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Original Article

Chromosomal Disturbances during Mitotic Activity of Root Tip Cells in *Allium* by Certain Commonly Used Antibiotics

Sanjay Kumar

ABSTRACT

Introduction: The certain commonly used antibiotics (cefixime, metronidazole, ciprofloxacin, cefpodoxime and cetirizine) purchased from the chemist shop in Mokokchung town, Nagaland and effects on mitotic activity of root tip meristematic cells of *Allium Cepa* were observed. **Methods:** The different concentrations were prepared by retaining the original effective concentrations (400, 400, 500, 200 and 10 mg) of the antibiotics and treated the root tips of *Allium* at different times (6, 12 and 24 h) to record the effects or abnormalities. **Results:** All the concentrations (ppm) and time (h) were effective to induce the chromosomal disturbances during the mitotic activity of root tip cells in *Allium*. **Conclusion:** The mean value (±S.E.) recorded for mitotic cells, mitotic stages, physiological and clastogenic abnormalities and showed a mixed response which could not predict dose response curve in actual.

Key words: *Allium cepa*, Antibiotics, Chromosomal disturbances, Physiological disturbances, Clastogenic abnormalities.

INTRODUCTION

Antibiotics or antibacterial are the anti-microbial drugs used for the prevention (growth inhibition) and treatment (killing of bacteria) of the bacterial infections. The broad-spectrum antibiotics administered based on the signs and symptoms of the patient for prevention of pathogen, when pathogen has not been identified and laboratory results may take several days to identify the pathogen which is also known as empirical therapy.[1] The narrow spectrum antibiotics are administered to the patients, when pathogen has been already identified and known as definitive therapy.[2] The broad spectrum antibiotics were so famous and easily available to the common people that without consultant of medical practitioner used by them. They consult only for the definitive therapy. A list of antibiotics is available at registered pharmacy in the market for different ailments caused by microbes. The antibiotics such as Chloroquine, Primaquine, Quinacrine, Chloramphenicol, Ciprofloxacin, Pyrimethamine, Dapsone, Mefloquine, Artemisinin, Trimethoprim, Antihistamines, atenolol, 3-Mix antibiotics, Metronidazole, Alprazolum, Anti-tumor antibiotics, Plant extract and Agricultural antibiotics were reviewed and discussed their uses and side effects on animal models, human beings and plants in the following paragraphs.

A review was done on the genotoxic potential of commonly used antimalarial drugs.[3] A note on the control of malaria was reported.[4] The drug chloroquine used in the treatment of malaria. The cytological effects of chloroquine were reported on the root meristem of *Allium Cepa*.[5] The chloroquine genotoxicity was reported on the liver cells of Rat.[6] The low dose radiation and vitamin C treatment was analysed on the chloroquine induced genotoxicity in mice.[7] It was reported that chloroquine has capability to unite with DNA and intercalates with guanine of dsDNA. The attachment with DNA and intercalation of chloroquine with guanine residue in dsDNA causes conformational change in the DNA topology which makes the drug (chloroquine) a possible mutagenic agent.

Primaquine used to treat malaria at early stage of development of *Plasmodium falciparum* in the liver. But, Primaquine primarily used to treat liver reservoirs or hypnozoites of *P. vivax* and *P. ovale*. The drug primaquine induced the differential gene expression in mice liver.[8] The overdose of Primaquine caused glucose-6-phosphate dihydrogen deficiency in humans. The side effects such as muta-genotoxicity of primaquine, pentaquin and pamaquine had been reported on *Salmonella typhimurium*.[9,10,11,12]

The antimalarial drug quinacrine is a derivative of acridine. The acridine derivatives were used as chemotherapeutic agents.[13] The mutagenic potentiality of Quinacrine was evaluated and reported.[14,15] The non-surgical female sterilant (Quinacrine dihydrochloride) induced dicentrics, rings and marker chromosomes in human peripheral blood lymphocytes.[16] The upper limit of toxicity was evaluated in aberration assay using cytotoxicity and chromo-

Sanjay Kumar

Department of Botany, Banaras Hindu University, Varanasi-221005, Uttar Pradesh, INDIA.

Correspondence

Sanjay Kumar

Department of Botany, Banaras Hindu University, Varanasi 221005, Uttar Pradesh, INDIA.

Phone No: 9436607170

E-mail: ksanjay79@gmail.com

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some aberrations.[17] The high number of aberrations may be analysed using comet assay.[18]

The use of quinacrine as an antimalarial drug was suppressed by other antimalarial drug because it has shown some severe side effects such as cyto-geno-muta-clastotoxicity in Ames *Samonella* assay, mouse lymphoma assay, chromosome aberration test (dicentrics, ring configurations, translocations, inversions, marker chromosomes, haploid, polyploidy and endoreduplication), micronucleus test, effects on Chinese hamster ovary cells, frame shift mutation in *Pneumococcus*, human lymphocytes, *Drosophila melanogaster*, altered nuclear structure and RNA synthesis, rat lymphocytes, and altered nuclear metabolism.[19,20,21] It is used now for the treatment of giardiasis, rheumatic diseases, anthelminthic and female sterilization.

Chloramphenicol (CAP) is a very much dynamic antibiotic with wide range actions. The wide range includes, especially the easy dispersion through the cells and tissues, also oozing out through the secretion pathway. Cytogenetic and haematological effects were observed in Calves after the application of antibiotic and dispersed broadly in the body because of non-ionized and extremely lipid-soluble nature of Chloramphenicol.[22]

The CAP inhibits the mitochondrial function and protein synthesis in eukaryotic cells. The inhibition of protein synthesis badly affects the immunoglobulin manufacture and production as well as cell reproduction, multiplication and development. The result causes tiredness and aplasia (failure of an organ or tissue to develop or to function normally) among humans and animals. The induction of leukemia had been observed after application of chloramphenicol in toads. The toxic side effects of CAP had been reported on the human bone marrow such as bone marrow depression (BMD) and bone marrow aplasia (BMA). The BMD was observed more commonly because it starts simultaneously along with the oral administration of the antibiotic, but reversible (over a period) and dose-dependent. The BMA was observed less common, because it occurs occasionally after the oral administration of the antibiotic, but irreversible (over a period) and becomes lethal.[23] Chloramphenicol induced the haemotoxicity in guinea pig. Also, BMD had been reported in household animals.[24]

Ciprofloxacin (CFX) is a fluroquinolone antibiotic drug with broad spectrum antibacterial and effective microbicidal activity. The antibacterial drug ciprofloxacin was evaluated for its genotoxic effects.[25] The antibacterial drug Ciprofloxacin increased the hepatic and lipid hydroperoxides level in mice.[26] The genotoxic and cytotoxic effects of Ciprofloxacin were observed in Human lymphocytes.[27] The antimicrobials quinolone showed genotoxic potentials using comet assay and micronucleus test.[28]

CFX antibiotic extended its effective range on urinary tract infections (UTI), g positive bacteria, bacterial topoisomerase II (DNA gyrase), bacterial DNA replication, repair, transcription, and other cellular functions because of this bacterial death occur. CFX antibiotic and its quinolone derivatives had many unfavourable and toxic consequences on central nervous system, cardiovascular system, biochemical and immunological changes in various cells, immunomodulatory effects on monocytes and macrophages, delay in cell cycle, sister chromatid exchange, unscheduled DNA synthesis, apoptosis, reproductive developmental toxicity, carcinogenicity, androtoxicity, phototoxicity and cyto-genotoxic effects on eukaryotic cells. The ciprofloxacin and roxithromycin caused apoptosis of T-cells. The immunomodulatory effects of Quinolones were reported.[29]

Pyrimethamine is a metabolically slow antibiotic and used for erythrocytic shizontocide, but it is less effective on the pre erythrocytic phase of *Plasmodium falciparum*. The adverse side effects of Pyrimethamine are megaloblastic anaemia and granulocytopenia at high doses. The megaloblastic anaemia results from inhibition of DNA synthesis during RBC production. When the DNA synthesis is disrupted, the cell cycle cannot progress from growth stage G_2 to mitosis (M) stage. The granulocytopenia is a marked decrease in number of granulocytes of white blood cells containing enzymes to digest microorganisms. The genotoxic effects of antimalarial drug Pyrimethamine was evaluated in mouse.[30] The long duration exposure of pyrimethamine was investigated and reported the genotoxic effects in the bone marrow and toxicity of spermatogenesis mice.[31,32] Pyrimethamine caused micronucleus induction in the hamster lung cells and bone marrow cells of mice and, dose-dependent effects on abnormal sperms, less epididymal sperm count, abnormal germ cells and genotoxicity in animal model mice.[33,34,35]

The combination (Pyremethamine+Sulfadoxin) is widely used for the treatment of *P. falciparum* resistant malaria. The use of the drug (fansidar a combination of Sulfadoxine-pyrimethamine) against resistant *P. falciparum* reported the cyto-genotoxic effects (micronucleus and sister chromatid exchange induction) of the drug on cultured human lymphocytes.[36]

Dapsone is used for the treatment of leprosy, dermatitis herpetiformis.[37] The combination (Dapson+pyrimethamine) used for malaria treatment. The side effects of the drug reported such as haemolytic anaemia, methemoglobinemia, toxic hepatic effects, cytogenic effects, micronucleus, clastogenic effects in mouse.[38]

The antimalarial drug (Mefloquine) is a shizonticide, which causes skeleton and muscular malformations at higher concentration in animal models such as rats, mice and rabbits.[39] The mefloquine had shown the potential for genotoxicity and mutagenicity.[40] The other side effects of Mefloquine (dose dependent) includes cyto-genotoxicity, polymorphonuclear neutrophils, decrease in phagocytosis, muta-genotoxicity, sister chromatid exchange, chromosomal aberrations, and lymphocytopenia in animal models (rats, mice and rabbits).[41,42]

The derivatives of artemisinin (artemether and artesunate) are active components of *Artimisia annua* (herb sweet worm wood). The chemistry, biology and history of quinolines and artemisinin were studied and reported.[43] The antimalarial drugs artesunate and artemether showed the cyto-genotoxicity, DNA damage, clastogenic effects, micronuclei induction, necrosis, apoptosis, gastric cell line cancer at higher dosage in animal model i.e. human lymphocytes and mice.[44,45] The drug artemisinin induced apoptosis, blocks prostate cancer growth and cell cycle arrest.[46,47] The chemical (anti-malarial trioxanes like artemisinin) mechanism of action and cytochrome p450 metabolism studies lead to the design of new anti-malarial peroxides.[48]

Trimethoprim is very close to the anti-malarial drugs, but it is not used for the treatment of malaria. It is most useful in the treatment of urinary tract infections (UTI). The antibiotic (Trimethoprim) produced cytotoxicity, genotoxicity and sensitivity in fish as well as mammalian cells. Cytotoxic and genotoxic effects of combination (Triclosan and Trimethoprim) were observed in hemocytes of zebra mussel.[49] The cyto-genotoxicity of the drug using micronucleus and comet assay test, sister chromatid exchange, single cell gel electrophoresis (SCGE), apoptosis, lysosomal membrane stability test, were reported on fish, mammalian cells, human lymphocytes, zebra mussel hemocytes, mouse.[50] Cyto-genotoxicity of the combination (Sulfamethoxazole + trimethoprim) such as micronucleus and DNA damage was reported in rats.[51] The micronuclei formation was observed in nourished and malnourished rats after treatment with Trimethoprim + sulfamethoxazole. The antimalarial compound artesunate showed genotoxicity and cytotoxicity in the somatic cells of mice and human lymphocytes.[52]

The drugs (Montelukast and levocetirizine) also known as antihistamines were used to cure and manage the sensitive to allergy, affected rhinitis and asthma indications. Montelukast and levocetirizine wedged the allergens and histamine receivers which causes allergic reactions and

asthmatic warning signs. The amalgamation of the drugs (Montelukast and levocetirizine) has been of good quality command over different kinds of allergies and asthmatic symptoms but the drawback of the drug includes the crossing of the placenta then into the foetus and embryo in the expectant women.[53]

The cytotoxic and antibacterial activity was evaluated using the combination of 3-antibiotics together. A 3-antibiotic combination (3Mix) is commonly exercised in endodontics for root canal disinfection and pulp revascularization trials. The cytotoxicity and antibacterial efficacy (dose and time dependent) of 3Mix antibiotic was higher as compared to the single dose antibiotic on cultured cells except Metronidazole.[54] The dose-dependent cytogenetic and metabolic effects on DNA synthesis and total cell protein of four antibiotics (benzylpenicillin, cefuroxime, dicloxacillin and erythromycin,) were reported on the cultured endothelial cells of human.[55]

The different Benzodiazepines showed mutagenic, genotoxicity and carcinogen toxicity activity.[56] The oxazepam showed genotoxicity using micronucleus test.[57] The Alprazolam and Lorazepam caused cytotoxicity.[58] The alprazolam and clonazepam caused differential effects on immune system and blood vesels of albino rats.

Atenolol, (a beta blocker drug) replaced the propranolol. The drug (propranolol), generally, utilized for the control of hypertension (abnormally high blood pressure or a state of psychological stress), angina (severe chest pain or intense localized pain), tachycardia (abnormally rapid heart rate), and acute myocardial infarction (heart attack) by the physicians.[59] Atenolol drug concentration ranged from 50-100 mg/day orally and the half-life of the drug was observed as 10h.[60] Atenolol absorbed speedily from the gut and highest concentration was observed in serum within 2-3h.[61] Atenolol is hydrophilic in nature and therefore its metabolic activity is slow. The slow metabolic activity causes the drug to be available (50%) in the circulatory system at any time.[62] There were reports on the unfavourable side effects or unavoidable consequences such as hepatotoxicity (drug induced liver damage), lupus erythematosus (autoimmune inflammatory diseases), septal panniculitis (a condition of subcutaneous fat affecting the layer of adipose tissue), memory impairment (ability to forget), breast pain (breast problems in women), swelling (abnormal enlargement of body parts), fetal growth retardation during pregnancy and induction of chromosome loss in *in vitro* and *in vivo*.[63,64,65,66,67,68,69,70,71]

A new drug or antitumor antibiotic (11-acetyl-8-carbamoyloxymethyl-4-formyl-14-oxa-1, 11-diazatetracyclo [7.4.1.0(2, 7).0(10, 12] tetradeca-2, 4, 6-trien-6, 9-diyl diacetate, FK973) illustrated tremendous cytotoxic effects on human glioblastoma, medulloblastoma, murine and malignant glioma cells.[72] The cytogenetic effects such as induction of micronuclei and chromosome breakage at metaphase stage of antitumor antibiotics (carminomycin, doxorubicin and daunomycin) of the anthracycline group were recorded.[73]

Allium Cepa had revealed its potential to measure the geno-mutatoxicity of various drugs in the past. The different concentrations of Alprazolam caused chromosome aberrations and irregular cell cycle in *Allium Cepa* root tip cells.[74] The Sao Goncalo Channel water showed increased mutagenic effects on the *Allium* root tip cells.[75] The benzo(α) pyrene induced the chromosomal aberrations in *Allium Cepa* root tip test.[76] Benzodiapines (BDZs) or Alprazolam used in medical practice for anxiety disorders (common mental illness such as feeling of uneasiness, worry and fear), panic disorders (sudden attack of fear and panic) and anxiety caused by depression (mental health disorders). Although, the drug has small half-life but gathered and collected nature of the drug was observed in human being. Alprazolam was reported with dose dependent and cyto-carcinogenic effects on *Allium* root meristematic cells at different concentrations (1, 10, 50 and 100 µg/ml).[77] The food preservatives caused the cytogenetic effects on the *Allium Cepa* root tip meristematic cells.[78]

The cyto-muta-genotoxic effects of metal compounds Ce (III) and Sm (III) in combination with an antibiotic, 3-(2-benzimidazol)-3-nitro-6-methyl chromen-4-one were reported on germination, survivality, seedling height and action of spinach (*Spinacia oleracea L.)* plant.

The plant extract of *Azadirachta indica*, *Alstonia boonei* and *Carica papaya* was an anti-malarial agent and, simultaneously, the anti-malarial drugs, Fansidar and Daraprim was used to observe anti-mitotic effect, if any, on the root tip mitosis of *Hippeastrum equestre*. Both the plant extracts and anti-malarial drugs had shown the anti-mitotic activity on the root tip mitotic cells.[79]

The agricultural antibiotic, Captan, in the concentration (50, 100, 400, 800, 1000 mg/kg) range of 50-1000 mg/kg induced cyto-mutagenetic effects (such as induction of micronuclei, chromosome break, and abnormal sperm morphology) on the mouse bone marrow and testicular cells. The cytogenetic effects were reported for the agricultural antibiotic (Captan) on mouse bone marrow and testicular cells.[80]

The present draft is an effort to consider the consequences of four antibiotics (Cefixime, Metronidazole, Ciprofloxacin hydrochloride, Cefpodoxime proxetil) and one anti allergic (Cetirizine) drug on the root tip mitotic activity of *Allium cepa*. The drugs are widely used by the common people, sometimes without the prescription of a medical practitioner. The good reason for using these drugs is their easy and extensive use for the treatment of illness. *A. cepa* has been selected because it has large number of chromosomes (2n=16), easy to manage the metaphase and other stages, highly thick and easily visible at metaphase stage, moreover, material is easily available in everyone's kitchen.

MATERIALS AND METHODS

The antibiotics [Cefixime (400mg), Metronidazole (400mg), Ciprofloxacin hydrochloride (500 mg), Cefpodoxime proxetil (200 mg)] and one anti-allergic Cetirizine (10 mg) were collected from the market chemist shop of Mokokchung Town, Nagaland. The company make of the antibiotics and anti-allergic is Cipla, Lupin, Alembic, Cipla and Alkem Laboratories LTD respectively.

The different concentrations (ppm) of the antibiotics and anti-allergic medicines were prepared in such a way that the original effective concentrations (400 mg, 400 mg, 500 mg, 200 mg and 10 mg) of the medicines should not be disturbed.

Preparation of different concentrations All the medicines were crushed into a powdered form and used for preparation of different concentrations without change in their effective dose. All the concentrations were made in 100 ml and stored in fridge for further use. The ppm conversion was used to convert mg into ppm (1ppm=mg/L). The different concentrations were cefixime and metronidazole (40, 80 and 120 ppm), ciprofloxacin hydrochloride (50, 100 and 150 ppm), cefpodoxime proxetil (20, 40 and 60 ppm) and cetirizine (1, 2 and 3 ppm) respectively. The lower concentration (40, 40, 50, 20 and 1 ppm) of each medicine is equivalent to the effective dose (400, 400, 500, 200 and 10 mg) of the respective antibiotics and anti-allergic medicines.

Treatment *Allium Cepa* bulbs were submerged in water at beaker or glass for the growth of the root tips (23±2 ^{0}C) in the laboratory. The root tips were cut when it reached 1-2 cm long. The root tip meristematic cells were treated with the different concentrations of different antibiotic and anti-allergic medicines for 6, 12 and 24 h.

Preparation of slides the root tip meristematic cells were rinsed (3×5 min) with distilled water. The root tips were fixed in 3:1 (ethanol: acetic acid) fixative overnight in fridge (4 ^{0}C). The root tips were rinsed (3×5 min) and treated with enzyme pectinase (1%) for 1 h at room temperature. The

tips were rinsed (3×5 min) and hydrolysed with HCl (5 N) for 30 min at room temperature. The tips were rinsed (3×5 min) and stained with acetocarmine (2%) for 15 min. It was squashed on the slide with cover slip and observed under microscope for different mitotic stages and data collection. The data was collected on the different kinds of mitotic stages, total number of mitotic cells, total number of dividing cells, total number of non-dividing cells, number of interphase, prophase, anaphase, telophase, cytokinesis and different abnormal stages such as stickiness, laggards, multipolar anaphase, anaphase bridges and micronucleus. The data was analysed statistically.

RESULT AND DISCUSSION

Number of mitotic cells

Control

The total number of cells (TNC), number of non-dividing cells (NDC) and number of dividing cells (DC) were counted for three different time (6, 12 and 24 h), recorded and reported the mean numbers TNC (509.33±51.42), NDC (469.67±54.95) and DC (39.66±4.25) from three different slides Table 1.

Cefixime

The treatment of root tip cells with cefixime for different h (6, 12 and 24 h) suggested that TNC were induced and showed a little higher value (614.67±19.78) over the control at the concentration (80 ppm) and time (12 h). It seems that the concentration (80 ppm) does not cause in the reduction of total number of cells and, it may not involve in the abnormal function of the cell cycle. But it caused the reduction in total number of cells, when the concentration increased (120 ppm) for 24 h. The increased concentration may have effect on the cell cycle.

The number of NDC has shown the similar trend as the TNC. The NDC increased at 80 ppm for 12h. It may be involved in the induction of NDC or interphase stages and hence increases the number of NDC over the control. The number of DC were recorded very less in control as compared to the treatment (320.67±75.51, 110.67±8.45 and 184.67±63.39) for all the time which suggest that all the concentration is highly effective in the induction of cell division cycle or mitosis.

Metronidazole

The metronidazole treatment (40, 80 and 120 ppm) to root meristematic cells indicated very high values (612.00±73.02, 810.33±93.26 and 969.00±259.52) and increasing trend for all the time (6, 12 and 24 h) as compared to the control. It suggests that the concentrations may be used to increase the TNC by inducing the cell division cycle of the plant but higher concentrations (80 and 120 ppm) equally increasing the number of NDC (710.33±89.83 and 853.33±217.32) as well as DC (100.00±20.66 and 115.67±52.98) over the control.

Cetirizine

The number of dividing cells (DC) showed higher mean value (53.33±11.31, 73.33±10.58 and 110.67±60.18) over the control at all the concentrations used (1, 2 and 3 ppm). It has shown an increasing trend from lower to higher concentrations. The concentrations may cause induction of the mitosis and help to increase the number of dividing cells. Also, it is a good indication to increase the number of cells in human beings suffering from cold and cough where many cells are damaged. It may help in growth and development of new cells or replaced the damaged or torn out cells.

The number of non-dividing cells (NDC) showed higher mean value (901.67±40.84) over the control at higher concentration (3 ppm). The concentration is highly effective to induce the non-dividing cells or to stop the cells to enter mitosis. It may be effective at the interphase stage (G1, S and G2) of the cell cycle. The other two concentrations are not effective as they have less value of cells than the control (469.67±54.95).

Ciprofloxacin

All the treatment has shown the increasing trend over the control. The concentrations (50, 100 and 150 ppm) were effective to increase the number of cells in terms of TNC (858.0±151.40, 1033.0±323.05 and 694.33±101.04), NDC (792.0±141.30, 628.67±101.57 and 628.67±101.57) and DC (66.0±11.71, 70.66±0.88 and 65.66±5.84) than the control (509.33±51.42, 469.67±54.95 and 39.66±4.25), although DC were recorded low in number as compared to the ND and TNC.

Cefpodoxime

The concentrations (40 and 60 ppm) showed the effect on the capacity of cell division, the lower concentration (20ppm) does not have much effect. The maximum effect was showed by the concentration 40 ppm which increases the maximum mean value of cells for TNC, NDC and DC. The higher concentration (60 ppm) showed the effect but the number of cells was counted less as compared to the 40-ppm concentration.

Number of mitotic stages

Control

The different mitotic stages [Interphase (I), Prophase (P), Metaphase (M), Anaphase (A), Telophase (T) and Cytokinesis (C)] were observed and mean value from three slides for control (14.66±5.78, 16.33±4.09, 4.00±1.15, 1.00±0.57, 3.00±2.00 and 0.33±0.33) was recorded respectively Table 2.

Cefixime

The mean value of all the mitotic stages was recorded higher than the control. The high mean value (214.00±58.28) of interphase (I) cells were recorded at 40 ppm than 80 (26.66±2.18) and 120 ppm (83.00±15.53). The mean value of prophase was almost constant at all the concentrations but higher than the control. The mitotic stages such as metaphase, anaphase and telophase showed the mixed response, but the mean value was higher side than the control. The maximum cytokinesis (7.66±2.90) was observed at higher concentration (120 ppm).

Metronidazole

All the concentrations have shown the decreasing trend in interphase and cytokinesis, but the values are higher side over the control. The mitotic stages P, M, A and T showed the mixed response and there was no decreasing or increasing trend but mean values are higher than the control.

Cetirizine

The interphase and prophase cells were not affected by the lower concentration (1 ppm), but higher concentration (2 and 3 ppm) showed increasing trend. The higher mean value of metaphases (13.00±4.93) and anaphases (4.60±2.33) was recorded at lower concentration (1 ppm) than the control. The higher concentrations (2 and 3 ppm) showed almost constant mean values. Telophase showed mixed response but higher values over the control. the cytokinesis was higher at the high concentration (3 ppm).

Ciprofloxacin

All the mitotic stages have showed the mixed response at all the concentrations (50, 100 and 150 ppm). Prophase and metaphase less affected by all the concentrations. The concentrations (50 and 100 ppm) favours the cytokinesis.

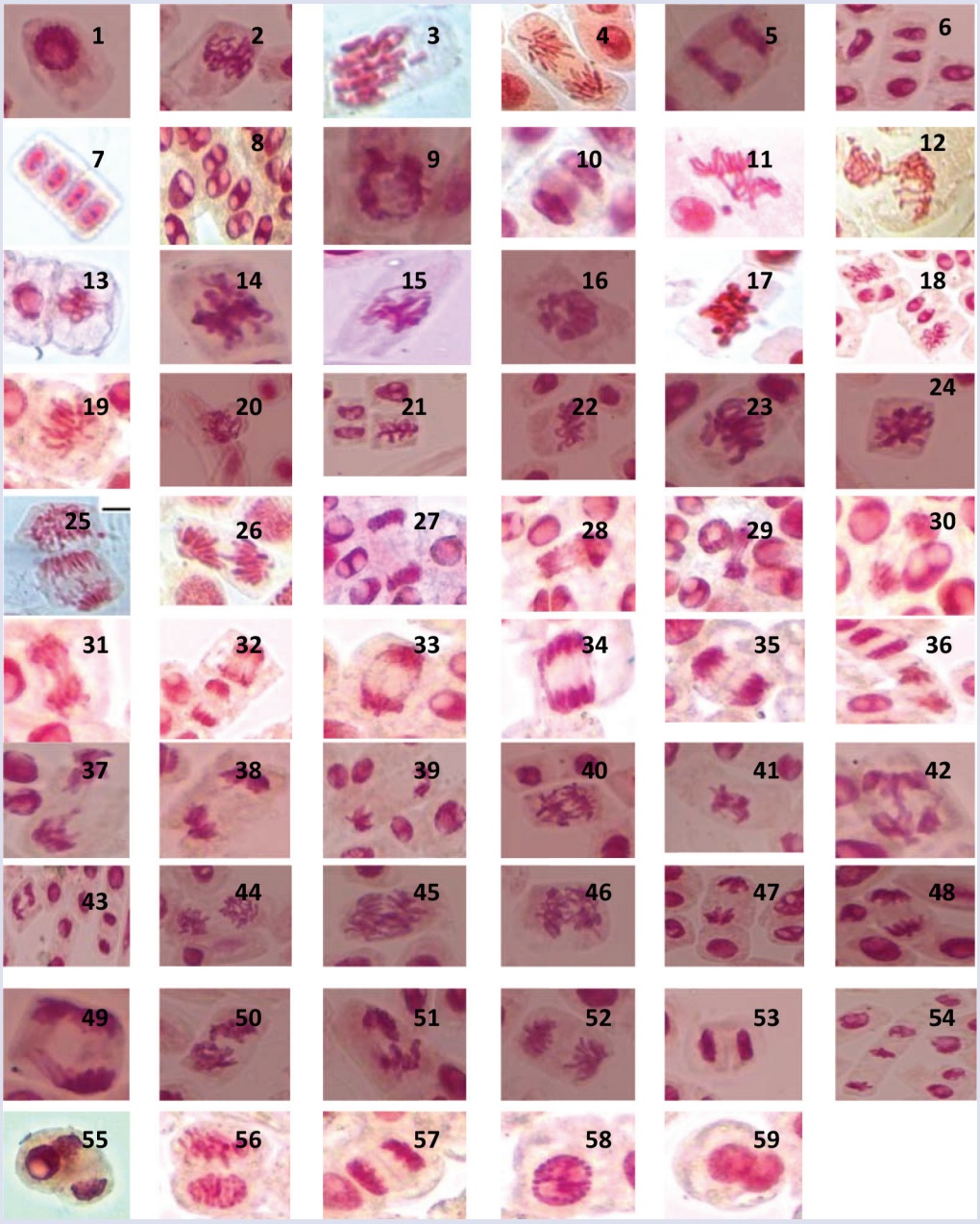

Figure 1: Miotic stages, Control 1-6; Interphase abnormities 7-10; Prophase abnormalities 11-16; Metaphase abnormalities 17-24; Anaphase abnormalities 25-52; Telophase abnormalities 53-55; cytokinesis abnormalities 56-57; others 58-59.

Cefpodoxime

The concentration (40 ppm) is active and showed good response as compared to the 20 and 60 ppm.

Physiological and Clastogenic effects

The different concentrations of antibiotics were studied for the chromosomal physiological and clastogenic abnormalities and recorded Table 2. The clastogenic abnormalities were recorded for the cefixime as micronuclei (1.00±1.00, 1.66±0.80 and 3.00±0.57), metronidazole as binucleate cells (1.00±1.00, 1.00±1.00 and 1.33±1.33) at all the concentrations (40, 80 and 120 ppm), and ciprofloxacin as micronuclei (0.66±0.33) at lower concentration (50 ppm). The antibiotic cefixime also showed chromosome exchange abnormalities (1.66±0.88 and 0.66±0.66) at lower and higher concentrations (40 and 120 ppm). The physiological abnormalities (stickiness, laggards and bridges) were recorded for almost all the antibiotics and at all the concentrations. The other physiological

Table 1: Mean ±S.E. (S.D.) value recorded on mitotic cells and stages after antibiotics treatment.

Antibiotics Treatment (ppm)	TNC	NDC	DC	I	P	M	A	T	Cy
				Mean±S.E. (S.D.)					
Control	509.33±51.42 (89.07)	469.67±54.95 (95.19)	39.66±4.25 (7.37)	14.66±5.78 (10.01)	16.33±4.09 (7.09)	4.00±1.15 (2.00)	1.00±0.57 (1.00)	3.00±2.00 (3.46)	0.33±0.33 (0.57)
Cefixim 6h 40	501.33±109.78 (190.14)	180.67±36.88 (63.88)	320.67±75.51 (130.79)	214.00±58.28 (100.95)	65.00±21.36 (37.00)	13.00±3.21 (5.56)	12.33±1.45 (2.51)	13.00±3.00 (5.19)	3.33±1.20 (2.08)
12 h 80	614.67±19.78 (34.26)	504.00±18.33 (31.74)	110.67±8.45 (14.64)	26.66±2.18 (3.78)	64.66±13.53 (23.43)	8.66±4.25 (7.37)	1.33±0.33 (0.57)	8.66±1.85 (3.21)	2.00±0.00 (0.00)
24h 120	488.00±1.51 (262.46)	303.33±89.80 (155.55)	184.67±63.39 (109.80)	83.00±15.53 (26.90)	64.33±34.10 (59.07)	12.66±6.69 (11.59)	4.00±3.05 (5.29)	13.00±5.56 (9.64)	7.66±2.90 (5.03)
Metronidazol 6h 40	612.00±73.02 (126.47)	403.67±34.71 (60.13)	208.33±43.97 (76.17)	119.33±15.71 (27.22)	61.33±19.53 (33.84)	19.33±3.17 (5.50)	10.00±3.21 (5.56)	7.66±3.17 (5.50)	2.66±0.66 (1.15)
12h 80	810.33±93.26 (161.54)	710.33±89.83 (155.59)	100.00±20.66 (35.79)	48.66±19.16 (33.20)	14.33±4.80 (8.32)	7.66±2.33 (4.04)	1.33±0.88 (1.52)	3.66±0.88 (1.52)	1.00±1.00 (1.73)
24h 120	969.00±259.52 (449.50)	853.33±217.32 (376.41)	115.67±52.98 (91.76)	33.66±8.41 (14.57)	20.66±5.23 (9.07)	9.66±1.76 (3.05)	9.33±3.28 (5.68)	5.66±1.66 (2.88)	0.33±0.33 (0.57)
Cetrizine 6h 1	439.67±90.24 (156.31)	386.33±79.27 (137.31)	53.33±11.31 (19.60)	12.33±1.45 (2.51)	16.33±3.17 (5.50)	13.00±4.93 (8.54)	4.60±2.33 (4.04)	8.00±3.78 (6.55)	0.66±0.66 (1.15)
12h 2	541.00±50.14 (86.85)	467.67±58.90 (102.02)	73.33±10.58 (18.33)	18.00±1.15 (2.00)	21.33±6.56 (11.37)	16.66±3.48 (6.02)	7.00±3.60 (6.24)	4.00±0.00 (0.00)	0.66±0.33 (0.57)
24h 3	101.23±86.91 (150.53)	901.67±40.84 (70.74)	110.67±60.18 (104.24)	25.33±14.34 (24.84)	26.33±9.83 (17.03)	16.66±10.80 (18.71)	8.00±5.50 (9.53)	14.33±4.33 (7.50)	4.00±2.51 (4.35)
Ciprofloxacin 6h 50	858.00±151.40 (262.24)	792.00±141.30 (244.74)	66.00±11.71 (20.29)	24.66±3.28 (5.68)	16.33±3.52 (6.11)	4.33±1.76 (3.05)	8.66±1.45 (2.51)	4.66±0.88 (1.52)	3.66±1.76 (3.05)
12h 100	1033.00±323.05 (559.55)	628.67±101.57 (175.93)	70.66±0.88 (1.52)	22.00±3.05 (5.29)	11.33±1.45 (2.51)	8.00±0.57 (1.00)	10.00±4.72 (8.18)	4.33±1.76 (3.05)	4.66±1.76 (3.05)
24h 150	694.33±101.04 (175.01)	628.67±101.57 (175.93)	65.66±5.84 (10.11)	30.66±2.40 (4.16)	12.66±4.09 (7.09)	3.66±0.33 (0.57)	6.00±2.00 (3.46)	3.00±1.52 (2.64)	1.33±0.66 (1.15)
Cefpodoxime 6h									

Table 1: Con									
20	402.33±205.96	209.67±50.20	25.66±4.17	21.66±11.34	14.33±2.96	0.33±0.33	0.00±0.00	0.00±0.00	0.00±0.00
	(356.73)	(86.96)	(7.23)	(19.65)	(5.13)	(0.57)	(0.00)	(0.00)	(0.00)
12h									
40	1473.70±111.02	1177.30±111.15	280.33±7.68	184.67±15.67	25.33±11.86	27.00±4.58	14.00±1.52	20.00±7.02	1.66±0.33
	(192.30)	(192.52)	(13.31)	(27.15)	(20.55)	(7.93)	(2.64)	(12.16)	(0.57)
24h									
60	1091.30±240.58	823.33±196.66	261.33±45.21	184.00±52.31	68.33±13.59	1.33±0.88	0.66±0.66	5.00±2.64	0.66±0.33
	(416.69)	(340.63)	(78.30)	(90.62)	(23.54)	(1.52)	(1.15)	(4.58)	(0.57)

TNC, total number of mitotic cells; NDC, non dividing mitotic cells; DC, dividing mitotic cells; I, interphase; P, prophase; M, metaphase; A, anaphase; T, telophase; Cy, cytokinesis.

Table 2: Abnormalities induced after application of different antibiotics at different concentrations.

Antibiotics treatment (ppm)	Abnormalities										
	Stickiness	Laggards	Vagrant Cells	Early Anaphase	Multipolar Anaphase	Late Anaphase	Bridges	Micronuclei	Chromosome Exchage	C-mitosis	Binucleate
					Mean±S.E. (S.D.)						
Cefixim											
6h											
40	14.33±6.38	3.00±1.52	4.00±0.57	2.66±1.33	2.00±0.57	1.00±0.00	1.33±0.66	1.00±1.00	1.66±0.88	-	-
	(11.06)	(2.64)	(1.00)	(2.30)	(1.00)	(0.00)	(1.15)	(1.73)	(1.52)		
12h											
80	5.00±1.52	1.00±0.57	-	0.66±0.33	-	-	2.33±1.45	1.66±0.88	-	-	-
	(2.64)	(1.00)		(0.57)			(2.51)	(1.52)			
24h											
120	3.33±1.20	1.00±0.57	2.33±1.45	-	-	1.66±1.66	2.33±1.85	3.00±0.57	0.66±0.66	-	-
	(2.08)	(1.00)	(2.51)			(2.88)	(3.21)	(1.00)	(1.15)		
Metronidazole											
6h											
40	6.66±3.38	-	-	-	-	1.33±0.33	1.33±1.33	-	-	-	1.00±1.00
	(5.85)					(0.57)	(2.30)				(1.73)
12h											
80	3.33±1.85	0.33±0.33	-	-	-	1.00±0.57	0.33±0.33	5.33±2.33	-	-	1.00±1.00
	(3.21)	(0.57)				(1.00)	(0.57)	(4.04)			(1.73)

Table 2: Con

24h											
120	5.33±1.85 (3.21)	0.66±0.66 (1.15)	-	0.33±0.33 (0.57)	-	0.66±0.66 (1.15)	0.66±0.33 (0.57)	-	-	0.33±0.33 (0.57)	1.33±1.33 (2.30)
Cetrizine											
6h											
1	5.00±2.51 (4.35)	0.33±0.33 (0.57)	-	-	-	-	-	-	-	-	-
12h											
2	3.33±0.88 (1.52)	-	-	-	-	-	2.33±0.33 (0.57)	-	-	-	-
24h											
3	10.33±9.83 (17.03)	1.00±1.00 (1.73)	-	-	0.33±0.33 (0.57)	-	4.33±2.84 (4.93)	-	-	-	-
Ciprofloxacin											
6h											
50	7.33±3.84 (6.65)	-	-	-	-	-	-	0.66±0.33 (0.57)	-	-	-
12h											
100	8.66±0.33 (0.57)	0.33±0.33 (0.57)	-	-	-	-	1.33±0.66 (1.15)	-	-	-	-
24h											
150	5.00±0.57 (1.00)	1.00±0.57 (1.00)	-	-	-	-	2.33±0.88 (1.52)	-	-	-	-
Cefpodoxime											
6h											
20	1.00±0.00 (0.00)	0.33±0.33 (0.57)	-	-	-	-	-	-	-	-	-
12h											
40	21.33±3.17 (5.50)	2.66±0.33 (0.57)	-	-	1.33±0.88 (1.52)	-	5.66±1.85 (3.21)	-	-	-	-
24h											
60	0.66±0.33 (0.57)	-	-	-	0.33±0.33 (0.57)	-	-	-	-	-	-

abnormalities were recorded such as vagrant cells, early anaphase, multipolar anaphase, late anaphase and c-mitosis.

Mitotic images abnormalities

The mitotic image abnormalities induced at different concentrations and time were photographed and reported in Figure 1. The normal mitotic (Interphase, Prophase, Metaphase, Anaphase, Telophase and Cytokinensis) images Figure 1-6, interphase (binucleate cells, interphase nucleoli, nuclear chromatin and interphase chromatin) abnormalities Figure 7-10, prophase (interlaced chromatin, micronucleus, intermingled, looplike structure, sticky, ring like structure, disturbed sticky) abnormalities Figure 11-16, metaphase (disturbed, micronuclei, sticky, interlaced, sticky equatorial and intermingled) abnormalities (17-24), anaphase (fragments, bridges, sticky, loose chromatids, chromatids dissolved type, bipolar at both poles, bipolar at one pole, multipolar, intermingled and dysjunct) abnormalities (25-52), telophase (telocytokinesis, telocytomixis, telocytonucleomixix) abnormalities (53-55), cytokinesis (cell notch, cell plate) abnormalities (56-57) and other (nuclear membrane granules, nucleomixis) abnormalities (58-59) were recorded.

CONCLUSION

All the doses are potent to induce the mitotic images disturbances and lead to different kinds of abnormalities.

Although the mean value recorded for the abnormalities showed a mixed response and the values are very less to predict the dose response curve. The antibiotics cefixime, metronidazole and ciprofloxacin could not be recommended at higher doses and for longer duration as it may damage the genetic constituent of the plant as well as animals.

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CONFLICT OF INTEREST

Author declare no conflict of interest.

ABBREVIATION USED

Ppm: Parts per million; **DC:** Dividing cells; **NDC:** non dividing cells; **TNC:** Total number of cells.

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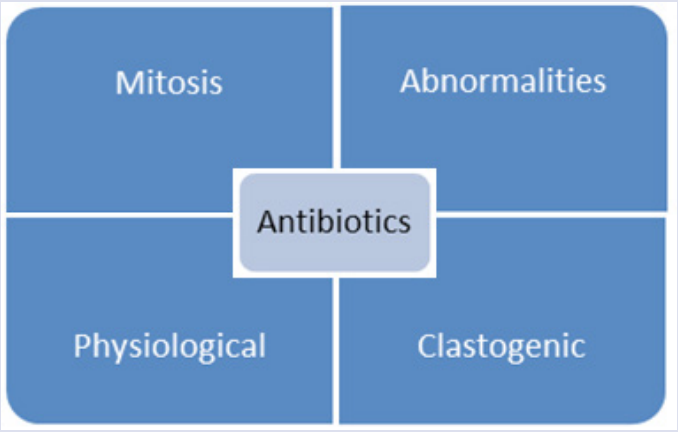
GRAPHICAL ABSTRACT



SUMMARY

- The different concentrations of commonly used antibiotics cefixim (40, 80 and 120 ppm), metronidazole (40, 80 and 120 ppm), ciprofloxacin hydrochloride (50, 100 and 150 ppm), cefpodoxime proxetil (20, 40 and 60 ppm) and citrizine (1, 2 and 3 ppm) applied to root tip cells of *Allium* and recorded the observations of various forms of abnormalities categorized into physiological and clastogenic which agrees with earlier reports.
- The lower concentration (40, 40, 50, 20 and 1 ppm) of each medicine is equivalent to the effective dose (400, 400, 500, 200 and 10 mg) of the respective antibiotics and anti-allergic medicines.

ABOUT AUTHORS

Dr. Sanjay Kumar has joined Banaras Hindu University recently, earlier he served Nagaland University, Nagaland. He obtained his post-graduation and Ph.D. (Botany) from Banaras Hindu University, Varanasi. His current research interests include Cytogenetics, population genetics, molecular genetics, biochemical and phytochemistry of plants and published many national and international research articles.

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