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Title of thesis: Effect of some natural compounds on arsenic and mercury altered cardiovascular and tracheal contraction

ABSTRACT

Arsenic and mercury toxicity is a global environmental health problem affecting millions of people across the globe. Acute exposure to arsenic or mercury is associated with cardiovascular and respiratory disorders but direct effect of arsenic/mercury on aortic and tracheal system is unknown. Natural compounds are investigated as smooth muscle relaxants, in addition to the investigation of pathways contributing to this relaxation.

Experiments were done to investigate the acute effect of varying concentrations of As and Hg on agonist-induced contraction and elucidation of hypercontraction pathways was done by incubating rings with modulators. Relaxation caused by these natural compounds was evaluated by incubating rings with modulators, followed by incubation with natural compounds. Ameliorative potential of natural compounds is assessed by co-incubating rings with As/Hg and natural compounds. SOD, GPx and NOS activities were also seen in aortic and tracheal muscles incubated with ofAs/Hg, natural compounds alone, or in combination of As/Hg and natural compounds.

Results obtained show that As and Hg cause hypercontraction of aortic as well as tracheal smooth muscle. In both, aortic and tracheal, smooth muscles As/Hg-caused hypercontraction is attributed to excessive ROS generation and NO depletion, with a minor role of calcium influx. Plant derived active principles: carvacrol, carvone, eugenol, linalool and thymol showed significant relaxation of aorta and trachea and saturating effect was seen at 100 µM for all compounds. Carvacrol and eugenol are found to mediate relaxation by

quenching ROS and elevating NO in both, aorta and trachea. Thymol mediates relaxation by ROS quenching in both aortic and tracheal muscles. Linalool caused relaxation could be attributed to inhibition of Ca^{2+}-influx and increase of NO in both muscle types. Carvone caused relaxation is mediated through inhibition of Ca^{2+}-influx and elevation of NO in trachea, and solely by Ca^{2+}-influx inhibition in aorta. Carvacrol, eugenol and thymol are found to be efficient ameliorators of As/Hg caused hypercontraction. Linalool and carvone are found to be good relaxant turn out to be poor ameliorators of As/Hg caused hyeprcontraction in both aortic and tracheal muscles. Ameliorative efficiency of all five natural compounds showed no significant differences in both tissue types whether muscle is co-incubated with natural compounds and metal ions or muscle pre-incubated with natural compounds followed by metal ions. A minor but significant change in SOD, GPx and NOS activities was seen for both muscle types on acute As/Hg exposure. However, aortic/tracheal incubation with natural compounds did not lead to any significant variation in activities of these enzymes. Activities of SOD, GPx and NOS for muscles co-incubated with natural compounds and metal ions was in the same range as that of As/Hg exposed muscles indicating that the natural compounds cause amelioration independent of these enzymes.

To conclude, it is shown that acute exposure to As/Hg cause an increase in agonist-induced contraction of aortic and tracheal smooth muscles; this hypercontraction is attributed to ROS generation and NO depletion majorly, with a minor role of calcium influx. All tested natural compounds are found to be efficient relaxant of both muscle types. Only carvacrol, eugenol and thymol act as ameliorators of As/Hg-induced hypercontraction of aorta and trachea. Since these molecule cause deleterious effect against alteration of pathways caused by As/Hg, therefore, act as ameliorators in aortic and tracheal smooth muscles. Result of

biochemical assays indicate that As/Hg-induced hypercontraction and natural compounds-caused amelioration does not originates from alteration in activities of SOD, GPx or NOS.