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Effect of *Ventilagodenticulata* bark extract against Cisplatin induced Genotoxicity

Shakeel Ahmad Bhat[1],Sulakshana Pal Singh[2],Vasundhara Saxena[2] , Harsh Rastogi[3]

[1]Pinnacle Biomedical Research Institute Bhopal (M.P),

[2]Sharda School of Pharmacy,Agra(U.P)

[3]Dr. K.N. Modi Institute of Pharmaceutical Education and Research, Modinagar, Ghaziabad, U.P.

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Abstract:cis-Diamminedichloroplatinum (II),generally brandedascisplatin (CDDP), is a first-line chemotherapeutic agent that has several uses in a wide choice of cancer conditions. The comprehensive prescription of cisplatin is concomitant with some less-known adverse effects such as genotoxicity, hepatotoxicity, nephrotoxicity and sperm toxicity etc. Cisplatin generates enormous quantity of free radicals which causesoxidative stress by different mechanism. Sperm and chromosome are repeatedly dividing cells, which when damage at their level, will directly imitate in the arrangement that can be identified by micronucleus and sperm structure study .The present investigation explores the probable potential of *Ventilago denticulata* bark extract against cisplatin inducing genotoxicity in bone marrow and sperm toxicity in testies of albino rats

Methodology: The genotoxicity study was conducted by using micronucleus assay method and sperm toxicity was studied under the parameters of sperm head and sperm neckbreakagewithhistologicalchangesintestis.Inboththeparameterscisplatin 6mg/kg i.p was used as inducer for genotoxicity. Ethanolic extract of *Ventilago denticulata* bark extract the test group of lower dose 200 mg/kg, and higher dose is 400 mg/kg.

Result: Statistically significant results were obtained during the genotoxicity study in boththemethod.Onlysingledoseofcisplatinwassufficienttoinducethegenotoxicityin both the method. The ethanolic extract of *Ventilago denticulata* bark was used as testdrug in the giving study. Genotoxicity was significantly reduced with the gradualincrease in the dose of test (Plant extract) drug and the study was conducted at 200mg/kg, 400 mg/kg of the ethanolic plant extract.

Key words: *Ventilago denticulata*, Genotoxicity, Cisplatin, Micronucleus Assay, Sperm Toxicity

INTRODUCTION

Cancer is nastiest disturbing diseases that affect worldwide. Today's lifestyle of human affectsthebodybrutally;evensocalledhealthynutrientfoodisfullofpesticidewithfull ofharmful chemical. Normal soil and water is contaminated with varieties of pollutant and food is indirectly affected which lead to specific dangerous diseases. Statistically proven data till date shows alarming cases of unexplained and unrecoverable cancer with high percentage of mortality rate. Several treatment and medication procedure are being invented every years to cure and treat cancer in which Chemotherapy is the one of the besttreatment. Asper theInternational Agency for Research onCancer (IARC) andJoint ResearchCentre(JRC)ofEuropeanCommissionforeseen,thatnewcancer incidenceand mortality rates from 2020 to upcoming year is progressively increasing (Ferlay, J *et.al* 2021). Anticancer drug produced numerous types of skin toxicity on single or long term treatment like dermatologic toxicity, dermal hypersensitivity reaction, vitiligo, psoriasis etc. Gastrointestinal toxicity like diarrhea or colitis is also being reported in some of the cases.Manyanticancer treatments arebeing usedinversatile wayandnewchemotherapy developed every day. (Mir, M. H *et.al* 2022)

Cisplatin is one of the first generation anti-cancer drug which is widely used in testicular cancer,ovariancancer,osteogenicsarcomaandneuroblastoma,ontheotherhandtheside effect caused by cisplatin are renal toxicity, hematologic toxicity, loss of hearingas well as genotoxicity. (Solernó, L. M., (2022) (Prestayko, A. W *et.al* 1979). Cisplatin also causes hepatotoxicity, endocrinopathies, thyroid toxicity, pituitary toxicity, pulmonary toxicity, rheumatologic toxicity, neurologic toxicity, ophthalmologic toxicity, cardiovascular toxicity, renal toxicity (Kennedy, L. B *et.al* 2020). In generalanti- neoplastic medication trigger ROS production as a result which in turn produce oxidative stress and caused different organ toxicity (Ranasinghe, R., Mathai, M., *et.al* 2023) (Khairnar, S. I., Kulkarni, Y. A.*et.al* 2024). Several metabolic pathways were discovered through with cisplatin produced oxidative stress at sertoli cells, leydig cells, and germ cells (Keshta, A. T., Fathallah, A. M., *et.al* 2023).

One of the dangerous toxic effect of cisplatin is genotoxicitywhich can be define as, the toxicityofgeneticmaterialinwhichchromosomesandnucleusofthecellisbeingaltered in number or structure. (Timmerman, D. M.*et.al* 2022). Genotoxicity at the sperm level affect the spermatogenesis aberration which leads to chromosomal destruction,permanent azoospermia, decreases motility rate, the penetration rate at zona pellucida is reduced and sperm structure is abberated.

Clinical data with respect to the usage of cisplatin showed that majorly affecting toxicity is genotoxicity therefore the present study was focused on genotoxicity and the options which can be used to reduce it.

Present study target *Ventilago denticulata* which is a traditionally explore plant and possesses proven significant medicinal activity in diuretics, arthritis, and hyperglycemia, anti HIV activity (Saisin, S., Panthong, K., *et.al* (2023) and antibacterial and antifungal activity. (Azizah, M., Pripdeevech, P.,*et.al* 2020). It also possesses antioxidant and

cytotoxic activity (Srimoon, R., Anartgnam, P. *et.al* (2020), phosphodiesterase inhibitor (Molee, W *et.al* 2018), anti acetylcholinesterase (Suksamrarn, S., *et.al* 2017) and anti-inflammatory activity (Panthong, K., Hongthong, S., *et.al* 2020). The pharmacological importance of plant can be explained , as the whole plant is enriched with phytochemical like steroids resins, tannins, glycosides, reducing sugar, carbohydrates, saponins, terpenoids, acidic compounds, phenols, alkaloids, flavonoids etc. (dos Santos Oliveira,E., Kohatsu, C. N.,*et.al* 2023). Therefore this plant was selected for the present study to exposure it against genotoxicity, using micronucleus assay method to evaluate the % of genetic material aberration at different cellular level like nucleus, chromosome andsperm.

MaterialandMethodology:

Plant collection and authentication: *Ventilago denticulata* plant bark was purchased from Sanjeevni Ayurved Bhopal M.P. India in powdered form. Invoice code 8250, dated 15 December 2014. Mfg. Lic. No. 25D/9/2005 (VINDHYA HERBALS)

Extraction process:In the current investigation, extraction was carried out using 'Soxhlation' continuous hot percolation method. A thimble of the Soxhlet apparatus was filled with 1000 g of *Ventilago denticulata's* dried ground bark and successive extraction was carried out using pet ether, ethanol and hydro alcohol. The dried extract was weighed, and % yield was calculated for each extract.

Acute oral toxicity of plant extract: The acute oral toxicity of each extract was conducted in accordance with OECD guideline 423. In the study four doses 5, 50, 300, and 2000 mg/kg bwt—were administered orally to the animals. Animals were observed for two hours continuously and animal mortality rate was record for the period of two days.

Experimentaldesign

Four groups of 6 animals each was chosen random from the total number of animals.
Group I (Control): Rats served as control and received normal saline for five days.
Group II (Inducer): received injection of cisplatin 6mg/kg b.wt. on the fifth day of the experiment(Neves,*et.al*2023)
GroupIII(Test1):Animalsweretreatedwithplantextract200mg/Kgb.wt.forfive consecutive days with cisplatin on the last day one hour after extract dose.
GroupIV(Test2):Animalsweretreatedwithplantextract400mg/Kgb.wt.forfive consecutive days with cisplatin on the last day one hour after extract dose.

Micronucleusassaymethodusingextractionofbonemarrowfromanimals:

Fetal calf serum was put into a 5 ml centrifuge tube before the animals were set to death. Both femur bones were extracted from the animals and freed from the muscles. Withcare, the proximal ends of both femurs were reduced until the marrow canal's modest aperture was apparent. An appropriate-sized needle was installed on a disposable plastic syringe, and around 0.2 ml of serum was drawn out of the tube. A few millimeters into theproximalendofthemarrowcanalwasthenenteredwiththeneedle.Tokeepthe

femur from coming off the needle, it was fully immersed in the serum and pressed up against the tube. The serum in the syringe was then injected into the aspirated bone marrow. The sample was evaluate with % of formation micronucleus (MN), % Micronucleus Polychromatice erythrocytes (MNPC).(Álvarez-Barrera *et.al* 2023)

Spermtoxicitystudyusingspermanalysisandhistologicalexaminationoftestis.

Sperm analysis: The right cauda epididymis was finely minced by scissors in 1 ml of isotonic saline in a Petridish and was incubated at room temperature for 4 hours to provide the movement of all spermatozoa from epididymal tissue to fluid. After that the fluid mixture was filtered and the supernatant was separated from tissue particles. Inorder to determine the percentage of morphologically abnormal spermatozoa, slides stained with eosin-nigrosin (1.67 g eosin, 10 g nigrosin, and 2.9 g sodium citrate per 100 ml distilled water) were prepared. Prepared slides were viewed under microscope (Olympus'CH20I'Trinocular)at40X.Atotalof300spermcells wereexaminedoneach slide (1800 cells in each group), and the head, tail, and total abnormality rates of spermatozoa were expressed as percentages.

Hispathologicalexaminationoftestis

At the last day of experiment in each group all animals were sacrificed and testis were removed and were fixed in 10% formalin for 24 h, and were embedded in paraffin; 5–6 μm sections were routinely stained with haematoxylin and eosin and examined the slide as compared to control group.(Brzoska, M. M *et.al* 2003)

Statisticalanalysis

The experimental results were expressed as mean ± SD. All the results were subjected to statistical analysis by one-way analysis of variance (ANOVA) to determine thesignificant difference between the groups. ANOVA was done with Sigma stat software. All pairwise multiple comparison procedures by Bonferroni's test method. $P<0.05$ and $P<0.001$ were considered as levels of significance.

RESULT:Fromtheexhaustedexperimentaltheworkfollowingdatawas obtained:

Acute oral toxicity study: The acute oral toxicity, ethanolic bark extract of ***Ventilago denticulata*** was not harmful during the acute toxicity test, and there were no fatalities reported up to the higher dose (2000 mg/kg body weight). Therefore, following study the safe and effective dose was chosen as for 1/10 part or 1/5 part of 2000mg/kg that is we had selected the dosage from 200-400 mg/kg for in vivo studies.

TABLE 1:Acute Oral Toxicity ofethanolic bark Extract offollowed theOECD-423 Guideline.

s.no	Extract(mg/kg/b.w)(o.p)	Observation after 24 hrs	Mortility
1.	5 mg/kg	Normal	Non/6
2.	50 mg/kg	Normal	Non/6
3.	300 mg/kg	Normal	Non/6
4.	2000mg/kg	Normal	Non/6

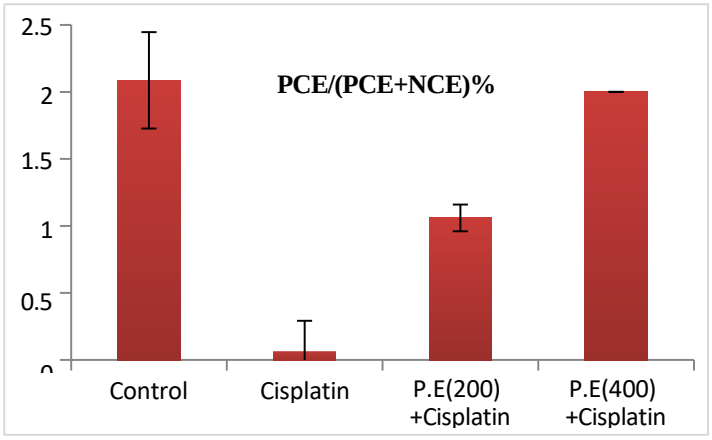
Micronucleusassaymethod:

In micronucleus assay method the four group which were randomly created and four differenttreatments asper table number 2weregiven to theWister rats. Thefollowing % MNPCE (Micronucleus Poly Chromatid Erythrocytes), PCE (Poly Chromatid Erythrocytes) and NCE (Non Chromatid Erythrocytes) were examined and mean calculated Total MNPCE /1000 and PCE/(PCE+NCE) %. Present data were presented in the (Mean ± SD) format. All data were evaluated by using statically examined by One Way ANOVA followed by Borfferoni's test. Data were significant or not we were examined as $P<0.005$ was measured as level of significance (n=6) when matching or comparing with control group. The value were presented by $P<0.001$ **, and $P<0.050$ is presented by * and "a" represent compare group between normal and inducer and "b" represent compare with inducer and extract groups

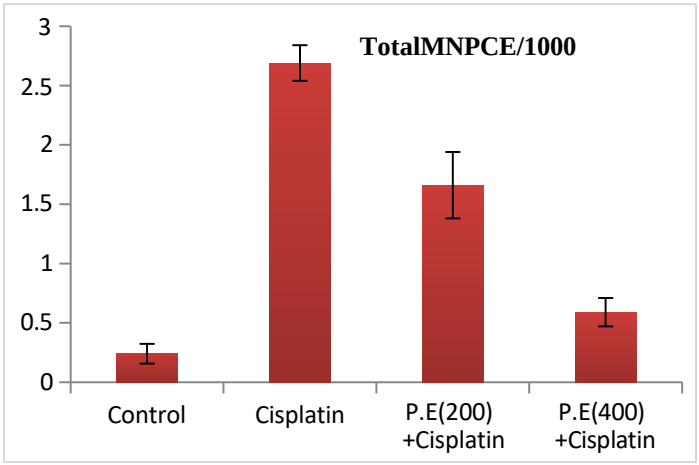
TABLE 2: Frequencies of MNPCE and Mitotic Activity (PCE/(PCE+NCE) %) in bone marrow of Wistar rats treated with Cisplatin and extract (mean ±SDs)

Group No.	Treatment	Total MNPCE /1000	PCE/(PCE+NCE) %
1.	NormalControl	0.24±0.083	2.087±0.36
2.	Cisplatin	$2.69\pm0.15^{*a}$	$0.072\pm0.22^{*a}$
3.	Plantextract(200mg/kg)+Cisplatin	$1.66\pm0.28^{*b}$	$1.060\pm0.10^{*b}$
4.	Plantextract(400mg/kg)+Cisplatin	$0.59\pm0.12^{*b}$	$2.001\pm0.00^{*b}$

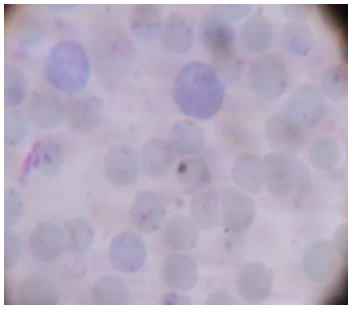
Graphs1:Representsfrequencies themitoticactivity (% PCE/(PCE+NCE)) in bone marrow of Wistar rats treated with Cisplatin and *Ventilago denticulata* extract (mean ±SD)



Graphs 2: Represents frequencies the Total MNPCEin bone marrow ofWistar rats treated with Cisplatin and *Ventilago denticulata* extract (mean ±SD)



Photographicalpresentationofmicronucleus



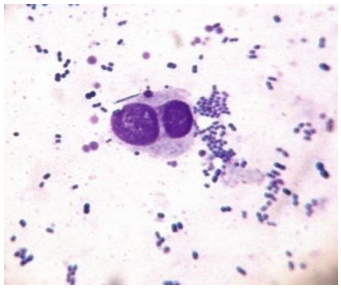


Fig1(a) **Fig1(b)**

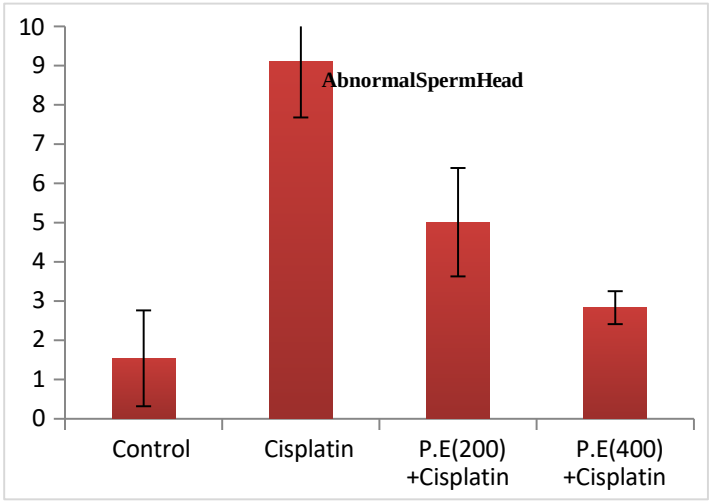
Fig1(a): Photomicrographshowingnormalnucleuswithoutmicronucleus.
Fig1(b): Photomicrographshowedpresenceofmicronucleus.

Testicular Toxicities and Sperm deformities study: In Testicular toxicities method the four group which were randomly created and four different treatments as per table number 3 were given to the Wister rats. The following % Head breakage, % Tail breakage, % Total abnormality in sperm was examined microscopically. Present data were presented in the (Mean ± SD) format. All data were evaluated by using statically examined by One Way ANOVA followed by Borfferoni's test. Data were significant or not we were examined as P<0.005 was measured as level of significance (n=6) when matching orcomparing with controlgroup. Thevaluewerepresented by P<0.001**, and P<0.050 is presented by * and "a" represent compare group between normal and inducer and "b" represent compare with inducer and extract groups

TABLE3:Effectof*Ventilagodenticulatabark*extractonTesticularaToxicitiesand Sperm deformities induced by Cisplatin in rats

Group No.	Group	%Head breakage	%Tail breakage	% Total abnormality
1.	NormalControl	1.54±1.22	2.25±0.24	3.79±1.36
2.	Cisplatin	9.10±1.42^{*a}	11.82±1.11^{*a}	20.92±2.55^{*a}
3.	Plantextract(200mg/kg) + cisplatin	5.01±1.38^{**b}	6.39±1.19^{**b}	9.30±2.57^{*b}
4.	Plantextract(400mg/kg) + cisplatin	2.83±0.42^{*b}	3.39±0.24^{*b}	5.71±0.62^{*b}

GRAPH 3: Graphical presentation of effect of *Ventilago denticulata* extract on abnormal Sperm Head induced by Cisplatin treated Wister rats.



Photographicalpresentationofabnormalspermstructure

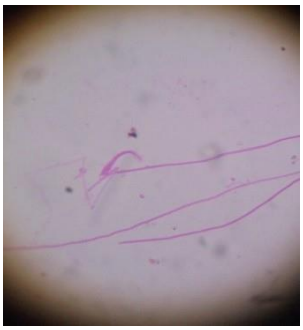


Fig2(a)

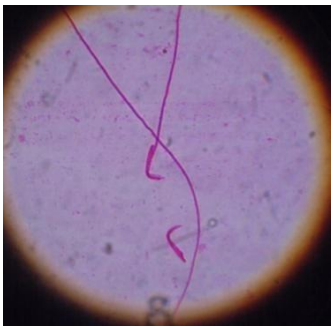


Fig 2(b)

Fig 2(a) and Fig 2(a) : Photomicrograph showing abnormal sperm head break and tailbreak

Histologicalevaluationoftesties

Histological examination of testis in different groups: During these study testies in all groupwere isolated and slides were prepared and examined under electron microscope at 40x magnification.

Controlgroup.

Fig3(a):Control groupnormal architect ofcell oftestis wereshownwith properarrangement of cells. Smooth muscles with no depletion and with no inflammation clearly visible.

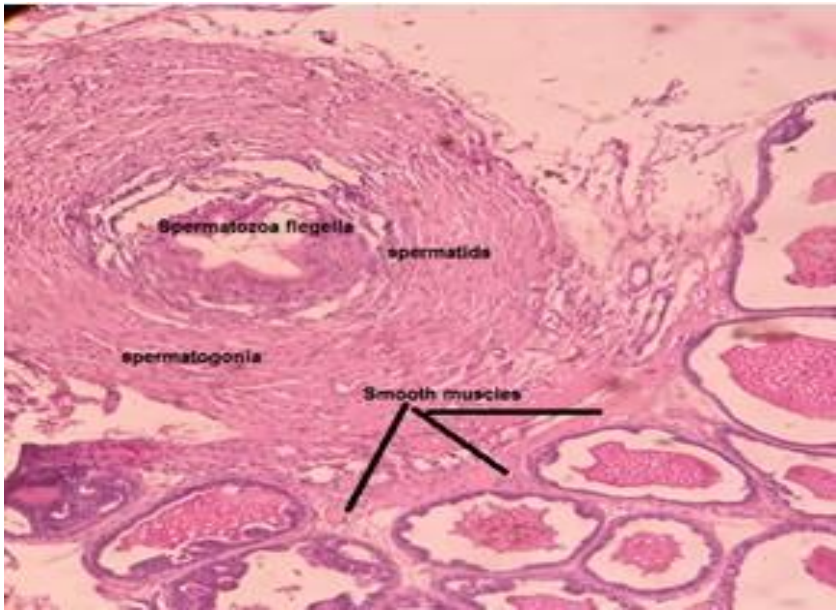


Fig3(a)

Cisplatingroup/inducergroup

Fig 4 (a), Fig 4 (b)**:** Photomicrographs of testis of rats treated with cisplatin showing severe testicular atrophy with degeneration of germ cells in seminiferous tubules and prominently thick testicular capsule. Also showing shrunken tubules and great depletion of germ cells. (40X, Haematoxylin-eosin stain).

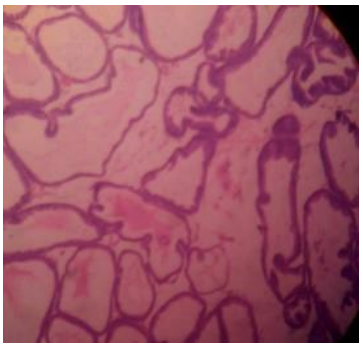


Fig4 (a)

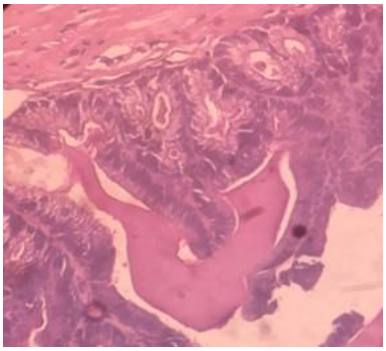


Fig4 (b)

Test1group(200mg/kgplantextract+cisplatin)

Fig 5 (a) and Fig 5 (b): Photomicrographs of testis of rats treated with plant extract (200mg/kg) and cisplatin showing less testicular atrophy and also uniform arrangement of germ cells in seminiferous tubules and normal diameter of tubules. (40X, Haematoxylin-eosin stain).

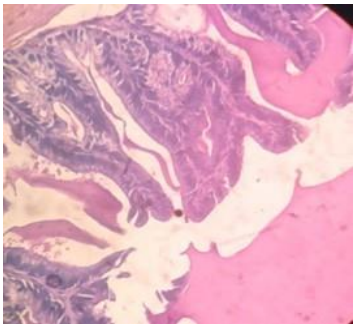


Fig5 (a)

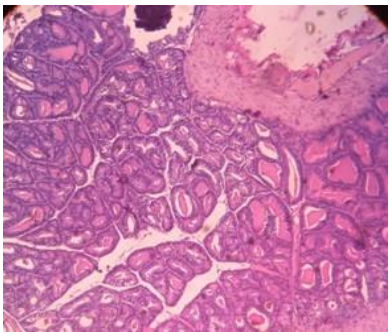


Fig5 (b)

Test2Group(400mg/kgplantextract+cisplatin)

Fig 6 (a) and Fig 6 (b)**:** Photomicrographs of testis of rats treated with plant extract (400mg/kg) and cisplatin showing normal arrangement of germinal and Sertoli cells. Normal diameter of testicular capsule and normal number of Leydig cells between the tubules. (40X, Haematoxylin-eosin stain).

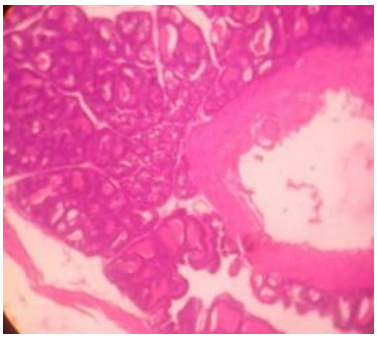


Fig6 (a)

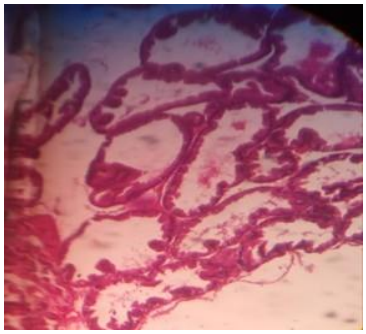


Fig6 (b)

Discussion

Cisplatin is prime choice as antineoplastic agent, which is used for the treatment of diverse cancers like neck, head cancer, ovarian cancer, cervical and lung. Frequently used cisplatin amplifies free radicals formation and successively leads different types of cellular damage at genetic level, which in turn can cause malignancies in normal cells. Many proven data represent that cisplatin undergoes aquation inside the cells, and the platinum atom covalently binds to the N7 position of purines nucleotides of DNA leading to mutation, intra-strand and inter-strand cross-linking and strand breaks**.**

Our present study shows that single i.p dose of cisplatin (6 mg/kg) enhanced the number of abnormal mitotic dividing stage of metaphase and caused formation of micronucleus at cellular level which directly produced genetic alteration or structure aberration of bone marrow cells.

Promising effect of ethanolic extract of *Ventilago denticulata* bark extract was studied at different parameters and as it was found safe during acute oral toxicity guideline 423.

According to the table 2, and graph 2 results of micronucleus assay the MNPCE (%) of control group, it was found to be 0.24±0.083 and after cisplatin treatment the frequency of formation of MNPCE (%) was significantly increased up to 2.69±0.15 which was c**omparative** high as compare to inducer group. However in the Group 3, the formation of MNPCE (%) was reduced as compared to cisplatin group which proves that plant had some potential which reduced the cisplatineffect,sopretreatmentwithplantextractsignificantly($P<0.01$)decreasedthe

micronucleus frequency from 2.69±0.15 to 1.66±0.28 and in group 4 where dose was 400 mg/kg given the MNPCE (%) was reduced from 2.69±0.15 to 0.59±0.12.

On the other hand the other parameter % mitotic index was thoroughly affected by cisplatin or pretreatment of extracts. The control group the value is about 2.087±0.36 and single dose of cisplatin reduced up-to 0.072±0.22 which is significantly very large different between control and cisplatin group. After pretreatment of plant extract 200 mg /kg and 400 mg/kg, value was improved up to 1.060±0.10 and 2.001±0.00 when compared with cisplatin group.

Throughthe microscopic examination fig 1(a)shows that control groupnotcontain anyMNPCE and in fig 1(b) where cisplatin group shows clear micronucleus formation.

In combination with cisplatin and *Ventilago denticulata* barks extract showed dose dependent potential and showed that reduction of the MN frequency with increased in doseof plant extract. Present study was emphasis arranged the aspects that service to understand the lessening of number of micronucleus formation.

According to the table 3 and graph 3 showed that in control group there were normal structure of sperm without any aberration and in cisplatin group testicular toxicities was directly visible with significant different so we said that changes in sperm architecture were significantly increased in formofbreakageofspermhead,tail.Thetotalabnormalities ofspermcomparedwiththecontrol group were also enhanced in cisplatin group. However the pretreatment of plant extract in 200mg/kgor400mg/kgbothwerehighlysignificantlypreventedascomparedtocisplatingroup.
Theabnormalspermhead(%)ofcontrolgroupratswasobservedtobe1.54±1.22.Thisabnormality got highly significantly ($P<0.001$) increased in cisplatin group up to 9.10±1.42. Conversely pretreatment of rats with plant extract 200 mg/kg showed a significant ($P<0.05$) decrease up to 5.01±1.38ascomparedtothecisplatinalonegroupandin400mg/kggroupvaluefurtherdecreased up to 2.83±0.42.
Inthesecondparametertheabnormalspermtail(%)ofcontrolgroupratswas2.25±0.24andvalue waselevatedsignificantlyupto11.82±1.11incisplatingroupwhichisveryhugedifferentbetween controlandcisplatingroup.Howeverintheplantextract200mg/kggroupthevaluewasdeclined from11.82±1.11to6.39±1.19andin400mg/kgthatvaluedeclinedfrom11.82±1.11to3.39±0.24.

Bothgroup200mg/kgand400mg/kgshowssignificantreductioninthenumbersofspermtail.

Thetotal sperm abnormality overall in control groupwasabout 3.79±1.36andwhentreated with cisplatinvaluewasincreasedupto20.92±2.55whichissignificantlyverylargedifferentcompared tocontrolgroup.Pretreatmentofplantextractgroupthevaluewasabout9.30±2.57for200mg/kg and 5.71±0.62 for 400 mg/kg extract.

Microscopicexaminationofspermshoweddifferenttypeofaberrationatspermlevelthatisclearly seen in fig 2 (a) and fig 2 (b).

Histology of testis supported our data with clear evidence. In fig 3 (a), fig 3 (b) in control group histopathological studies of normal group it was showed normal testicular architecture with an orderlyarrangement ofgerminal andSertoli cells andnormalarrangement ofLeydigcells. There was absent of any type of inflammation .On the other side in fig 4(a), fig 4(b)histopathological evaluation of cisplatin group showed moderate to severe testicular atrophy with degeneration of germ cells. Seminiferous tubules and testicular capsule was prominently thick. The tubules were shrunken and greatly depleted of germ cells. There were depleted numbers of Leydig cells between the tubules. A drastic reduction in tubular diameter was also evident from this group. Overall we said that cisplatin was disturbed the normal architect of any testis and due to which spermatogenesis was affected.

In fig 5 (a), fig 5 (b) plant extract (200 mg/kg) showed less testicular atrophy and also uniform arrangement of germ cells in seminiferous tubules. Normal diameter of tubules was also seen in this group. In plant extract 400 mg/kg in fig 6 (a) and fig 6 (b) showed visible testicular protection as was clearly evident from normal arrangement of germinal and sertoli cells, normal diameter oftesticularcapsule.Normalnumberofleydigcells betweenthetubules.Largenumber of germ cells in sertoli cells was also seen. Thus indicating the significant testicular protection against cisplatin induced testicular atrophy.

Conclusion

Chemotherapy showed very serious side effect on patient body among which some are fatal and formed different disease. It is very necessary to work over it and will find simple potential product which reduced chemotherapy caused problems. Study indicated that cisplatin caused serve effect on genetic material and caused aberration on bone marrow cells, sperm and testis architecture. Through the exhaustive pharmacological experimental work on Ventilago denticulata with respect to genotoxicity, it proves significant results. The plant has the potential toreduceorreversedthetoxicityatnewdividingcellphaseswhichisresponsibleforthe

formationofgenotoxicityonnext celldivisioncycle.Statisticallyprovendatasoonobtainin these experimental works can be used for the future endeavor.

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