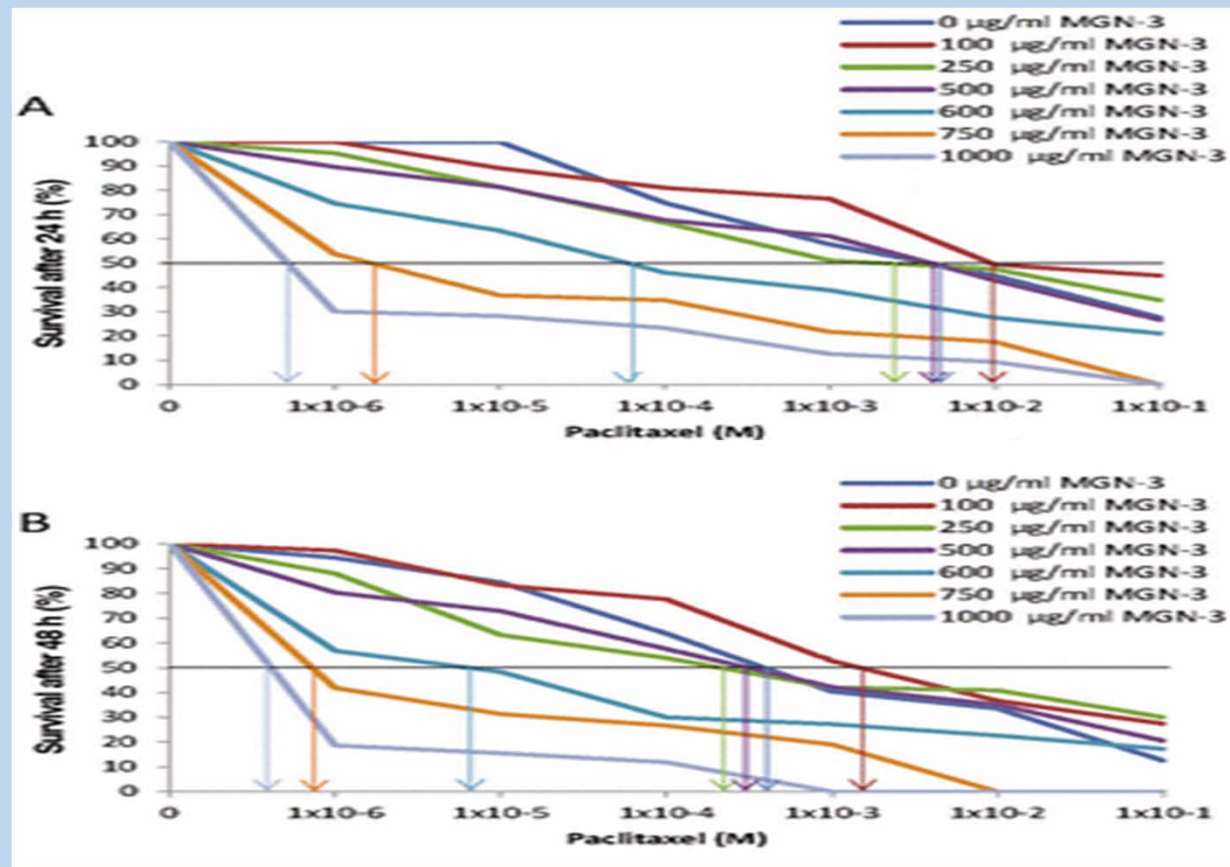


BioBran = ImunoBran

10. MCF-7 human adenocarcinoma cells.

MCF-7 is a human breast cancer cell line with estrogen, progesterone and glucocorticoid receptors. It is derived from the pleural effusion of a 69-year-old Caucasian metastatic breast cancer (adenocarcinoma) in 1970.

11. Co-culture of MCF-7 cells with BioBran plus paclitaxel caused a more marked reduction than paclitaxel alone. The sensitizing effect of BioBran follows a dose-dependent pattern. At 24 h, the paclitaxel IC_{50} value decreased by a factor of over 100 at BioBran concentrations of 600, 750, and 1000 $\mu\text{g/ml}$, as compared with paclitaxel alone. Further reduction of IC_{50} can be seen at 48 h.

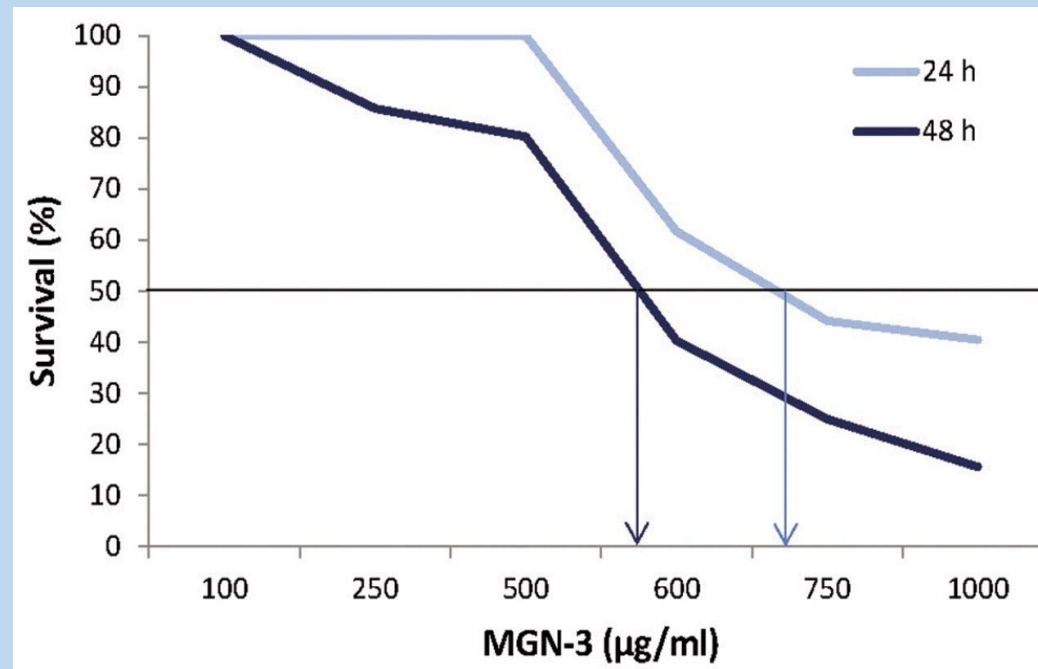


BioBran = ImunoBran

12. 4T1 Cell Line

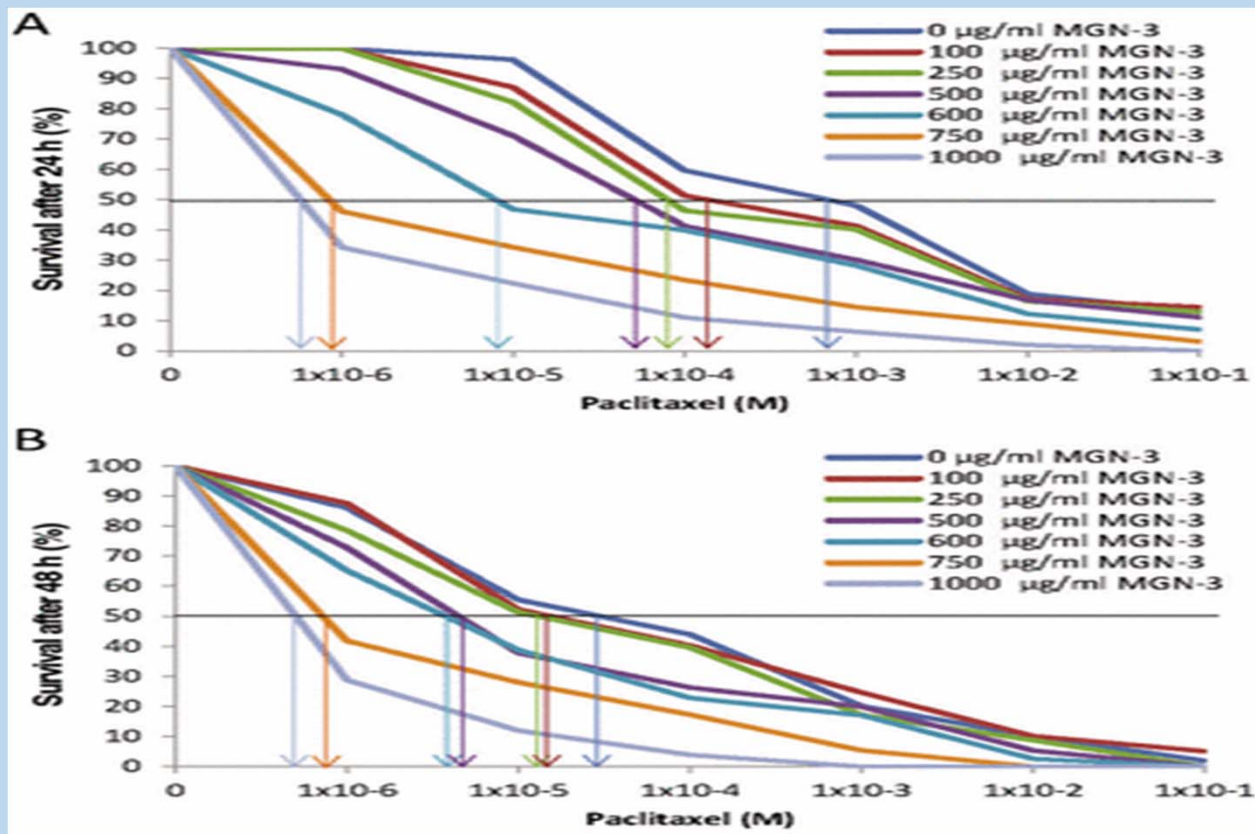
4T1 is a triple-negative mouse breast cancer cell line. The tumor growth and metastatic spread of 4T1 cells in BALB/c mice very closely mimic human breast cancer. This tumor-derived cell line is an animal model for stage IV human breast cancer.

13. BioBran reduced 4T1 cell survival in a dose-dependent fashion as examined by MTT assay. We noted a remarkable cytotoxic effect by BioBran at 24 h: the IC₅₀ was approximately 700 µg/ml. At 48 h post-culture of 4T1 cells with BioBran, the IC₅₀ value further decreased to approximately 580 µg/ml.



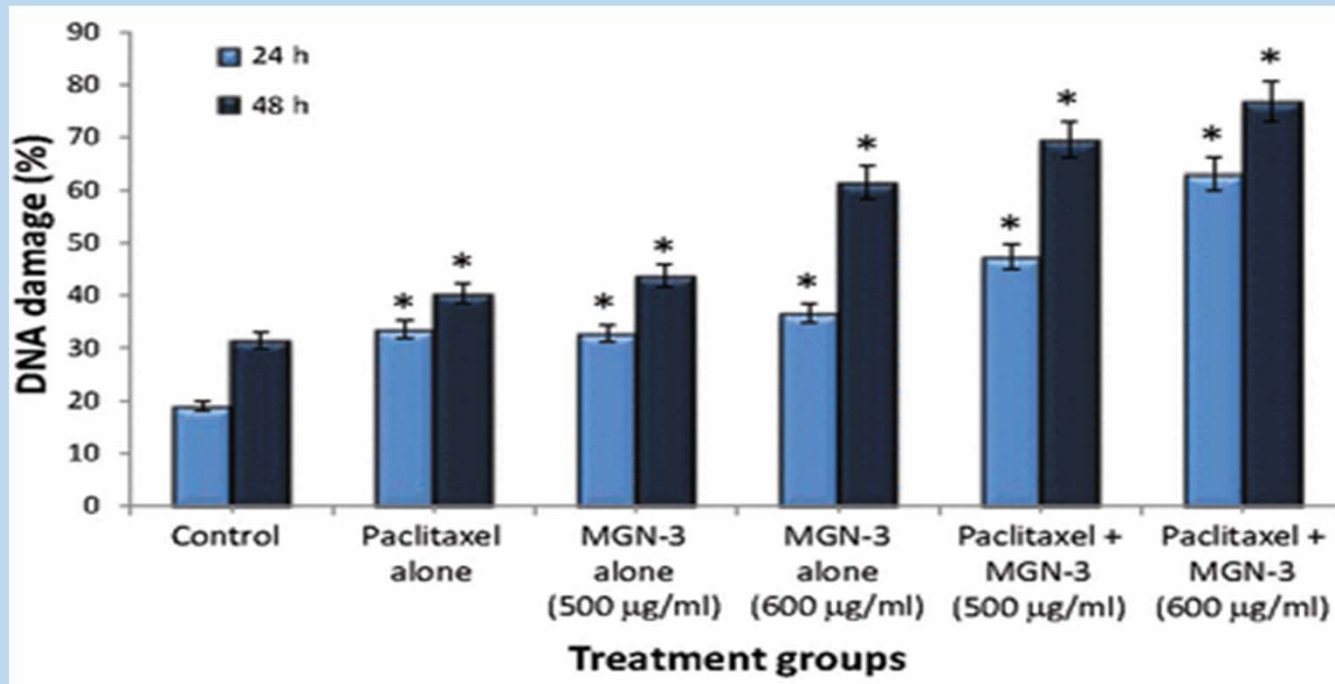
BioBran = ImunoBran

14. The survival of 4T1 cells post-culture with paclitaxel alone was inhibited; however, further inhibition was noticed post-culture with BioBran-plus-paclitaxel. The sensitizing effect of BioBran follows a dose-dependent pattern.

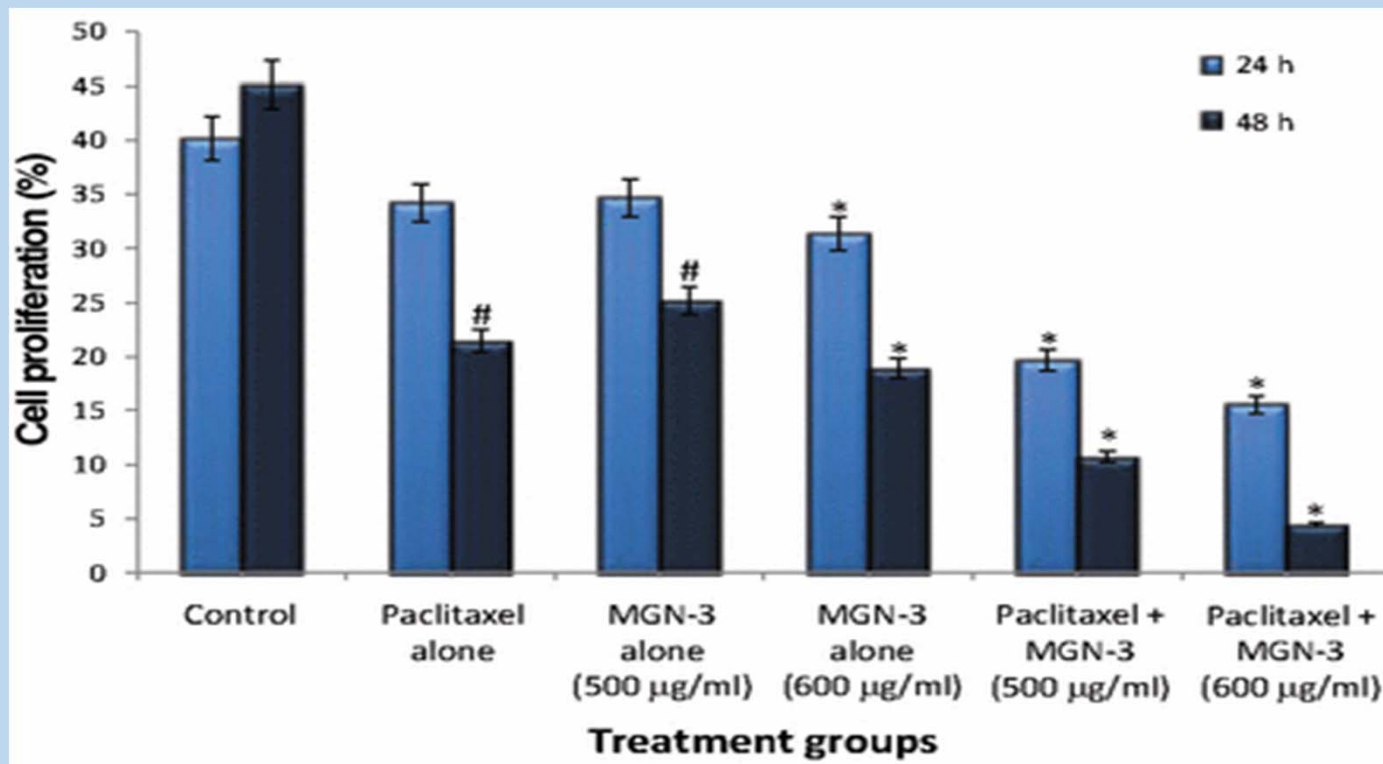


BioBran = ImunoBran

15. DNA damage of 4T1 cells

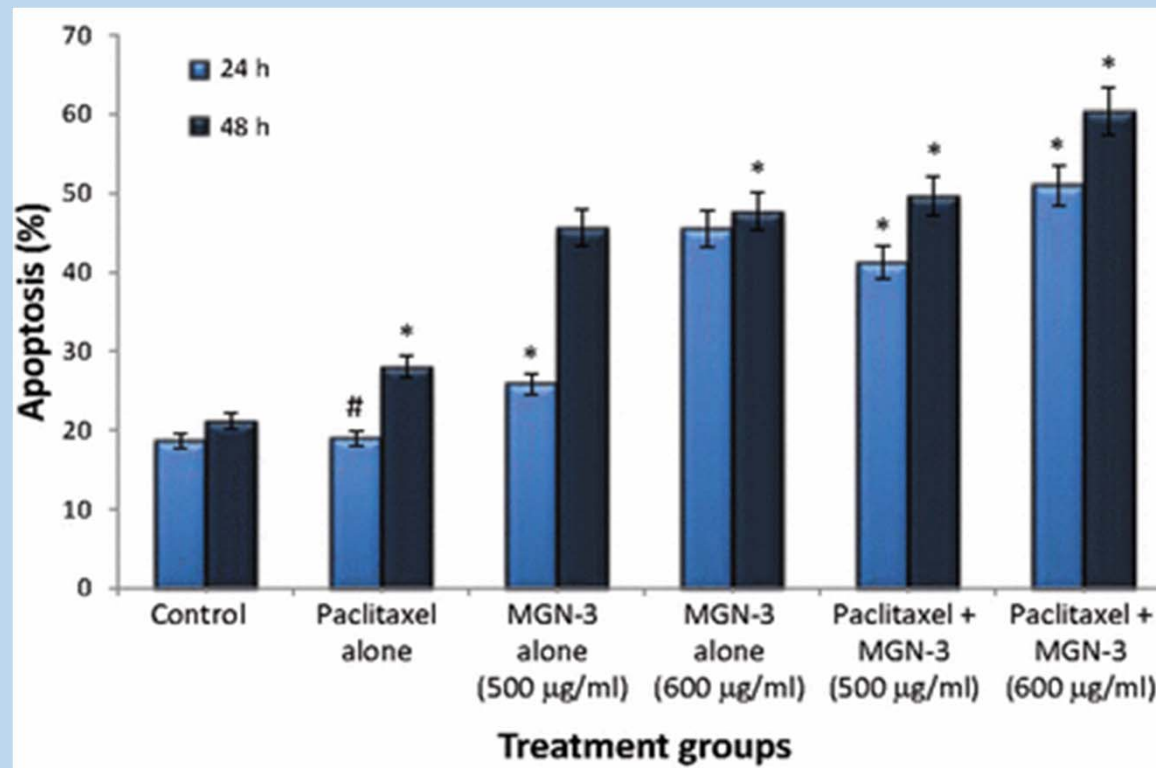


16. Percentage of 4T1 cell proliferation



17. Treatment of 4T1 cells with paclitaxel alone significantly increased the percentage of DNA damage ($p<0.01$) as compared with control untreated 4T1 cells.

Exposure of 4T1 cells to both paclitaxel plus BioBran resulted in a marked increase in a percentage of DNA damage higher than that with either agent alone.



BioBran = ImunoBran

18. Summary of Results

- BioBran increased the susceptibility of both types of cancer cells to paclitaxel by over 100-fold.
- BioBran works synergistically with paclitaxel causing DNA damage, enhancing apoptosis, and inhibiting cell proliferation in 4T1 cells.

19. Properties of BioBran

BioBran (MGN-3, ImunoBran) is an arabinoxylan extracted from rice bran and possesses immunomodulatory function for different immune cells, such as dendritic cells (DC), NK cells, T- and B-cells, and macrophages.

It increases the production of cytokines such as tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ). In addition, BioBran has demonstrated characteristics as a novel antitumor agent able to sensitize human leukemia cells to death receptor (CD95)-induced apoptosis

Conclusion

Data from this study indicate the potential of BioBran in reducing the chemotoxic effects of paclitaxel *via* reducing the concentration required for killing cancer cells. The IC₅₀ value for paclitaxel was reduced by over *100-fold* for both MCF-7 and 4T1 cells in the presence of MGN-3.

The results of this study showed that BioBran exerts a paclitaxel-sensitizing effect on metastatic 4T1 cells.