Understanding the Role of Herbal Plants and Their Secondary Metabolites Associated With Drugs Induced Genotoxicity"

Sulakshana Pal Singh & Dr. Lokesh Verma (Professor)

[1&2] SAGE University Bhopal (M.P) ,Sahara Bypass Road Katara Hills , Extension ,Bhopal , Madhya Pradesh 462022, India.

Corresponding author : **Dr. Lokesh Verma (Professor)**

Abstract:
The modern person cannot do admirations to his health in this age of modernization. He is being enmeshed in a muck of ailments as a result of his way of life. The unique plants that can be used to maintain health were known to our ancestors. However, allopath develops with time. People became interested in allopath because the results were immediately apparent, but there were also several negative effects that occasionally surfaced. Sometimes these adverse effects were so bad that people began tightening new illnesses. Cancer is a fatal illness that affects people worldwide. Cancer has been around for a very long time. As result of this, there are numerous additional problems like (organ toxicity) kidney, liver toxicity etc. The anticancer medicine has an influence on the cell cycle, which affects both normal and cancer cells' genes. As a result, the patient's gene structure begins to deteriorate, normal dividing cells experience genotoxicity, and more mutagenesis occurs. Nevertheless, the anticancer drug can be used to treat the disease. Numerous studies are being conducted constantly to eliminate this genotoxicity. In this examination, we'll explore the similarities that are largely present in all of those herbal plants and extracted substances effect on the genotoxicity caused due to any reason.
Keyword: Cancer, Genotoxicity, Organ toxicity

Introduction

India is a country rich in culture and endowed with many traditional remedies that were passed down from ancestors. During ancestor time they were blessed with the god gift or herbal knowledge. Ayurveda is the conventional treatments that are used today but allopathic treatment hamper its image. Allopathic treatment is useful in fast relief but with time the list of side-affect also seen in patients. Some side effect are irreversible and it harm brutally and create other

problem that should resolved on time otherwise it may develop different type of disorderand as a result, we have more fatal diseases like cancer, asthma, and others side effect like organ toxicity (nephrotoxicity, hepatotoxicity, cardio toxicity), genotoxicity etc.

It is anticipated that conditions will be worse than they are now, 29.5 million new cases of the disease will be reported per year. [1]

In 2020, GLOBOCAN will examine cancer cases and deaths that are associated to them. Statistics said that 19.3 million new cases of cancer and 10.0 million of death. [2] Many other techniques are being studied for the treatment of cancer, such as the (CAR) T cell therapy [3].Cancer is a disease requires long-term treatment, which causes organ toxicities as well as genotoxicity and sometime secondary cancer [4]. Genotoxicity are the elements that formed genetic knockout that cause mutation and all those substances that are capable of damaging and interacting to the genome are called as genotoxin [5] Mutations in somatic cells may cause cancer, while mutations in germ cells may be passed on to offspring. Mutations in somatic cells may cause cancer, while mutations in germ cells may be passed on to offspring. Mutations in somatic cells may cause cancer, while mutations in germ cells may be passed on to offspring [5]

1. Genotoxicity is caused like environmental toxin substance arsenic that caused chromosomal aberration and micronucleus formation after regular or long exposure [6]
2. Streptonigrin is anticarcenogin in nature and it work on the DNA, RNA of cancerous cell like mitomycin C, porfiromycin, all showing genotoxicity [7]
3. Carbon black nanoparticle also showed genotoxicity [8]
4. Food habits also causes genotoxicity like fried meat[9]
5. Additive also showed genotoxicity like titanium dioxide is used to prepared different formulation [10]
6. Molybdenum, lithium, and tungsten all are produced pulmonary toxicity and then genotoxicity [11]
7. 1,2-Dichloroethane EDC is generally present in all environmental condition and it produced genotoxicity [12]
8. Nitrogen oxides is present in pollution and it is genotoxic [13]
9. Some of antihypertensive agents caused genotoxicity [14]
10. Industrial wastage caused genotoxicity [15]
11. Psychotropic drugs can caused the genotoxicity [16]
12. Chromium (III),(IV)both showed genotoxicity [17]
13. Cadmium (Cd) is one of compound of pollutant air can also produce genotoxicity [18]

Several indirect mechanism is also responsible to create genotoxicity in cell like ROS production, disturbing of lipid peroxidase, superoxidase and indirect disturbing of oxidative stress inside the cell is also responsible indirectly of cellular genetic material damage[19]. Many flavoring agents also have genotoxic in nature [20].Many potent agents will causes genotoxicity but many repair mechanism [21]

Anthracyclines anticancer medications repeatedly produced side effects like myelosuppression, neutropenia, cardiomyopathy, nausea, and the stimulation of secondary tumors. Anthracyclines can under go one-electron reduction and structure formed semi quinone which formed free hydroxyl that harm the lipid membrane and DNA strand and break into pieces and caused DNA abberation. [22]

Plant bioassays are well known used system help to screening and observing chemical moiety with mutagenic and carcinogenic in nature. Plant bioassay determine the chromosomal damage, exchange of sister chromatid exchange, DNA strand breakage. Plant in vitro culture evaluation of genotoxic compound is determine with the help of root of different sensitive plant like *allium cepa* assay *vicia faba,*and *crepis capillaries* [23]

Several other method identify the genotoxicity and mutagenic compound like RAPD (random amplified polymorphic DNA), AP-PCR(arbitrarily primed polymerase chain reaction) and DAF (DNA amplification fingerprinting), all method are observed genetic mapping. [24].Insect used to determine genotoxicity is Drosophila melanogaster [25].

Flash-comet assay: Single cell gel electrophoresis it take lesser time and reduced the risk of laboratory indirectly induced DNA hydrolysis in the alkaline medium[26]. Yeast cell growth for genotoxic study [27]

Comet assay: Modified forms of the ordinary protocol identify oxidized DNA bases and can be used to expose positions of DNA base damage. Different methods like chromosomal aberration assay, micronucleus assay both in blood and sperm cells [28], [29]

Micronuclei (MN): Measured number of condensed fragments of acentric chromosome or whole chromosome. Micronucleus formation frequency index is a parameter to identify the genotoxic nature of any compound *in vivo*[30]

Table 1

Basic mechanism of genotoxicity due to anticancer drug

Doxorubicin is DNA intercalated of cancerous cell as well as normal cell. Doxorubicin caused cellular membrane damage after formation of hydroxyl radical and superoxide ions [41]

Cyclophosphamide andcisplatinits metabolite induces oxidative stress which leads to DNA damage of normal cells and toxicities to various target organs and it active the ROS and NO production which ultimately damages the lipids, proteins and DNA inside the cell [42][43]

TABLE 2 ,TABLE 3 ,TABLE 4

Conclusion

As per above review many publication, researcher and investigation directly and indirectly indicated the role of plants and their secondary metabolites. Every plants have many chemical constitutes and have large list of pharmacological benefits with limited or no side effect. Our todays lifestyle is ruined with the time and many fatal diseases come into by these loopholes and person suffer with many diseases at very lower age many fatal diseases like cancer need proper treatment and it treatment is long termed and due to it long term medication destroyed their body

with different other diseases like hepatotoxicity, nephrotoxicity, sometime genotoxicity and it also caused secondary cancer due to genotoxicity. Today review is based on that categories in which herbal plant and their isolated compound are worked the genotoxicity and their other problem.

Table 1 List of plant that is genotoxic in nature

S.no	Plant	Part used	Extract	Method	
1	*Antidesma venosum*	Whole plant	Dichloromethane, 90% methanol	Ames test, Vitotox ® test, Comet, MN	[31]
2	*Salix alba*	Bark		Comet assay	[32]
3	*Bauhinia platypetala extract*	Leaves	Ethanol	Comet assay	[33]
4	*Chenopodium ambrosioides*				[34]
5	*Pterolobium stellatum Otostegia integrifolia Vernonia amygdalina*	Root	Chloroform, 80%methanol	Comet assay	[35]
6	*Lythrum salicaria*			Mussel MN	[36]
7	*Teucrium arduini L. Teucrium flavum L*		Methanol	Comet assay	[37]
8	*Achyrocline satureoides Iodina rhombifolia Desmodium incanum*		Aqueous	*Ames* test	[38]
9	*Nepeta meyeri (catmint)*	Aerial parts	Oil extract		[39]
10	*Hypericum adenotrichum*		Methanol	MN, comet assays.	[40]

TABLE 2 List of anticancer drug that produced genotoxicity

s.no	Name Of Drug	
1	Cis-tetraammine(oxalato)ruthenium(III) dithionate	[44]
2	Cyclophosphamide and 5-Fluorouracil	[45]
3	Cisplatin	[46]
4	Cyclophosphamide	[47]
5	Fluorinated trifluoromethyl 4-thiazolidinone	[48]
6	Oxaliplatin	[49]
7	Methotrexate	[50]
8	Bendamustine	[51]
9	Imatinib mesylate	[52]
10	Mitomycin C	[53]

TABLE 3 List of plant that reduced the risk of genotoxicity

s.no	Plant name	Part of plant	Extract used	Method used to identified genotoxicity	References
1	*Roylea cinerea*	Leaves	Aqueous	Allium cepa	[54]
2	*Ranunculus acris (*Buttercup family*)*	Flower	Aqueous	Allium cepa	[55]
3	*Moringa peregrine*	Leaves	Aqueous	CA, MN	[56]
4	*Ficus carica*	Leaves	Methanol	CA, MN	[57]
5	*Ginkgo biloba*	Leaves		CA, MN	[58]
6	*Myrciaria jaboticaba*	Seed		CA	[59]
7	*Rhus verniciflua stokes*	Fruit Extract			[60]
8	*Myrciaria dubia* (camu–camu)	Fruit juice		Comet assay	[61]
9	*Circuma longa*	Rhizomes		CA, MN	[62]
10	*Aegle marmelos*	Plant material	Methanol	CA	[63]
11	*Psathyrella candolleana and agaricus bisporus*	Fruit bodies	Aqueous	CA ,MN and comet assays	[64]
12	*Artemisia judaica* ("Shih kharasani)	Leaves	70% ethanol	MN, comet assay	[65]
13	*Rubus niveus*	Aerial parts		MN, comet assay	[66]
14	*Chenopodium album*	All part	Methanol	CA	[67]
15	*Nigella sativa*	Seeds	Aqueous-ethanol	MN	[68]
16	*Cactus cladode*	Whole plant part	Juice	CA, SOS Chromotest	[69]
17	*Garlic extract*	Bulbs	Ethanol	CA in germ cells	[70]

18	*Hemidesmus indicus*	Root	Ethanol	Sister chromatid exchanges, CA and MN	[71]
19	*Helicteres isora*	Fruits	Pet ether, methanol	CA and MN	[72]
20	*Phyllanthus maderaspatensis.*	Whole plant	Ethanol	MN.	[73]
21	*Sea-buckthorn*	Juice		MN	[74]
22	*Phyllanthus emblica*	Dried fruits	Aqueous	Cytokinesis-block micronucleus (CBMN) assay	[75]
23	*Myristica fragrans*		Aqueous	Allium cepa assay	[76]
24	*Glycyrrhiza glabra*	Root	Juice	CA	[77]
25	*Coleus aromaticus*		Ethanol	CA, MN	[78]
26	*Terminalia chebula*	Fruit dried	50% Methanol	CA, MN	[79]
27	*Cajanus cajan* (Pigeon pea)	Seed	Flavonoid portion	CA, Comet assay	[80]
28	*Grape seed*	Seed	Oil extract	CA	[81], [96]
29	*Coccinia indica*	Leaves	Petroleum ether, 70% methanol	CA, MN	[82]
30	*Haberlea rhodopensis*	Leaves	70% ethyl alcohol,	CA	[83]
31	*Equisetum arvense* (horsetail)	Aerial part	Ethanol	CA	[84]
32	*Persea americana Mill(avocado)*	Fresh fruits	50% methanol	CA	[85]
33	Turmeric	Rhizomes		CA	[86]
34	*Salacia oblanga*	Root-bark	Methanol	CA	[87]
35	*Viscum album*	All part	Methanol	CA	[88]
36	*Solanum lycopersicum*	Fruit	Aqueous	CA	[89]
37	*Egyptian sweet marjoram*	Leaves	Aqueous	CA	[90]
38	*Ocimum sanctum*	Leaves	Nanoparticles	CA	[91]
39	*Lepidium sativum*	Leaves	Methanolic	CA	[92]
40	*Foeniculum vulgare*	Seed	Oil	CA,MN	[93]
41	*Solanum lycocarpum*	Whole plant	Hydro alcoholic	CA,MN	[94]

42	*Fucus vesiculosus*	Whole plant	Aqueous	CA, Comet assay	[95]
43	*Baccharis dracunculifolia*	Leaves	Ethyl acetate	CA	[97]
44	*Cassia occidentalis*		Aqueous	CA	[98]
45	*Allium tuncelianum*	Buds	Ethanol	CA	[99]
46	*Roylea cinerea*	Leaves	Aqueous	Allium cepa assay	[100]
47	*Parquetina nigrescens*	Leaves	Aqueous	Allium cepa assay	[101]
48	*Mentha spicata*	Leaves	Aqueous	CA	[102]
49	*Pomegranate peel*	Peel	Ethanol/water	CA, MN	[103]
50	*Bauhinia variegate*	Bark	50 % methanol	CA, MN	[104]
51	*Origanum majorana*	Leaves		*Vicia faba*assay	[105]
52	*Salvia officinalis*		Oil	MN,CA, comet assay	[106]

TABLE 4 List of isolated herbal compound reduced the risk of genotoxicity

s.no	**Chemical constituents**	**Pharmacological activities**	**Assay**	**References**
1	Nordihydroguaiaretic acid	Diabetes	MN, CA	[107]
2	Lycopene	Antioxidant	MN, CA	[108]
3	Curcumin	Antioxidant	CA	[109]
4	Vitamin C	Antioxidant	CA	[109]
5	Caffeic acid phenethyl ester	Antioxidant	CA	[110]
6	Bixin		CA	[111]
7	olive and canola oils		CA	[112]
8	Pycnogenol	Anti-inflammatory	CA	[113]
9	Quercetin	Anti-tumor	CA, MN	[114]
10	Resveratrol	Anti-apoptotic		[115].
11	Rutin	Anticancer	CA, MN	[116]
12	Zerumbone	Anti-inflammation	CA	[117]
13	Genistein	Antioxidant	CA	[118]
14	Gallic acid	Immunomodulatory	MN	[119]
15	Lutein	Antioxidant	CA	[120]

16	Glycyrrhizic acid		MN	[121]
17	*Pinus eldarica*		Comet assay,MN	[122]
18	Herniarin		MN	[123]
19	Piperine		CA	[124]

Reference

1. Perse M. Cisplatin Mouse Models. (2021), Treatment, Toxicity and Translatability. Biomedicines. ;9(10):1406.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2020) Global Cancer Statistics, GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin ;71(3):209-249.
3. Mohanty R, Chowdhury CR, Arega S, Sen P, Ganguly P, Ganguly N.(2019) CAR T cell therapy: A new era for cancer treatment (Review). 42(6):2183-2195.
4. Yin W, Wang J, Jiang L, James Kang Y. Cancer and stem cells (2021)Exp Biol Med (Maywood) ;246(16):1791-1801.
5. Radhika, P., & Jyothi, Y. (2019). A review on genotoxicity, its molecular mechanisms, regulatory testing in drug development process. Sereal Untuk, 10(9), 4054-69.
6. Gebel, T. W. (2001). Genotoxicity of arsenical compounds. International Journal of Hygiene and Environmental Health, 203(3), 249-262.
7. Bolzán, A. D., & Bianchi, M. S. (2001). Genotoxicity of streptonigrin: a review. Mutation Research/Reviews in Mutation Research, 488(1), 25-37.
8. Di Ianni E, Jacobsen NR, Vogel UB, Møller P (2022), Systematic review on primary and secondary genotoxicity of carbon black nanoparticles in mammalian cells and animals. Mutat Res Rev Mutat Res 790:108441.
9. Sanz-Serrano J, López de Cerain A, Garayoa R, Azqueta A, Vettorazzi A(2020). Genotoxicity evaluation of fried meat: A comprehensive review. Food Chem Toxicol. ;136:110943.
10. Kirkland D, Aardema MJ, Battersby RV, Beevers C, Burnett K, Burzlaff A, Czich A, Donner EM, Fowler P, Johnston HJ, Krug HF, Pfuhler S, Stankowski LF Jr.(2022) A weight of evidence review of the genotoxicity of titanium dioxide (TiO2). Regul Toxicol Pharmacol. ;136:105263..
11. Hadrup N, Sørli JB, Sharma AK. Pulmonary toxicity, genotoxicity, and carcinogenicity evaluation of molybdenum, lithium, and tungsten (2022) A review. Toxicology.
12. Gwinn MR, Johns DO, Bateson TF, Guyton KZ. (2011), A review of the genotoxicity of 1,2-dichloroethane (EDC). Mutat Res. ;727(1-2):42-53.
13. Victorin K. Review of the genotoxicity of nitrogen oxides. (1994) Mutat Res ;317(1):43-55.

14. Brambilla G, Martelli A. (2006) Genotoxicity and carcinogenicity studies of antihypertensive agents. Mutat Res. ;612(2):115-49.
15. Claxton LD, Houk VS, Hughes TJ (1998). Genotoxicity of industrial wastes and effluents. Mutat Res. ;410(3):237-43.
16. Durnev AD, Eremina NV, Zhanataev AK, Kolik LG. Genotoksichnost' psikhotropnykh lekarstv v eksperimental'nykh i klinicheskikh issledovaniyakh (2022), Genotoxicity of psychotropic drugs in experimental and clinical studies. ;122(10):7-16.
17. Sawicka E, Jurkowska K, Piwowar A. (2021) Chromium (III) and chromium (VI) as important players in the induction of genotoxicity - current view. Ann Agric Environ Med.18;28(1):1-10.
18. Galal, O. A. (2015). Role of ellagic acid against cadmium-induced genotoxcity in drosophila melanogaster. The egyptian journal of experimental biology (zoology), 7(1), 77-77.
19. Povirk, L. F., & Austin, M. F. (1991). Genotoxicity of bleomycin. Mutation Research/Reviews in Genetic Toxicology, 257(2), 127-143.
20. Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., & Urasawa, S. (1982). Genotoxicity of flavoring agents. Mutation Research Letters, 105(6), 387-392.
21. Choudhuri S, Kaur T, Jain S, Sharma C, Asthana S. (2021) A review on genotoxicity in connection to infertility and cancer. Chem Biol Interact. ;345:109531
22. Błasiak, J., Gloc, E., & Warszawski, M. (2002). A comparison of the in vitro genotoxicity of anticancer drugs idarubicin and mitoxantrone. Acta Biochimica Polonica, 49(1), 145-155.
23. Abdelmigid, H. M. (2013). New trends in genotoxicity testing of herbal medicinal plants. New insights into toxicity and drug testing. InTech, 89-120.
24. Atienzar, F. A., & Jha, A. N. (2006). The random amplified polymorphic DNA (RAPD) assay and related techniques applied to genotoxicity and carcinogenesis studies: a critical review. Mutation Research/Reviews in Mutation Research, 613(2-3), 76-102.
25. Panchal K, Tiwari AK. (2017) Drosophila melanogaster "a potential model organism" for identification of pharmacological properties of plants/plant-derived components. Biomed Pharmacother. ;89:1331-1345.
26. Bivehed E, Hellman B. (2020) Flash-comet assay. MethodsX. ;7:101161.
27. Toussaint M, Conconi A.(2006) High-throughput and sensitive assay to measure yeast cell growth: a bench protocol for testing genotoxic agents. Nat Protoc.;1(4):1922-8.
28. Gülkaç, M. D., Akpinar, G., Üstün, H., & Özön Kanli, A. (2004). Effects of vitamin A on doxorubicin-induced chromosomal aberrations in bone marrow cells of rats. Mutagenesis, 19(3), 231-236.
29. Watanabe, H. (2018). Risk of chromosomal aberration in spermatozoa during intracytoplasmic sperm injection. Journal of Reproduction and Development, 64(5), 371-376.

30. Shahrim, Z., Baharuddin, P. J. N. M., Yahya, N. A., Muhammad, H., Bakar, R. A., & Ismail, Z. (2006). The in vivo rodent micronucleus assay of Kacip Fatimah (Labisia pumila) extract. Tropical Biomedicine, 23(2), 214-219.
31. Elgorashi, E. E., Taylor, J. L. S., Maes, A., De Kimpe, N., Van Staden, J., & Verschaeve, L. (2002). The use of plants in traditional medicine: potential genotoxic risks. South African Journal of Botany, 68(3), 408-410.
32. Maistro EL, Terrazzas PM, Perazzo FF, Gaivão IOM, Sawaya ACHF, Rosa PCP. Salix alba (white willow) medicinal plant presents genotoxic effects in human cultured leukocytes. (2019) J Toxicol Environ Health A. ;82(23-24):1223-1234.
33. Santos FJ, Moura DJ, Péres VF, Sperotto AR, Caramão EB, Cavalcante AA, Saffi J. (2012) Genotoxic and mutagenic properties of Bauhinia platypetala extract, a traditional Brazilian medicinal plant. J Ethnopharmacol ;144(3):474-82.
34. Gadano A, Gurni A, López P, Ferraro G, Carballo M. (2002) In vitro genotoxic evaluation of the medicinal plant Chenopodium ambrosioides L. J Ethnopharmacol. 2002 Jun;81(1):11-6.
35. Kahaliw W, Hellman B, Engidawork E. (2018) Genotoxicity study of Ethiopian medicinal plant extracts on HepG2 cells. BMC Complement Altern Med.1;18(1):45.
36. Eck-Varanka B, Kováts N, Hubai K, Paulovits G, Ferincz Á, Horváth E.(2015) Genotoxic effect of Lythrum salicaria extract determined by the mussel micronucleus test. Acta Biol Hung. ;66(4):460-3.
37. Grujičić D, Marković A, Vukajlović JT, Stanković M, Jakovljević MR, Ćirić A, Djordjević K, Planojević N, Milutinović M, Milošević-Djordjević O. (2020) Genotoxic and cytotoxic properties of two medical plants (Teucrium arduini L.and Teucrium flavum L.) in relation to their polyphenolic contents. Mutat Res Genet Toxicol Environ Mutagen. 2020 Apr;852:503168.
38. Vargas VM, Guidobono RR, Henriques JA. (1991) Genotoxicity of plant extracts. Mem Inst Oswaldo Cruz. ;86 Suppl 2:67-70.
39. Kekeç G, Mutlu S, Alpsoy L, Sakçali MS, Atici Ö.(2013) Genotoxic effects of catmint (Nepeta meyeri Benth.) essential oils on some weed and crop plants. Toxicol Ind Health.;29(6):504-13.
40. Sarimahmut M, Balikci N, Celikler S, Ari F, Ulukaya E, Guleryuz G, Ozel MZ.(2016) Evaluation of genotoxic and apoptotic potential of Hypericum adenotrichum Spach. in vitro. Regul Toxicol Pharmacol. ;74:137-46.
41. Mohamed, E. K., Osman, A. A., Moghazy, A. M., Rahman, A. A. S. A., & AS, A. (2021). Propolis protective effects against doxorubicin-induced multi-organ toxicity via suppression of oxidative stress, inflammation, apoptosis, and histopathological alterations in female albino rats. Biointerface Res. Appl. Chem, 12, 1762-1777.
42. Tripathi, D. N., & Jena, G. B. (2009). Intervention of astaxanthin against cyclophosphamide-induced oxidative stress and DNA damage: a study in mice. Chemico-biological interactions, 180(3), 398-406.

43. Mundhe, N., Dahiya, V., Budhani, M. K., Mishra, N., Reddy, J., & Lahkar, M. (2015). The Study of protective effect of Nordihydroguaiaretic acid (NDGA) on cisplatin induced genotoxicity and nephrotoxicity by attenuating oxidative stress in Swiss albino mice. World Journal of Pharmaceutical Sciences, 232-240.
44. Rezende, M. D. R. M., de Souza Velozo-Sá, V., Vilanova-Costa, C. A. S. T., & de Paula Silveira-Lacerda, E. (2020). Cytotoxic, clastogenic and genotoxic effects of cis-tetraammine (oxalato) ruthenium (III) dithionate on human peripheral blood lymphocytes. Acta Scientiarum. Biological Sciences, 42, 1-10.
45. Gupta, S., Das, D., Mitra, P. K., Halder, S., & Datta, A. K. (2020). Assessment of cytotoxicity induced by hazardous chemotherapeutic drugs cyclophosphamide and 5-fluorouracil in Allium cepa assay for ecological safety. Cytologia, 85(2), 151-155.
46. Sioud, F., Ben Toumia, I., Lahmer, A., Khlifi, R., Dhaouefi, Z., Maatouk, M., ...& Chekir-Ghedira, L. (2020). Methanolic extract of Ephedra alata ameliorates cisplatin-induced nephrotoxicity and hepatotoxicity through reducing oxidative stress and genotoxicity. Environmental Science and Pollution Research, 27, 12792-12801.
47. Ghosh, A., Rabbani, S. I., Asdaq, S. M. B., Mohzari, Y., Alrashed, A., Najib Alajami, H., ... & Khalid Alanazi, A. (2021). Morus alba prevented the cyclophosphamide induced somatic and germinal cell damage in male rats by ameliorating the antioxidant enzyme levels. Molecules, 26(5), 1266.
48. Javvaji, K., Mamilla, J., Kongari, L., Kosurkar, U. B., Kumbhare, R. M., & Misra, S. (2023). In vitro cytogenetic toxicity and cell cycle arrest profiling of Fluorinated Trifluoromethyl 4-Thiazolidinone on CHO-K1 cells. Archives of Clinical Toxicology, 5(1), 1-8.
49. Ganaie, M. A., Jan, B. L., Khan, T. H., Alharthy, K. M., & Sheikh, I. A. (2019). The protective effect of naringenin on oxaliplatin-induced genotoxicity in mice. Chemical and Pharmaceutical Bulletin, 67(5), 433-438.
50. Ch, A., & Mustak, M. S. (2019). Antigenotoxic effects of rutin against methotrexate genotoxicity in Swiss albino mice. Current Trends in Biotechnology and Pharmacy, 13(2), 163-177.
51. Pereira, T. S., Sant'anna, J. R. D., Morais, J. F., Yajima, J. P. R. D. S. A., Mathias, P. C. D. F., Franco, C. C. D. S., & Castro-Prado, M. A. A. D. (2019). Assessment of bendamustine-induced genotoxicity in eukaryotic cells. Drug and Chemical Toxicology, 42(4), 394-402.
52. Gajski, G., Gerić, M., Domijan, A. M., Golubović, I., & Garaj-Vrhovac, V. (2019). Evaluation of oxidative stress responses in human circulating blood cells after imatinib mesylate treatment–Implications to its mechanism of action. Saudi Pharmaceutical Journal, 27(8), 1216-1221.
53. Al-Dualimi, D. W., Shah Abdul Majid, A., Al-Shimary, S. F. F., Al-Saadi, A. A., Al Zarzour, R., Asif, M., ... & Abdul Majid, A. M. S. (2018). 50% Ethanol extract of

Orthosiphon stamineus modulates genotoxicity and clastogenicity induced by mitomycin C. Drug and Chemical Toxicology, 41(1), 82-88.

54. Rashid F, Singh D, Attri S, Kaur P, Kaur H, Mohana P, Quadar J, Vig AP, Bhatia A, Singh B, Walia H, Arora S.(2022) Modulation of atrazine-induced chromosomal aberrations and cyclin-dependent kinases by aqueous extract of Roylea cinerea (D.Don) Baillon leaves in Allium cepa. Sci Rep.
55. Smirnova, M. V., Koygerova, A. A., & Tsvetov, N. S. (2023). Influence of Ranunculus acris Flower Extract on Allium cepa Root Meristem. International Journal of Plant Biology, 14(1), 91-99.
56. Alyamani, N. M. (2023). The potential antimutagenic effect of Saudi moringa oleifera (Moringa peregrina) leaves extract on the bone marrow of male albino mice. Journal of Biotech Research, 14, 106-114.
57. Fahmy, M. A., Hassan, E. E., Ibrahim, N. E., Hassan, E. M., Hassan, Z. M., & Omara, E. A. (2020). Protective role of ficus carica extract against hepato-testicular side effects and genotoxicity induced by cisplatin. Pharmacognosy Journal, 12(3).
58. Prasad, R., Kumar, M. K., & Rudrama Devi, K. (2020). Antimutagenic activity of ginkgo biloba leaf extract in cisplatin induced chromosomal aberrations in somatic cells of mice.
59. Do Carmo, M. A. V., Fidelis, M., de Oliveira, P. F., Feitoza, L. Q., Marques, M. J., Ferreira, E. B., ...& Azevedo, L. (2021). Ellagitannins from jabuticaba (Myrciaria jaboticaba) seeds attenuated inflammation, oxidative stress, aberrant crypt foci, and modulated gut microbiota in rats with 1, 2 dimethyl hydrazine-induced colon carcinogenesis. Food and Chemical Toxicology, 154, 112287.
60. Nozza, E., Melzi, G., Marabini, L., Marinovich, M., Piazza, S., Khalilpour, S., ...& Sangiovanni, E. (2020). Rhus coriaria L. fruit extract prevents UV-A-induced genotoxicity and oxidative injury in human microvascular endothelial cells. Antioxidants, 9(4), 292.
61. da Silva, F. C., Arruda, A., Ledel, A., Dauth, C., Romão, N. F., Viana, R. N., ... & Pereira, P. (2012). Antigenotoxic effect of acute, subacute and chronic treatments with Amazonian camu–camu (Myrciaria dubia) juice on mice blood cells. Food and chemical toxicology, 50(7), 2275-2281.
62. CH, L. N., Dheeraj, G., Sukumar, B., Harish, P., & Sanjana, S. Protective effects of circuma longa on induced genotoxic effects of doxorubicin on bone marrow cells of mice.
63. Ch, P. R., Rudrama Devi, K., & Reddy, K. P. (2015). Incidence of chromosomal aberrations by doxorubicin and its protection by aegle marmelos.
64. Al-Habib, M. N., Holliday, J., & Aladahmy, M. S. (2018). Psathyrella candolleana and Agaricus bisporus extracts provide protection against DNA oxidative damage induced by doxorubicin. International Journal of Medicinal Mushrooms, 20(8).

65. Linjawi, S. A. (2016). Evaluation the protective effect of Artemisia judaica extract against doxorubicin induced genetic toxicity and histopathology in male. Advances in Environmental Biology, 10(1), 250-258.
66. Tolentino, F., de Araújo, P. A., de Souza Marques, E., Petreanu, M., de Andrade, S. F., Niero, R., ...& Maistro, E. L. (2015). In vivo evaluation of the genetic toxicity of Rubus niveus Thunb.(Rosaceae) extract and initial screening of its potential chemoprevention against doxorubicin-induced DNA damage. Journal of ethnopharmacology, 164, 89-95.
67. Panigrahy, S. K., Jatawa, S., & Tiwari, A. (2012). Modulatory effect of chenopodium album extract against cyclophosphamide induced genotoxicity damage in cultured mammalian cells. Mutagenesis, 35, 191-200.
68. Abajy, M. Y. (2020). Investigating the protective effect of Nigella sativa against the cyclophosphamide induced genotoxicity in rats. Research Journal of Aleppo University, 138, 1-8.
69. Brahmi, D., Ayed, Y., Hfaiedh, M., Bouaziz, C., Mansour, H. B., Zourgui, L., & Bacha, H. (2012). Protective effect of cactus cladode extract against cisplatin induced oxidative stress, genotoxicity and apoptosis in balb/c mice: combination with phytochemical composition. BMC Complementary and Alternative Medicine, 12(1), 1-14.
70. Anuradha, S., & Devi, K. R. (2011). Anti-genotoxic effects of crude garlic extract on cisplatin induced toxicity on germ cells and morphology of sperms in in vivo mouse. Journal of Cell and Animal Biology, 5(13), 279-282.
71. Ananthi, R., Chandra, N., Santhiya, S. T., & Ramesh, A. (2010). Genotoxic and antigenotoxic effects of Hemidesmus indicus R. Br. root extract in cultured lymphocytes. Journal of ethnopharmacology, 127(2), 558-560.
72. Sharma, S., Bhargava, S., & Mehta, A. (2017). Cytoprotective role of helicteres isora in chromosomal aberrations and micronucleus frequencies in rat bone marrow cells against cisplatin induced genotoxicity. European Journal of Biomedical and Pharmaceutical Sciences, 4, 588-591.
73. Chandrasekar, M. J. N., Bommu, P., Nanjan, M. L. J., & Suresh, B. (2006). Chemoprotective effect of Phyllanthus maderaspatensis. In modulating cisplatin-induced nephrotoxicity and genotoxicity. Pharmaceutical biology, 44(2), 100-106.
74. Nersesyan, A., & Muradyan, R. (2004). Sea-buckthorn juice protects mice against genotoxic action of cisplatin. Exp. Oncol, 26(2), 153-5.
75. Guo, X. H., Ni, J., Xue, J. L., & Wang, X. (2017). Phyllanthus emblica Linn. fruit extract potentiates the anticancer efficacy of mitomycin C and cisplatin and reduces their genotoxicity to normal cells in vitro. Journal of Zhejiang University. Science. B, 18(12), 1031.
76. Akinboro, A., Mohamed, K. B., Asmawi, M. Z., Sulaiman, S. F., & Sofiman, O. A. (2011). Antioxidants in aqueous extract of Myristica fragrans (Houtt.) suppress mitosis and cyclophosphamide-induced chromosomal aberrations in Allium cepa L. cells. Journal of Zhejiang University Science B, 12, 915-922.

77. Sharma, V., & Agrawal, R. C. (2015). Evaluation of anticlastogenic effects of Glycyrrhiza glabra root extract against cyclophosphamide induced chromosomal aberration in Swiss albino mice. Journal of Applied Pharmaceutical Science, 5(6), 127-132.
78. Prasad, S., Naik, P., & Vijayalaxmi, K. K. (2002). Efficiency of Coleus aromaticus extract in modifying cyclophosphamide and mitomycin-C induced clastogenicity in mouse bone marrow cells. Indian Journal of experimental biology, 40(9), 1020-1025.
79. Raja, W., Pandey, S., & Agrawal, R. C. (2011). Studies on the anticlastogenic effect of Terminalia chebula extract on cyclophosphamide-induced micronucleus formation and chromosome aberrations in Swiss albino mice. Int J Gen, 1(2), 13-17.
80. Abo-Zeid, M. A., Abdel-Samie, N. S., Farghaly, A. A., & Hassan, E. M. (2018). Flavonoid fraction of Cajanus cajan prohibited the mutagenic properties of cyclophosphamide in mice in vivo. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 826, 1-5.
81. Abd El-Rahim, A. H., & Hafiz, N. A. (2009). Investigation on the protective effect of grape seed and linseed oils against cyclophosphamide induced genotoxicity in mice. Global Veterinaria, 3(5), 377-382.
82. Nitharwal, R. K., Patel, H., Karchuli, M. S., & Ugale, R. R. (2013). Chemoprotective potential of Coccinia indica against cyclophosphamide-induced toxicity. Indian Journal of Pharmacology, 45(5), 502.
83. Popov, B., Georgieva, S. V., & Gadjeva, V. (2011). Modulatory effects of total extract of Haberlea rhodopensis against the cyclophosphamide induced genotoxicity in rabbit lymphocytes in vivo. Trakia Journal of Sciences, 9(1), 51-57.
84. Kour, J., Ali, M. N., Ganaie, H. A., & Tabassum, N. (2017). Amelioration of the cyclophosphamide induced genotoxic damage in mice by the ethanolic extract of Equisetum arvense. Toxicology reports, 4, 226-233.
85. Paul, R., Kulkarni, P., & Ganesh, N. (2011). Avocado fruit (Persea americana Mill) exhibits chemo-protective potentiality against cyclophosphamide induced genotoxicity in human lymphocyte culture. J Exp Ther Oncol, 9(3), 221-30.
86. Mukhopadhyay, M. J., Saha, A., & Mukherjee, A. (1998). Studies on the anticlastogenic effect of turmeric and curcumin on cyclophosphamide and mitomycin C in vivo. Food and chemical toxicology, 36(1), 73-76.
87. Srinivas, H. R., Muralidhar, S. T., Javed, A., Ishwarya, M. S., Manish, J. M., Shruthi, B. M., & Narayanaswamy, S. Y. (2013). Protective effect of Salacia Oblanga and quercetin on cyclophosphamide-induced chromosome aberrations in rat bone marrow cells. International Journal of Engineering Inventions, 2(5), 36-43.
88. Sekeroğlu, V., Aydin, B., & Sekeroğlu, Z. A. (2011). Viscum album L. extract and quercetin reduce cyclophosphamide-induced cardiotoxicity, urotoxicity and genotoxicity in mice. Asian Pac J Cancer Prev, 12(11), 2925-31.

89. Raja, W., Agrawal, R. C., & Ovais, M. (2010). Effects of Solanum lycopersicum Fruit Extract on Cyclophosphamide-induced chromosome aberrations in mouse bone marrow cells. Pharmacologyonline, 1, 909-914.
90. Ramadan, G., Nadia, M., & Zahra, M. M. (2012). Egyptian sweet marjoram leaves protect against genotoxicity, immunosuppression and other complications induced by cyclophosphamide in albino rats. British Journal of Nutrition, 108(6), 1059-1068.
91. Vijaya, P. P., Rekha, B., Mathew, A. T., Syed Ali, M., Yogananth, N., Anuradha, V., & Kalitha Parveen, P. (2014). Antigenotoxic effect of green-synthesised silver nanoparticles from Ocimum sanctum leaf extract against cyclophosphamide induced genotoxicity in human lymphocytes—in vitro. Applied Nanoscience, 4(4), 415-420.
92. Kassem, I. A., Farghaly, A. A., Ghaly, N. S., Hassan, Z. M., & Nabil, M. (2020). Composition and genoprotective effect of the flavonoidal content of Lepidium sativum L. methanolic seed extract against cyclophosphamide-induced DNA damage in mice. Pharmacognosy Journal, 12(1).
93. Tripathi, P., Tripathi, R., Patel, R. K., & Pancholi, S. S. (2013). Investigation of antimutagenic potential of Foeniculum vulgare essential oil on cyclophosphamide induced genotoxicity and oxidative stress in mice. Drug and Chemical Toxicology, 36(1), 35-41.
94. Tavares, D. C., Munari, C. C., de Freitas Araújo, M. G., Beltrame, M. C., Furtado, M. A., Gonçalves, C. C., ... & Veneziani, R. C. S. (2011). Antimutagenic potential of Solanum lycocarpum against induction of chromosomal aberrations in V79 cells and micronuclei in mice by doxorubicin. Planta medica, 77(13), 1489-1494.
95. Leite-Silva, C., Gusmão, C. L. S., & Takahashi, C. S. (2007). Genotoxic and antigenotoxic effects of Fucus vesiculosus extract on cultured human lymphocytes using the chromosome aberration and Comet assays. Genetics and Molecular Biology, 30, 105-111.
96. Yalcin, E., Oruc, E., Çavuşoğlu, K., & Yapar, K. (2010). Protective role of grape seed extract against doxorubicin-induced cardiotoxicity and genotoxicity in albino mice. Journal of medicinal food, 13(4), 917-925.
97. Munari, C. C., Resende, F. A., Alves, J. M., de Sousa, J. P. B., Bastos, J. K., & Tavares, D. C. (2008). Mutagenicity and antimutagenicity of Baccharis dracunculifolia extract in chromosomal aberration assays in Chinese hamster ovary cells. Planta medica, 74(11), 1363-1367.
98. Sharma, N., Trikha, P., Athar, M., & Raisuddin, S. (1999). Protective Effect of Cassia occidentals Extract on Chemical-Induced Chromosomal Aberrations in Mice. Drug and chemical toxicology, 22(4), 643-653.
99. Ozkan, O., Gul, S., Kart, A., Cicek, B. A., & Kilic, K. (2013). In vitro antimutagenicity of Allium tuncelianum ethanol extract against induction of chromosome aberration by mutagenic agent mitomycine C. Kafkas Univ Vet Fak Derg, 19(2), 259-62.

100. Rashid, F., Singh, D., Attri, S., Kaur, P., Kaur, H., Mohana, P., ...& Arora, S. (2022). Modulation of atrazine-induced chromosomal aberrations and cyclin-dependent kinases by aqueous extract of Roylea cinerea (D. Don) Baillon leaves in Allium cepa. Scientific Reports, 12(1), 12570.
101. Alabi, O. A., Atanda, H. C., & Olumurewa, J. A. (2022). Cytogenotoxicity of the aqueous extract of Parquetina nigrescens leaf using Allium cepa assay. Protoplasma, 259(6), 1417-1425.
102. Saleem, M. A., & Al-Attar, M. S. (2013). Protective effects of mentha spicata aqueous extract against ifosfamide induced chromosomal aberrations and sperm abnormalities in male albino mice. Trends Biotechnol. Res, 2(1).
103. Elwej, A., Ben Salah, G., Kallel, C., Fakhfakh, F., Zeghal, N., & Ben Amara, I. (2016). Protective effects of pomegranate peel against hematotoxicity, chromosomal aberrations, and genotoxicity induced by barium chloride in adult rats. Pharmaceutical biology, 54(6), 964-974.
104. Agrawal, R. C., & Pandey, S. (2009). Evaluation of anticarcinogenic and antimutagenic potential of Bauhinia variegata extract in Swiss albino mice. Asian Pac J Cancer Prev, 10(5), 913-6.
105. Qari, S. H. (2008). In vitro evaluation of the anti-mutagenic effect of Origanum majorana extract on the meristemetic root cells of Vicia faba. Journal of Taibah University for Science, 1, 6-10.
106. Diab, K. A., Fahmy, M. A., Hassan, Z. M., Hassan, E. M., Salama, A. B., & Omara, E. A. (2018). Genotoxicity of carbon tetrachloride and the protective role of essential oil of Salvia officinalis L. in mice using chromosomal aberration, micronuclei formation, and comet assay. Environmental Science and Pollution Research, 25, 1621-1636.
107. Mundhe, N., Dahiya, V., Budhani, M. K., Mishra, N., Reddy, J., & Lahkar, M. (2015). The Study of protective effect of Nordihydroguaiaretic acid (NDGA) on cisplatin induced genotoxicity and nephrotoxicity by attenuating oxidative stress in Swiss albino mice. World Journal of Pharmaceutical Sciences, 232-240.
108. Sendão, M. C., Behling, E. B., Dos Santos, R. A., Antunes, L. M. G., & Bianchi, M. D. L. P. (2006). Comparative effects of acute and subacute lycopene administration on chromosomal aberrations induced by cisplatin in male rats. Food and chemical toxicology, 44(8), 1334-1339.
109. Antunes, L. M. G., Araújo, M. C. P., Darin, J. D. A. C., & Maria de Lourdes, P. B. (2000). Effects of the antioxidants curcumin and vitamin C on cisplatin-induced clastogenesis in Wistar rat bone marrow cells. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 465(1-2), 131-137.
110. Ramazan Yılmaz, H., Uz, E., Altunbaşak, A., Sakallı, E., & Özçelik, N. (2010). Anticlastogenic effect of caffeic acid phenethyl ester on cisplatin-induced chromosome aberrations in rat bone marrow cells. Toxicology and Industrial Health, 26(1), 33-37.

111. Silva, C. R., Antunes, L. M. G., & Maria de Lourdes, P. B. (2001). Antioxidant action of bixin against cisplatin-induced chromosome aberrations and lipid peroxidation in rats. Pharmacological Research, 43(6), 561-566.
112. Evangelista, C. M. W., Antunes, L. M. G., Francescato, H. D., & Bianchi, M. L. P. (2004). Effects of the olive, extra virgin olive and canola oils on cisplatin-induced clastogenesis in Wistar rats. Food and Chemical Toxicology, 42(8), 1291-1297.
113. Aydin, B., Unsal, M., Sekeroglu, Z. A., & Gülbahar, Y. (2011). The antioxidant and antigenotoxic effects of Pycnogenol® on rats treated with cisplatin. Biological trace element research, 142, 638-650.
114. Attia, S. M. (2010). The impact of quercetin on cisplatin-induced clastogenesis and apoptosis in murine marrow cells. Mutagenesis, 25(3), 281-288.
115. Attia, S. M. (2012). Influence of resveratrol on oxidative damage in genomic DNA and apoptosis induced by cisplatin. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 741(1-2), 22-31.
116. Prasad, R., & Prasad, S. B. (2021). Modulatory Effect of Rutin on the Antitumor Activity and Genotoxicity of Cisplatin in Tumor-Bearing Mice. Advanced Pharmaceutical Bulletin, 11(4), 746.
117. Al-Zubairi, A. S. (2017). In vitro genotoxic effects of zerumbone and cisplatin combination in CHO cell lines. Asian Pacific Journal of Cancer Biology, 2(4), 101-107.
118. Beg, T., Siddique, Y. H., & Afzal, M. (2012). Protective action of flavonoids genistein and gingerol against cisplatin toxicity in vitro. Journal of Young Pharmacists: JYP, 4(2), 124.
119. Shruthi, S., & Bhasker Shenoy, K. (2018). Genoprotective effects of gallic acid against cisplatin induced genotoxicity in bone marrow cells of mice. Toxicology research, 7(5), 951-958.
120. Serpeloni, J. M., Grotto, D., Mercadante, A. Z., de Lourdes Pires Bianchi, M., & Antunes, L. M. G. (2010). Lutein improves antioxidant defense in vivo and protects against DNA damage and chromosome instability induced by cisplatin. Archives of toxicology, 84, 811-822.
121. Arjumand, W., & Sultana, S. (2011). Glycyrrhizic acid: a phytochemical with a protective role against cisplatin-induced genotoxicity and nephrotoxicity. Life sciences, 89(13-14), 422-429.
122. Sharifan, A., Etebari, M., Zolfaghari, B., & Aliomrani, M. (2021). Investigating the effects of bark extract and volatile oil of Pinus eldarica against cisplatin-induced genotoxicity on HUVECs cell line. Toxicology Research, 10(2), 223-231.
123. Salehcheh, M., Safari, O., Khodayar, M. J., Mojiri-Forushani, H., & Cheki, M. (2022). The protective effect of herniarin on genotoxicity and apoptosis induced by cisplatin in bone marrow cells of rats. Drug and Chemical Toxicology, 45(4), 1470-1475.
124. Wongpa, S., Himakoun, L., Soontornchai, S., & Temcharoen, P. (2007). Antimutagenic effects of piperine on cyclophosphamide-induced chromosome

aberrations in rat bone marrow cells. Asian Pacific Journal of Cancer Prevention, 8(4), 623-627.