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Chapter

Natural Drugs in DNA Repair

Thulasi G. Pillai, Cherupally K. Krishnan Nair and P. Uma Devi

Abstract

Natural products have been used in medicine right from the ancient civilisation. Natural products are used in many types of diseases, together with chemotherapy and radiotherapy. Many products are used against cancer. Many diseases are genetically derived. The drugs which have the capacity to act at genome level gains significant importance in any disease scenario. The genetic information essential for the identity and function of eukaryotic cells exist in DNA and during the lifetime of the cell DNA can be repeatedly damaged due to different factors. The stability and the fidelity of the replication process are meant to be the most remarkable features of the genetic material. The stability can be affected at any time. Compound which can enhance the DNA repair are applicable in many disease condition. Our study was focussed on the DNA repair enhancing property of a glucan from the macro fungi *Ganoderma lucidum*. Comet assay and chromosomal aberrations in mouse bone marrow were used as end points of study. Glucan was found to have DNA repair enhancing property in human lymphocytes.

Keywords: natural products, *Ganoderma lucidum*, glucan, mushroom, DNA repair

1. Introduction

The word 'Natural' has gained tremendous importance in the twenty-first century. Products obtained from nature are known to be natural. The Father of Medicine, Hippocrates has quoted that 'Let your food be our medicine and medicine be our food'. The incorporation of medicinal herbs and extract as food has been practiced long ago. In the present scenario, herbals are seen as potential medicine for a variety of diseases often viewed to super cede the pharmacological efficacy of allopathic drugs [1]. Natural products has become an extremely valuable commodity for the world today. The developing countries miss the modern medicine as they cannot afford it. Natural drugs were already there is use in Chinese medicine, Indian Ayurveda, Arabic Unani medicine and various other indigenous medicine. The two most important classics describing about more than 700 botanicals along with their classification, pharmacological and therapeutic properties are Charak Samhita and Sushrut Samhita (100–500 BC) [2, 3]. Recent reports have substantiated the general belief that traditional medicine is affordable as compared to modern medicine [4]. Natural products play a major role as 'drugs' and as 'lead structures' for the development of synthetic molecules [5]. Ancient people were fully aware of rich potential of herbs for curing different types of ailments. The twentieth century made invaluable contributions to the domain of medical sciences. The discovery of the fascinating molecule, DNA double helix and completion of human genome project were marvellous achievements that had no parallel.

Different modalities of DNA repair mechanisms are offered by natural drugs in mammalian system like base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), SSB repair, which includes BER and DNA-PK-mediated ligation; DSB repair, which includes NHEJ and HR; inter-strand cross-link repair and DPCs (DNA-protein cross links) repair. The drugs act even as a biological catalyst where the rate of the repair process is enhanced [6]. An important cell pathology determinant is the rate of DNA repair. Shortened lifespan and increased cancer incidence has been observed in experimental animals with genetic deficiencies in DNA repair. Mice deficient in the dominant NHEJ pathway and in telomere maintenance mechanisms get lymphoma and infections more often, and consequently have shorter lifespans than wild-type mice [7]. Mice with deficient key repair mechanisms and DNA helices unwinding transcription protein have premature onset of aging-related diseases and shortening of lifespan [8]. Few natural products with DNA protective activity are phenolic compounds, essential oils, alkaloids, caratenoids, glutathione and glucans. Polyphenols and phenolic compounds have the capacity to donate electrons and scavenge free radicals [9, 10].

Phenolic compounds have the capacity to donate electrons and directly scavenge free radicals [9, 10]. The extracts of *Geranium sanguineum* are rich with polyphenol compounds are found to exhibit anti-mutagenic and free radical scavenging capacities [11, 12]. Essential oils, are antioxidants. The essential oil from ginger is a natural antioxidant [13]. Alkaloids, are antioxidants. Carotenoids are lipophilic compounds. Lycopene present in tomatoes and other red fruits like red carrots, red bell peppers, watermelons, and papayas has good antioxidant capacity [14]. Glutathione is a free radical scavenger by either reacting directly with free radical molecules or by acting as proton donor for protection of active molecules as DNA [15]. Glucan is an important carbohydrate from plants, bacteria and fungi. It is discussed in detail here due to their diverse activity. Somehow the antioxidant activity is related to DNA repair mechanism as most of the compound which can repair DNA damage are found possess antioxidant capacity.

Macro fungi are distinguished as important natural resources with therapeutic potential. Studies were conducted on the glucan isolated from the medicinal mushroom and the macrofungi, *Ganoderma lucidum*. *Ganoderma* is popularly known as 'The mushroom of longevity and immortality'1. *Ganoderma lucidum*, commonly known as reishi, a mushroom like fungus which grows on logs or tree stumps is one of the most popular medicinal mushrooms in China, Japan and the United States (**Figure 1**). It has a shiny, hard, asymmetrical cap that ranges in colour from yellow to black. Species of the genus *Ganoderma* P. Karst (Ganodermatales) are important wood decaying mushrooms occurring throughout the world, mainly on tropical trees. Over 250 species of this mushrooms are known. The fruiting

Figure 1.
Ganoderma lucidum growing in wild.

bodies of *Ganoderma lucidum* contain a variety of chemical substances. The polysaccharides of *G. lucidum* are the other major source of its biological activity and therapeutic use. This mushroom has attracted great attention owing to its antitumor and hypoglycemic activities [16]. Many fungal polysaccharides have been reported to be active in humans. More than 180 chemical substances have been isolated from *Ganoderma*, which include polysaccharides, triterpenes, nucleosides, ergosterols, fatty acids, proteins, peptides and trace elements. *Ganoderma* has been extensively used as mushroom of immortality in China and other Asian countries. *Ganoderma* has been reported to have numerous pharmacological effects including immunomodulating, anti-inflammatory, analgesic, anticancer, anti-lipidemic and hepatoprotective antihypertensive effects [8, 17]. It is widely accepted that pharmacological effects of *Ganoderma* depends on its colour, on the stage of development and the environment in which it grows. The fruiting bodies of *Ganoderma lucidum*, commonly known as reishi have long been prescribed in Chinese medicine as a tonic and sedative [18]. In Chinese folklore reishi has been regarded as a panacea for all types of diseases, perhaps owing to its demonstrated efficacy as a popular medicine. *Ganoderma* is also used in treating conditions of the nervous system. The ability of bioactive polysaccharides and polysaccharide-bound proteins to modulate immune cells can be due to the structural diversity and variability of these macromolecules. The bioactive glucanes and proteoglucans isolated from medicinal mushrooms are the most promising class of immunoceutics. Unlike proteins and nucleic acids, polysaccharides contain repetitive structural features which are polymers of monosaccharide residues joined to each other by glycosidic linkages. Glucan appear to be beneficial to humans with impaired immune systems, and those suffering from infectious diseases and cancer, as well as in helping patient recovery from chemotherapy and radiotherapy.

The basic mechanism of DNA replication, recombination and DNA repair are conserved throughout evolution. The complementarity of strands of DNA and the double stranded nature of DNA plays the major role in all the process. Damage to DNA by physical, chemical and biological factors influences the extraordinary accuracy of the entire process. At each cell division a handful of error is introduced per billion bp. Treatment modalities for cancer like chemo and radiotherapy affect DNA in many ways. Drugs of natural origin are capable of increasing the rate of DNA repair. The chapter will focus on the natural drugs and their influence on DNA repair mechanism. In the hierarchy of targets of reproductive death, DNA must be surely placed at the top, though membrane damage should be considered as the second important target with eukaryotic cells which contain their DNA in the nucleus, little lethal damage is observed as long as the radiation is absorbed only by the outer membrane and cytoplasm. There is a drastic increase as soon as the ionizing radiation reaches the nucleus and hence DNA. The DNA damages produced by ionizing radiation can be intra- or inter-strand cross linking and single and double strand breaks (**Figures 2** and **3**). The cellular reactions include halt in cell cycle, advancement at cell cycle checkpoints and the stimulation of DNA repair. An unrepaired or misrepaired DNA damage can result in genetic or genomic variability, changes in cellular individuality and role, cell death, and in multi-cellular organisms, neoplastic transformation.

Humanities use of mushrooms extends as early to 5000 B.C. About 2000 species of edible mushrooms are known all over the world. The total production of the edible mushroom is about 3.75 million tonnes. However they are rich source of high quality protein, vitamins and minerals. The average protein content is 10–40% on dry weight basis and low in fat content. Extracts and powders of mushrooms (mycelia and sporocarps) in the form of sugar coated tablets are being marketed on commercial scale for treatment of diseases such as diabetes, cancer, etc. Medicinal macro fungi modulate immune system and possess antitumor, antimicrobial,

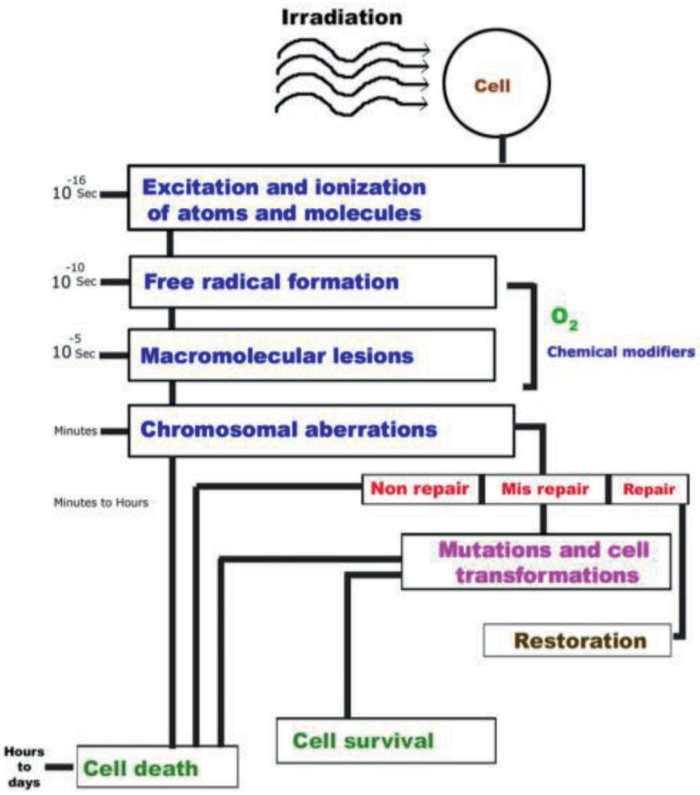

Figure 2.
Effect of radiation on cell.

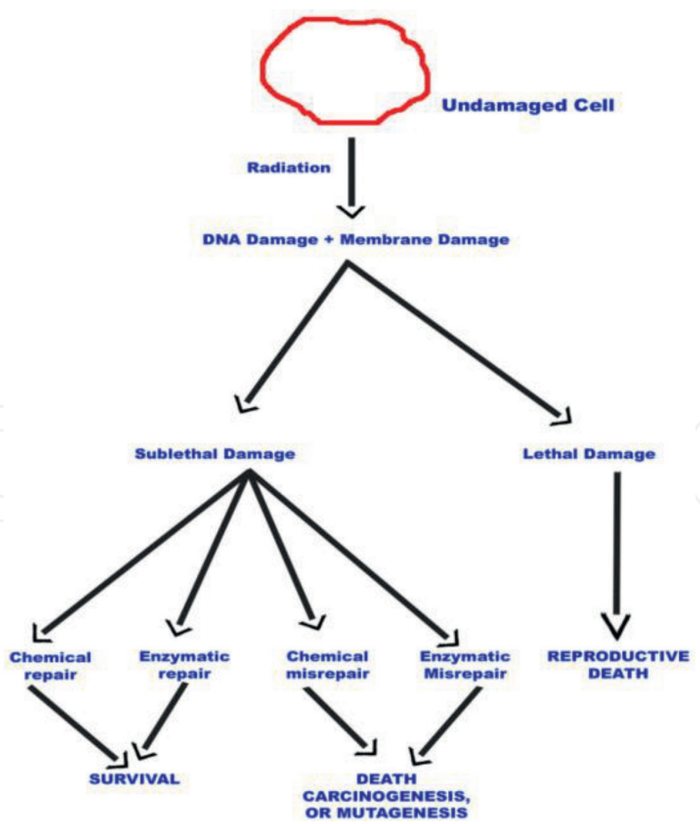

Figure 3.
Different types of damages in cell after radiation exposure.

anti-inflammatory activities. Attempts are done to explore the use of mushrooms and their metabolites for the treatment of a variety of human ailments [19]. More than 100 medicinal mushrooms have been identified.

Ganoderma lucidum, commonly known as reishi, the mushroom of immortality is one of the most popular medicinal mushrooms. The fruiting bodies of *Ganoderma lucidum* contain a variety of chemical substances including polysaccharides, triterpenes, nucleosides, ergosterols, fatty acids, proteins, peptides and trace elements. The polysaccharides of *G. lucidum* are the other major source of its biological activity and therapeutic use. This mushroom has attracted great attention owing to its antitumor and hypoglycemic activities [6]. Many fungal glucan have been reported to be active in humans.

2. Materials and methods

2.1 Animals

Swiss albino mice, were kept for a week under environmentally controlled conditions with access to standard food and water. Recommendations of the ethical Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) instituted by the Animal Welfare Division of the Government of India were followed.

2.2 Irradiation

Gamma cell facility of Bhabha Atomic Research Centre, Trombay was used for irradiation. Whole body irradiation to mice was given to unanesthetized animals, which were kept in well-ventilated Perspex boxes and was exposed at a dose rate of 1 Gy/min. *Ex vivo* irradiation of human peripheral leukocytes was done in Junior Theratron unit with a dose rate of approximately 0.4 Gy/min. Chemicals were obtained from Sigma Chemicals (St. Louis, Missouri) and purchased from Merck India Ltd., Mumbai.

3. Methods

3.1 Isolation of glucan

Ganoderma lucidum were collected from Southern parts of India. The polysaccharides were isolated from the fruiting bodies by the method of Mizuno [20]. Purification of the compound was done by ion-exchange chromatography. Qualitative confirmation was done by anthrone [21] and phenol sulphuric acid reagent [22]. Further characterization of the compound was done by IR and NMR, mass spectra, gel filtration and acid hydrolysis.

3.2 Comet assay

Comet assay was performed by the method of Singh with modifications [23]. DNA damage in blood leukocytes was estimated. Ten microliters of heparinised whole blood, is mixed with 200 μl of low melting point agarose at 37°C and layered on frosted slides pre-coated with 200 μl high melting point agarose. The slides were pre-chilled in lysing solution and the standard protocol was followed [24].

CASP software was used for the quantitation of the DNA strand breaks of the stored images by which the percentage DNA in tail, tail length, tail moment, and olive tail moment [25]. The tail length of comet specifies the extent of damage as the smaller molecules move faster on the agarose gel. The longer tails of the comets

indicate that the strand breaks are more frequent. The tail moment normalizes the difference in the size of the nucleus studied, which is product of the percent DNA in the tail of the comet and tail length. Calculation of olive tail moment distance of centre of gravity of DNA is considered rather than usual tail length.

3.3 Metaphase preparation

Six groups of six animals each were used. At 22 h after irradiation all the animals were injected i.p. with 0.025 colchicine and sacrificed 2 h later by cervical dislocation. Bone marrow from the femur was aspirated, washed in saline, treated hypotonically (0.565% KCl), at 37°C for 30 min, fixed in 3:1::methanol:acetic acid, spread on clean slides and stained with 4% Giemsa [26].

The aberrations were scored with the help of a light microscope. Per animal 500 metaphases were scored. Chromatid breaks, chromosome breaks, fragments, rings and dicentrics as well as cells showing polyploidy and severely damaged cells (SDC), cells with 10 or more aberrations of any type, the different types of aberrations were scored. In 'chromosome type' aberration, breaks involved both the chromatids and in 'chromatid type' aberration involved only one chromatid. Fragments are those deleted portion having no apparent relation to any particular chromosome [27]. Data are mean ± (S.E).

3.4 Treatment of animals

Group I—double distilled water (DDW).
Group II—300 mg/kg body wt. of amifostine i.p. (30 min prior to irradiation).
Group III—20 mg/kg body wt. of glucan orally (5 min after irradiation).
Group IV—DDW + 4 Gy radiation (RT).
Group V—300 mg/kg body wt. of amifostine (30 min before irradiation) + RT 4 Gy.
Group VI—RT 4 Gy + 20 mg/kg body wt. glucan orally (5 min after irradiation).

4. Results and discussion

The compound isolated from *G. lucidum* answered anthrone and phenol sulphuric tests giving typical colour reactions indicating the presence of carbohydrates. From the IR spectrum, pyranoid form was suggested to be present due to the presence of three absorption bands at 1153.4, 1091.6 and 1029.9 cm^{-1}. In the HNMR spectrum H^{-1} signals were observed at less than 4.8 ppm (4.762, 4.683, 4.667, 4.658, 4.402 ppm), which suggest that component sugars have beta configuration. From gel filtration chromatography, the molecular weight of the compound was found to be 1.5×10^6 Daltons. From the acid hydrolysis treatment for the detection of monosaccharides, the sugars present in the compound were found to be glucose, mannose and rhamnose. The compound was identified to be beta-glucan.

4.1 DNA repair enhancement

The repair process in lymphocytes was found to be enhanced by the glucan at 50 μg/ml concentration. The percent DNA, tail length, tail moment and olive tail moment was reduced significantly. At 2 Gy 0 min, the comet parameters increased. Fifteen minutes after irradiation the comet parameters were reduced. The presence of glucan reduced the comet parameters further. After 2 h of irradiation the comet parameters were reduced by the glucan to the control level (**Figure 4** and **Table 1**).

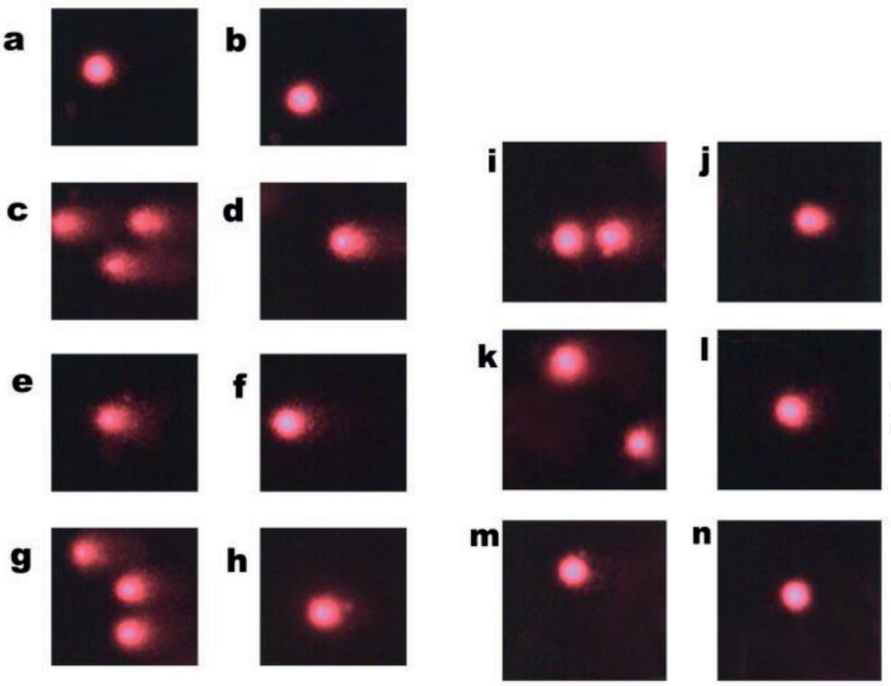

Figure 4.
DNA repair enhancement by glucan in human lymphocytes (comet assay). Untreated: (a) control; (c) 2 Gy 0 min; (e) 2 Gy 15 min; (g) 2 Gy 30 min; (i) 2 Gy 45 min; (k) 2 Gy 60 min; (m) 2 Gy 120 min. Treated with glucan: (b) control; (d) 2 Gy 0 min; (f) 2 Gy 15 min; (h) 2 Gy 30 min; (j)2 Gy 45 min; (l) 2 Gy 60 min; (n) 2 Gy 120 min.

Treatment (per 500 cells)	Fragments	Chromatid break	Chromosome break	Rings	Dicentrics
DDW (control)	6.3 ± 2.5	0.16 ± 2.5	0	0	0
Amifostine (alone)	8.0 ± 1.7	2.3 ± 0.3	0	0	0
Glucan (alone)	7.3 ± 0.8	1.0 ± 0.5	0	0	0
RT 4 Gy (alone)	384.1 ± 16.4[g]	13 ± 2.3[g]	8.5 ± 1.5[g]	3.8 ± 0.6[g]	11.3 ± 1.6[g]
RT 4 Gy + amifostine	31.5 ± 4.0[a,i]	9.5 ± 1.8[e]	2.3 ± 0.4[b,i]	0.8 ± 0.4[b]	2.1 ± 0.4[a,i]
RT 4 Gy + glucan	38.6 ± 4.6[a]	8.1 ± 0.7[e,k]	2.8 ± 0.4[a]	0.8 ± 0.3[b]	1.3 ± 0.4[a]

Datas are mean ± S.E. n = 6.
[a]P < 0.0001.
[b]P < 0.001.
[c]P < 0.01.
[d]P < 0.05.
[e]Marginally significant, compared to RT alone.
[f]P < 0.05 compared to RT + amifostine.
[g]P < 0.0001 compared to DDW.
[h]P < 0.001 compared to amifostine alone.
[i]P < 0.01 compared to amifostine alone.
[j]P < 0.05 compared to amifostine alone.
[k]P < 0.0001 compared to glucan alone.
[l]P < 0.001 compared to glucan alone.

Table 1.
*Effect of **G. lucidum** glucan and amifostine on the induction of different chromosomal aberrations in mouse bone marrow after whole body γ-irradiation (4 Gy).*

4.2 Chromosomal aberrations

Sham treated control showed 1% aberrant cells. Compared to control glucan or amifostine alone did not induce any significant changes. There was significant increase in the percentage of aberrant cells treated with radiation. Treatment with glucan after irradiation and amifostine before irradiation resulted in significant

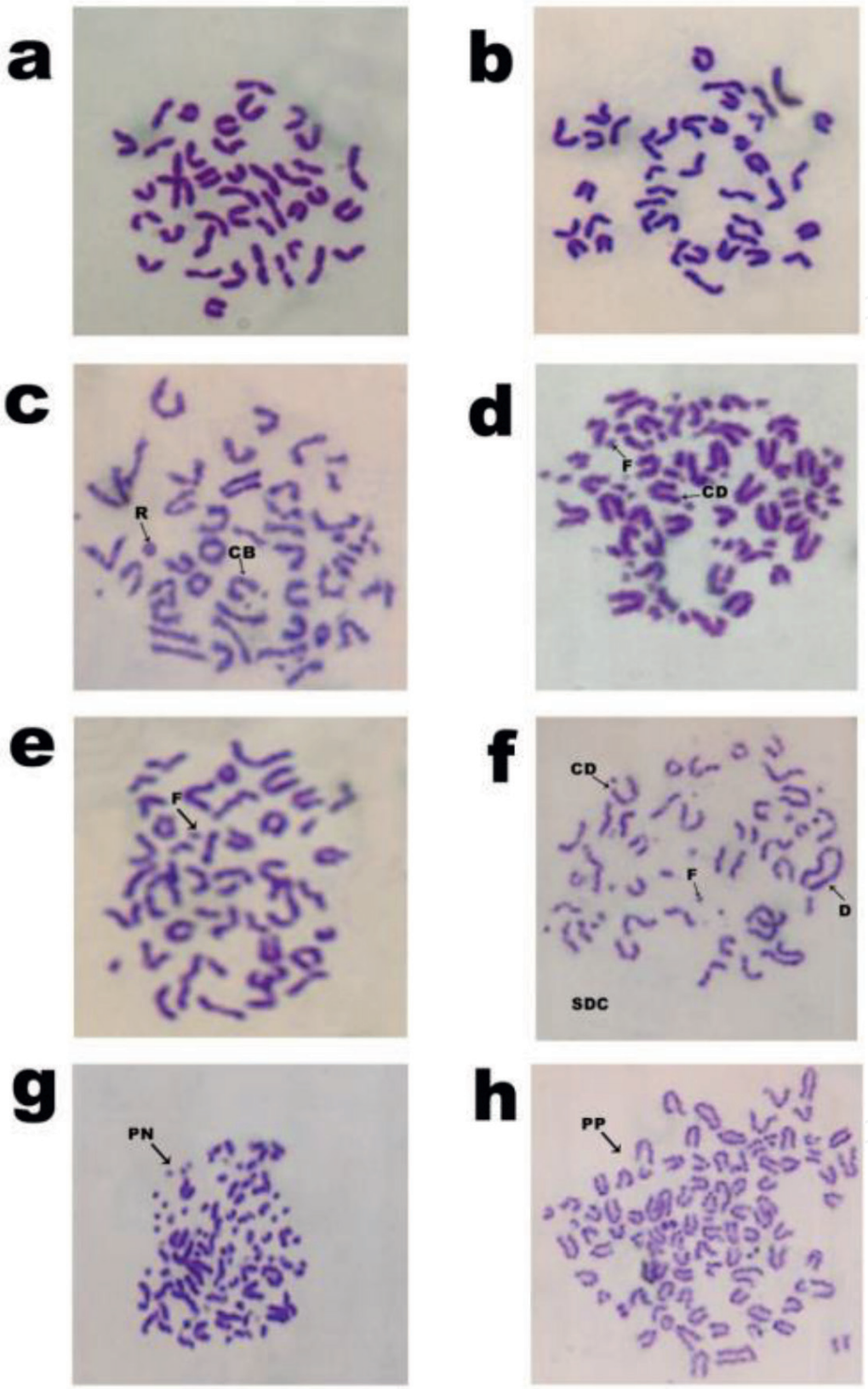

Figure 5.
Different types of chromosomal aberrations in mouse bone marrow. F, fragments; CD, chromatid break; CB, chromosome break; PN, pulverisation; SDC, severe damaged cell; PP, polyploidy; D, dicentrics; R, rings.

decrease in the percentage of aberrant cells and number of aberrations per cell compared to the group which received radiation alone. A decrease in all types of aberrations, as well as polyploidy and cells with pulverisation was observed. The number of severe damaged cells (SDC) significantly reduced to about 1.5 times after glucan treatment. The number of cells with multiple and complex damage was

Treatment	Polyploidy	SDC	Pulverised cells
DDW (control)	0	0	0
Amifostine (alone) (300 mg/kg body wt.)	0.6 ± 0.66	0	0
Glucan (alone) (20 mg/kg body wt.)	0	0	0
RT 4 Gy (alone)	4.8 ± 0.60[g]	14 ± 1.3[g]	10.6 ± 1.3[g]
RT 4 Gy + amifostine (300 mg/kg body wt.)	0.83 ± 0.40[a]	3.6 ± 0.71[a,i]	1.6 ± 0.33[a,j]
RT 4 Gy + glucan 20 mg/kg body wt.)	0.5 ± 0.22[a]	2.0 ± 0[a,f]	1.5 ± 0.22[a,l]

Datas are mean ± S.E. n = 6.
[a]P < 0.0001.
[b]P < 0.001.
[c]P < 0.01.
[d]P < 0.05.
[e]Marginally significant, compared to RT alone.
[f]P < 0.05 compared to RT + amifostine.
[g]P < 0.0001 compared to DDW.
[h]P < 0.001 compared to amifostine alone.
[i]P < 0.01 compared to amifostine alone.
[j]P < 0.05 compared to amifostine alone.
[k]P < 0.0001 compared to glucan alone.
[l]P < 0.001 compared to glucan alone.

Table 2.
Effect of G. lucidum polysaccharides and amifostine on the induction of polyploidy, SDC and pulverization in mouse bone marrow after whole body γ-irradiation (4 Gy).

Time	Olive tail moment without glucan	Olive tail moment with glucan
0 Gy 0 min	3.9444 ± 0.2582	3.677 ± 0.2362
2 Gy 0 min	26.1602 ± 0.5566	26.001 ± 0.3345
2 Gy 15 min	15.6947 ± 0.5193	15.0996 ± 0.7832
2 Gy 30 min	10.0415 ± 0.5287	7.9954 ± 0.57714
2 Gy 45 min	7.2821 ± 0.5541	6.1824 ± 0.5673
2 Gy 60 min	7.5109 ± 0.5966	4.4504 ± 0.3189
2 Gy 120 min	6.2424 ± 0.3847	3.6330 ± 0.3214

Table 3.
Effect of glucan on enhancement of DNA repair in human lymphocytes after 2 Gy gamma irradiation (comet assay).

significantly decreased by glucan post-treatment indicating that the former may help in the repair of the DNA breaks (**Figure 5**, **Tables 2** and **3**).

The lifespan of cells to radiation leading to a loss of cell viability can be greatly influenced by the ability of cells to repair injured DNA. The hazard in mammals exposed to ionizing radiation is to the haemopoetic system. Radiation induced damage to DNA can temporarily affect DNA replication allowing repair to happen involving a well-coordinated event of DNA repair enzymes such as DNA repair polymerase, DNA ligase and PARP [28]. The factors that influence the response of living cells to radiation are the DNA repair status, the physiological state of cells, the presence of oxygen and chemicals as well as pre and post-irradiation treatments [29].

By examining the comet parameters of human peripheral blood leucocytes the effect of polysaccharides on DNA repair was ascertained. Through the initial 30 min, most of the DNA repair processes were completed. The presence of polysaccharide boosted the process of DNA repair. The comet parameters were more at 30 min post-irradiation, in irradiated control and polysaccharide treated group which can be attributed to the commencement of excision repair process [30]. After 45 min

there was not much difference in the comet parameters, in control group. The comet parameters kept on reducing in the presence of polysaccharides and at 120 min the comet parameters were almost similar to the unirradiated control. Re-joining of DNA strand breaks by most cell types is known to be a rapid process within few seconds-minutes [31] and this kinetics are seen in comet assay too. In freshly isolated lymphocytes repair by Hydrogen peroxide induced breaks takes place very slowly which can be due to the additional DNA breakage as a result of quick exposure to atmospheric oxygen in the repair incubation period [32]. At the same time repair of endonuclease III- or FPG-sensitive sites (i.e., oxidized purine and pyrimidines) by base excision repair, is much slower process, taking few hours [33].

Background levels of DNA damage in normal cells, the variation in DNA repair capacity within human populations, and the regulation of DNA repair at the molecular level within the nucleus can be monitored by comet assay [34].

5. Conclusion

The integrity of DNA molecule at structural level has to be protected and preserved for the effectual transmission of the genetic information contained to progeny. Distinctions in the arrangement of nucleotides or changes in the configuration of bases or sugars, in the double helix of DNA can impede the replication or transcription of genome.

Multilation to DNA molecule is the crucial factor for cell death. Mechanisms of repair of damaged DNA molecules play a vital role in cell survival. No medicine has been invented that could successively be applied in DNA damage. Our study indicates that the polysaccharides from *G. lucidum* enhance the repair process.

5.1 Advances in area of DNA repair

Prevention is better than cure and cancer induction is greatly influenced by nutrition. The unaffordable discovery cost and failures at the completion of discovery pipeline makes medicines arbitrary to the developing countries. Newer technologies like reverse pharmacology, systems biology which are charming give innovation opportunities based on investigational wisdom and universal viewpoint of translation medicine. Chemotherapy and SSRI revolutionised longevity and quality of life in therapeutics. The Human Genome Project opened understanding towards personalised medicine. Glucan from *G. lucidum* possess immunomodulating activities and regulate a number of undiscovered cellular genes. New studies are needed to unravel these molecular targets giving insights into the interactions of the fungi like *G. lucidum* with our body system and provide strategies for the discovery of effective and safe approaches for drugs from natural sources.

Glucan was isolated from the mushroom *Ganoderma lucidum*, a basidiomycete white rot macro fungus that has been used extensively for therapeutic use in China and Japan for years. The compound was characterised by different chromatographic techniques, done by IR, NMR, and paper chromatography, gel filtration chromatography and spectroscopic techniques like infra-red spectrum and nuclear magnetic resonance spectrum.

The molecular weight of the isolated glucan was 1.6×10^6 Daltons. The rate of DNA repair in the presence and absence of the compound was determined. Comet assay was performed using the method of Singh in human lymphocytes. Chromosomal aberration was studied in mouse bone marrow. After radiation exposure, the comet parameters, percent DNA, tail length, tail moment and olive tail moment were changed in the presence of glucan. Chromosomal aberrations and

individual aberrations were also reduced by glucan. The result of present investigation reveals the potential application of glucan from *G. lucidum* in increasing the rate of DNA repair which makes it useful in medical scenario.

The path of science is always fascinating giving deep intuitions with new technologies. The term 'DNA repair' gained more significance in last decade. The beautiful discoveries in essential mechanisms of DNA repair extended Nobel prize in Chemistry in 2015 to T. Lindahl, P. Modrich and A. Sancar. Their discovery defined three pathways that essentially correct DNA damage, protecting the integrity of genetic code assuring perfect replication through generations allowing correct cell division. The mechanisms behind base excision repair, mismatch repair and nucleotide excision repair was explained. Since then the number of drugs and targeted pathways has increased remarkably. The DNA repair enzyme was declared as the molecule of the year in 1994. Though the studies from model organisms serve as a basis to elucidate of repair mechanism, the utilisation of cutting edge technology has channelled in a new era of DNA repair research. The DNA repair pathways have also become better understood. The accessibility of a wide-ranging spectrum of drugs with known molecular targets will provide the rationale to use those drugs in relation to various disease conditions and to combine DNA damaging agents with the appropriate DNA repairing agent. The journey of DNA repair continues. Our current research is carried out in this direction.

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