Arsenic based traditional herbometallic nanodrug targeting energy metabolism in metastatic breast cancer: a therapeutic approach

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ABSTRACT

Background: Cancer cells are highly energy-dependent and solely rely on neighboring cells for energy supply due to inability in energy production. Again, it is evidenced that around 80-90 % of energy supply in metastatic cancer comes from intracellular fatty acid beta-oxidation. Thereby, limitations in both energy production and fatty acid oxidation may pave the way for cancer treatment.

Aim(s): Herein, we have tried to introduce an arsenic-based herbometallic nanodrug, Rasa Manikya (RM) prepared from Ayurveda Bhasma showing an excellent in-vitro and in-vivo anticancer activity through energy depletion in metastatic breast cancer.

Results: Physico-chemical chemical characterization of RM along with balance organic and inorganic fractions, has resulted an increased bio-availability followed by cell penetrable size confirmation and cell viability analysis. The Mito and Glyco-stress analysis has resulted in a clear depletion in mitochondrial respiration as well as glycolytic rate inducing energy reduction in the form of ATP. Also, an explicit limitation in fatty acid oxidation was hypothesized in the presence of RM initiating the downregulation of fatty acid synthase (FASN). Following this, an excessive dose-dependent reactive oxygen species (ROS) generation, anti-metastatic activity initiation followed by the DNA damage, and apoptosis have resulted successfully. The RM intervened antitumor activity supported by the management of the oxidative stress parameter has further signified the possibilities of RM as a potential chemotherapeutics.

Conclusion(s): Arsenic based traditional preparation has successfully initiated the energy reduction, which in turn enhanced the ROS followed by DNA damage and apoptosis. Also, the in-vivo oxidative stress management in the presence of RM influenced the antitumor activity successfully.

Keywords: Metastatic cancer; Fatty acid beta oxidation; Herbometallic; Mito and Glyco-stress;
Apoptosis; Chemotherapeutics.

Abstract category: Cancer cell metabolism and immunotherapy

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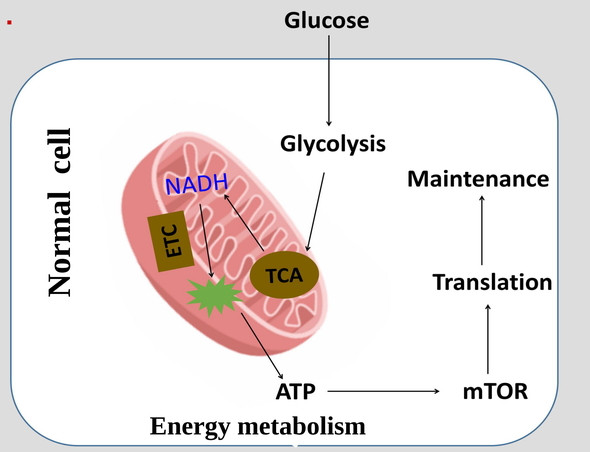
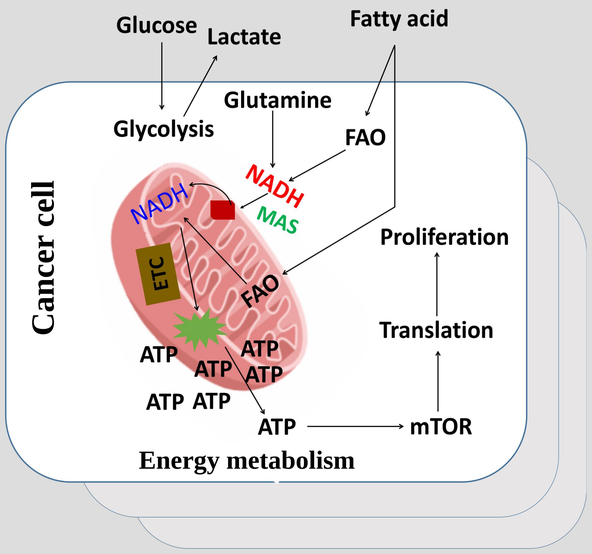
INTRODUCTION





OBJECTIVES

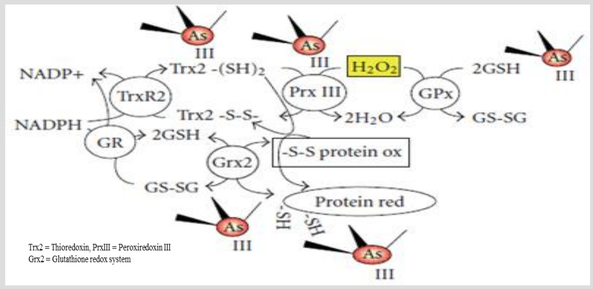
- ❖ Introduction of naturally synthesized arsenic based metallodrugs limiting metastatic cancer growth without any toxicity.
- ❖ Limiting of successive energy supply in metastatic breast cancer cells via the active interference in the energy producing pathway.
- ❖ Blocking of fatty acid oxidation or limitation in fatty acid uptake during cancer progression.

METHODS AND MATERIALS

- ○ Compound characterization were done using standard protocol and instrumentation followed by the synthesis via soxhlet methods.
- ○ Sea horse energy efflux assay measured the Glyco and Mito-stress invitro.
- ○ Intracellular ROS, NADPH/GSH, cell death apoptosis, relative gene expression etc. were checked following standard protocol.
- ○ Invivo animal assay were performed according to ethical guidelines.

RESULTS and DISCUSSION

Working Scheme:



Physicochemical Characterization:

Elements Measured	Mean ppm of an individual element in Arsenic based metallodrugs (using ICP-OES)	Water-soluble mean ppm of an individual element in Arsenic based metallodrugs (using AAS)
Fe	753.310 ± 3	90 ± 2
S	34213.135 ± 10	-
Zn	3.914 ± 0.3	bd
Cu	3.212 ± 0.4	bd
Cd	0.002 ± 0.001	-
Pb	0.001 ± 0.0005	-
Hg	0.003 ± 0.001	-
As	10994.776 ± 10	bd

Table 1. Cation constituents of totally acid digested RMNP and its water-soluble portion. bd means below detection level; (-) means not measured;

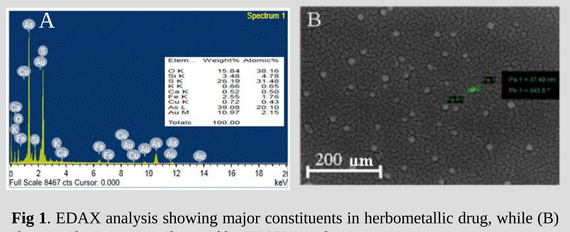


Fig 1. EDAX analysis showing major constituents in herbometallic drug, while (B) showing the exact size observed by FESEM analysis.

In-vitro Biological assay:

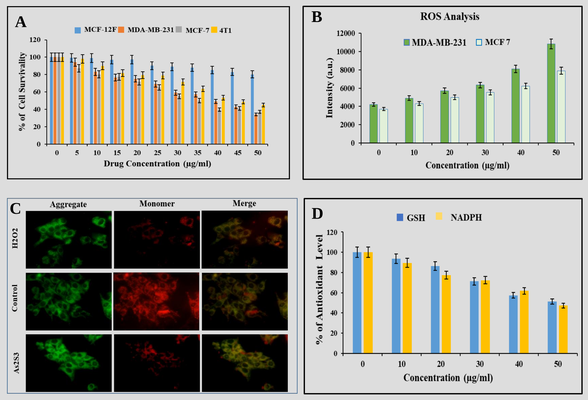


Fig 2. (A) Cell cytotoxicity assay, (B) showing excessive ROS generation, (C) indicating a significant changes in mitochondrial membrane potential, while (D) showing a depletion in antioxidant level, manifesting the anticancer capabilities of As2S3.

Cell metabolism fate:

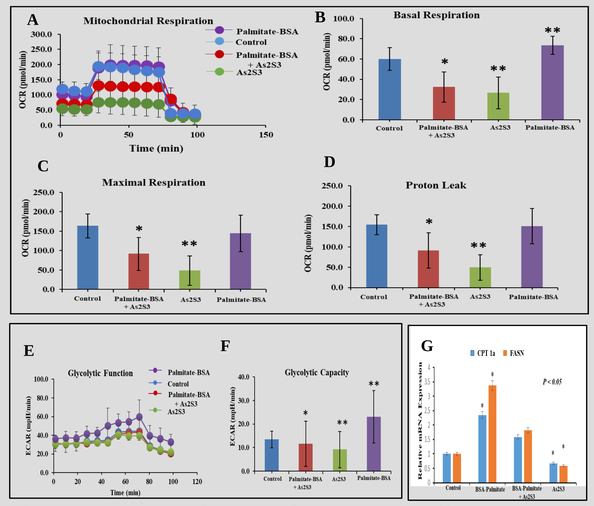


Fig 3. (A). Figure (A-D) showing significant Mito-stress profiling in presence of As2S3 followed by the Glyco-stress (E) along with comparative glycolytic activity observation (F). Fig (G) showing comparative gene expression associated with this phenomenon.

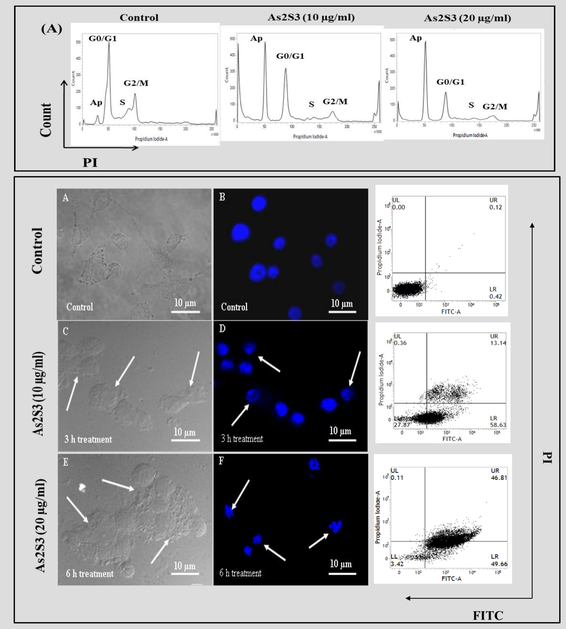


Fig 4. Significant changes in Cell cycle and apoptosis analysis in presence of As2S3 respectively.

In-vivo Biological assay:

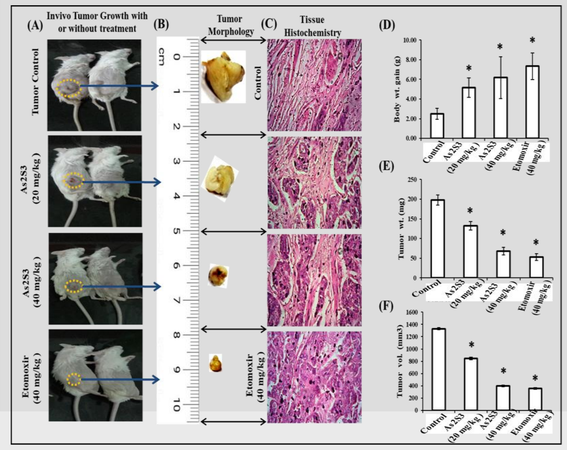


Fig. 5. Significant antitumor activity in female BALB/c breast cancer model.

CONCLUSIONS

- ✓ Arsenic based a traditional herbometallic preparations has been demonstrated successfully without any severe side effects.
- ✓ It has a remarkable control over the energy metabolism in metastatic breast cancer.
- ✓ It is highly capable to induce DNA damage and apoptosis successfully in cancer cells .
- ✓ It has shown an excellent antitumor activity.

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