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SAFETY OF AYURVEDIC FORMULATIONS AT GENETIC LEVELS THROUGH GENOTOXICITY STUDIES

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ABSTRACT:

Background: Ayurvedic formulations are routinely used in the therapeutics without any noticeable side effects. But doubts regarding their safety are always raised on scientific platforms. Considering this, there is need to evaluate safety of such Ayurvedic formulations containing heavy metals as an integral component. Materials and methods: Published research work on genotoxicity of Ayurvedic formulations have been screened and reviewed from different search engines and reputed databases in addition, dissertation works done at the Institute are also complied in the study. Results and conclusion: Results of Current research work has revealed that total nine safety studies have been published on genotoxicity of Ayurvedic formulations. In all the studies, formulations like Swarna Makshika Bhasma, Rasamanikya, Tamra Bhasma, Brahma Rasayana, Hridayarnava Rasa, Garbhapala Rasa, Abhraka Bhasma, Naga Bhasma, Trivanga Bhasma and Makaradhwaja were found to be safe when accessed for their genotoxic potential though containing heavy metals as an integral component.

KEYWORDS: *Ayurveda, Genotoxicity, Heavy metals, safety and toxicity*

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INTRODUCTION:

Since the prehistoric period, man has been using different sources of drugs for protection of health and treatment of diseases. These drugs in Ayurveda are obtained from natural sources such as plants, animals, and minerals. Use of metals and minerals in therapeutics has been found since Vedic period, which became an important part of Ayurvedic therapeutics due to their additional advantages like smaller doses, quick action etc.[1] They are used in the clinical practice since ages without negligible side effects that itself is ultimate proof for their safety. But many controversies and concerns have been raised by the scientific community regarding safety of such Ayurvedic formulations due to mere presence of metallic and mineral contents as an integral ingredient of that formulations. So, there is need to generate safety profile of such formulations those comprising metals and minerals as component. In addition to the existing toxicity studies, Government of India expressed the need on conducting genotoxicity studies of different metal- or mineral-based drugs.[2] Sperm abnormality assay and chromosomal aberration (CA) assay are one of commonly used methods to evaluate the genotoxic potential of drugs.[3] Till date, very few studies have been carried out in this direction, and there is a need to extend such studies with all drugs of metal or mineral in origin. Considering this, current research work has been planned to screen and compile those published research works which directly evaluate the safety of Ayurvedic formulations at genetic level through genotoxocity studies.

Materials and Methods: Published research works on genotoxicity of Ayurvedic formulations have been screened and reviewed from different search engines and reputed databases like google scholar, Pub med, Scopus etc. In addition, dissertation works done at the Institute are also complied in the study.

DISCUSSION:

Swarna Makshika Bhasma: In current research work, safety of *Swarna Makshika Bhasma* (SMB) has been evaluated at genetic level through chromosomal aberration study and sperm abnormality assay on Swiss albino mice. Samples of SMB prepared from *Swarna Makshika* procured from three different mines were administered at therapeutic dose of 4.5 mg/kg body weight along with honey and distilled water (1:1.5) for 14 consecutive days. Cyclophosphamide (CP) was kept as positive control and administered as single-dose of 25 mg/kg body weight intra peritoneal 24h prior to sacrifice.All treatment groups showed signifi cant weight gain as compared to positive control. All the test drug groups were devoid of any sperm head and tail abnormality such as amorphous, hook less, banana-shaped, curved head. No any chromosomal aberration was also found in all the test drug groups. In contrary, Positive control group showed sperm abnormality and chromosomal aberration with particular emphasis on chromosomal and chromatid gaps, breaks, and centered scatter chromosomes.[4]

Hridayarnava Rasa: In this study, genotoxicity of *Hridayarnava Rasa* prepared by using S*hodhita Tamra Bhasma* [STBHR] and *Ashodhita Tamra Bhasma* [ATBHR] was carried out on adult swiss albino mice at the dose of 32.5 mg/kg body weight of mice through chromosomal aberration study and sperm abnormality assay.[5] The animals were randomized into five groups consisting of five animals in each group. Group I served as normal control (NC) receiving tap water and normal food. Group II served as positive control and treated with CP single dose 25 mg/kg intra-peritoneally 24 hour prior to

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termination.[6 7] Group III served as vehicle control (VC) and treated with honey 10 ml/kg body weight. Group IV and V were treated with test drugs [stock solution 10 ml/kg body weight (containing test drug 32.5 mg/kg body weight and honey 10 ml/kg body weight)] for 14 consecutive days. In present study, different chromosomal abnormalities like gap, ring formation, stickiness etc., were observed in CP treated group along with a greater number of aberrations in the form of chromosome breaks and centric fusion. Trial drugs did not show any of the sperm and chromosomal abnormalities. The tested preparations were free from sperm abnormalities, proving their non-toxicity to sperm.[8]

Tamra Bhasma: Safety of *Tamra Bhasma* has been evaluated through genotoxicity study. The animals were randomized into five groups consisting of five animals in each group for evaluating the influence of TB and TBA (*Tamra Bhasma* with and without *Amritikarana)* on CA and sperm morphological abnormality. Group I served as normal control (NC) receiving tap water and normal food. Group II served as positive control and treated with CP single dose 25 mg/kg intra-peritoneally 24 h prior to termination.[9 10] Group III served as vehicle control (VC) and treated with honey 10 ml/kg body weight. Groups IV and V were treated with both test drugs 7.8 mg/kg body weight along with honey for 14 consecutive days and sacrificed on the 15th day. Body weight of animals showed significant normality before and after drug administration, indicating that the drug tested had no toxic degenerative potential. The CP-treated group showed a maximum number of sperm abnormalities in the head and tail such as banana-shaped, hooked, amorphous and wavy head and double-tailed and twisted tail abnormalities. Increased frequency of chromosomal aberrations such as chromatid break, gap, stickiness and ring were also observed in the CP-treated group. Both drugs tested show no aberrations in the sperm and chromosome test.[11]

Rasamanikya: To evaluate safety of *Rasamanikya* at genetic level, albino rats were categorized into six groups, each consisting of six animals. Group I was served as the vehicle control (VC) received honey and *Ghrita* in distilled water. Group II served as positive control treated with two doses of cyclophosphamide (CP) (40 mg/kg, *ip*) 48 and 24 h prior to termination of the study. Group III and IV were treated with test drug, KSHRM (*Kushmanda Swarasa Shodhita Haratala Yukta Rasamanikya)* with *Guduchi Ghana* in the vehicle at TED (90 mg, *po*) and TED×5 (450 mg, *po*) levels respectively. Group V and VI were treated with test drug, CSHRM (*Churnodaka Shodhita Haratala Yukta Rasamanikya)* with *Guduchi Ghana* in the vehicle at TED (90 mg, *po*) and TED×5 (450 mg, *po*) respectively. Test drugs and vehicle were administered for 60 consecutive days. Any abnormal behavioral changes were not observed in treated groups in comparison to the control group. No mortality was observed in both the samples of *Rasamanikya* along with GG at TED and TED×5 dose levels. Weight gain was observed in all control and treated rats during study period. But, the percent change in body weight pattern in treated groups did not differ significantly from the changes observed in the normal control group. Both the test drugs along with adjuvant did not produce any chromosomal aberration in bone marrow of albino rats at TED and TED×5 dose levels. Evaluation of bone marrow cellularity suggests that test drugs did not possess the mutagenic effect on rats at both the dose level. Both the trial drugs along with adjuvant were studied on bone marrow cellularity in histopathology. The test drugs did not affect the cell count of

polychromatic normoblast, erythrocytes and normoblast showing micronuclei at both dose levels studied, in comparison with the control group. In addition of this, both the drugs showed the almost same number of normal sperms as observed in the vehicle control group.[12]

***Brahma Rasayana* (BR):** *Brahma Rasayana* is one such important *Rasayana* (rejuvenator) formulation comprising more than 35 different plant extracts. Its main ingredients are extracts of *Terminalia chebula* and *Emblica officinalis*. It is reported to retard brain aging, and help in regeneration of neural tissues, besides producing antistress, adaptogenic and memory enhancing effects.[13] The older mice (9 months) were orally fed with *Rasayana* for 8 weeks. Dosages (1g to 4g) were between 2.5% and 13% of body weight (30-40 g) i.e., 25 g to 130 g/kg body weight, so that the ingredient *Embilica officinalis* was being consumed at a comparable rate, and might be expected to have conferred a similar degree of protection on the experimental animals. Results revealed no evidence for BR induced chromosomal aberrations. Overall, data show no evidence for BR induced chromosomal aberrations. The great proportion of observed abnormalities are chromatid breaks the frequencies of which are equal to those of controls at the 2 g and 4 g levels, where most effects would be expected. BR confers protection against certain kinds of sperm abnormality. Moreover, sperm count data in *Rasayana*-treated animals consistently showed slight but not significant increases in sperm count compared to controls. Similarly, Mitotic analysis showed consistent increases in the number of mitotic cells in all three treatment groups of which none reached significance. Together with our results, they suggest that BR does not possess genotoxic effect.[14]

***Naga Bhasma*:** 30 and 60 *Puta Naga Bhasma* was evaluated for genotoxicity study and administered for consecutive 45 days. Group I was served as normal control received vehicle as honey in water (5ml/kg,po). Group II served as positive control received cyclophosphamide (40mg/kg, ip). Group III and V received 30 and 60 *Puta Naga Bhasma* with *Nisha Amalaki,* TED (33.7 mg/kg, po) respectively. Group IV and VI: 30 and 60 *Puta Naga Bhasma* with *Nisha Amalaki,* tedx5 (168.75mg/kg, po) respectively. All treated groups exhibited progressive gain in body weight during experimental period. Gain of body weight is indicating that test drugs are not bearing degenerative potentials. The chromosome aberration test, recommended by regulatory authorities for the assessment of genotoxicity and mutagenicity of many chemicals and natural compounds, has provided positive data.[15] In the present study, cyclophosphamide increased the number of chromosome aberrations in the given dose with relatively high frequencies of chromosome breaks, centric fusion, centric attenuation, deletion, fragmentation, end to end and polyploidy shape when compared to control group. Gap, ring formation as well as stickiness were also frequent in cyclophosphamide treated group. This is may be due to the fact that almost all the rats have chromosomes are acrocentric. These types of chromosomes have the exceptional facility to merge with each other. Only structural aberrations were enumerated in the cyclophosphamide treated group, with special emphasis on Chromosome and chromatid gap, breaks and centric diffusions. Both test drugs i.e., NB 30 and NB 60 at both dose levels of TED and tedx5 did not produce any adverse changes/ chromosomal aberration in bone marrow of albino rats in comparison to control group. Morphological abnormalities of sperms described in two types as head and tail abnormalities. The

head abnormality included amorphous shape, without hook, banana shaped and folded head. Tail abnormality included the coiled tail and double tail. Cyclophosphamide treated group showed the significant increase in number of sperm abnormalities in both head and tail in comparison to control group. Amorphous shaped head, hook less head and coil tailed abnormalities were more frequent than other abnormalities of head and tail in cyclophosphamide treated group. Test drugs, NB 30 and NB 60 at both dose levels of TED and tedx5 did not produce any adverse changes/abnormality on sperm in comparison to control group showing non-toxic to sperms. Further, cyclophosphamide treated group showed severe decrease in spermatogenesis and loss of cytoarchitecture in testis. NB 30 and NB 60 at both dose levels of TED and tedx5 did not produce any adverse changes on cytoarchitecture of testis in rats when compared with control group.[16]

Garbhapala Rasa: Thirty wistar strain male albino rats weighing 200±20g were selected in the experimentation and divided randomly into five groups, Group I was served as control group received *Draksha Jala* as adjuvant. Group II was positive control group received distilled water (5ml/kg, po) with cyclophosphamide (40mg/kg, ip). Group III, IV and V received *Garbhapala Rasa* at TED (22.5 mg/kg, orally), tedx5 (112.5 mg/kg, orally) and tedx10 (225 mg/kg, orally) dose levels. The *Garbhapala Rasa* was administered orally once a day for 90 consecutive days All the animals were dosed with constant dose volume (10 ml/kg body weight). Body weight was noted down before commencement of the study and afterwards every 14 days along with general behavior pattern by exposing each animal to open arena. All treated groups exhibited progressive gain in body weight during experimental period. Cyclophosphamide (Cp) is a covalent DNA-binding agent. Its cyto-genotoxicity has been reviewed and updated by Anderson,[17] and its use as a positive control chemical in genotoxicity tests has been recommended.[18] In the present study, cyclophosphamide increased the number of chromosome aberrations in the given dose with relatively high frequencies of chromosome breaks, centric fusion, centric attenuation, deletion, fragmentation, end to end and polyploidy shape when compared to control group. Gap, ring formation as well as stickiness were also frequent in cyclophosphamide treated group. Test drug *Garbhapala Rasa* along with adjuvant at all dose levels of TED and tedx5 and TEDX10 did not produce any adverse changes/ chromosomal aberration in bone marrow of albino rats in comparison to control group. The number of hook less head, folded and amorphous head, banana, unusual head, and coiled sperm was found statistically significant higher in cyclophosphamide treated group in comparison to control group. *Garbhapala Rasa* at all dose levels dose levels did not produce any sperm head and tail shape abnormalities in comparison to control group.[19]

***Makaradhwaja*:** Safety of *Makaradhwaja* was evaluated in male wistar albino rats categorized into five groups. Group I has received vehicle as betal leave juice in water (5ml/kg,po) and served as control group. Group II was positive control group received distilled water (5ml/kg, po) with cyclophosphamide (40mg/kg, ip). Group III, IV and V received *Makaradhwaja Rasa* with adjuvant at TED (33.75 mg/kg, po), tedx5 (168.75 mg/kg, po) and tedx10 (337.5 mg/kg, po) dose levels. 90-days oral chronic genotoxicity study of *Makaradhwaja* along with *Sahapana* was evaluated by employing *in vivo* chromosomal aberration (CA) assay and abnormal sperm assay (ASA). All treated groups exhibited progressive gain

in body weight during experimental period. Gain of body weight is indicating that test drugs are not bearing degenerative potentials in albino rats. In the present study, cyclophosphamide increased the number of chromosome aberrations at the given dose with relatively high frequencies of chromosome breaks, centric fusion, centric attenuation, deletion, fragmentation, end to end and polyploidy shape when compared to control group. Gap, ring formation as well as stickiness were also frequent in cyclophosphamide treated group. This is may be due to the fact that almost all the rats have chromosomes are acrocentric. These types of chromosomes have the exceptional facility to merge with each other. Only structural aberrations were enumerated in the cyclophosphamide treated group, with special emphasis on Chromosome and chromatid gap, breaks and centric diffusions. Centric fusion is a process that leads to a decrease in chromosome number. Two acrocentric chromosomes join together to produce a metacentric chromosome. Fusion and fission are the main mechanisms by which the chromosome number can be decreased and increased during evolution of the majority of animals and in some groups of plants. The alterations of chromosome structure can however be detected through comparative analysis of karyotypes. The gross chromosomal changes and their location can conveniently be studied through clarification of chromosomal details and their comparison with unaltered genotypes. Cyclophosphamide treated group showed the significant increase in number of sperm abnormalities in both head and tail in comparison to control group. Amorphous shaped head, hook less head and coil tailed abnormalities were more frequent than other abnormalities of head and tail in cyclophosphamide treated group. Test drugs, *Makaradhwaja* along with *sahapana* at all dose levels of TED, tedx5 did not produce any significant increase in adverse changes/abnormality on sperm in comparison to control group showing non-toxic to sperms. Whereas in *Makaradhwaja* along with *sahapana* particularly at higher dose of TEDX10 the coiled tailed shaped sperm has increased compared to control group but it is non-significant compared to control group. Further, cyclophosphamide treated group showed severe decrease in spermatogenesis and loss of cytoarchitecture in testis. *Makaradhwaja* along with adjuvant at all dose levels of TED, tedx5 and TEDX10 did not produce any adverse changes on cytoarchitecture of testis in rats when compared with control group. Result of present study showed that, test drugs i.e., *Makaradhwaja* along with *sahapana* at all dose levels of TED and tedx5 and TEDX10 did not produce any adverse changes/chromosomal aberration in bone marrow of albino rats in comparison to control group.[20]

Abhraka Bhasma: In present experiment, mice were categorized into a control group received normal food and water, *Abhraka Bhasma* treatment group with dose 120 mg,360 mg/kg, 2000mg and 5000 mg/kg body weight orally for 7 days respectively and they were observed for a period of 14 days. The physical parameters including the body weight were monitored throughout the experimental period. The genotoxicity of these mice was analyzed by examining chromosomal aberrations, sperm count and sperm abnormalities, and mitotic index. There was a decreasing trend with increasing the dose was observed for induction of chromosomal aberrations. The reproductive toxicity of the *Abhraka Bhasma* has been assessed by using sperm shape abnormalities and sperm count. The results have shown that there were no significant changes ($p < 0.05$) in the number of sperms

and sperms with abnormalities when compared to control mice indicating that *Abhraka Bhasma* did not induce reproductive toxicity in mice.[21]

Trivanga Bhasma: Thirty wistar strain male albino rats weighing 200±20g were selected and divided randomly into five groups, Group I was served as vehicle control group received honey as adjuvant. Group II was positive control group received distilled water (5ml/kg, po) with cyclophosphamide (40mg/kg, ip). Group III, IV, V received *Trivanga Bhasma* at TED (33.75 mg/kg, orally), tedx5 (168.75 mg/kg, orally) and tedx10 (337.5 mg/kg, orally) dose levels. The vehicle and test drugs were administered for 90 consecutive days to respective groups. Animals were examined throughout the experimental period for signs of gross toxicity. Progressive increase in body weight of all treated groups was observed during the experimental study. Cyclophosphamide treated group showed a significant increase in the number of sperm abnormalities in both head and tail in comparison to the control group. *Trivanga Bhasma* at dose level of TED, tedx5, and TB x10 did not produce any adverse changes/abnormality on sperm, cytoarchitecture of testis and chromosomal aberration in the bone marrow on repeated administration of 90 days when compared with the control group.[22]

CONCLUSION:

Results of Current research work has revealed that total ten safety studies have been published on genotoxicity of Ayurvedic formulations. In all the studies, formulations like *Swarna Makshika Bhasma, Rasamanikya, Tamra Bhasma, Brahma Rasayana, Hridayarnava Rasa, Garbhapala Rasa, Abhraka Bhasma, Naga Bhasma, Trivanga Bhasma* and *Makaradhwaja* were found to be safe when accessed for their genotoxic potential though containing heavy metals as an integral component.

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