Naringenin and Metformin Enhance the Antitumor Effect of Doxorubicin Against Experimental Models of Breast Carcinoma

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Abstract

Breast cancer is the most common malignancy in women worldwide and is curable in patients at an early stage. The present work is aimed to evaluate the potential of naringenin and metformin concomitant addition with doxorubicin chemotherapy against experimental breast carcinoma models. The antitumor potential of drugs under the study was evaluated in vivo against methylnitrosourea (MNU)- induced breast cancer in rats and 4T1- induced orthotropic mouse model. Tumor-bearing animals were randomly divided into various groups to assess the effect of each single drug and concomitant drug treatments. Parameters like tumor growth, body weight, survival rate, blood glucose, hematology and histology study were determined. There was significant reduction in tumor weight and an observed decrease in tumor multiplicity in naringenin and metformin concomitant addition with doxorubicin treatment as compared to doxorubicin alone against MNU-induced breast carcinoma. Likewise, significant reduction of tumor volume and tumor weight was also observed in 4T1 mouse model suggesting combination treatment enhanced antitumor activity in vivo. Further, histology of tumor biopsies presented enhanced antitumor activity of doxorubicin through increasing tumor necrosis. Hematological parameters, body weight and survival data presented better safety of combination treatment without compromising efficacy using lower dose of doxorubicin as compared to large dose of doxorubicin alone. These results demonstrate that naringenin and metformin enhanced the antitumor effect of doxorubicin in animal models of breast carcinoma and useful as an adjunct to increase the effectiveness of doxorubicin at lower dose.

Full Text

This preprint is available for download as a PDF.

Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

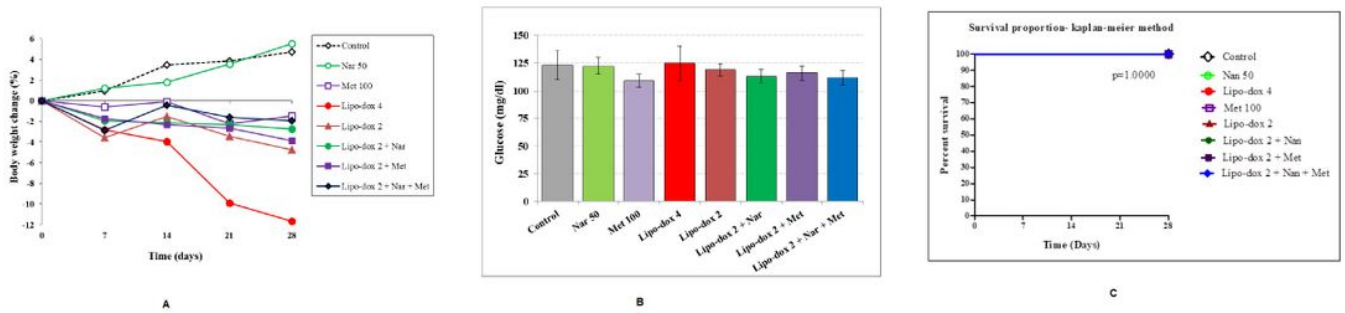
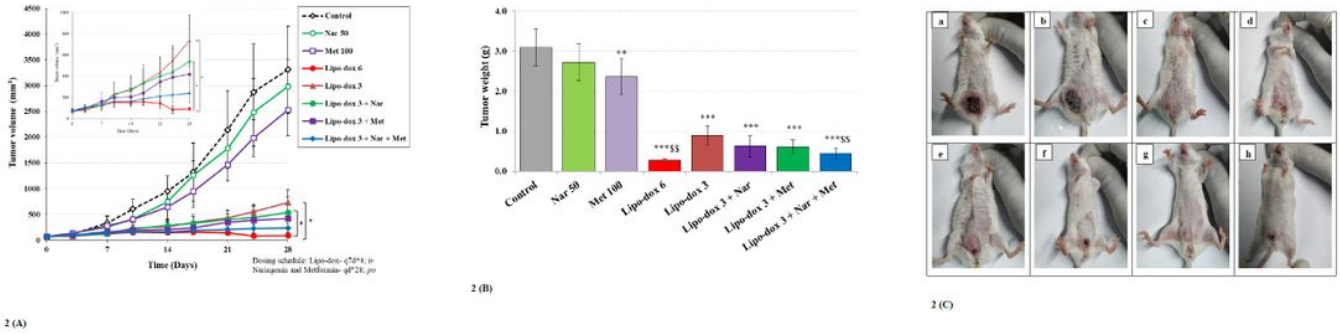


Figure 1

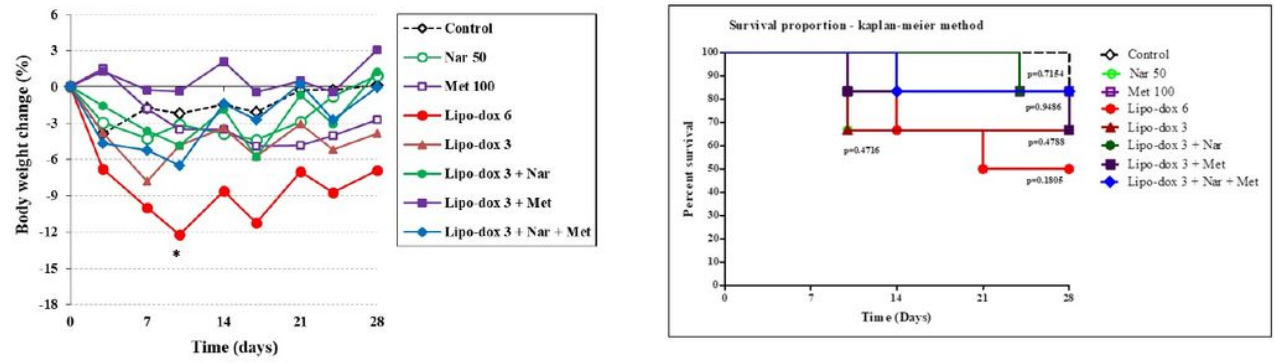
Effect of single or combination treatment of naringenin, metformin and liposomal doxorubicin on (A) body weight (B) glucose levels and (C) survival in MNU- induced rat model Body weight data are expressed as % change in body weight from initial body weight. n=6. The data was analyzed using One way ANOVA followed by dunnet's posttests. *p < 0.05, compared to initial body weight of same group. A dose producing a weight loss ≥15% of initial body weight was considered toxic. No significant change in body weight was observed in any treatment group. Survival was estimated using the kaplan-meier method, and differences were analyzed by log-rank test. n=6. No mortality was observed in any treatment group. Nar- Naringenin, Met- Metformin, Lipo-dox- Liposomal doxorubicin



2 (A) 2 (B) 2 (C)

Figure 2

Effect of single or combination treatment of naringenin, metformin and liposomal doxorubicin in 4T1 mouse model (A) tumor volume (B) tumor weight (C) representative images tumor bearing mice Data are expressed as mean ± SD. n=6. Tumor volume data was analyzed using Two way ANOVA followed by Bonferroni posttests. *p<0.05 compared to Lipo-dox 3 alone. Tumor weight data was analyzed using One way ANOVA followed by dunnet's posttests.*p < 0.05, **p < 0.01, ***p < 0.001 compared to control group. $$p < 0.01 compared to Lipo-dox 3 alone group. Groups (a) Nar 50, (b) Met 100, (c) Lipo-dox 6, (d) Lipo-dox 3, (e) Lipo-dox 3 + Nar, (f) Lipo-dox 3 + Met and (g) Lipo-dox 3 + Nar + Met Nar- Naringenin, Met- Metformin, Lipo-dox- Liposomal Doxorubin hydrochloride, q7d*4- total 4 dose at weekly interval.qd*28- daily for total 28 days.



3 (A) 3 (B)

Figure 3

Effect of single or combination treatment of naringenin, metformin and liposomal doxorubicin on (A) body weight and (B) survival in 4T1 mouse model Body weight data are expressed as % change in body weight from initial body weight. The data was analyzed using One way ANOVA followed by dunnet's posttests. *$p < 0.05$, compared to initial body weight of same group. A dose producing a weight loss ≥15% of initial body weight was considered toxic. No significant change in body weight was observed in any treatment group except Lipo-dox 6. Survival was estimated using the kaplan-meier method, and differences were analyzed by log-rank test. No statically significant difference was observed in survival data. Nar- Naringenin, Met- Metformin, Lipo-dox- Liposomal Doxorubin hydrochloride, q7d*4- total 4 dose at weekly interval.qd*28- daily for total 28 days.

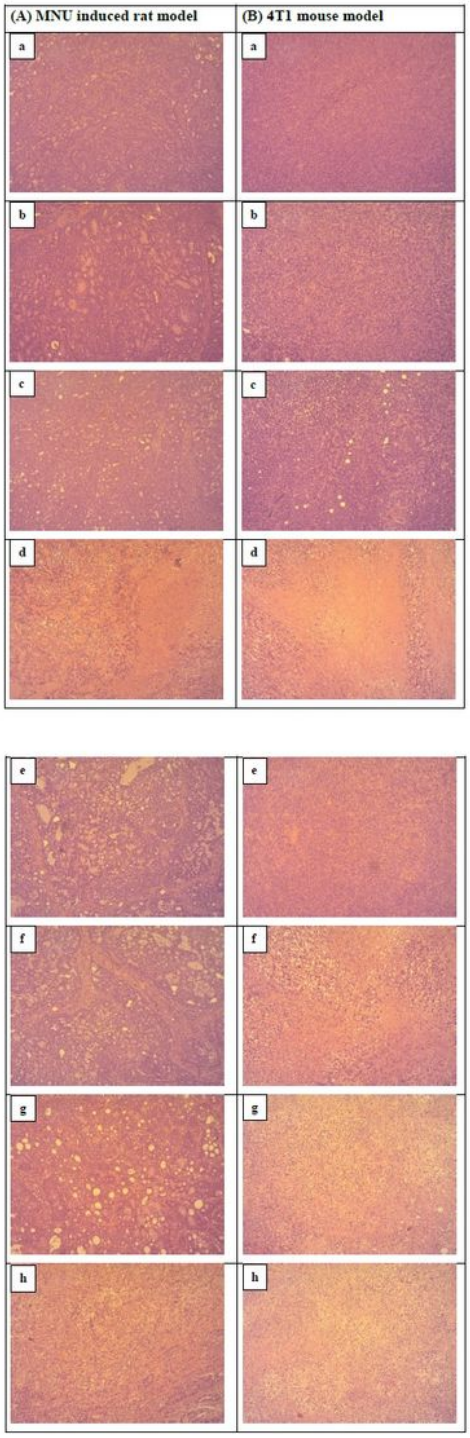


Figure 4

Representative images of tumor sections using histology (H&E) (A) MNU- induced rat model and (B) 4T1 mouse model: Groups (a) Nar 50, (b) Met 100, (c) Lipo-dox 6, (d) Lipo-dox 3, (e) Lipo-dox 3 + Nar, (f) Lipo-dox 3 + Met and (g) Lipo-dox 3 + Nar + Met, (100x magnification, scale bars = 50μm)

Supplementary Files

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- Tablesandfigures.pdf
- Supplementarydatafiles.xlsx